

Blue Nails: A Case of Minocycline-Induced Hyperpigmentation

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Summary

Minocycline-induced hyperpigmentation is a rare but documented side effect of the drug. It has an approximate incidence of 3-15%. Patients being treated with minocycline for rosacea have a 15% incidence of developing hyperpigmentation. Patients treated with minocycline for acne have a lesser incidence of 3%. While specific causation remains unconfirmed, there appears to be a strong correlation noted in the literature of dose- and duration-dependent development. There are three main types of minocycline-induced hyperpigmentation. Type I has been seen as early as a few weeks after initiation of minocycline treatment, whereas type II and III appear to develop after several months for cumulative doses of 70-100 grams. Type II is thought to be due to minocycline or its oxidation products being deposited into insoluble complexes within the cutaneous tissue. Discontinuation of minocycline usually results in resolution of hyperpigmentation in few months. Type III has been known to cause permanent changes.

Patient Presentation

A 60-year-old male on minocycline for acne suppressive therapy presented with progressive 3-month bluish discoloration of his fingernails. He recalled no recent fingernail trauma and denies dyspnea, shortness of breath, fatigue, and syncope. He had no history of congenital cardiac conditions other than bileaflet mitral valve with mild mitral insufficiency, noted on outpatient echocardiogram 10 years prior. He had no history of smoking, pulmonary disease, or rheumatologic disease. The pigmentation was non-palpable, non-pruritic, and non-tender. On physical examination, bluish pigmentation was also noted on patient's gingiva and cutaneous tissue of medial aspect of ankle. The patient had been taking minocycline for forty years but his dose was doubled 2 years prior to presentation. Of note, 3 years prior he had noticed hyperpigmentation over his ankles. The patient was advised at that time to discontinue minocycline and switch to doxycycline. However, he continued taking minocycline and 9 months later developed leukopenia of 3.3 K/ μ L, decreased from his baseline of 4.5 K/ μ L.

Diagnosis

Minocycline-Induced hyperpigmentation type II.

The patient may fit the classification of type II, which is often seen on healthy cutaneous tissue as brown-gray or blue-black coloration of shins, ankles and arms. The patient agreed to switch to doxycycline. After 5 months, the patient continued to have bluish discoloration of his fingernails and gingiva although improved to faint bluish coloring of nailbeds.

Testing

An echocardiogram was performed to evaluate for cardiac causes of cyanosis. Workup for cardiac causes were negative.

Five months after discontinuation of minocycline his bluish discoloration faded which usually it is seen in Minocycline-Induced Hyperpigmentation type II.

Treatment

Switched his minocycline to doxycycline. After 5 months, the patient continued to have bluish discoloration of his fingernails and gingiva although improved to faint bluish coloring of nailbeds.

Patient Outcomes

With switching his minocycline to doxycycline his nail discoloration got better. He also validated the cutaneous findings as a result of minocycline use.

Lessons Learned

1. Recognition of cutaneous findings as a result of minocycline induced hyperpigmentation.
2. Differentiated sub-types of minocycline-induced hyperpigmentation and distinguish variations in resolution of symptoms.

Reduce unnecessary diagnostic evaluations

Complete patient education regarding the minocycline side effect when prescribing as a new medication

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Selective Cannabis Strain Allergy in a Patient Presenting with a Local Allergic Reaction

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Summary

RATIONALE: Cannabis use is growing domestically due to recent legalization in many jurisdictions. Although there are many reports of cannabis allergy in the literature, to our knowledge, there is no published report of selective cannabis strain allergy.

RESULTS: A 31-year-old male presented for allergy testing due to an episode of periorbital swelling after direct contact with cannabis. He observed that he was more reactive to certain strains of cannabis. He brought in various strains of cannabis for skin testing and had positive testing to the three of the five strains.

CONCLUSIONS: We believe this is the first reported case of selective cannabis strain allergy based on patient history and skin prick testing. This case report outlines the variability in different strains of cannabis and stresses the importance of further research into cannabis allergen identification. Multiple cannabis allergens should be included and incorporated into commercial extracts when they become routinely available.

Patient Presentation

A 31-year-old male was referred for allergy assessment to cannabis. He had observed several episodes of pruritus and erythema on his skin after contact with varying strains of cannabis and noted that the severity of his reaction appeared to be strain dependent. He developed a severe local reaction involving bilateral periorbital swelling shortly after coming into direct contact with one particular strain of cannabis (believed to be "Blue Moonshine", but unsure). This particular episode was associated with dyspnea, but no other systemic symptoms. For this reaction he presented to a local emergency department and was treated with antihistamines and corticosteroids with good effect. He had never had an immediate reaction after smoking cannabis. After this particular episode and prior to his allergy consultation, he continued to smoke cannabis without adverse reaction but avoided direct contact. His past medical history was notable for asthma and seasonal rhinoconjunctivitis.

Diagnosis

The patient was diagnosed with recurrent local allergic reactions after direct contact with particular cannabis strains. He had suspected selective cannabis strain allergy based on his clinical history.

Testing

Skin testing was performed to environmental inhalants and the patient had positive reactions to dust mite, grass pollen and tree pollens. The patient also brought in various strains of cannabis for skin testing including "Blue Moonshine" (Cannabis indica dominant strain), "Blue Dream" (Hybrid strain that is largely Cannabis sativa dominant), "Sweet Island Skunk" (Cannabis sativa dominant strain), "Sweet Skunk" (Hybrid) and "Blueberry Haze" (Hybrid). The cannabis strains were mixed with small aliquots of water for skin testing. Fresh testing was required due to the absence of commercially available

abstracts. He had positive testing to the strains “Blue Dream” (7 mm), “Sweet Island Skunk” (10 mm) and “Blueberry Haze” (6 mm) while he had negative testing to “Blue Moonshine” and “Sweet Skunk”.

Treatment

The patient was advised to avoid direct cutaneous or mucosal contact with cannabis due to his reported clinical history and skin testing. Due to the inconsistencies in strain identification by history and skin testing, he was advised to avoid all strains. An epinephrine autoinjector was prescribed in case he developed a more severe systemic reaction on repeat exposure.

Patient Outcomes

A telephone follow-up visit was conducted 6 months after the initial consultation. The patient endorsed that he was still smoking cannabis regularly but had not had any new significant reactions. He continued to use all above tested strains of cannabis in addition to a few new ones. He was still avoiding direct contact if possible.

Lessons Learned

Cannabis use is prevalent across the world. However, in response to recent legalization in many jurisdictions, more information regarding its potential medical side effects are becoming evident. There are two main species of cannabis (*Cannabis sativa* and *Cannabis indica*) from which all current strains are believed to be descendants.[1] Strains are produced by crossbreeding existing strains to take advantage of particular drug effects. A hybrid strain is considered to contain components of both *Cannabis indica* and *Cannabis sativa*. There are nearly 3000 different strains listed on some commercial websites which are organized into three dominant classes (Indica, Sativa, Hybrid).[2]

Various studies have linked cannabis use to hypersensitivity reactions including exacerbations of asthma, allergic rhinitis, contact dermatitis, anaphylaxis and urticaria. [3-6] There is currently only one allergen (Can s 3) listed in the WHO/IUIS Allergen Nomenclature Sub-committee, and it is estimated that only 72% of patients with a reported allergy to cannabis are sensitized to this allergen.[7] With rising use of cannabis, the ability to accurately detect individuals with cannabis allergy on skin prick testing will be important.

This case report highlights the wide range of cannabis strains which may be implicated in hypersensitivity. Despite the fact that all current strains of cannabis are believed to be descendants of two plants, there is immense variability amongst strains. This patient had positive testing in three of five strains he was tested against, and the strains that the patient was sensitized to did not appear to have any obvious similar characteristics. Complicating the situation, the strain that the patient believed was the trigger for his initial severe reaction (Blue Moonshine) was negative on skin testing.

We believe this is the first reported case of selective cannabis strain allergy based on patient history and skin prick testing. However, there was discrepancy in identification of the likely causative strain. In the near future, cannabis extracts will likely be available for clinical use. As there is currently only one confirmed allergen from cannabis plants, this report also emphasizes the importance of further research into determining the specific allergens implicated in cannabis allergy. Having a larger number of identified allergens available will likely increase the specificity of testing. Accurate identification of cannabis allergens and incorporation into commercial extracts will undoubtedly be a difficult task given the complexity and variability of currently available commercial strains.

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ATYPICAL CASE OF KAWASAKI DISEASE

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Summary

Peripheral gangrene must be regarded as an important sign of infantile Kawasaki disease early treatment of which can prevent severe permanent coronary involvements and sequels.

Patient Presentation

Early diagnosis and treatment of Kawasaki disease as the most common cause of acquired heart disease in childhood, may significantly improve the prognosis.

We present the case of a 1year 7 months male patient previously Healthy with history of high fever during 5 days, eyes with non exudative billateral conjuntivitis, big fisures on mouth, edema of both hands and feet with vasculitis changes, generalized rash on trunk, and genital erytema. No changes on BCG vaccine scar, or palpable lymph nodes. The patient was irritable with high grade fever. CBC : Hb 10.3, Hct 31, Leu 16,620, Neu 74 % , Linf 18 % , Mono 5 % , Eos 1.5 % , Plt 386,000, PCR 213. AST 26, ALT 28, Bilirrubine 0.41, BI 0.25, BD 0.16, GGT 32, DHL 1040, FA 183. The patient presented with noticeable drop on platelet Count from 386,000 to 41,000 and dramatic leucocyte elevation from 16,630 to 57,270. Hiponatremia was recorded 131 mg dl. The patient was diagnosed with vasculic process compatible with Kawasaki Disease complicated with cutaneuos vasculitis and peripheral gangrene. Five criteria were found on the patient (fever, eye, oral, extremities, exhanthem). Prominente Leucocytosis, thrombocytopenia (prognosis factor), elevation of PCR, hyponatremia. Infection was ruled out explaining the leucocytosis, thromocytopenia and extremities changes.

Treatment was done initially with high doses of immunoglobuline)(2 grams kg), high doses of aspirine, systemic steroids (methylprednisolone 30 mg kg dose), enoxaparine.

Diagnosis

The patient was diagnosed with vasculic process compatible with Kawasaki Disease complicated with cutaneuos vasculitis and peripheral gangrene.

Testing

Dilation of Right coronary artery 4 mm

Skin Biopsy showing cutaneous vasculitis with fibrosis..

Treatment

Treatment was done initially with high doses of immunoglobuline)(2 grams kg), high doses of aspirine, systemic steroids (methylprednisolone 30 mg kg dose), enoxaparine.

Patient Outcomes

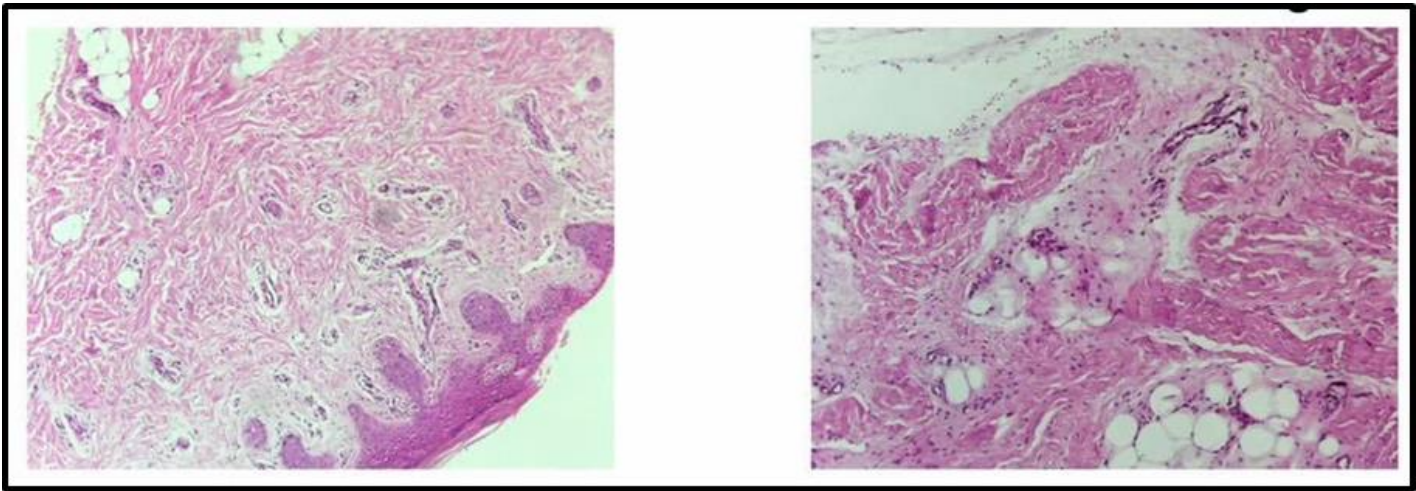
After adequate treatment, peripheral gangrene, arterial dilations and aneurysms improved, but during 12 months follow-up coronary aneurysms did not improve completely.

Lessons Learned

Early diagnosis and treatment of Kawasaki disease as the most common cause of acquired heart disease in childhood, may significantly improve the prognosis.

Cutaneous vasculitis could present in patients with Kawasaki disease as a form of atypical clinical manifestations.





Allergy Evaluation in a Patient with Atopic Dermatitis and Narcolepsy Type 1

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Summary

Atopic dermatitis (AD) and narcolepsy type 1 (NT1) are two distinct diseases that have not been classically shown to be related. The potential connection between the known immunological etiology of AD and the proposed autoimmune pathophysiology of dysregulation in NT1, however, is the subject of ongoing speculation and debate with advances in gene sequencing and technology. Here, we present a case of a patient with concomitant refractory AD and NT1, and review the current research on their immunological relationship and the challenges in management relative to disease burden and psychiatric comorbidities. She was trialed on a course of dupilumab and is following with her primary care for NT1 management.

Patient Presentation

A 19-year-old Asian American female with NT1 and AD presented to the allergy clinic for evaluation of food and environmental allergies. Her past medical history was significant for diagnosis of AD at age 9, in which shortly after, she began having symptoms suggestive of narcolepsy, with excessive daytime fatigue, occasional hypnagogic hallucinations, and sleep paralysis. She did not mention her sleep symptoms until the age of 16 and was formally diagnosed with NT1 when she developed increasingly excessive daytime sleepiness followed by cataplexy several months later. Coupled with her clinical presentation, recent polysomnogram and multiple sleep latency tests further supported the diagnosis of NT1 with short REM latency and sleep-onset rapid eye movement periods during all nap intervals respectively. Since her NT1 diagnosis, the patient has reported sleeping an average of 6 hours each night with 2 daytime naps. She has previously been prescribed stimulants such as modafinil, methylphenidate, and amphetamine salts, but is following with her primary care on creating a sustainable management regimen.

Her AD has been conservatively managed for several years with minimal improvement on dietary control, topical corticosteroids, tacrolimus and over the counter emollients. The pruritis associated with her eczematous lesions, particularly on her antecubital regions, have frequently disrupted her sleep, with intense flares-up occurring every 3-4 months. She had attributed these flare-ups with environmental allergies and food sensitivities, but has never been formally identified. The patient denies any history of asthma or allergic rhinitis, with crisaborole as the sole pharmacological treatment of her AD. For management of sleep disruption secondary to pruritus, the patient has trialed several first and second-generation antihistamines but all were discontinued secondary to increased daytime somnolence and worsening of her narcolepsy symptoms. She endorsed frequent feelings of depression and anxiety secondary to poor management of her medical illnesses, but denies any thoughts of suicidality or homicidality. Patient Health Questionnaire-2 was negative and mild anxiety was noted on the Hamilton Anxiety Scale (score of 14).

Diagnosis

Physical exam was consistent with atopic dermatitis and eczema, which had been previously known to the patient and her mother. Testing at this visit was done to identify specific triggers that could worsen her AD and be related to her flare-ups or associated with her narcolepsy.

Testing

Laboratory values were significant for serum IgE of 982 and RAST test positive for dust mites (including *D. Pteronyssinus* and *D. Farinae*), common birch, hazelnut, cat dander, and several other antigens. Of note, the patient has tested positive for HLA DQB1*06:02. She has no family history of autoimmune diseases or atopy. She tested negative for ANA, anti-dsDNA, RF, anti-SM, anti-SSA, anti-SSB, and anti-CCP and her CRP, ESR, TSH, and Hgb A1c were all within normal limits. Physical examination revealed thick, erythematous oozing plaques of the antecubital regions and the neck. On assessment, she had an Eczema Area and Severity Index Score (EASI) of 3.45 and Scoring Atopic Dermatitis Score (SCORAD) of 37.

Treatment

The patient tested positive for several environmental and food allergies, most notably dust mites. Dust mites are the most common allergen known to aggravate AD and avoidance can greatly reduce exacerbations and long term sequelae. With the patient's long history of AD and its refractory nature to standard interventions, reduction of allergen exposure had only marginally improved her symptoms. Options such as allergen-specific immunotherapy (SIT) against dust mite species were discussed, however immunotherapy has been cautioned in patients with autoimmune conditions, as no studies to date have evaluated the safety of allergen-specific immunotherapy in patients with comorbid autoimmune conditions. She was ultimately trialed on a course of dupilumab, which is an IL-4 receptor alpha antagonist that is the only FDA-approved monoclonal antibody for the treatment of AD not adequately controlled with topical prescription therapies.

Patient Outcomes

Upon consultation at the clinic, the patient decided to manage her AD with dupilumab before revisiting her NT1 treatments. Next allergy follow-up is pending patient return.

Lessons Learned

Atopic dermatitis and narcolepsy type 1 are two unique disease processes that affect different body systems. Both may share an immunological connection and various comorbidities, which can complicate treatment and management options as physicians must take into account what the standard pharmacological intervention is and how it can impact other disease processes. Future research is needed to better understand treatment options for patients with refractory eczema and comorbid autoimmune disease. In this case, and for similar cases involving multiple specialists, a multimodal, physician-patient team approach is needed to ensure optimal success. As advances in genetics and gene associations occur, this further highlights the need to reassess diseases that previously were not previously deemed as related, thus providing future avenues for precision medicine and patient care. More research is needed to evaluate an immunological mechanism of NT1 and any potential overlap with atopic or autoimmune disease. Efforts to elucidate the immunopathogenesis of diseases such as AD and NT1 should be done in conjunction with trials for development of new immunotherapeutic interventions. Thus far, case series and longitudinal follow-ups of patients receiving immune-targeted treatments such as IVIg, plasmapheresis, or alemtuzumab have been conflicting or inconclusive.





An Abraxane (C) Accident

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Summary

A young Caucasian woman with recently-diagnosed metastatic breast cancer developed Stevens-Johnson Syndrome (SJS) after one infusion of albumin-bound paclitaxel, a formulation of paclitaxel specifically formulated to minimize the risk of infusion reactions. Her early symptoms of a localized skin rash and oral ulcers were treated with steroid cream and supportive care initially. She rapidly deteriorated to develop a diffuse, painful rash with more extensive destruction of her oral mucus membranes. After skin biopsy confirmed the diagnosis of SJS, she was treated with high-dose IV steroids and recovered without ocular impairment or circulatory collapse. Following recovery, she struggled with malnutrition due to pain from oral ulcers and has yet to resume treatment for her metastatic breast cancer.

Patient Presentation

The patient is a 30-year-old Caucasian female with obesity and depression, who was recently diagnosed with metastatic breast cancer. Family history was unremarkable for Stevens-Johnson Syndrome or other known drug reactions. She received an intravenous infusion of albumin-bound paclitaxel, also known as abraxane, as treatment of her breast cancer following progression on hormonal therapy. She had no history of allergies to any medications and had not recently been started on any new medications in 3 months after a trial of different hormonal therapies for breast cancer. Two days following the abraxane infusion, she developed a maculopapular rash on her wrist, as well as oral ulcers. At that point, she was advised to use a steroid cream on her rash and medicated mouthwash for her oral ulcers. Over the ensuing 48 hours, her rash rapidly spread to her thighs, neck, face, and mouth. When describing the rash, the patient said it was increasingly painful, rather than pruritic. She presented to her local community hospital where she was found to be severely septic. Initially, she was thought to have a viral infection or mucositis causing the sepsis and was treated accordingly with acyclovir in addition to broad-spectrum antibiotic therapy. Due to a lack of improvement in her condition and the rapid spread of the rash, she was transferred to the nearest academic medical center.

Diagnosis

The patient was ultimately diagnosed with Stevens-Johnson Syndrome. The fact that her rash, even from its initial localized presentation on her wrist, was painful rather than pruritic raised suspicion for a serious systemic drug reaction. Additionally, she had mucus membrane involvement and her rash spread and darkened with great rapidity. As a result of these clinical characteristics there was a high suspicion for Stevens-Johnson Syndrome.

Testing

Skin biopsy was performed, which was consistent with Stevens-Johnson Syndrome. This test was chosen due to the high clinical suspicion for this disease as well as the fact that delay in diagnosis of this condition would be fatal.

Treatment

The patient was treated with intravenous methylprednisolone 150 mg per day for 4 days. She underwent prompt ophthalmologic evaluation including fluorescing staining to assess for loss of ocular surface epithelium. Though she had no ocular involvement, aggressive topical lubrication was implemented to prevent ocular membrane breakdown. The data surrounding the use of intravenous immunoglobulin, alone or in combination with corticosteroids, is limited in the case of SJS. Due to her relative neutropenia at presentation and initial concern for sepsis, she was not treated with cyclosporine or anti-TNF-alpha biologic agents, though there is emerging data supporting the efficacy of these agents at slowing the destruction of skin in SJS.

Patient Outcomes

The patient's rash regressed rapidly following initiation of intravenous steroids. She did not develop ocular involvement with SJS and never required intubation. Although her oral ulcers improved dramatically, she still struggled to maintain an appropriate level of intake to support herself nutritionally and lost over 20 pounds during her hospitalization. Ultimately, parenteral nutrition was initiated until percutaneous gastrostomy can be placed. She will resume treatment for metastatic breast cancer following her hospitalization and further recovery, though the use of any taxane agents is now precluded.

Lessons Learned

In the practice of allergy/immunology, clinicians are often tasked with evaluating localized maculopapular eruptions that can have a broad range of etiologies that vary greatly in their morbidity and mortality. Concurrent mucus membrane involvement should trigger consideration of Stevens-Johnson Syndrome (SJS) as a potential etiology. This case also highlights how pain associated with an otherwise seemingly unremarkable rash can be an early clue with regards to the presence of an underlying serious systemic drug reaction, such as SJS. Furthermore, any medication can theoretically trigger SJS. Despite the fact that this patient's only recent exposure was a taxane designed to be less prone to causing drug-reactions, early skin biopsy was the appropriate course of action given her clinical presentation and allowed for her to avoid ocular complications, intubation, and circulatory collapse. There have been no other cases of SJS occurring in reaction to albumin-bound paclitaxel described in the literature; however, cases have been published of patients developing SJS after receiving docetaxel and paclitaxel. A 53-year-old gentleman developed SJS after his second dose of paclitaxel. In the case of the patient who received docetaxel, he first manifested skin eruptions after only 1 dose of the chemotherapeutic before he subsequently developed SJS with mucus-membrane involvement.

Diagnosing Pulmonary Actinomyces: Next Generation Sequencing as an Alternative to Culturing/Staining for Actinomyces

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Summary

A 16 year old female presented with recurrent pneumonia of 1.5 years. Initial evaluation for autoimmune, immunodeficiency, and infectious etiologies was negative. Despite no growth of pulmonary actinomyces on tissue culture, next generation sequencing (NGS) of the patient's bronchoalveolar lavage was positive for actinomyces timonensis. Empiric therapy with a short course of penicillin improved fever and respiratory symptoms. The patient was ultimately treated successfully with daily penicillin V K over 12 months.

Patient Presentation

A previously healthy 16-year old female presented with recurrent fever and pulmonary nodules. Symptoms began with right upper quadrant pain, fatigue, and dyspnea. She also complained of intermittent blurry vision, rash, and joint pain. Family history was notable for mother with recurrent pyelonephritis. Physical exam demonstrated decreased breath sounds in the right lower lung, malar rash, and axillary adenopathy. She was initially treated for presumed pneumonia with clarithromycin, but had symptoms recur with 5 hospitalizations over an 18-month period.

Diagnosis

The initial differential diagnosis for the patient's recurrent fever, pneumonia, and pulmonary nodular disease included primary immunodeficiency, infection (e.g. non-tuberculosis mycobacterium, NTM), and rheumatologic disorders (e.g. sarcoidosis). For immunodeficiency, isolated NTM infection in the lungs would have been an atypical presentation for Mendelian susceptibility to mycobacterial disease. In addition, IL-12 interferon gamma pathway flow cytometry was normal. These results included normal activation of IFN gamma stimulated pSTAT1 in monocytes, normal absolute lymphocyte count, normal absolute B cell count, normal expression of CD119/IFN γ R on monocytes, and normal expression of CD212/IL-12R on lymphocytes. Other pertinent immune testing included normal: absolute CD3, CD4, CD8, and NK cells; serum immunoglobulins; and NADPH oxidase activity. Invitae primary immunodeficiency gene panel was notable for a heterozygous variant of uncertain significance in IL12RB1(p.Leu258Val), which was not clinically relevant.

Infectious workup was negative including blood cultures; cultures for acid fast bacteria and fungi; Cocci IgM and IgG; HIV antibody; Mycoplasma IgM and IgG; PPD; TB quantiferon; and, respiratory PCR panel. As the patient complained of a malar rash and joint pains - rheumatoid factor, ANA, ANCA, DAT polyspecific, DNA antibody, ACE and myeloperoxidase antibody were assessed and returned normal. Due to the patient's changes in vision, she was evaluated by ophthalmology to assess for uveitis related to Blau syndrome or granulomatous uveitis related to JIA; fortunately no abnormalities were noted on exam.

Testing

Fine needle aspiration of the pulmonary nodules revealed necrotizing granulomas. Since the patient showed characteristic clinical features of pulmonary actinomycosis including fever, fatigue, dyspnea, chest pain, night sweats, and loss of appetite, cultures for actinomyces were obtained. Tissue culture and staining was negative for mycobacteria and actinomyces. However, 16S/NGS of the BAL was positive for actinomyces timonensis on two separate occasions. This proved crucial for determining treatment.

Treatment

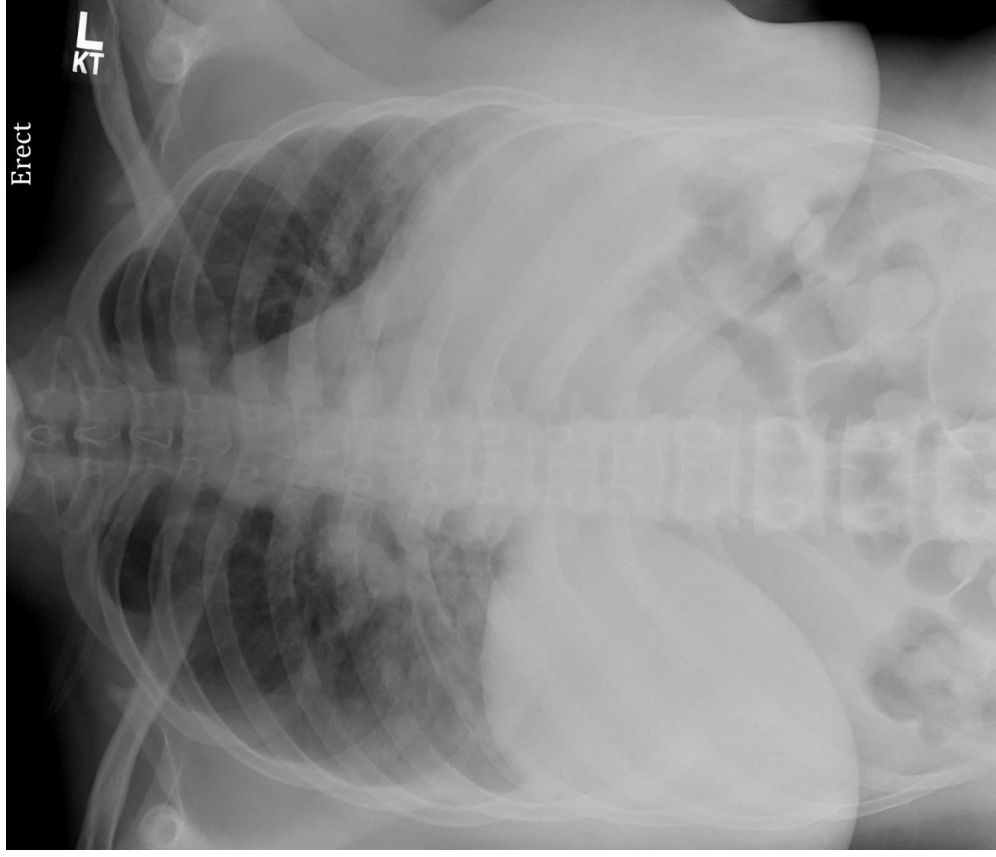
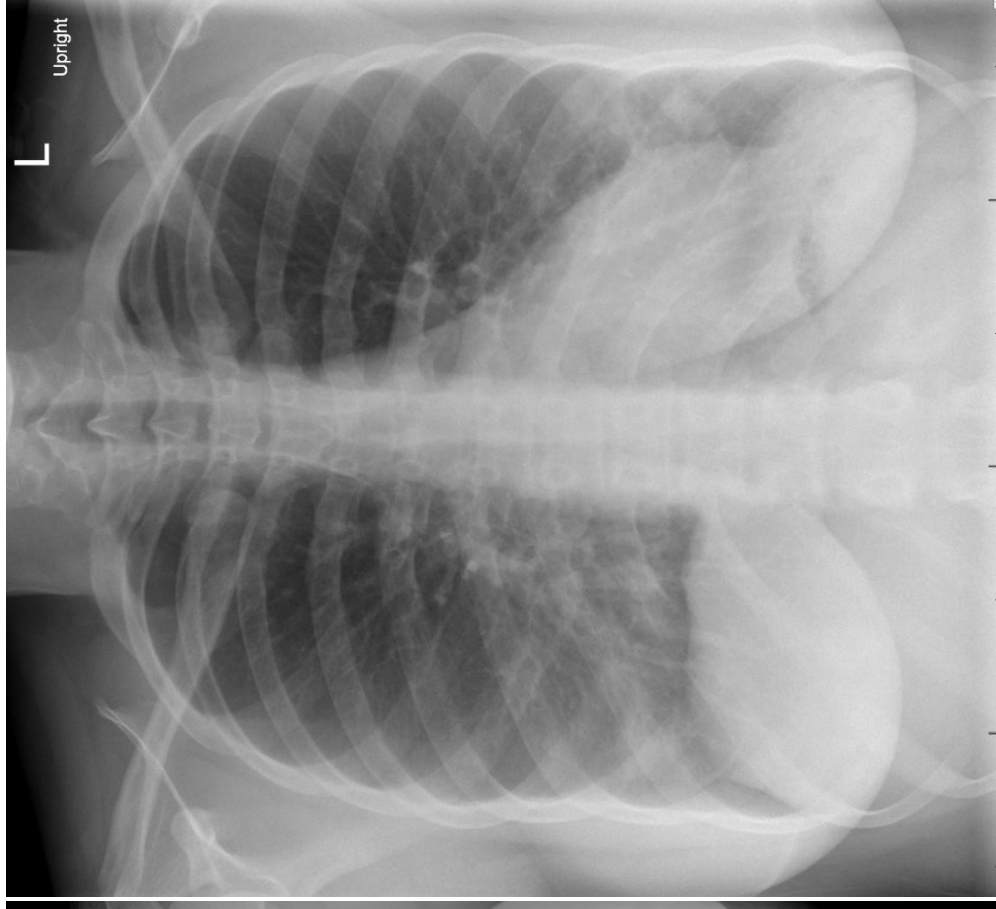
The patient was prescribed empiric therapy with a short course of penicillin which subsequently improved her fever and respiratory symptoms. She then continued therapy for presumed pulmonary actinomycosis with high-dose penicillin for 6-12 months.

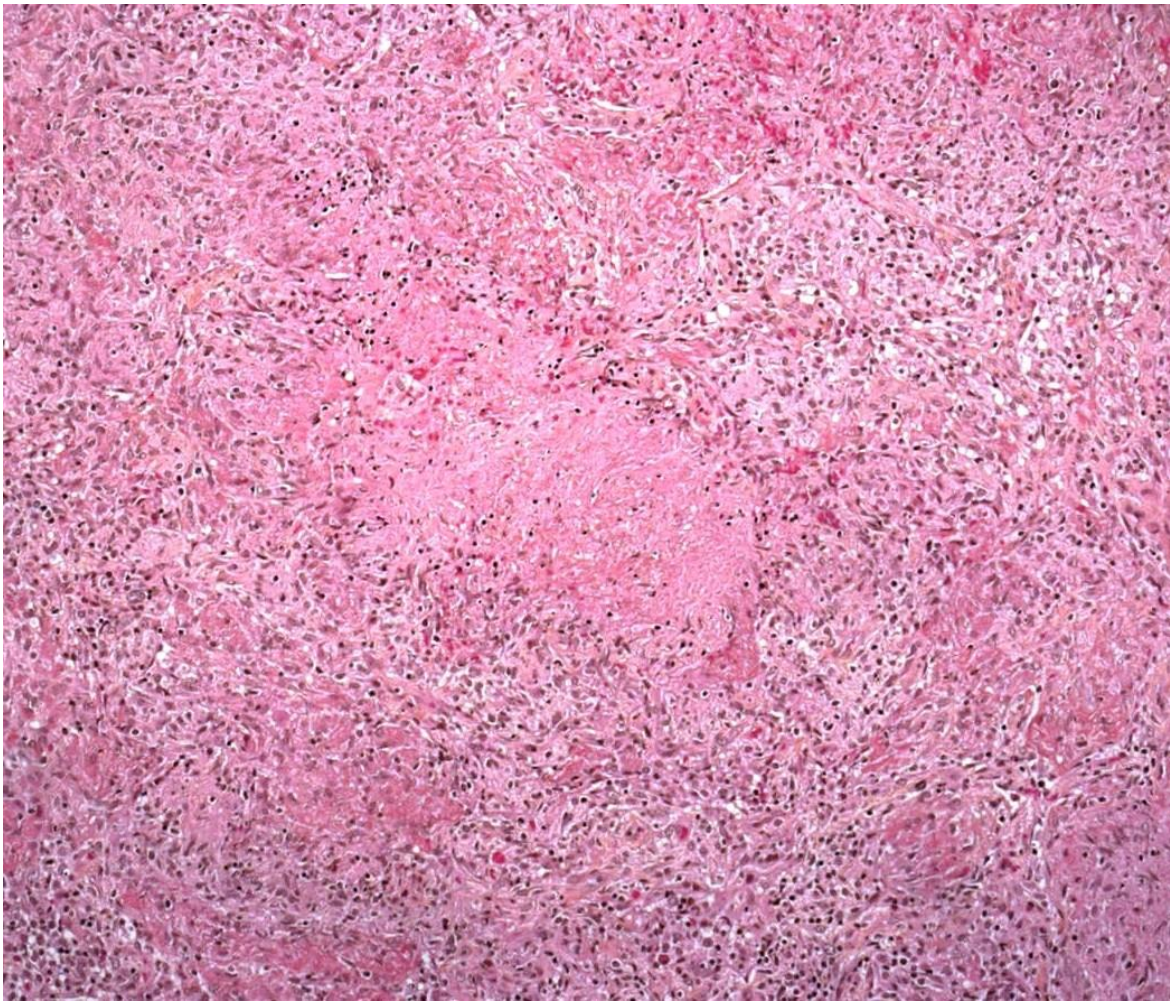
Patient Outcomes

Since the patient previously completed a 14 day treatment of penicillin with improvement of symptoms, she received treatment with penicillin VK given 4 times per day for 12 months with resolution of symptoms. The patient's chest pain persisted but was significantly improved without need for analgesics or anti-inflammatories. Fever, chills, sweats, cough, sputum production, and chest congestion have resolved. Exercise tolerance has normalized. Repeat CT scan at the end of treatment showed complete resolution of pulmonary nodules.

Lessons Learned

Pulmonary actinomycosis requires a combination of several factors including: a positive culture, demonstration of sulphur granules in infected tissue, clinical and radiological correlation with active disease, and response to antibiotic treatment per the European Respiratory Journal. In this case, the patient did not demonstrate sulphur granules, however NGS was positive twice for actinomyces on BAL and the patient's recurrent pneumonia and other clinical symptoms were responsive to penicillin. Diagnosis of actinomycosis is difficult since cultures from BAL may reflect commensal species of actinomyces rather than active disease. NGS is a rapid and effective tool for identification of infectious organisms that are difficult to identify by culture. The patient's resolution of symptoms with treatment shows that NGS was able to detect active actinomycosis vs. a commensal species. This is relevant to the practice of allergy/immunology because it presents another approach to ruling out an infectious process that may be mimicking primary immunodeficiency.





Anaphylaxis to platelets associated with antibodies to IgA in a non-deficient IgA patient

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Summary

Our patient is a 17-year-old male with Ewing's sarcoma who had hypersensitivity to platelet transfusions. Anaphylaxis to blood products can be seen in IgA deficient patients. Our patient, however, had normal IgA levels with elevated IgG antibody to IgA. This case is extremely rare, as less than five reports exist in the literature.

Patient Presentation

A 17-year-old male with Ewing's sarcoma developed hypersensitivity to platelet transfusions. He tolerated his first packed red blood cell (pRBC) transfusion. Weeks later, he developed pruritus and a forearm hive after his next pRBC transfusion. Subsequently, he received multiple pRBC infusions, which he tolerated. He also tolerated his first platelet transfusion. During the next platelet transfusion, however, he developed significant urticaria with pruritus of the throat and ears. Despite premedications with hydrocortisone and diphenhydramine, he developed pruritus, urticaria, and coughing minutes into his third platelet transfusion. He received epinephrine intramuscularly, and symptoms resolved within 30 minutes. Platelet infusion with hydrocortisone and diphenhydramine premedication was re-attempted later that day, and he reacted with similar symptoms 35 minutes after the transfusion began. He again was given epinephrine with resolution of symptoms. None of the blood or platelet products had been washed. The patient denied any history of food allergies, asthma, or reactions to other medications. He mentioned a history of seasonal allergic rhinitis.

Diagnosis

Anaphylaxis to platelets with antibodies to IgA in a non-deficient IgA patient.

Testing

Tryptase: <2 g/L

Since at least two cases of underlying systemic mastocytosis have been unmasked by anaphylactic reactions to platelet transfusions a tryptase level was ordered.

Anti-IgA antibody: 247 U/mL (normal <99 U/mL)

We wanted to evaluate the patient to see if he made antibodies against IgA. To our knowledge there is no test available to evaluate for IgE against IgA.

IgA level: 137 mg/dL

It was vital that we measure patient's serum IgA level as IgA deficient patients can have anaphylaxis to blood products that contain trace amounts of IgA.

Treatment

We used the protocol established by the American College of Radiology for pretreatment of patients with radiocontrast reactions, as we were unable to find a protocol for prevention of anaphylaxis to

blood products. This protocol recommends oral prednisone 0.5 to 0.7 mg/kg (with maximum of 50 mg per dose) at 13, 7, and 1 hour(s) prior to administration plus oral, intramuscular, or intravenous diphenhydramine 1.25 mg/kg (maximum 50 mg) 1 hour prior to administration; or intravenous methylprednisolone 1 mg/kg (maximum 32 mg per dose) at 12 and 2 hours prior to administration plus oral, intramuscular, or intravenous diphenhydramine 1.25 mg/kg (maximum 50 mg) 1 hour prior to administration. In addition, all blood products were ordered to be washed.

Patient Outcomes

The patient tolerated subsequent platelet and blood transfusions after following the protocol listed above along with washed blood products.

Lessons Learned

IgE or IgG anti-IgA antibodies are often implicated in severe anaphylactic reactions during pRBC or platelet transfusions in IgA deficient patients, as both blood products contain IgA, but this phenomenon remains quite rare. Upon consultation, we ordered an anti-IgA antibody titer by ELISA, IgA level, and a serum tryptase concentration. No clinical testing is available to assess IgE antibodies against IgA. Our patient exhibited an elevated IgG antibody (247 U/mL) to IgA despite having a normal serum IgA level of 137 mg/dL. In a previous report, IgG against IgA was present in 3 out of 142 non-IgA deficient women. The report did not mention whether any of these 3 individuals had reactions when given blood products or IVIG. At least one case of underlying systemic mastocytosis has been unmasked by anaphylactic reactions to platelet transfusions, but the serum tryptase level in our patient was normal. We cannot completely account for his ability to tolerate most pRBC transfusions, but the higher plasma concentration in platelet preparations may serve as a contributing factor. We therefore present a rare case of anaphylaxis after platelet transfusions in a non-IgA deficient patient who has antibodies against IgA.

Successful Desensitization of a Patient to Omalizumab after Anaphylactic Reaction

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Training Program University of Chicago, Internal Medicine

Summary

Omalizumab is effective as an adjunct therapy for moderate to severe persistent asthma. However, anaphylaxis is a known adverse event related to omalizumab that may prevent patients from its use. Here, we describe a successful desensitization protocol to omalizumab.

A 13 year old boy with allergic rhinitis, atopic dermatitis, food allergy and severe persistent asthma presented to clinic after developing a rash and wheezing immediately after receiving omalizumab at an outside facility. His asthma had been well controlled on a combination of mepolizumab and omalizumab in addition to controlled inhalers and montelukast. After the reaction, he was taken off omalizumab therapy and his asthma worsened, requiring recurrent courses of oral steroids. A 10-step desensitization protocol was successfully completed with the patient. He is now receiving omalizumab regularly, and his asthma is again better controlled.

Patient Presentation

A 13 year old boy with a history of allergic rhinitis, atopic dermatitis, food allergy and severe persistent asthma presented to allergy clinic after experiencing an anaphylactic reaction immediately following an omalizumab injection. He was diagnosed with asthma at the age of 2 years and his initial therapy included albuterol and inhaled corticosteroids. He continued to experience severe asthma exacerbations, triggered by allergens and/or recurrent sinusitis. By the age of 12 years, his therapy had been escalated to include inhaled corticosteroids, a long acting beta-agonist, montelukast, oral anti-histamines, and azalastine. In response to the gradual worsening of his symptoms and frequent exposure to oral steroids, he was started on mepolizumab therapy. Despite this, his asthma remained poorly controlled and he was ultimately started on omalizumab therapy in addition to the above medications.

He tolerated the first six doses of omalizumab without any issues. Within minutes of receiving the seventh injection he developed a diffuse urticarial rash on his chest and the injection site, difficulty breathing and wheezing. He was given intramuscular epinephrine, diphenhydramine, and prednisone and transferred to the emergency department, where he was monitored for several hours and did well. Omalizumab therapy was discontinued, and unfortunately, his asthma symptoms worsened. He began missing school frequently and having asthma exacerbations once a month, requiring several courses of oral steroids. He was then referred to allergy clinic for further management.

Diagnosis

Prior to starting biologic therapy, testing was performed to further investigate the patient's diagnosis of asthma and to better characterize his asthma. Testing was also performed to exclude alternative diagnoses like acute bronchopulmonary aspergillosis. An environmental allergy skin prick test was done to understand which environmental triggers could be reduced to improve his asthma control.

His complete blood count with differential was remarkable for elevated eosinophils of 1402 cells/ul. His IgE level was 3372 kU/L. ABPA panel was negative.

His pulmonary function testing showed airway obstruction with FEV1/FVC 70% of predicted value and a positive response to bronchodilator. The environmental allergy skin test showed the following: weeds +, grass +, dog +, cat +.
Skin testing to omalizumab was not done.

Testing

Omalizumab has a black box warning for anaphylaxis.

The history of immediate urticarial rash and difficulty breathing following omalizumab injection is consistent with an anaphylactic reaction to omalizumab.

Treatment

As the patient's asthma was better controlled when he was on a combination of mepolizumab and omalizumab therapy, we proceeded with omalizumab desensitization procedure to allow him to use omalizumab again. His prior dose was 375mg every other week, based on his weight and total IgE level. The patient received 10 doses of subcutaneous omalizumab in increasing amounts every 30 minutes for a total dose of 188mg. He was given 0.05ml of diluted omalizumab stock solution at a concentration of 150mg/1.2ml, dose of 6.25mg, the dose was then increased every 30 minutes to a maximum dose of 55mg. He received 10 subcutaneous injections total, 5 injections in the right arm and 5 injections in the left arm.

He did begin coughing 30 minutes after the 7th injection (0.32ml of 150mg/1.2ml concentration, dose of 40mg) and an albuterol-ipratropium nebulizer treatment was administered. His coughing resolved and the final two doses of omalizumab were administered without any further issues.

His peak flow was checked every 30 minutes a well. His baseline peak flow was 400ml and improved to 430ml after the procedure was completed.

Patient Outcomes

Subsequently, he received a dose of 188mg of omalizumab 1 week after the desensitization procedure without any issues. The following week he tolerated a full dose of 375mg and he is now receiving omalizumab 375mg every other week.

Six months after resuming omalizumab his asthma symptoms are better controlled. His frequency of asthma exacerbations, hospital and primary care office visits has decreased, he has only required 1 course of oral steroids for an asthma exacerbation in the last 6 months.

Lessons Learned

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody that has been shown to be an effective adjunctive therapy for moderate to severe persistent allergic asthma. It has a known adverse reaction of anaphylaxis and since its approval for allergic asthma there have been many reported cases of anaphylaxis after omalizumab injection. Such a reaction may deprive patients who were previously benefiting from omalizumab of its use. There have been two other reported cases in the literature that have described subcutaneous desensitization to omalizumab after an anaphylactic reaction (Dreyfus D, et al and Owens G et al). We describe a 10-step desensitization protocol to omalizumab that allowed this patient to continue to benefit from the medication after desensitization.

Infection frequency decreased with aeroallergen immunotherapy in a patient with mannose-binding lectin deficiency

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Summary

This is the first reported case of aeroallergen immunotherapy (AIT) decreasing the frequency of infection in a patient with mannose-binding lectin (MBL) deficiency. This innate immunodeficiency is reported in approximately 5–30% of the population and is often asymptomatic; however, a subset of patients experience recurrent infections requiring multiple courses of antibiotics. Our patient presented with a history of recurrent sinusitis, otitis media, and pneumonia requiring hospitalization and up to 18 courses of antibiotics within 1 year. She began an aeroallergen immunotherapy program for allergic rhinitis. Within the first 6 months she noted fewer illnesses and after one year reported marked improvement with only 2 episodes of sinusitis. The following year she reported no antibiotic requiring illnesses. This benefit has been sustained now for 3 years while receiving AIT.

Patient Presentation

Our patient is a 65 year old female with a history of allergic rhinitis, recurrent sinusitis and otitis media, pneumonia requiring hospitalization, mild persistent asthma, GERD, obesity, and hypertension who presented to the allergist office with severe allergies and multiple recurrent respiratory infections. Aeroallergen immunotherapy was initiated to optimize her allergy symptom control.

Diagnosis

Our patient was diagnosed with seasonal and perennial allergic rhinitis and MBL deficiency.

Testing

With multiple upper respiratory symptoms refractory to conservative therapy, she was skin tested for environmental allergies. Testing demonstrated sensitization to dust mite, cat, dog, tree, grass, weed, and mold. Her history of recurrent respiratory infections requiring frequent antibiotic use and hospitalizations prompted an evaluation of her immune status. Quantitative and qualitative immunoglobulins were normal with protective pneumococcal titers. MBL deficiency was identified with a level of 6 ng/mL.

Treatment

With shared decision making, risks and benefits of immunotherapy were discussed to improve control of her rhinitic symptoms. The role of MBL deficiency contributing to her frequent infections was also reviewed. Treatment options included prophylactic antibiotics to prevent her recurrent infections and hospitalizations. She was informed that MBL replacement was still an experimental therapy. The patient chose to initiate aeroallergen immunotherapy and hold on further treatment of her MBL deficiency.

Patient Outcomes

A welcomed benefit occurred for our patient while receiving aeroallergen immunotherapy. Not only were her allergy symptoms improved, but the frequency of her infections, antibiotic use and

hospitalizations had significantly decreased. She started noticing symptom improvement within the first 6 months, followed by only 2 episodes of sinusitis after one year, and was both infection and antibiotic free after 2 years. Now after three years of aeroallergen immunotherapy, this benefit has continued. The only change in her medical regimen was the initiation of allergen immunotherapy. Our patient experienced a marked decline in infection frequency while receiving aeroallergen immunotherapy.

Lessons Learned

Our patient was quite symptomatic with frequent infections attributed to MBL deficiency. There was concurrent allergic rhinitis treated with immunotherapy with a marked decrease in infections. Currently, there are no studies examining the role of allergen immunotherapy in the setting of MBL deficiency. Treatment for symptomatic patients with MBL deficiency is limited to prophylactic antibiotics, avoidance of infectious contacts, handwashing hygiene, and appropriate vaccines. Current research is focused on MBL replacement therapy as treatment for MBL deficiency. However, as evidenced in this case, aeroallergen immunotherapy for atopic patients with symptomatic MBL deficiency may be a novel treatment option providing a safe, effective means to indirectly treat patients with symptomatic MBL deficiency.

The Immune Function of 3 Siblings with ITCH E3 Ubiquitin Ligase Deficiency

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Summary

3 Amish siblings with ITCH E3 ubiquitin ligase deficiency were referred to pediatric pulmonology and allergy/immunology for evaluation and treatment of asthma and recurrent sinopulmonary infections. Their genetic condition has most widely been described in mouse models with rare reports of its effects in humans. ITCH E3 ubiquitin ligase is thought to play a role in multiple cell signaling pathways for Treg differentiation and T cell anergy, and deficiency is associated with multiorgan autoimmune inflammation. Immune evaluation showed no frank immune deficiency. The patients' social situation resulted in numerous barriers to care, including difficulty in providers communicating with the family outside of clinic and financial difficulties accessing medication as well as physical barriers to medication delivery such as lack of electricity for nebulizers or physiotherapy vests. Some solutions were available to provide access to care but the family was ultimately lost to follow-up.

Patient Presentation

Patient A is an 8-year-old male. Patient B is a 7-year-old female. Patient C is a 4-year-old male. All 3 children presented with failure to thrive and chronic chest congestion, wheezing, and wet cough associated with post-tussive emesis. They had all been treated with multiple antibiotic courses for recurrent pneumonia, otitis media, and sinusitis.

Medical/surgical history: All children in the family have remained unvaccinated because of the family's religious beliefs. The 3 siblings all carried diagnoses of reactive airways disease requiring frequent use of albuterol and oral steroid courses, as well as allergic rhinitis. Patient B also has mild eczema. All 3 were born at term and had uncomplicated deliveries. Patient A has speech delay and Patient C has gross motor delay. Patient B has a history of appendectomy for acute gangrenous appendicitis with rupture at age 4. Patient C has a history of hospitalization at age 6 weeks for bronchiolitis requiring mechanical ventilation and another admission at 5 months for wheezing with hypoxic respiratory failure.

Social history: All 3 siblings live at home with mother, father, and 6 additional sisters and 5 additional brothers in a rural Amish community. No exposure to pets or tobacco smoke but home is heated with a wood stove. They have been unable to afford certain medications such as budesonide, montelukast, and cetirizine as family has no insurance or social security numbers. They also do not have a phone at home and require medical transportation arrangements as they live 1 hour away from clinic and have no car. Communication with the family is facilitated by calling their insurance caseworker who travels to the family's home to speak to them directly. They have no electricity at home, so nebulizer treatments are delivered with the use of an oxygen tank. The parents speak English and Pennsylvania Dutch but the children speak Pennsylvania Dutch only. They recently enrolled in state-funded insurance for the children to facilitate filling of prescriptions and transportation to appointments.

Family history: 2 siblings died at ages 11 months and 2 years who also had ITCH E3 ubiquitin ligase deficiency. Maternal grandmother had asthma.

Physical exam: All 3 patients have dysmorphic features including frontal bossing, dolichocephaly, orbital proptosis, flattened mid-face, small chin, and low posteriorly-rotated ears. All have rhonchi on lung auscultation and hepatosplenomegaly. None have digital clubbing. Patient B has severe thoracolumbar

scoliosis and bulging erythematous left TM with purulent fluid. Patient C has purulent drainage from bilateral ears obstructing view of the TMs.

Diagnosis

Autoimmune lung disease and rhinitis due to ITCH E3 ubiquitin ligase deficiency causing severe asthma-like picture as well as recurrent rhinosinusitis leading to recurrent sinopulmonary infections.

Testing

Due to recurrent diagnoses of bacterial infection, patients had screening immune evaluation, CXR, and sputum cultures ordered. Aspergillus precipitins and total IgE were also ordered to rule out ABPA due to severe asthma symptoms with chronic wheezing and wet cough. Due to failure to thrive with chronic wet cough and recurrent sinusitis, sweat chloride testing was to be scheduled for a return visit to evaluate for cystic fibrosis, as it could not be done in clinic. Lymphocyte proliferation to antigen/mitogen and NADPH oxidative burst were planned for a future visit as it was too late in the day to send specimens to the reference lab. Patients A and B also had spirometry performed to assess for airway obstruction but had difficulty with the maneuvers. Due to difficult venous access, Patient C could only have quantitative immune globulins, S pneumoniae titers, and sputum culture done. All 3 patients had normal quantitative immunoglobulins. Patient A had protective titers to 59% of S pneumoniae serotypes, whereas Patient B had to only 18%. Patient C had protective titers to none of the serotypes, and undetectable antibody titer to 11 of them. Patients A and B had absent titers to diphtheria and tetanus, normal MBL level, and essentially normal numbers of T/B/NK cells, with negative aeroallergen IgE panel and total IgE within normal limits. Patient A had absolute eosinophil count of 800, and patient B had 1800. They both had negative Aspergillus precipitins and negative sputum AFB smear/culture and RT-PCR for M avium complex. Patient C's sputum grew pan-susceptible Klebsiella pneumoniae and MDR Elizabethkingia meningoseptica. CXR in each patient showed coarsened central pulmonary markings, thought to be consistent with reactive airways disease vs related to autoimmune lymphocytic infiltration.

Treatment

Patient B had mild respiratory distress in clinic and was treated with nebulized albuterol-ipratropium, and was given a prescription for amoxicillin-clavulanate for otitis media and oral prednisone for asthma exacerbation. Patient C was also treated for otitis media with Augmentin and oral prednisone for asthma exacerbation. Parents were taught techniques for manual chest physiotherapy (as no electricity available to use vest) and all 3 patients were prescribed airway clearance twice daily with albuterol, to increase to 4 times daily when sick. They were also prescribed BID budesonide and daily montelukast and additionally started on 3x weekly azithromycin prophylaxis [off-label use]. When Patient C's sputum culture results were available, he was switched from amoxicillin-clavulanate to levofloxacin.

Patient Outcomes

Because of family's religious beliefs, vaccine boosters with post- titers were not a diagnostic option. Patients have been lost to follow-up as they preferred to continue care with local pediatrician rather than travel 1 hour each way to get specialty care at our clinic, even with insurance-provided transportation and medication coverage. Therefore, lymphocyte proliferation, NADPH oxidative burst, and further workup for patient B's elevated eosinophil count could not be completed.

Lessons Learned

This case illustrates some of the unique challenges in treating patients of the Amish community, and provides a detailed look at the immune function of patients with the rare condition of ITCH E3 ubiquitin ligase deficiency. Previous case reports by Lohr et al (Am J Hum Genet 2010) and Kleine-Eggbrecht (Pediatrics 2019) focused on the autoimmune gastrointestinal and pulmonary manifestations of this deficiency.

A Rare Instance of Adult-Onset Food Protein-Induced Enterocolitis Syndrome

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Training Program Marshfield Clinic Pediatrics (Fedt); Marshfield Clinic Internal Medicine-Pediatrics (Timothy, Ender)

Summary

This patient presented for evaluation after two episodes of severe reactions occurring after consumption of eggs. Careful history with negative skin-prick testing for allergy to eggs supported a diagnosis of Food Protein-Induced Enterocolitis Syndrome. There was no interest in oral food challenge due to severity of symptoms. Patient was therefore advised to avoid consumption of the food that induced symptoms, lightly cooked egg. There has been no reported recurrence as of this time.

Patient Presentation

This patient presented for evaluation after two episodes of severe reactions occurring after consumption of eggs. The patient had previously eaten eggs without symptoms for six decades. The first episode occurred four hours after ingestion of an omelet, with symptoms consisting of abdominal pain with 30 minutes of projectile vomiting. This resolved without intervention. Following ingestion of scrambled eggs one week later, he again experienced the same symptoms four hours after eating. Neither episode included cutaneous, respiratory, or cardiovascular involvement. Patient had no history of atopic dermatitis, nasal/ocular allergies, or asthma. He was not on oral antihistamines. There was no family history of similar symptoms.

Diagnosis

Patient initially presented with concern for egg allergy, suspected to be IgE-related, but timeline (4 hours) and description of symptoms were better correlated with the clinical features of Food Protein-Induced Enterocolitis (FPIES), with abdominal pain, lethargy, and projectile vomiting following 4 hours after egg ingestion on multiple occasions.

Testing

Skin-prick testing to egg was negative. There was no interest in oral food challenge due to severity of symptoms, and the fact that patient had experienced these symptoms multiple times at home following ingestion of eggs.

Treatment

Patient was advised to avoid consumption of egg.

Patient Outcomes

He was provided with information regarding his diagnosis, and with food avoidance, patient has had no recurrence of symptoms in 3 months. He is to follow up in Allergy Clinic in 1 year or sooner if interested in oral food challenge.

Lessons Learned

Our case highlights the need for a high index of suspicion for this disease process in an age group outside the typical range and involving unusual food groups in that age group. It also highlights the

difficulty of a definitive diagnosis when gold standard testing involves induction of symptoms. Review of literature suggests lack of interest in oral food challenge is a common theme among adult patients, and in fact, we were able to find only 1 case of FPIES in adults related to eggs which was confirmed with oral food challenge.

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Hsu P, Mehr S. Egg: A frequent trigger of food protein–induced enterocolitis syndrome. *Journal of Allergy and Clinical Immunology*. 2013;131(1):241-242. doi:10.1016/j.jaci.2012.08.045

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A Missed Diagnosis of Vocal Cord Dysfunction of Over 13 Years

Author Keturah Baker

Training Program Marshfield Medical Center

Summary

We present a teenaged patient with 34 Emergency Room visits, 7 Urgent Care visits, and 9 hospitalizations over the course of a decade for symptoms eventually found to be consistent with vocal cord dysfunction. A diagnosis of vocal cord dysfunction was considered early on, but rhinoscopy done without provocation challenge was negative, and patient continued to be treated for multiple episodes of presumed anaphylaxis and asthma exacerbations. Patient was at last again referred to allergist for these symptoms, and a repeat rhinoscopy was done. This showed normal vocal cords at rest, but at the mere smell of peanut butter, patient developed the classic “posterior chinking” of the vocal cords. Following correct diagnosis, patient was treated appropriately and experienced incredible improvement in quality of life.

Patient Presentation

Patient is a 16 year old male with a past medical history significant for multiple anaphylactic reactions thought to be due to peanuts, and asthma reactions requiring hospitalizations and intubation who presented to our facility for tongue swelling, shortness of breath and lightheadedness after drinking cow's milk which he had previously tolerated. Patient self administered Epinephrine as he felt as though he was having an anaphylactic reaction. EMS was called and when arrived, administered another dose of Epinephrine. Prior to transport to the Emergency Room, patient felt nauseous and vomited nonbloody nonbilious vomitus. Patient's condition subjectively improved by the time he presented to the Emergency Room. Patient was given a bolus of normal saline, 50mg of oral Benedryl, 4mg of oral Zofran, 125mg of IV Methylprednisolone, and 20 mg of oral Famotidine. Patient was transferred to the Pediatric General Floor where he did not have any further symptoms and was discharged two days later.

Diagnosis

Hospital followup with Allergy and Immunology Clinic again raised suspicion for Vocal Cord Dysfunction. Of note, clinical suspicion of Vocal Cord Dysfunction was raised years prior and discounted because of visualization of vocal cords through rhinoscopy did not reveal any abnormalities at rest. Given the high clinical suspicion of Vocal Cord Dysfunction, a repeat rhinoscopy performed in the Allergy and Immunology Clinic with provocation.

Testing

Repeat rhinoscopy was performed at rest and with the presence of a provoking stimuli of peanut butter odor from a nearby opened container. Within 10-15 seconds of breathing in the odor of peanut butter, patient began to cough. After another 15 seconds, patient experienced inspiratory stridor. Visualization of the vocal folds during symptoms revealed the classic posterior “chink” of the vocal folds. Scope was then removed and patient was placed on Heliox via face mask and within 30 seconds, patient's symptoms resolved.

Treatment

Patient received Speech Therapy to manage symptoms.

Patient Outcomes

Patient was able to utilize learned therapies. Patient had a dramatic improvement in quality of life and was now able to maintain a job and partake in social activities.

Lessons Learned

A high index of suspicion is needed when diagnosing Vocal Cord Dysfunction. It is especially important to perform rhinoscopy with provoking stimuli

An unusual presentation of Systemic Mastocytosis

Author Syed Rizvi

Training Program Pediatrics

Summary

58 year old female with past medical history of osteoporosis who presents with 7 year history of non palpable erthematous papules measuring 2-3mm initially scattered across anterior thighs, progressing slowly over years, up to her abdomen and chest. Due to progression and increasing number of papules and increasing complaints of skin flushing, skin biopsy is obtained which showed telangiectasia macularis eruptiva perstans.

Patient Presentation

58 year old female with past medical history of osteoporosis who presents with 7 year history of non palpable erthematous papules measuring 2-3mm initially scattered across anterior thighs, progressing slowly over years, up to her abdomen and chest. Due to progression of presentation and increasing complaints of skin flushing, skin biopsy is obtained which showed telangiectasia macularis eruptiva perstans. Her skin flushing would be exacerbated by hot temperatures, certain foods including shellfish, alcohol, and spicy foods. She denied having any dizziness (hypotension) or diarrhea with these episodes. Skin Biopsy was CD117 positive which lead to obtaining serum tryptase levels which were elevated at 31.4.

Bone marrow biopsy was obtained next with Kit D816V mutational analysis on BMB being negative, allowing us to rule out systemic mastocytosis. With a negative KitD816V analysis, she was diagnosed with indolent systemic mastocytosis in the presence of telangiectasia macularis eruptiva perstans. After diagnosis, she was referred to Allergy/Immunology specialists where she was serum tryptase levels were rechecked and continued to be elevated at 31.2. After food and respiratory allergen testing, she was started on daily antihistamines, mast cell stabilizers, and requested to carry Epi-Pen at all times, and was followed up every season with serial tryptase levels which stabilized with treatment in high 20's.

Diagnosis

Telangiectasia Muscularis Eruptiva Perstans and Indolent Systemic Mastocytosis

Testing

Skin Biopsy which showed mastocystosis, consistent with TMEP. Bone marrow biopsy was also obtained with KIT816V analysis being negative. Tryptase levels were obtained prior to and during initial A/I consultation which remained elevated. Food and respiratory allergen testing was also obtained but were only positive for dust mites.

Treatment

Initiation of daily antihistamines BID, mast cell stabilizer (Cromolyn) due to history of asthma, and Epi-pen prescription.

Patient Outcomes

Serial tryptase levels obtained every 3 months showed stabilization around 27-29.

Lessons Learned

Cutaneous mastocytosis is a proliferation of mast cells on the skin without other organ involvement. Though TPEM is a manifestation of cutaneous mastocytosis, it may progress to systemic involvement. Typical symptoms are insidious and providers should gather a thorough history and physical, and have a multidisciplinary approach with dermatology, hematology and allergy/immunology to track disease progression.

Desensitization to Intravenous Iron following Severe Anaphylaxis

Author Richard Wu, M.D.

Training Program National Institutes of Health

Summary

Patients who develop severe anaphylaxis to IV iron products may not receive adequate iron supplementation. We performed a literature based novel protocol was developed for IV iron desensitization. Patients with severe anaphylaxis to IV iron may receive subsequent iron products through careful selection of a low osmolar iron compound, a slow desensitization protocol and a comprehensive pre-medication regimen.

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Case was supervised by Dr. Lawrence DuBuske.

Patient Presentation

A 41-year-old African American female developed severe anaphylaxis to the first dose of intravenous (IV) sodium ferrous gluconate in sucrose (Ferrlecit®), within 5 minutes having generalized pruritus then diffuse arthralgias, 2 minutes later tachypnea (respiratory rate 36) with diffuse hives and bilateral leg swelling. Symptoms resolved upon infusion discontinuation, and receiving IV diphenhydramine 25 mg and IV methylprednisolone 125 mg. 6 weeks later labs showed a hemoglobin 9.1 g/dL (12.0-16.0 g/dL), MCV 75.7 fL (80.0-100.0 fL), RDW 17.0% (11.5-14.5%), absolute eosinophil count 180/mcL (0-200/mcL), Immunoglobulin E 63 IU/mL (6-495 IU/mL), and normal serum tryptase (2.3 mcg/L) with electrolytes, liver enzymes, ESR and CRP normal. Serum iron and ferritin showed severe iron deficiency. A literature review identified non- dextran iron products with low osmolality as safer; a 16 step desensitization protocol was devised with addition of pre-medication. The patient successfully received 2 doses of IV ferumoxytol (Feraheme®) 510 mg via this 16-step desensitization. IV ferumoxytol was initially administered at 2mL/hr (concentration of 0.002 mg/mL), up-titrated every 15 minutes to a final rate of 80mL/hr (concentration of 2.024 mg/mL). She received pre-medication using IV methylprednisolone 60mg, oral famotidine 20mg, oral cetirizine 10mg and oral montelukast 10mg.

Diagnosis

Severe Anaphylaxis to IV Iron

Testing

A 41-year-old African American female developed severe anaphylaxis to the first dose of intravenous (IV) sodium ferrous gluconate in sucrose (Ferrelecit®), within 5 minutes having generalized pruritus then diffuse arthralgias, 2 minutes later tachypnea (respiratory rate 36) with diffuse hives and bilateral leg swelling. Symptoms resolved upon infusion discontinuation, and receiving IV diphenhydramine 25 mg and IV methylprednisolone 125 mg. 6 weeks later labs showed a hemoglobin 9.1 g/dL (12.0-16.0 g/dL), MCV 75.7 fL (80.0-100.0 fL), RDW 17.0% (11.5-14.5%), absolute eosinophil count 180/mcL (0-200/mcL), Immunoglobulin E 63 IU/mL (6-495 IU/mL), and normal serum tryptase (2.3 mcg/L) with electrolytes, liver enzymes, ESR and CRP normal. Serum iron and ferritin showed severe iron deficiency.

Treatment

A literature review identified non-dextran iron products with low osmolality as safer; a 16-step desensitization protocol was devised with addition of pre-medication. The patient successfully received 2 doses of IV ferumoxytol (Feraheme®) 510 mg via this 16-step desensitization. IV ferumoxytol was initially administered at 2mL/hr (concentration of 0.002 mg/mL), up-titrated every 15 minutes to a final rate of 80mL/hr (concentration of 2.024 mg/mL). She received pre-medication using IV methylprednisolone 60mg, oral famotidine 20mg, oral cetirizine 10mg and oral montelukast 10mg.

Patient Outcomes

Patient tolerated IV iron infusion by desensitization with pre-medication.

Lessons Learned

Patients with severe anaphylaxis to IV iron may receive subsequent iron products through careful selection of a low osmolar iron compound, a slow desensitization protocol and a comprehensive pre-medication regimen.

Positive to negative basophil histamine release assay conversion in a patient with chronic spontaneous urticaria

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Summary

The use of the basophil histamine release assay has expanded its use from being a diagnostic tool for the autoimmune subtype of chronic spontaneous urticaria, to depicting disease duration and severity, depending on a positive or negative assay result. We describe a patient, diagnosed with chronic spontaneous urticaria, autoimmune subtype, treated with anti-histamine therapy until disease remission. Conversion of the assay to negative correlating with disease remission was observed. This is the first description, in current literature, that a positive to negative conversion has been observed. This case suggests further research into the utility of the basophil histamine release assay as a biomarker for disease remission in the subset of patients with a positive assay at the time of diagnosis should be considered.

Patient Presentation

A 50-year-old female was referred to the allergy and immunology clinic at the Health Science Centre in Winnipeg, Manitoba with a history of daily, pruritic raised wheals over a 6-week period. She described the individual wheals as lasting less than 24 hours, however, they were following by a violaceous hue lasting up to 72 hours. The daily episodes of urticaria were not associated with any identifiable physical trigger. Her past medical history was unremarkable. She denied any previous drug or environmental allergies. Medications taken during the development of urticaria were aspirin 81 mg daily, and a multi-vitamin, both of which were discontinued without any change in her urticaria frequency. There was no associated angioedema. Prior to being seen in the allergy clinic, the patient had trialed Diphenhydramine 50mg prior to bedtime, 0.1% betamethasone cream applied three times daily, and a 5 day course of prednisone 50 mg once daily to control her pruritus. Physical examination was unremarkable, with no urticaria, or hyperpigmentation noted. Blood work analysis included a complete blood count, creatinine, and electrolytes. A skin biopsy was completed, which revealed features only consistent with urticaria with no evidence of a vasculitic process. Additionally, an extended nuclear antibody screen and urinalysis returned as negative. A diagnosis of chronic spontaneous urticaria (CSU) was made. The patient was prescribed cetirizine 20mg orally every morning and 10mg orally every afternoon, along with Singulair 10mg orally once daily. IgE autoantibody testing revealed a positive basophil histamine release assay result, classifying this patient as an autoimmune variant of CSU. Her daily urticaria resolved, and over the next two years, she was able to discontinue her Singulair, and taper her cetirizine use to 5mg orally as needed. At her three year follow up, she was in complete remission, with no urticaria over the proceeding 12 months. A repeat IgE autoantibody test was done, which revealed a negative basophil histamine release assay result, correlating with her disease remission state. This patient remains in complete remission approximately 9 years after testing negative with the basophil histamine release assay.

Diagnosis

Physical examination was unremarkable, with no urticaria, or hyperpigmentation noted. Blood work analysis included a complete blood count, creatinine, and electrolytes. A skin biopsy was completed, which revealed features only consistent with urticaria with no evidence of a vasculitic process. Additionally, an extended nuclear antibody screen and urinalysis returned as negative. A diagnosis of chronic spontaneous urticaria (CSU) was made. IgE autoantibody testing revealed a positive basophil histamine release assay result, classifying this patient as an autoimmune variant of CSU.

Testing

As outlined above in diagnosis.

Treatment

The patient was prescribed cetirizine 20mg orally every morning and 10mg orally every afternoon, along with Singulair 10mg orally once daily. IgE autoantibody testing revealed a positive basophil histamine release assay result, classifying this patient as an autoimmune variant of CSU. Her daily urticaria resolved, and over the next two years, she was able to discontinue her Singulair, and taper her cetirizine use to 5mg orally as needed. At her three year follow up, she was in complete remission, with no urticaria over the proceeding 12 months.

Patient Outcomes

At her three year follow up, she was in complete remission, with no urticaria over the proceeding 12 months. A repeat IgE autoantibody test was done, which revealed a negative basophil histamine release assay result, correlating with her disease remission state. This patient remains in complete remission approximately 9 years after testing negative with the basophil histamine release assay.

Lessons Learned

We describe the first identification of conversion of the assay from positive to negative in conjunction with disease remission. It is possible conversion could be an indicator of disease remission in patients, as opposed to disease fluctuation by temporary stabilization of histamine release from mast and basophils during treatment only (Berti et al. 2017). The significance of the conversion remains unclear, however, in this case report it appears correlated to long term disease remission, as shown by our patient's disease course. In the search for new parameters to aid in depicting disease response to therapies, we suggest that further research into the use of using the BHRA as an adjunctive test to identify disease remission could be considered. Some limitations for using the BHRA stem from the methodology of the assay relying on donor basophils, and the need for donor blood samples to be tested within 24 hours of submission (Hamilton et al. 2004). In addition, its lack of widespread availability, delayed testing results, and cost associated with it compared to recurrent attempts to wean therapy may limit its overall utility, though we postulate there may be value in difficult to treat cases.

Fresh Fruit Skin Prick Testing in the Diagnosis of Fruit Allergies: The True Test?

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Summary

Classic food allergies are IgE-mediated hypersensitivity reactions that are the result of sensitization to direct stimulation to an allergen found in foods. In contrast, oral allergy syndrome (OAS) is an IgE-mediated hypersensitivity reaction attributed to an uncooked, plant-based food's structural antigenic similarity to pollen. Although primarily limited to oropharyngeal symptoms, 8.7% of patients with OAS will experience systemic symptoms outside the gastrointestinal tract, 3% will experience systemic symptoms without oral symptoms, and 1.7% will experience anaphylactic shock. A patient's tolerance of the same foods when cooked highlights the instability of the allergenic proteins that cause this cross-reaction. In our patient skin prick testing with commercial extracts (CSPT) was negative despite having a history classic for oral allergy syndrome; repeat skin prick testing with fresh fruit (FFSPT) were positive. The following case questions the utility of CSPT and calls into question whether FFSPT should be the true test for fruit allergies.

Patient Presentation

The patient was a 13-year-old girl with medical history significant for seasonal allergies, eczema, and psoriasis who was brought to the clinic by her father for food allergy evaluation. She would oropharyngeal numbness after eating most fruits and some vegetables immediately upon ingestion that completely resolved within 20 minutes. She felt the sensation of numbness was most intense when eating plums, bananas, apples, grapefruit, blueberries, raspberries, peach, pineapple, green peas, and potato. She denied any associated ocular, nasal, respiratory, gastrointestinal, or dermatologic symptoms as well as any prior episodes of anaphylaxis. Of note, she would not experience any symptoms when ingesting the same fruits when cooked. Although mild, the family expressed anxiety regarding food choices and risk for severe reaction.

Diagnosis

With both a strong supporting history and objective confirmation, patient was diagnosed with oral allergy syndrome.

Testing

Skin prick testing (SPT) has been the mainstream diagnostic tool for diagnosing IgE mediated hypersensitivity due to its convenience, rapidness, and simplicity. Furthermore, SPT traditionally has a high sensitivity making it a great test for quickly ruling out allergies. CSPT was initially performed, revealing only sensitization to green peas and potato. As all fruits tested were non-reactive (histamine 3mm, saline non-reactive) but the patient had a strong history for IgE-mediated process, RAST was performed and the decision was made to perform fresh fruit skin prick testing. RAST results were as follows: raspberry and blueberry were class 0; kiwi and pineapple were class 0/I; plum was class I; banana was class II; peach, apple, and pear were class IV. Wheal sizes during FFSPT were as follows: apple 9mm, banana 7mm, blueberry 3mm, kiwi 14mm, peach 11mm, pear 9mm, pineapple 0mm, plum 9mm, and raspberry 0mm (with histamine 7mm and saline 3mm).

Treatment

Although there is no specific treatment for OAS, patient was advised to avoid eating the raw form of these foods and to be mindful for the development of systemic symptoms if accidental ingestion were to occur.

Patient Outcomes

Not Available.

Lessons Learned

Skin prick testing (SPT) has been the mainstream diagnostic tool for diagnosing IgE mediated hypersensitivity due to its convenience, rapidness, and simplicity. Furthermore, SPT traditionally has a high sensitivity making it a great test for quickly ruling out allergies. Although Blackley was the first to introduce the technique of skin tests in 1873 by means of scarification, SPT as we think of it today was first documented by Lewis and Grant in 1924. By 1936 Tuft and Blumstein noted extracts of concentrated fruit extracts failed to elicit skin reactions in individuals with histories strongly suggestive for allergy and in whom symptoms could be induced by ingestion. Six years later they would note performing SPT with fresh fruit juices without alteration for extract creation preserved the immunologic response.

We know today that false negative reactions during CSPT are thought to occur secondary to instability of allergenic proteins in the fruit or under-representation of minor allergens. The lack of standardization of allergen content in commercial extracts and additional allergenic proteins found in the fruit's skin (depending on the fruit in question) may also have an impact on false negative CSPT. This said, extensive review of the literature reveals few studies have investigated the differences in sensitivity between differences between CSPT and FFSPT. There are two main studies that are quoted. The first was performed by Ortolani et al. in 1989 that showed the difference in sensitivity for CSPT and FFSPT to be 2.3% vs 81.1% for apple, 25% vs 25% for banana, 40% vs 100% for cherry, 26.7% vs 66.7% for orange, and 13.7% vs 59.1% for peach. The second was written by Zivanovic et al. that found the sensitivity of CSPT and FFSPT for Kiwi fruit to be 15% and 100%, respectively.

In evaluating a diagnostic test, one should question its utility, feasibility, and cost-effectiveness. If CSPT is intended for ruling out food allergies, then it's sensitivity must be reliably high. FFSPT, at least for fruits, appears to be higher than CSPT. Commercial extracts may be readily available, however the 2010 finding that SPT with frozen fruit performed similar to FFSPT enhances the test's feasibility for clinical application. And the relative price difference between fresh fruit versus their commercial extract counterpart may help to lower the overall cost of testing. There is little literature looking at the sensitivity of skin prick testing for fruit antigens. However, if the role of skin prick testing is to aid in ruling out allergies, should FFSPT – and not CSPT – be the true test for evaluating fruit allergies?

A Peculiar Reaction to a Homemade Smoothie: Anaphylaxis from Parsley

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Summary

A 44 year-old male with HIV presented to allergy clinic after having an anaphylactic reaction consisting of pruritus, flushing, lip angioedema and shortness of breath minutes after drinking a homemade smoothie. The patient underwent skin prick which was negative. The patient subsequently underwent multiple oral food challenges to help elucidate the etiology; with parsley challenge, he developed an itchy throat, nasal congestion, ocular lacrimation as well as urticaria within one hour of consuming parsley. The patient was subsequently diagnosed with anaphylaxis to parsley.

Patient Presentation

A 44 year-old male with HIV presented to the emergency room with a diffuse burning sensation beginning in his ears, diffuse erythematous skin lesions consistent with urticaria, lip angioedema, as well as dyspnea minutes after drinking a homemade smoothie with cucumber, celery, parsley, apple, orange, lemon, aloe vera gel, and turmeric. Vital signs upon presentation included a blood pressure of 123/83 mmHg, pulse of 118 bpm, respiratory rate of 18 and oxygen saturation of 95% on room air. He was treated in the emergency room with IV diphenhydramine and steroids as well as IV fluids. He was ultimately discharged with a prescription for prednisone 60mg for 5 days and an EpiPen. One week later, he followed up at the University of California Irvine (UCI) Allergy clinic for evaluation of his symptoms. He had been avoiding the previously reported ingredients since his presentation to the emergency room. Pertinent allergic history included a dust mite allergy well controlled with flunisolide, azelastine and montelukast. He had no prior history of urticaria, angioedema, or latex allergy. Other past medical history was significant for HIV well controlled on emtricitabine, tenofovir and dolutegravir, hyperlipidemia on atorvastatin, and hypertension well controlled on amlodipine. There were no changes in his medications and all were prior medications he had been taking consistently for multiple years.

Diagnosis

Based on the criteria for diagnosing anaphylaxis by the National Institutes of Health and the Food Allergy and Anaphylaxis network, the patient was determined to have an anaphylactic reaction to parsley given the acute onset of illness with involvement of skin, mucosal tissue and associated dyspnea when he presented to the emergency room.

Testing

The patient underwent skin prick testing as a primary diagnostic technique to determine any possible food allergy, especially in the setting of consuming a smoothie with multiple ingredients. His skin prick test was negative to celery, apple, orange, lemon, cucumber as well as turmeric, barley grass, and collagen. He returned for another visit where he had dermatographic urticaria which confounded testing during that visit with weak positive results to aloe vera and ginger. His repeat test when urticaria subsided, was negative to ginger and parsley. He had consumed aloe vera, barley grass and collagen at home with no reactions. To help elucidate the etiology, the patient underwent multiple graded food challenges in allergy clinic. No reactions were observed after celery, apple, orange, cucumber, lemon, orange, turmeric and ginger challenges. The patient, however, experienced nasal symptoms as well

pruritus within about one hour of consuming parsley. Vitals remained stable, and no dyspnea was observed.

Treatment

After reporting allergic symptoms following ingestion of parsley, the patient received 50mg intramuscular diphenhydramine as well as steroids with improvement of symptoms. He was closely observed in clinic for 1 hour with improvement of allergic symptoms. The patient was educated and counseled on avoidance of parsley.

Patient Outcomes

In summary, this patient presented with erythematous skin lesions, lower lip swelling and shortness of breath shortly after drinking a homemade smoothie with multiple ingredients. He subsequently followed with UCI Allergy Clinic to undergo skin prick testing, which did not elucidate an etiology. Oral food challenge testing was done to elicit the specific allergens responsible for his reaction. He was ultimately found to have a positive allergic response during parsley oral food challenge. This is the first case of an individual with HIV that had an anaphylactic reaction to parsley.

Lessons Learned

Few studies have been reported regarding anaphylaxis to parsley. Only one study published in Medical Archives from Turkey by Arslan et al. describes one other case of near-fatal anaphylaxis to parsley from 2014. Other scattered reports have also reported allergic reactions such as urticaria and facial swelling after consuming parsley, although many of these reports did not include a graded food challenge with isolated parsley. Interestingly, one report by Cordobés-Durán et al. in the Journal of Investigational Allergology and Clinical Immunology in 2007 performed western blotting of protein extract from parsley with a polyclonal rabbit antiserum raised against the peach lipid transfer protein Pru p 3 and serum from a patient who developed urticaria and acute rhinoconjunctivitis from parsley. This study found that serum from the patient contained an allergen resembling a lipid transfer protein, which is a vegetable panallergen mainly found in the outer layers of plants. This suggests that sensitization to lipid transfer proteins may be responsible for the allergic reactions elicited in some patients from parsley. Herbal products are gaining popularity in a growing movement of integrative and alternative medicine, and parsley is not an uncommon ingredient for nutritional supplements, healthy alternatives, and even cosmetic products such as shampoos and soaps. The case presented here is an important reminder to take into consideration daily herbal products (such as parsley) and vegetables in the evaluation of patients with suspected food allergy, as these products have the potential to cause adverse allergic reactions.

A Rare Case of Anaphylaxis to Mulberry in a patient with Pollen-Food Allergy Syndrome

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Summary

Pollen-food allergy syndrome (PFAS)/Oral Allergy Syndrome is characterized by mouth/throat symptoms after ingestion of raw fruits or vegetables that cross-react with pollens. This may be due to increased sensitivity/reactivity to labile proteins or reactions to stable proteins. Mulberry fruit is a member of the Moraceae family (e.g. fig, jackfruit), with the pathogen-related allergen (PR10) in this family of fruits cross-reacting with the birch-pollen protein Bet-v-1. Mulberry allergy is a rarely described entity, but is typically mild and related to birch pollen allergy. Anaphylaxis is a rare outcome from ingestion of allergens usually associated with PFAS. This is the second case of anaphylaxis to mulberry reported, raising awareness for potential severe outcomes. Patient recovered after timely management of anaphylaxis.

Patient Presentation

A 19-year-old female with a past medical history of food allergy (peanut and tree nuts), PFAS (apple, peaches, and plums), and seasonal rhinoconjunctivitis ingested several dried mulberries in June 2019. Immediately following ingestion, she experienced abdominal pain followed by vomiting, shortness of breath, wheezing and diffuse urticaria. She took 50mg of diphenhydramine without improvement. She was taken to an emergency room and received 0.3 mg of intramuscular epinephrine and albuterol, with symptom resolution. On follow up, a skin prick test was performed with the dried mulberry (wheal 7mm). Serum IgE for mulberry was 0.15 kU/L. Birch pollen serum level was 97.40 kU/L. Mulberry avoidance was recommended.

Diagnosis

Mulberry-induced anaphylaxis

Testing

Skin prick testing and serum specific IgE to mulberry; The selection of tests was based on clinical history that suggested an IgE-mediated allergic reaction.

Treatment

Patient received 0.3 mg of intramuscular epinephrine and albuterol, with symptom resolution in emergency room. In our clinic, we provided Epinephrine autoinjector prescription and refills, anaphylaxis action plan and instruction based on the severity of reaction and proven hypersensitivity to mulberry.

Patient Outcomes

Patient was recovered from anaphylactic reaction after proper and timely treatment in emergency room. Allergy testing in our clinic suggested high likelihood of IgE-mediated allergy to mulberry. Future

care including Epinephrine autoinjector prescription with instruction, anaphylaxis recognition and action was provided.

Lessons Learned

Mulberry allergy is a rarely described entity, but is typically mild and related to birch pollen allergy. In even rarer situation, mulberry can cause anaphylaxis, raising awareness for potential severe outcomes.

Metastatic Dedifferentiated Liposarcoma In An Adolescent In The Setting Of Hypereosinophilia

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Summary

Metastatic liposarcoma associated with eosinophilia is described in adults, however there are limited number of cases reported in the pediatric population. This case highlights the importance of including malignancy in the differential of hypereosinophilia in a child. A 17-year-old male presented with incidental findings of multiple bilateral pulmonary nodules on computed-tomography (CT) of the chest, and hypereosinophilia (maximum absolute eosinophilic count (AEC) 7,029). Biopsy of the lung nodule showed high-grade metastatic sarcoma. A PET-CT demonstrated a 7.9-cm mass in the left thigh, with biopsy revealing dedifferentiated liposarcoma. Subsequently, the patient was diagnosed with liposarcoma, with metastases to the lungs, mediastinum, and brain. He completed 6 cycles of ifosfamide/doxorubicin, followed by surgical resection of primary thigh tumor and brain lesion. Given widely metastatic disease, he received palliative chemotherapy, and later transitioned to hospice. Patient died of respiratory failure from malignant pleural effusions.

Patient Presentation

A 17-year-old male with mild persistent asthma initially presented to the emergency room following a head trauma, with unremarkable head imaging. He additionally mentioned intermittent cough, and incidentally found to have a 1.8 cm nodule in his left middle lung and a 1-cm nodule in the right lung base on chest x-ray. To further characterize these findings, a CT chest was obtained, showing multiple bilateral pulmonary nodules (largest 2.1-cm). Per Fleischner Society's guidelines for evaluating small pulmonary nodules, patient had follow-up imaging 3 months later, showing enlargement of previous nodules by few millimeters, and appearance of new nodules as large as 3.3-cm in the left upper lobe (Figure 1)[1]. At initial encounter, patient did not endorse any respiratory symptoms, weight loss, night sweats, fatigue, fevers or chills. He denied tuberculosis risk factors, sick contacts, recent travel or smoking exposure. Complete blood count (CBC) was notable for WBC of 22, 33% eosinophils, AEC 7029.

Diagnosis

Given findings of pulmonary nodules and eosinophilia, investigation of idiopathic hypereosinophilia was initiated. An infectious work-up was essentially unremarkable, with negative fungal and parasitic serologies, and stool ova and parasites. Myeloproliferative diseases were ruled out with a negative bone marrow biopsy, and lymphoproliferative diseases and immunodeficiencies were ruled out with negative T-cell, B-cell, and NK-cell (TBNK) cell clonality testing. Additional testing to evaluate for an underlying rheumatologic condition also came back negative, including normal ANCA, ANA, ESR/CRP.

Testing

In addition to the general work-up for hypereosinophilia (Figure 2), including TBNK testing, bone marrow biopsy, parasitic/fungal serologies, and tryptase levels, a BAL and lung biopsy was warranted given the uncertainty of the diagnosis. BAL showed eosinophilia. Lung nodule biopsy revealed high-grade metastatic sarcoma with overexpression of MDM2. Further staging scans were completed, including a

PET-CT, demonstrating a 7.9-cm mass in the left posterior thigh with metastases to the brain, lungs and mediastinum (Figure 3). Biopsy of the thigh mass revealed dedifferentiated liposarcoma, confirming the primary tumor.

Treatment

After 4 cycles of chemotherapy with ifosfamide/doxorubicin, patient underwent resection of the primary thigh tumor and craniotomy for resection of brain metastatic lesion, followed by gamma knife therapy. He completed two more cycles of ifosfamide/doxorubicin, however had persistent lung nodules. Repeat wedge resection of the lung continued to show viable disease, and was started on pazopanib. Given MDM2 amplification of tumor, he was enrolled in a clinical trial with palbociclib. Unfortunately, patient continued to show progression of disease and was started on gemcitabine/docetaxel, and later switched back to pazopanib. Patient and family eventually opted for home hospice.

Patient Outcomes

Repeat imaging after induction chemotherapy and surgery showed stable lung disease. He was continued on same regimen, and restaging with second lung biopsy showed viable tumor. He was briefly enrolled in a clinical trial with palbociclib, but continued to have disease progression. He was switched to a palliative regimen, and later transitioned to hospice. Unfortunately, patient developed malignant pleural effusions, requiring several hospitalizations. Patient met his demise secondary to increased tumor burden causing respiratory distress.

Lessons Learned

Hypereosinophilia (AEC > 1500) is present in numerous conditions including infections, allergies, immune dysregulation/deficiencies and malignancies. Hypereosinophilic syndrome (HES) is a group of rare blood disorders associated with hypereosinophilia with evidence of end-organ dysfunction. HES is a diagnosis of exclusion. Hence, it is crucial to rule out other conditions that can mimic symptoms of HES, as treatment is different. Through this case, we illustrate the importance of including a full malignancy work-up in children.

Sarcomas make up about 10% of malignancies in children, rhabdomyosarcoma being the most common. In adults, sarcomas comprise 1% of malignancies, with leiomyosarcomas, liposarcomas and undifferentiated sarcomas being more common. Liposarcomas generally affect adults in their 5th decade of life [2]. Eosinophilia in the context of metastatic liposarcoma is rare and there is paucity of data in the pediatric population. Previous case reports review soft tissue sarcomas and its association with peripheral eosinophilia in adults [3,4]. One case report presents a 17-year-old boy with a cervical mass and eosinophilia, found to have myeloid sarcoma [5]. Through this case, we display the finding of hypereosinophilia in an adolescent found to have metastatic dedifferentiated liposarcoma, initially presenting with multiple lung nodules. To best of our knowledge, there are no reports of eosinophilia associated with metastatic liposarcomas in children and young adults.

This case highlights the importance of performing appropriate lung imaging and bronchoscopy with biopsy when a patient presents with pulmonary nodules and hypereosinophilia. Lung biopsy in this patient was critical in establishing the diagnosis of metastatic liposarcoma.

References:

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Hyper-eosinophilia Work-up	
TEST	RESULT
Absolute Eosinophilic Count	7029
Total IgE	147
CMP	Normal
ESR	Normal
FIP1L1/PDGFR mutation	Normal
T-cell clonality test	Normal
B-cell clonality test	Normal
Tryptase level	Normal
B12 level	Normal
O & P	Deferred
Trichinella serology	Normal
Toxocara serology	Normal
Strongyloides serology	Normal
Troponin	<0.01
Bone marrow biopsy	Unremarkable
Cardiac echo	Normal
EKG	Sinus rhythm
PFTs	Normal, no obstructive or restrictive pattern
CT Chest	Bilateral pulmonary nodules
CT Abdomen/Pelvis	2 small splenic calcifications
Tissue Biopsy	Left Thigh: dedifferentiated liposarcoma; Lung: metastatic high grade sarcoma with overexpression of MDM2
T cell CD3-CD4+, CD3+CD4-CD8-, and CD4+CD7-.	Normal

Figure 2: Hyper-eosinophilia work-up. Lung nodule and thigh mass biopsy findings were critical to the diagnosis of secondary eosinophilia from metastatic malignancy.

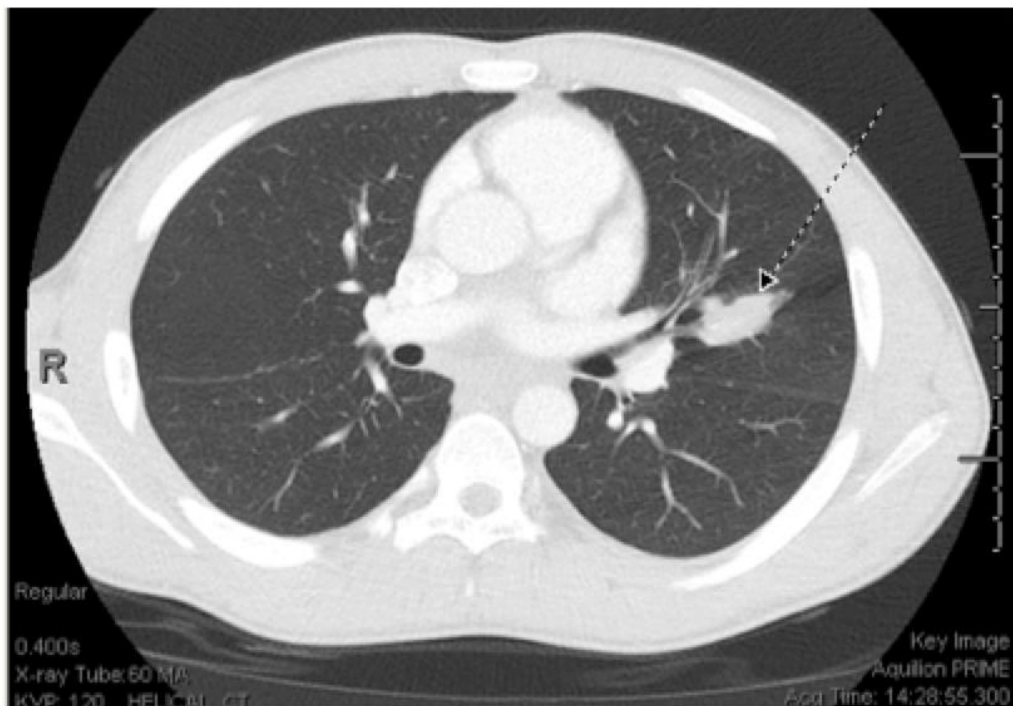


Figure 1: CT chest showing multiple bilateral centrilobular pulmonary nodules with an elongated lesion in the left upper lobe suggesting mucoïd impaction, measuring 3.3-cm.



Figure 3: Whole body PET demonstrating diffuse metastatic disease in the lungs, mediastinum, brain and left femoral lymph nodes, with left popliteal mass.

Angioedema: A diagnostic dilemma

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Summary

Ms. S is a 74-year-old female with a history of metastatic renal cell carcinoma to the liver and lung as well as longstanding recurrent syncope that is presumed to be secondary to autonomic insufficiency. She presented to hospital with an episode of syncope and angioedema of the face and extremities. Given her clinical presentation, she was treated for anaphylaxis. She had no respiratory or gastrointestinal symptoms. It was noted that one month prior, captopril was added onto her medication regimen, and this was thought to be the trigger for her angioedema; however, she was found to have low levels of functional C1 inhibitor and complement C4. Ms. S also confirmed a history of discrete episodes of isolated extremity swelling every couple of months over the course of many years. Genetic testing revealed a heterozygous variant to gene SERPING1, confirming a diagnosis of type 1 hereditary angioedema.

Patient Presentation

Ms. S was seen in the allergy and immunology clinic following her admission to hospital at the end of June 2019. It was noted that she was diagnosed with renal cell carcinoma in 2008, that later became metastatic, with involvement of the liver and lungs. She provided a history of recurrent episodes of syncope that had been thoroughly investigated and determined to be related to autonomic insufficiency.

Ms. S presented to a Vancouver hospital on June 25th, 2019 with an episode of syncope and angioedema of the face and extremities. At around lunchtime that day, she noticed the onset of left leg and right arm swelling. Approximately one hour later, she noticed facial swelling of her cheeks and lips. Several hours later, when she was going to the washroom, she collapsed. She does not recall this incident. At the time of EHS arrival, her blood pressure was 50 on 0 and given her angioedema, she was treated as anaphylactic shock with epinephrine. When in the emergency department, she was given Benadryl and Solu-Medrol with little effect. In regard to her angioedema, she had no airway compromise, dysphagia, or pruritis. It was noted that on her previous admission at the beginning of June, she had the addition of captopril onto her medication regimen, and this was thought to be the trigger.

While in the clinic that day, she mentioned that she presented to hospital with her first episode of facial swelling in 2018, but no further treatment or work-up was completed. A functional C1 inhibitor and complement levels were not done. Since last year, Ms. S describes discrete episodes of isolated extremity swelling every couple of months. They disappear on their own and she has not presented to hospital for these episodes.

Ms. S's family originates from Sri Lanka. One of her brothers reports an adverse reaction to lentils requiring epinephrine. She also has a grandson who has anaphylactic reactions to peanuts and carries an EpiPen. Ms. S also has a niece with a history of hand swelling that she associates with food. She mentioned that no one in her family has been diagnosed with hereditary angioedema.

Diagnosis

The patient's repeat bloodwork revealed a persistently low C1 esterase inhibitor level of 0.32 U and low C4 of 0.33 g/L. These results led us away from the previously suspected diagnosis of ACE inhibitor-induced angioedema. Approval for genetic testing was completed and it showed a heterozygous variant to gene SERPING1, confirming the diagnosis of type 1 hereditary angioedema.

Testing

The initial diagnosis made by the admitting internal medicine team at the beginning of June was ACE inhibitor-induced angioedema, as she was recently started on captopril. Unfortunately, C1 inhibitor and complement levels at that time were not done. On her readmission to hospital on June 25th, 2019, the functional C1 inhibitor was < 0.10 U and complement C4 was < 0.03 g/L. Due to this finding, we were considering the possible diagnosis of either hereditary angioedema – given her interesting family history – or acquired angioedema – given her history of metastatic cancer. In order to finalize our diagnosis, we repeated her bloodwork, including repeat levels of C1 esterase inhibitor and C4. We also submitted an application for genetic testing, given her family history of anaphylaxis and swelling.

Treatment

The treatment we provided our patient was based on the following four principles:

- a. Disease awareness and trigger avoidance: We counseled her on avoiding certain medications that interfere with bradykinin metabolism, such as ACEI, DDP4 inhibitors and neurolysin inhibitors, as well as notifying her healthcare providers of any dental or medical procedures, as these could trigger acute attacks.
- b. Treatment of acute attacks: We arranged for Ms. S to have education to self-administer icatibant injections for future acute angioedema episodes.
- c. Short term prophylaxis: Ms. S would require plasma derived C1 inhibitor at the time of medical/dental procedures to prevent attacks.
- d. Long term prophylaxis: The patient was given danazol over the short term until she was trained to use a C1 inhibitor.

Patient Outcomes

The patient was agreeable to be seen in clinic in one month's time, or sooner if there were any concerns with her diagnosis. She was trained by a nurse to administer C1 inhibitor 3000 units SC injections biweekly and icatibant injections for acute attacks. She was also advised to contact her family members regarding genetic testing given that there is a 50% chance of inheritance for this autosomal dominant condition.

Lessons Learned

When first encountering a patient with angioedema, it is important to obtain a thorough history while keeping a broad differential diagnosis in mind. It is imperative to note in this case that the medical team initially caring for the patient identified the use of captopril and immediately concluded the diagnosis to be ACE inhibitor related. As a result of that diagnosis, angioedema bloodwork was not done, the work-up was not completed and the patient's treatment was delayed. An important learning point from this case is to understand that ACE inhibitors can exacerbate an acute attack in those with hereditary angioedema and it is essential for medical specialists and physicians in allergy/immunology to obtain C1 inhibitor and complement levels in these patients. As this patient also has renal cell cancer and given

her age of presentation, acquired angioedema was also considered. Genetic testing however confirmed hereditary angioedema.

B cell Lymphoma as a Cause of Acquired Angioedema due to C1 Inhibitor Deficiency

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Summary

A 59 years-old female was referred to our Allergy Clinic for investigation of angioedema. At age 57, she presented facial angioedema and dysphonia 5 hours after dental procedure. She received oxygen and adrenaline at the Emergency Department, and angioedema resolved after 5 days. She had a similar episode 20 days later associated with abdominal pain. Complement tests revealed low C4, low quantitative and functional C1-INH and normal C3 levels. The Allergist she had consulted previously prescribed oxandrolone 5 mg once daily, and at our clinic she was switched to danazol. Therapy with attenuated androgens resulted in complete remission of angioedema. Fifteen months after regular follow up, she reported weight loss, weakness, night sweats, and presented splenomegaly on physical examination. Blood counts showed anaemia and thrombocytopenia. Haematological investigation revealed diagnosis of splenic lymphoma of the marginal zone. Patient underwent splenectomy and since then has remained asymptomatic without further episodes of angioedema.

Patient Presentation

At my initial encounter with the patient, she reported weight loss, weakness and night sweats in the last 3 months, and splenomegaly was found on physical examination. She had received care in our clinic for the past 15 months, with regular follow up visits every 3 months. During this time, she had been treated with danazol, 100 mg twice daily tapered to once daily, with no further episodes of angioedema. Her medical history at her first visit in our clinic was of 2 severe episodes of angioedema, one with dysphonia after dental procedure and the other associated with significant abdominal pain, both unresponsive to adrenalin, corticosteroids and antihistamines. Physical exam was completely normal at that time. Initial records indicated that the patient had no previous diseases. She had 2 pregnancies and underwent caesarean sections without complications. She had used estrogen-containing oral contraceptives (OCPs) for 15 years without any symptoms and she was an ex-smoker (20 years/pack). She denied cases of angioedema in the family.

Diagnosis

Although the patient had no family history of angioedema, HAE was our initial diagnosis, since patient's symptoms did not alleviate with antihistamines nor adrenalin and complement testing revealed very low quantitative and functional C1-INH levels, with normal C3. Although very uncommon, there are reports of patients with HAE due to C1-INH deficiency with no mutation detected in SERPING1. Diagnosis of acquired idiopathic angioedema was also considered despite inconsistencies in C1q levels, because of patient's age (57), lack of family history of angioedema, lack of symptoms associated with estrogen exposure (pregnancies and OCP use) and the 20% gamma-globulin peak. Although elevated C1q could be a good marker for Acquired Angioedema due to C1-INH deficiency, it has been reported that high levels of C1q are present in 70% of the patients with this condition. In both conditions, treatment with attenuated androgens could have resulted in complete remission of angioedema symptoms.

Testing

Initial laboratory tests were performed, and showed: complete blood count (CBC) without any cytopenias, negative antinuclear (ANA) and anti-thyroperoxidase antibodies, normal erythrocyte sedimentation rate (ESR) (8mm/first hour). Initial complement tests were performed revealing C4 less than 0.4 mg/dL (reference values, 12-36 mg/dL), C3 110mg/dL (reference values 90-170mg/dL), quantitative C1 inhibitor less than 2.8 mg/dL (reference values 15-34mg/dL), functional C1 inhibitor less than 10% (reference values 70-130%) and low levels of C1q, 72.3 mg/dL (reference values 118-244mg/dL). Upon repetition of the tests, results were consistent, with the exception of levels of C1q which showed normal levels, 141mg/dL (reference values 118-244mg/dL). Genetic test for Hereditary Angioedema (HAE) was performed, but no mutation in SERPING1 gene was found. She presented a 20% peak in the gamma-globulin zone of protein electrophoresis, and her Kappa free light chain was slightly elevated, 27.3 (reference values 6.7-22.4 mg/dL), with normal kappa/lambda ratio, 1.10 (reference values 0.31 – 1.56). Skull and long bones radiographs were normal. Computed tomography of chest and abdomen showed no abnormalities.

By the time I saw the patient for the first time, after 15 months of follow up in our clinic, I started the investigation of her symptoms of weight loss, weakness, night sweats, and of her splenomegaly with a CBC and differential, which showed Hb 11.3 g/L Ht 35% leukocytes 4,300/mm³ (22% neutrophils, 35% lymphocytes, 1% basophils, 2% monocytes, 0% eosinophils) platelets 51,000/mm³, revealing anaemia, neutropenia, and marked thrombocytopenia as compared to previous tests. Danazol was withdrawn, and new CT scans of abdomen and chest were performed revealing marked splenomegaly (28.8cm in the largest diameter). She was referred to haematology consultation. Bone marrow biopsy revealed hypercellular bone marrow with mature B cell lymphoid infiltrate. The diagnosis of marginal zone splenic lymphoma (MZL) was made and splenectomy was indicated.

Treatment

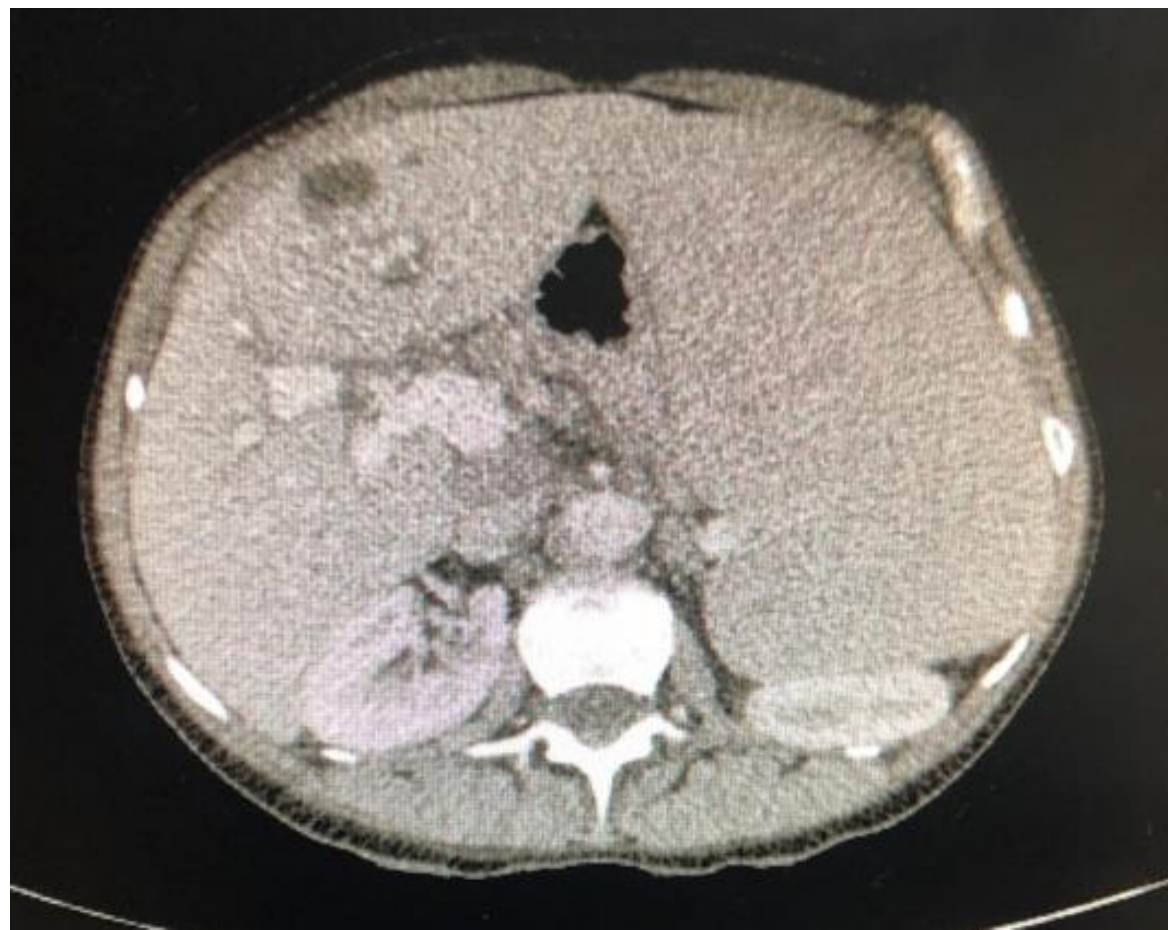
We decided to start the patient on attenuated androgen (Danazol 100mg initially twice daily, tapered to once daily as the patient showed good control of her symptoms) due to the hypothesis of HAE. Since the hypothesis of acquired angioedema was not ruled out, regular medical visits and general exams such as CBC and ESR were performed every 3 months in order to detect potential lymphoproliferative or autoimmune diseases.

Patient Outcomes

After evaluation by the Haematology group, the patient underwent splenectomy 18 months after the first visit to our clinic. Biopsy of the spleen confirmed MZL. Patient remained asymptomatic after splenectomy without further episodes of angioedema (6 months follow up).

Lessons Learned

This case report prompted me to always look for an underlying cause, especially lymphoma, in patients with isolated angioedema, particularly when it starts in adult life. Also, it reinforced the need for a close follow up of the patients, since new symptoms and signs can appear at any time. In my literature review I found the description of 72 patients with acquired angioedema, of whom 15 (20%) were associated with splenic marginal zone lymphoma (Castelli R et al, British Journal of Haematology 2016).





Recurrent lymphoma in an adenosine deaminase deficient patient receiving long-term enzyme replacement therapy

Author Erika Lee, MD

Training Program Clinical Immunology and Allergy

Summary

Adenosine deaminase (ADA) is a ubiquitous enzyme important for the degradation and salvage of purine metabolites. ADA deficiency causes severe combined immunodeficiency (SCID) and non-immune manifestations like sensorineural deafness and neurological/behavioural problems. ADA deficiency is often lethal in infancy without allogeneic hematopoietic stem cell transplant or gene therapy. When neither option is available, ADA enzyme replacement therapy (ERT) has been considered. Herein, we describe a 28-year-old woman diagnosed in infancy with ADA deficiency who has been receiving ADA ERT since one year of age. She has suffered significant comorbidities, including two separate episodes of primary lymphomas, Guillain-Barre Syndrome and two life-threatening opportunistic infections. She recovered from these comorbidities and continues with life-long intravenous immunoglobulin (IVIG) replacement and prophylactic antibiotics in addition to ERT. Our case illustrates that the long-term correction of the immune system with ADA ERT in ADA deficiency may not be adequate, resulting in continued morbidity.

Patient Presentation

At one year of age, our patient of Somali descent was diagnosed with SCID due to ADA deficiency after she presented with recurrent multi-system infections and failure to thrive. She was found to have homozygous nonsense ADA mutation Q3X, common in the Somali population. Because neither HLA-matched sibling donor nor closely matched unrelated donor was available at the time, her family chose to proceed with ERT. She continued to have recurrent acute otitis media and various viral infections caused by CMV, Herpes simplex virus and varicella zoster virus. She also suffered from developmental delay and bilateral hearing loss. At 14 years of age, she was diagnosed with extra-nodal diffuse large B cell lymphoma of the right hip. She achieved complete remission following treatment with chemotherapy and Rituximab. Monthly IVIG replacement was also initiated as her CD20+ B cells numbers remained extremely low. At 16 years of age, she was diagnosed with Guillain-Barre Syndrome (GBS); she received supportive treatment and had complete recovery. At 22 years of age, she was diagnosed with Mycobacterium Genavense infection of the gastrointestinal tract that resolved with quadruple antibiotic treatment. She has remained on lifelong azithromycin and trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxes, in addition to ERT and IVIG. At 26 years of age, she developed nausea, vomiting, decreased appetite and weight loss. As part of the follow-up for her chronic nontuberculous mycobacterial (NTM) infection of the gastrointestinal tract, Magnetic resonance imaging (MRI) abdomen was done and showed multiple liver lesions. She was subsequently admitted to the hospital for expedited workup of her liver mass.

Diagnosis

Our patient was diagnosed with stage IV diffuse large B cell lymphoma of the liver. Although she had lymphoma involving the hip previously, it was thought this one was a new primary as opposed to a relapse of her previous lymphoma.

Testing

The patient's bloodwork was notable for elevated CRP (158mg/L, normal 0-5) and LDH (1091U/L, normal 100-195). MRI of her abdomen showed multiple soft tissue masses within the liver with the largest lesion measured at 7.4x5.0x5.0 cm. Positron Emission Tomogram (PET) showed numerous metabolically active masses within the liver with the largest lesion measured 9.5x7.2cm and maximal SUV of 50.7 (Photo 1). Ultrasound-guided liver biopsy showed predominantly necrotic tissue with small viable focus of large B-cell lymphoma.

Treatment

The patient received 8 cycles of modified R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; Doxorubicin dose was reduced due to prior exposure to Anthracycline). Radiation was omitted due to concerns for increased risk of secondary malignancy in the background of primary immunodeficiency, and particularly ADA deficiency. During her chemotherapy treatment, she also received G-CSF and acyclovir prophylaxis, in addition to continuing ADA ERT, IVIG replacement, TMP-SMX and azithromycin prophylaxes.

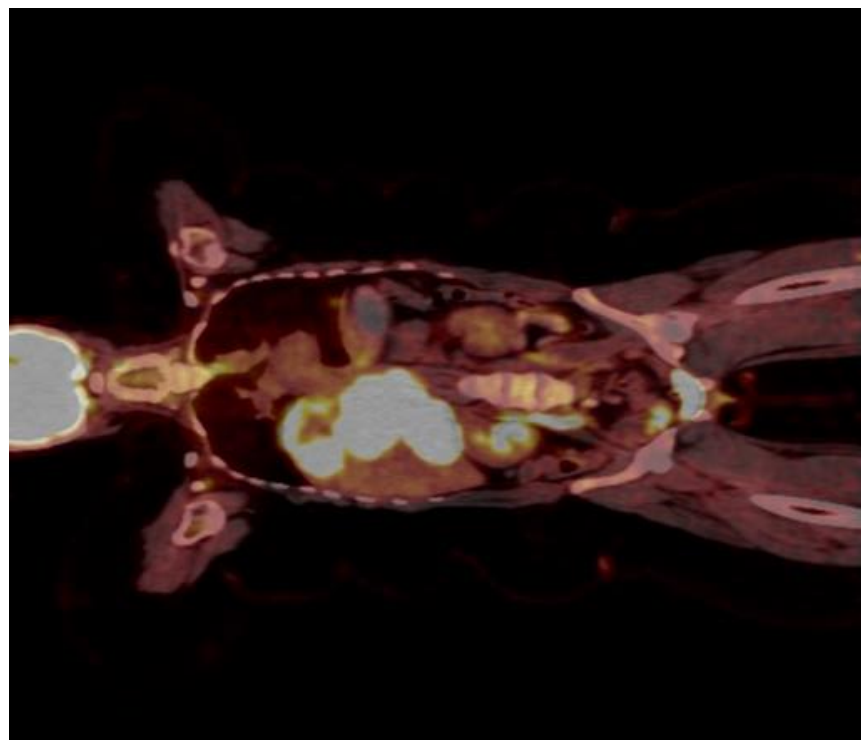
Patient Outcomes

After the completion of her chemotherapy, a repeat PET showed significant interval decrease in the size, degree and extent of abnormal metabolic activity of the hepatic lesions, with the residual smaller lesions showing no abnormal metabolic activity (Photo 2). Several months later, the patient complained of persistent headache. CT head showed multiple intracranial lesions with surrounding vasogenic edema. A brain biopsy, eventually grew *Mycobacteria Genavense* which was treated again with quadruple. The patient's clinical and radiographic abnormalities improved rapidly and she continues to remain in clinical remission from her lymphoma at the one-year follow-up. Throughout the 27 years of ADA ERT, the patient's plasma ADA activity has always remained within therapeutic range and her trough IgG level has remained above 8g/L consistently (while receiving IVIG). She has persistent lymphopenia (less than $0.2 \times 10^9/L$).

Lessons Learned

: The clinical course of our patient demonstrated significant comorbidities while receiving long-term ERT. Her recurrent life-threatening opportunistic infections suggest that ADA ERT may not be sufficient to rescue the immune system for extended periods. Her recurrent lymphomas and life-threatening autoimmunity support the concern for the emergence of serious complications with prolonged ERT. In conclusion, we report an ADA-deficient patient who received 27 years of ADA ERT who experienced serious immune and extra-immune complications.

ADA ERT can lead to temporary immunologic recovery in patients with SCID caused by ADA deficiency. ERT is also generally well tolerated and patients remain free of opportunistic or abnormally frequent infections. However, the immune reconstitution often declines while receiving long-term ERT for unknown reasons, resulting in the development of serious complications like lymphoproliferative diseases or serious infections. Hence, patients with ADA deficiency should be offered definitive treatment like allogeneic hematopoietic stem cell transplant or autologous gene therapy (Kohn et al, 2019).



Severe Anaphylaxis to Cow's Milk in Partially Hydrolyzed Formula in an Infant with Glycogen Storage Disease Type 1a

Author Tina M. Banzon, M.D.

Training Program Boston Children's Hospital

Summary

We describe an 11-month-old male with glycogen storage disease type 1a (GSD1a), food allergies to peanut and egg, atopic dermatitis, intermittent urticaria, and eyelid hemangioma managed on oral propranolol who presented with acute hypoglycemia (glucose 30 mg/dL), apnea, tachycardia, hypotension, acute urticaria, vomiting, diarrhea, and lethargy following his first ingestion of PediaSure Peptide 1.0 (partially hydrolyzed milk-based formula). Previously, he had been tolerating Enfamil Prosobee (soy-based formula). He also had fever for 3 days prior. Patient was on CPAP briefly, given IV fluid boluses and dextrose-containing IV fluids, and was admitted to the Intensive Care Unit. He recovered fully despite not receiving epinephrine. Patient had elevated specific IgE for milk (83.7 kU/L), casein (69.2 kU/L), alpha-lactoalbumin (3.08 kU/L), beta-lactoglobulin (21.8 kU/L), and elevated tryptase (77.4 mcg/L; normalized 3 days later).

Patient Presentation

On day of admission, mother had given patient PediaSure Peptide 1.0 via G-tube for the first time. He had never previously ingested cow's milk in any form. The patient had non-bilious, non-bloody emesis immediately following the feed, which was typical of his usual once daily emesis. He developed full-body hives 5 minutes later, which differed from his baseline intermittent hives, which were typically isolated and 1-2 in quantity. Patient then had cyanosis and cessation of breathing. Mother checked his blood glucose, which was 30 mg/dL. Of note, patient had a similar episode of respiratory distress at 4 months of age due to hypoglycemia associated with his underlying GSD1a. Mother gave patient rescue breaths for 5 minutes, called 911, and EMS manually resuscitated patient using bag valve mask and oral glucose. In the ED, vital signs were notable for tachycardia (HR 150s) and hypotension (BP 60s/30s). Exam was notable for ashen appearance, poor respiratory effort, and responsive only to painful stimuli; at that time, hives had resolved. He was briefly placed on CPAP for respiratory support and given fluid boluses and started on dextrose-containing IV fluids to manage his hypotension and hypoglycemia. His home propranolol therapy for right eyelid hemangioma (dose 6.42 mg PO BID) was held given his hypotension. Allergy was consulted after admission to the ICU for concern for allergic reaction to newly-introduced partially hydrolyzed milk-based formula. Patient had known peanut and egg allergy, diagnosed by positive skin prick testing performed at the request of the family due to his underlying atopic dermatitis. He had never previously ingested peanut or egg or experienced an allergic reaction. Epinephrine autoinjectors had been prescribed and the family had them in the home on the day of his reaction but did not use them, as they had assumed his symptoms were due to his hypoglycemia.

Diagnosis

Differential diagnosis for this episode included anaphylaxis, metabolic derangements related to his underlying GSD1a, or viral/infectious etiology. The patient had fever for 3 days, diarrhea for 1 day, vomiting, and positive sick contact, as father had URI symptoms for 1 week. Previously, patient had had a similar episode of apnea and respiratory distress at 4 months of age due to hypoglycemia. GSD 1a is

due to deficiency of the enzyme glucose-6-phosphatase, causing inability to convert glucose-6-phosphate (G6P) to glucose, leading to severe hypoglycemia and excess G6P shunted to alternative pathways, including lactate production. Consequent lactic acidosis can cause weakening of respiratory muscles and impair breathing. The patient's hypotension could have been exacerbated by his daily home medication of propranolol. Given the patient's clinical presentation of multisystem involvement in the setting of trialing cow's milk for the first time, and lab-work up compelling for an IgE mediated reaction (profoundly elevated tryptase, elevated specific IgE to milk proteins), a diagnosis of anaphylaxis to cow's milk was made.

Testing

Though the differential was initially broad due to patient's underlying GSD1a and his intercurrent febrile illness, his multisystem involvement (apnea, tachycardia, hypotension, acute urticaria, vomiting, diarrhea, and lethargy) in the setting of newly-introduced partially hydrolyzed cow's milk-based formula was concerning for IgE-mediated anaphylaxis. Review of ingredients in PediaSure Peptide 1.0 included whey protein hydrolysate and tuna oil as potential allergens; thus, specific IgE for milk and fish panels were sent. He had no known previous exposure to cow's milk or fish. Specific IgE was elevated for cow's milk (83.7 kU/L), casein (69.2 kU/L), alpha-lactoalbumin (3.08 kU/L), and beta-lactoglobulin (21.8 kU/L). Specific IgE to fish panel, including tuna, was negative. Total IgE was elevated (1045 units/mL). Tryptase was collected 6 hours after PediaSure Peptide 1.0 was given. While it is more useful when timed closer to reaction and less commonly elevated in food anaphylaxis, tryptase returned highly elevated at 77.4 mcg/L. The patient's elevated tryptase was thought to be due to his severe presentation of anaphylaxis, but given its profound elevation, underlying mastocytosis was also considered. Repeat tryptase 3 days later was normal (6.3 mcg/L), and thus, further work up for mast cell disorders was not pursued.

Treatment

Based on lab work-up, which included elevated specific IgE for milk (83.7 kU/L), casein (69.2 kU/L), alpha-lactoalbumin (3.08 kU/L), beta-lactoglobulin (21.8 kU/L), and elevated tryptase (77.4 mcg/L) with multisystem involvement concerning for anaphylaxis to cow's milk, patient was advised strict avoidance of cow's milk, including in partially hydrolyzed formula. The patient remained hospitalized in the ICU for two additional days for reinitiation of feeds and monitoring of blood glucose due to his underlying GSD1a. The patient tolerated reintroduction of Prosobee formula. No biphasic reactions developed during his admission. Family was advised to have epinephrine auto-injectors with patient at all times. Signs and symptoms of anaphylaxis and indications for epinephrine administration were reviewed with the family.

Patient Outcomes

Despite not receiving epinephrine for anaphylaxis, our patient recovered fully from the episode with supportive measures, including non-invasive ventilation and aggressive IV fluid hydration. Given that up to 20% of patients with anaphylaxis can have a biphasic reaction within 24 hours, or in some case reports 72 hours, after the episode of anaphylaxis, it was advised to the primary medical team to have low threshold to give epinephrine should the patient later on present with multisystem involvement after the initial episode.

Lessons Learned

Anaphylaxis to hydrolyzed formula is uncommon. Our patient's hypoglycemia, viral illness and daily propranolol may have contributed to his severe anaphylaxis. While metabolic derangements in disorders such as GSD1a can mimic anaphylaxis, IM epinephrine is prudent to administer in the setting of signs consistent with anaphylaxis.

Well's syndrome related to *Mycoplasma pneumoniae* in a 5-year-old boy

Author Hye-Young Kim

Training Program Fellow in training (Korea)

Summary

A 5-year-old boy was hospitalized with 3 days history of a pruritic, erythematous and edematous lesion on ankles, feet and shin. He also reported a mildly productive cough for 5 days. His body temperature on admission was 38.3°C. Biopsy of the nodule on the right shin showed diffuse eosinophilic infiltration in the dermis, consistent with eosinophilic cellulitis. Initially, *M. pneumoniae* IgG level was 3.5 AU/mL, but two weeks later, *M. pneumoniae* IgG level was > 100 AU/mL. These results finally led to the diagnosis of *M. pneumoniae* infection. Gradual clinical improvement was observed after the initiation of oral clarithromycin (15 mg/kg/day in 2 divided doses for 10 days) and oral prednisolone (1 mg/kg/day for 5 days). The patient was followed-up over the course of a year, and no relapse was observed.

Patient Presentation

A 5-year-old boy was hospitalized with 3 days history of a pruritic, erythematous and edematous lesion on both ankles and feet. He also reported a mildly productive cough for 5 days. His body temperature on admission was 38.3°C. Physical examination revealed tender, erythematous wheal-like plaques on both ankles and feet and an erythematous nodule on the right shin. Pulmonary examination revealed scattered crackles in the right upper lung zone. He denied a history of insect bites, medication use, recent vaccination, travel, or allergy. Chest radiography showed pneumonic consolidation in the right upper lung zone.

Diagnosis

We performed the skin biopsy of the module on the right shin. The result showed diffuse eosinophilic infiltration in the dermis, consistent with eosinophilic cellulitis.

And initial *M. pneumoniae* IgG level was 3.5 AU/mL, but two weeks later, *M. pneumoniae* IgG level was > 100 AU/mL.

Well's syndrome was confirmed by a skin biopsy with *M. pneumoniae* infection.

Testing

Chest radiography showed pneumonic consolidation in the right upper lung zone. His initial peripheral white cell count was 15,360 cells/mm³ (51.5% neutrophils, 26.7% lymphocytes, and 18.8% eosinophils), erythrocyte sedimentation rate was 45 mm/hour (0–15 h), and serum C-reactive protein was 5.9 mg/dL (0–0.5 mg/dL). A peripheral blood smear showed hypereosinophilia without immature cells.

Laboratory investigations revealed normal serum and urine chemistry and immunoglobulin and complement component levels, as well as normal perinuclear and cytoplasmic antineutrophil cytoplasmic antibody, antinuclear antibody, and anti-DNA antibody titers. The Serological tests for parasitic infestations, as well as parvovirus B19, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus infections showed negative results. A nasopharyngeal swab for RT-PCR of respiratory viruses showed negative results but *M. pneumoniae* was positive. Initially, *M. pneumoniae* IgG level was 3.5 AU/mL, but two weeks later, *M. pneumoniae* IgG level was > 100 AU/mL.

Treatment

Because the patient was diagnosed with *M. pneumoniae* infection, we prescribed oral clarithromycin (15 mg/kg/day in 2 divided doses for 10 days) .

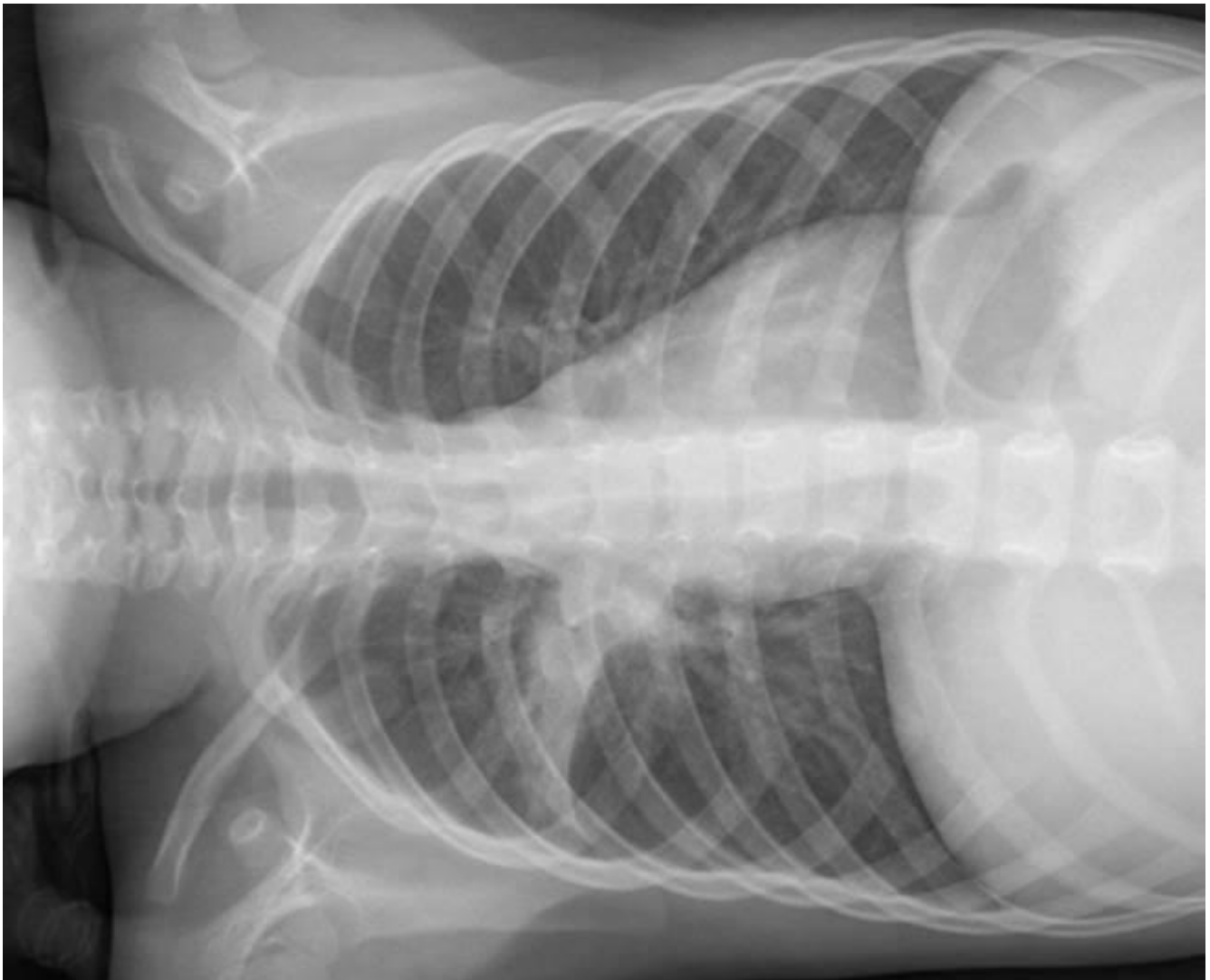
And the patient took oral prednisolone (1 mg/kg/day for 5 days).

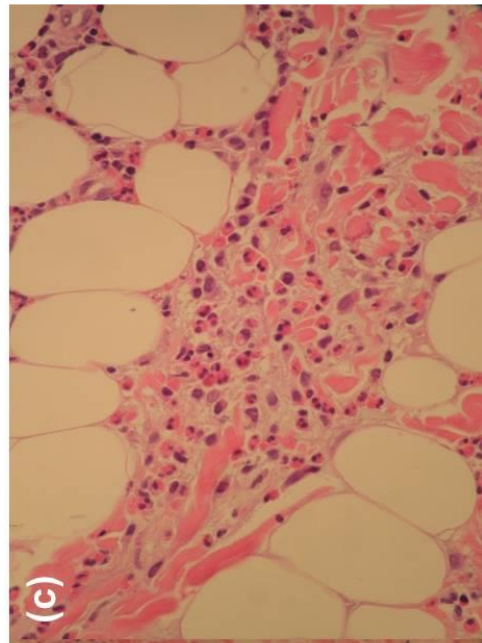
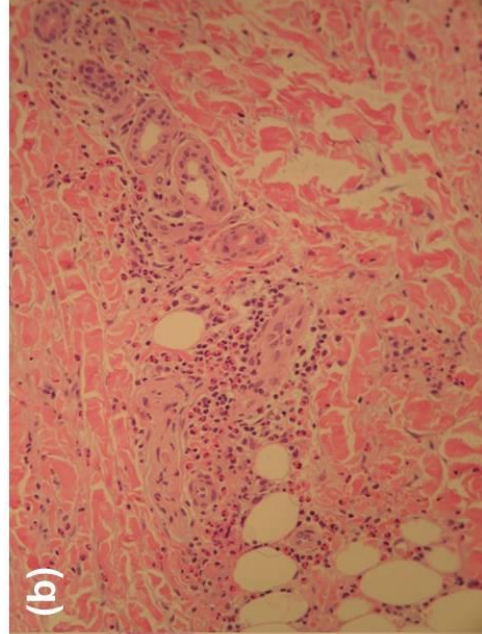
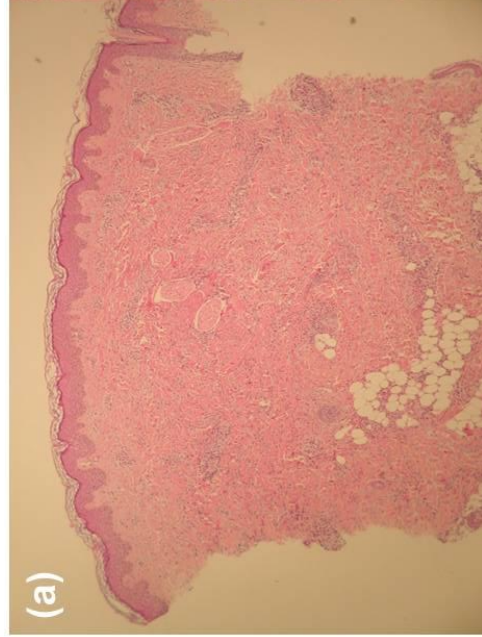
Patient Outcomes

Eosinophils count in the peripheral blood was 3% after 2 weeks. The patient was followed-up over the course of a year, and no relapse was observed.

Lessons Learned

This is the first report to describe the association between Well's syndrome and *M. pneumoniae* infection. Enquiry regarding possible causes for Well's syndrome should include *M. pneumoniae* infection.





Dupilumab Therapy Revealed an Underlying Cause of Hypereosinophilia in a Child

Author Osman M. Numair, MD; Diana Munoz-Mendoza, MD; Sami L. Bahna, MD, DrPH

Training Program Louisiana State University (Shreveport) - Allergy and Immunology

Summary

A 7yo female with severe atopic dermatitis (AD), moderate persistent asthma (controlled on budesonide nebulization 0.25 mg BID), and multiple food allergies (egg, peanuts, seafood) who didn't improve on skin moisturizers, medium potency steroid creams, and antihistamines. Oral cyclosporine 4 mg/kg/day was initiated but discontinued after 4 mo due to lack of improvement. She was enrolled in dupilumab trial; received 600 mg subcutaneous as a first dose followed by 300 mg every 4 wk. At 3 mo, she developed eosinophilia count of 11,398/ μ L (up from 801/ μ L) and lower extremities pain, which limited her daily activities. Ultrasound of her lower extremities was normal. Serology was negative for Toxocara IgG but positive to Strongyloides which was treated with Ivermectin. Patient dropped out from the dupilumab trial at 4 mo due to poor response of her AD and the development of bilateral leg pain and the Strongyloides infestation. 3 mo after discontinuation of dupilumab eosinophilic count dropped to 1,960/ μ L. Patient had improvement of her AD and extremities pain.

Patient Presentation

A 7yo female with severe AD, moderate persistent asthma (controlled on budesonide nebulization 0.25 mg), and multiple food allergies (egg, peanuts, seafood), the latter was based on a strong history and positive specific serum IgE. The mother was also eliminating milk, soy, and wheat suspected to exacerbate the dermatitis. Patient didn't improve on topical moisturizers 2-3 times daily, topical steroid creams (desonide 0.05% BID or tramcinolone 0.1% BID), and anti-histamines (oral diphenhydramine 12.5 mg QHS or hydroxyzine 2 mg/kg every 6 hr). Patient had normal vital signs, dry, scaly skin with areas of hyper and hypopigmentation of the extremities. CBC showed an eosinophil count 801/ μ L and total serum IgE 15,300 IU/mL. Patient was initiated on cyclosporine 50 mg BID (4 mg/kg/day) orally which was discontinued after 4 mo due to lack of improvement. She was enrolled in the dupilumab trial 600 mg subcutaneous first dose, followed by 300 mg q 4 wks. At 3 mo, she developed eosinophil count of 11,398/ μ L and bilateral lower extremity intermittent pain, which limited her daily activities.

Diagnosis

Persistent hypereosinophilia while on dupilumab in patient with severe atopic dermatitis and well controlled moderated persistent asthma

Testing

WBC count 25.33 K/ μ L, Hb 12.4 G/dL, Hct 36.9% and a platelet count 490 K/ μ L. The patient WBC differential was significant for an eosinophilia 11,398/ μ L and lymphocytes 4,053/ μ L. CRP was 9.64 mg/dL and total serum IgE 15,300 IU/mL. Ultrasound of her lower extremities was normal. Spirometry showed an FEV1 1.32L (124%), 1.74L (139%) and an FEV1/FVC of 75%. She had negative Toxocara IgG but positive Strongyloides IgG antibodies. EKG showed a normal sinus rhythm. Chest X-Ray showed no acute cardiopulmonary lesions.

Treatment

Patient received dupilumab 600 mg subcutaneously as first dose, followed by 300 mg every 4 wk for a total of 4 mo. After confirmation of *Strongyloides* infestation, patient was treated with oral Ivermectin 6 mg for 2 days. She was dropped from the dupilumab trial after 4 mo due to poor response and the development of bilateral leg pain and presumptive *Strongyloides* infection.

Patient Outcomes

Patient had improvement of AD and leg pain as well as a drop in eosinophilia to 1,960/ μ L 3 mo after discontinuation of dupilumab and ivermectin treatment

Lessons Learned

Transient hypereosinophilia on dupilumab has been reported in some patients. In our patient, it is not clear if the increase in eosinophilia count was due to dupilumab treatment or due to *Strongyloides* infestation.





Immune Overactivation: CTLA-4 haploinsufficiency with autoimmune infiltration (CHAI)

Author Matthew M. Farley, M.D.

Training Program Mayo Clinic Arizona Internal Medicine Residency Program

Summary

A 36-year-old previously healthy female presented with lymphocytic colitis, idiopathic thrombocytopenic purpura, middle ear soft tissue density, dermatitis, splenomegaly/axillary lymphadenopathy, and follicular bronchiolitis. Genomic sequencing for primary immunodeficiency disorders revealed a mutation in CTLA-4. Considering her clinical manifestations and the CTLA-4 mutation, she was diagnosed with CTLA-4 haploinsufficiency with autoimmune infiltration (CHAI). Treatment with sirolimus and abatacept was initiated, and her clinical response to the treatment will be monitored.

Patient Presentation

A 36-year-old previously healthy female presented to Allergy & Immunology clinic for immunodeficiency evaluation. Four years prior, she developed chronic watery diarrhea and biopsy of the colon was consistent with lymphocytic colitis. All other GI workup was negative, including serology for celiac disease. The following year, she developed immune thrombocytopenic purpura (ITP) during pregnancy with platelets as low as 80,000 and mild splenomegaly noted on CT abdomen. One year ago, she developed hearing loss and vertigo. ENT evaluated her and a CT temporal bone showed a soft tissue density within the left middle ear. Additionally, there was a soft tissue density within the left anterior and inferior mastoid air cells. The patient was treated with an oral steroid taper with dramatic improvement in her hearing loss and vertigo. Amidst the vertigo and hearing loss, she developed shortness of breath, fevers, chills, and night sweats. She failed to respond to antibiotic therapy and a CT chest was performed which showed multiple pulmonary nodules with axillary lymphadenopathy (Figure 1). No infectious or rheumatologic etiologies were identified; therefore, a video-assisted thoracic surgery (VATS) with biopsy was performed. Pathology demonstrated lymphoplasmacytic inflammatory infiltrate with non-necrotizing granulomas consistent with follicular bronchiolitis. The patient also developed an erythematous, pruritic rash with associated thick silvery scale (Figure 2). Skin biopsies showed spongiotic dermatitis. Her rash improved significantly after initiation of prednisone. Of note, the family history was negative for primary immunodeficiency or similar autoimmune manifestations.

Diagnosis

The patient's clinical presentation and genetic findings are consistent with CTLA-4 haploinsufficiency with autoimmune infiltration (CHAI). Literature review of previous CHAI case reports indicate that manifestations include autoantibody-mediated cytopenias, lymphadenopathy, splenomegaly, hypogammaglobulinemia, and lymphocytic infiltration of non-lymphoid organs, most commonly the GI tract, lungs, and skin. In CTLA-4 haploinsufficiency with autoimmune infiltration, patients have heterozygous loss-of-function mutations in CTLA-4. CTLA-4 is a critical T-cell inhibitory receptor primarily expressed on Tregs cells. It suppresses T-cell proliferation by negative signaling or competing with CD28, the main T-cell costimulatory module. To date, there are 21 published cases of this disease but none with the mutation that our patient has. [1]

Testing

IgG and IgM were mildly decreased with normal IgA and absent IgE. The tetanus and diphtheria titers were normal. For *s. pneumoniae* IgG, 8/23 serotypes were >1.3. After receiving Pneumovax, only one additional serotype IgG increased for a total of 9/23. Immunophenotyping was unremarkable except for the absolute number of CD27+ IgM-IgD- class switched memory cells was decreased. Genetic sequencing (Invitae Primary Immunodeficiency Panel) identified a variant of uncertain significance in CTLA4, Exon 2, c.439A>G (p.Thr147Ala). The report stated that this variant is not present in population databases (ExAC no frequency). Algorithms developed to predict the effect on protein structure and function all suggested that this variant is likely to be disruptive, but these predictions have not been confirmed by published functional studies.

Treatment

We started treatment with sirolimus and abatacept. She was loaded with Sirolimus 6mg, then maintained on 1.5mg daily thereafter. She is receiving Abatacept 750mg IV infusion once every 2 weeks for the first 4 weeks. Thereafter, she will receive once monthly infusions. This regimen was decided on with the assistance of experts at National Institutes of Health (NIH), whom have successfully treated 8 patients with this combination. She will also continue her prednisone taper. In vitro studies demonstrate that CTLA-4-Ig fusion protein (i.e. abatacept) suppresses T cell proliferation. [2] Human studies of abatacept have also shown clinical improvement in subjects with CHAI. [3] Furthermore, sirolimus has also been reported to alleviate symptoms in these patients. Sirolimus, a mTOR inhibitor, is widely known to suppress T cell function while allowing Tregs to expand and function appropriately. [1] For severe, refractory cases, hematopoietic stem cell transplant (HSCT) is an option. Eight patients treated with HSCT for severe immune dysregulation were retrospectively found to have CTLA deficiency. Of these, 6 of 8 patients are alive and well. Unfortunately, one patient died from graft-versus-host disease and another from diabetic ketoacidosis two years following HSCT. [4]

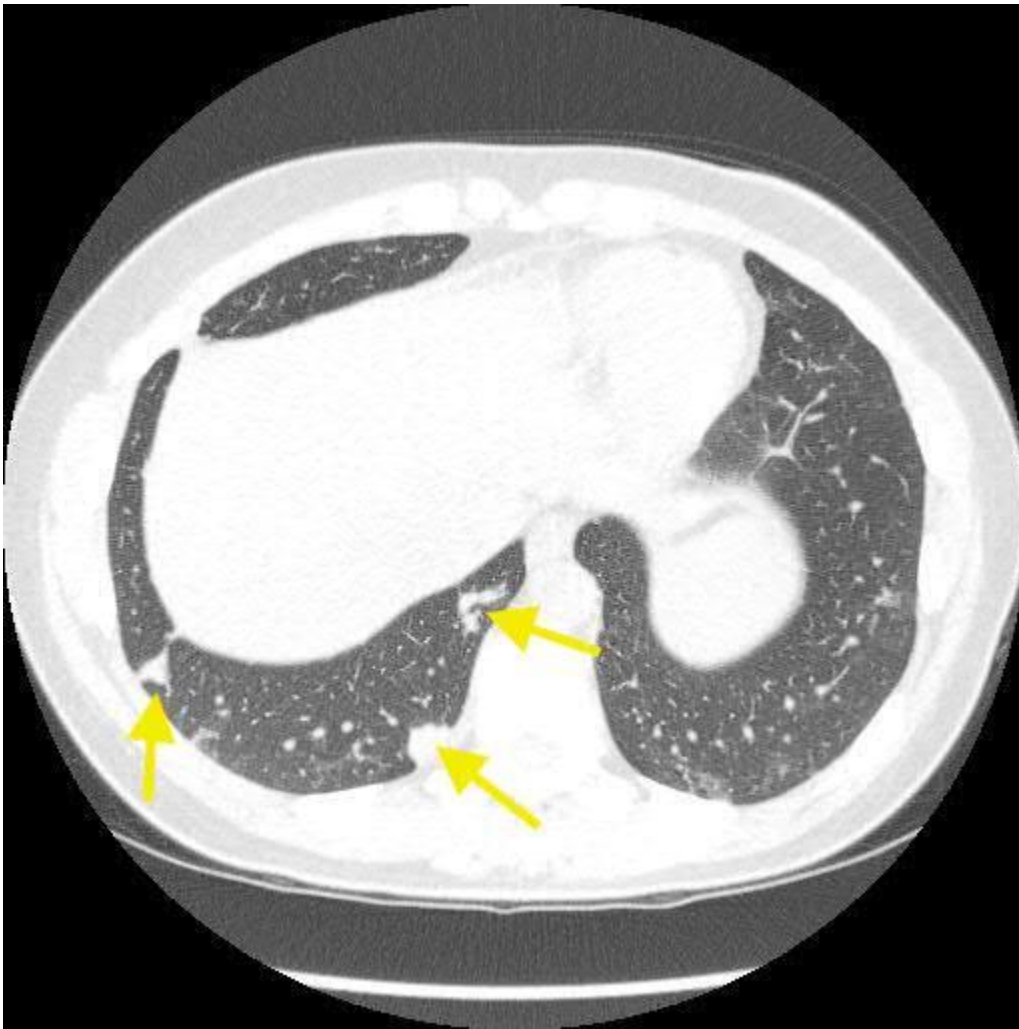
Patient Outcomes

The patient has just recently been initiated on the above mentioned treatment regimen. Her clinical improvement will be monitored with frequent office visits and with the assistance of multiple specialties including GI, Pulmonology, ENT, and Dermatology.

Lessons Learned

Lessons Learned:

- Consider CHAI in patients presenting with lymphocytic infiltration of non-lymphoid organs and other autoimmune features.
- Genetic testing is useful when immunodeficiency is suspected and the functional tests are not definitive.
- There are no standardized treatment protocols for CHAI, only successful case reports for abatacept, sirolimus, and HSCT. Therefore, further investigation and research are needed.
- Abatacept and sirolimus may suppress T cell activity/proliferation that drives the underlying disease pathogenesis.



Alpha-1 antitrypsin deficiency with heterozygous and homozygous mutations associated with an underlying immune deficiency

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Training Program The Children's Hospital at Montefiore

Summary

Mother and daughter presented with severe recurrent respiratory infections, productive cough, wheezing and shortness of breath as classical presentation of autosomal recessive alpha-1 antitrypsin deficiency (AATD). The mother who was severely pulmonary compromised and on constant oxygen therapy was heterozygote while her daughter was homozygote with a PI*ZZ genotype. Patients with heterozygote deficiency as noted in the mother are usually asymptomatic or mildly symptomatic.

Patient Presentation

Mother presented to our clinic at the age of 69 years with oxygen dependent COPD, chronic sinusitis, recurrent pulmonary infections and psoriatic arthritis. Patient was a former smoker for 40 years (1ppd). Her daughter presented to our clinic at the age of 40 years with a 10-year history of chronic cough, recurrent sinusitis and pneumonias. Patient was never a smoker and there was no clinical history or recent exposures to tuberculosis.

Diagnosis

Mother was found to have hypogammaglobulinemia, lymphopenia and exhibited poor antibody response to streptococcus pneumoniae serotypes. Genotyping and sequencing demonstrated the patient to be a heterozygote for AAT mutation.

Daughter had a computed tomography of chest reveal bilateral bronchiectasis and compromised pulmonary function. Immunologic work up showed as in her mother low serum immunoglobulins with poor specific antibody responses to polysaccharide antigens. Patient was found to be homozygous for an AAT mutation.

Testing

Mother was found to be heterozygous for alpha-1 antitrypsin deficiency with a normal trypsin level of 147 mg/dl. Her daughter was homozygous for the PI*ZZ genotype with a low level of trypsin at 40 mg/dl.

Treatment

Both patients are on AAT replacement therapy. Both patients are also on gamma-globulin therapy. Initially started on IVIG and over time switched to SCIG.

Patient Outcomes

Both patients pulmonary condition improved on weekly intravenous AAT therapy. The concurrent use of subcutaneous gamma-globulin due to the underlying immune deficiency has by and large controlled the associated infections. Both patients had positive bronchial cultures for pseudomonas and were treated with nebulized Tobramycin and Kanamycin respectively.

Lessons Learned

Patients with heterozygote AAT mutations are also prone to develop severe lung disease especially with an associated history of smoking. Although the mother has AAT heterozygote mutation and had normal AAT blood levels, she responded to intravenous AAT therapy. Alpha-1 anti-trypsin levels should be monitored in all patients with COPD. Therapy with intravenous AAT can be effective even in advanced lung disease and decrease the progression of decline of pulmonary function.

Complement Factor I Deficiency in a Patient with Recurrent Cellulitis

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Summary

This is a case of a 27-year-old otherwise healthy female with adult onset recurrent skin and soft tissue infections in the absence of unusual exposures and despite appropriate and repeated courses of antimicrobial therapy found to have complement factor I (CFI) deficiency. After referral to allergy and immunology for immunological assessment, the patient was found to have intact innate and adaptive immune systems with the notable exception of low alternative complement pathway activity (AH50) and CFI. Vaccination history was reviewed and updated, and management consisted of extensive counseling on early recognition and antimicrobial intervention with regard to future signs and symptoms of infection. An official letter was provided to the patient to carry with her and present to primary care or emergency department providers should she develop signs of infection.

Patient Presentation

A 27-year-old otherwise healthy female with two remote episodes of cellulitis as a teenager and a subsequent near decade long infection-free period developed four episodes of SSTIs within a one year period. Two of these infections included purulent abscesses requiring drainage with one requiring inpatient admission and surgical debridement—later confirmed as methicillin-resistant *Staphylococcus aureus* (MRSA) via a culture of drained purulent fluid. This MRSA infection developed despite a MRSA decolonization protocol being completed only several months prior after an SSTI that was treated empirically as MRSA but without microbiological confirmation. The patient required multiple courses of antibiotics for treatment of her infections but developed repeated infections despite appropriate therapy. She otherwise did not report unusual environmental exposures or notable social history. Family history included a cousin who suffered a severe soft tissue infection and died of unclear complications in her twenties. No immediate family members were reported to suffer from frequent infections or immunodeficiency. Given the history, a referral was made to allergy and immunology for further assessment of the patient's immune system.

Diagnosis

The diagnosis of CFI deficiency was made via broad immunologic assessment after a careful history eliciting recurrent SSTIs despite lack of exposures and appropriate antimicrobial therapies. Given the alternative complement pathway (AH50) returned low on initial labs, CFI was assessed as part of a more detailed laboratory analysis of the alternative complement pathway. The diagnosis of Factor I deficiency was made after demonstration of reproducibly low AH50 and low quantitative CFI. Of note, the diagnosis was not of a complete deficiency of CFI but instead simply a low value.

Testing

Given the history of recurrent SSTIs, a defect in complement or oxidative burst was favored over humoral defects in the differential. Nevertheless, a broad work-up was completed to reduce the possibility of missing the diagnosis. Initial immunologic testing, in addition to a basic CBC with differential and a CMP, included the dihydrorhodamine (DHR) flow cytometric test to rule out chronic granulomatous disease, CH50, AH50, lymphocyte proliferation studies, flow cytometry of T, B, and NK

cells, quantitative immunoglobulins, isohemagglutinins, tetanus and diphtheria antibodies, and pneumococcal antibody levels. All labs returned within normal limits with the exception of AH50 and pneumococcal antibody levels. 23-valent pneumococcal vaccine was administered and specific antibody levels showed appropriate antibody response on reevaluation four weeks later. AH50 was repeated and properdin and complement factors B, D, and I were assessed. Inadequate sample quantity was obtained for factor H analysis. On three occasions, each separated by two to three months, AH50 returned consistently low at values of 73, 72, and 44 units/mL [77 – 159 units/mL]. CFI was then found to be low at 26 mcg/mL [29.3 – 58.5 mcg/mL] with all other specific complement factors falling within their normal respective quantitative ranges.

Treatment

The patient was vaccinated appropriately. Prophylactic antibiotics were considered; however, the risk to benefit ratio was deemed unfavorable unless her SSTIs were to progress and become continuously and recurrently morbid. Annual or more frequent monitoring was instituted to maintain close observation of the patient's condition.

Patient Outcomes

The patient has not suffered any additional SSTIs since the time of last office visit.

Lessons Learned

This patient's case highlights the entity of low CFI and the less typical clinical phenotype of late onset recurrent SSTIs. The astute allergist should consider low CFI on the differential when evaluating a patient with recurrent SSTIs in the absence of unusual exposures and despite appropriate and repeated courses of antimicrobial therapy. Cases reviewed include those published by Shields et al in June 2019 in the journal, *Frontiers in Immunology*.

An unusual case of a neutrophilic urticarial dermatosis

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Summary

An 81 year old man presented with right periorbital erythematous swelling and associated erythematous plaques on his torso and lower extremities, as well as a two year history of urticaria associated with systemic symptoms. These symptoms had previously been treated as a drug reaction. Laboratory studies revealed elevated ESR and CRP, as well as pancytopenia. Etiologies including vasculitis and chronic idiopathic urticaria were considered, and the patient underwent trials of hydroxychloroquine and omalizumab without improvement in symptoms. An extensive work up, including skin and bone marrow biopsy, was performed which revealed neutrophil-rich urticaria and myelodysplastic syndrome. After initial improvement on oral prednisone, the patient's symptoms returned and potassium iodide was started by dermatology as an alternative treatment for neutrophilic urticaria.

Patient Presentation

An 81-year-old man presented with right periorbital erythematous swelling along with scattered blanchable erythematous plaques on his upper torso and lower extremities and legs. For two years prior to presentation, he had recurrent episodes of a similar rash lasting one to two weeks at a time, occurring over all parts of his body, and often leaving bruising and desquamation. He endorsed associated episodic fatigue. He reported tongue swelling once, and occasional hoarseness, though he never reported dyspnea. Under the care of dermatology over the past two years, the patient had undergone multiple medication changes to target possible drug etiologies for the rash, though none of these medication changes led to resolution of these episodes. Trials of cetirizine and hydroxyzine provided no clinical improvement. Examination at the time of his presentation to our service was significant for non-tender erythematous indurated plaques covering the right periorbital area and cheek without overlying scale, a few blanchable erythematous edematous plaques on his upper back with several smaller erythematous macules scattered on mid and lower back, and erythematous plaques on his bilateral anterior lower extremities, some with overlying scale. At the time of initial presentation to us, the patient was admitted to the hospital for acute management of periorbital swelling and was subsequently discharged on oral steroids. He was referred to Allergy/Immunology to consider omalizumab for treatment of refractory urticaria. His medical history was significant for pancytopenia, Grave's disease, diabetes mellitus and atrial fibrillation.

Diagnosis

Initial clinical features of the rash were most suspicious for urticarial vasculitis. However, biopsies did not support a diagnosis of vasculitis, workup for systemic vasculitis by rheumatology was negative, and empiric treatment with high-dose prednisone and hydroxychloroquine were ultimately ineffective. Chronic idiopathic urticaria was unlikely given history, clinical characteristics of the rash, and lack of response to oral antihistamines, prednisone, and omalizumab (for three months). Skin biopsies demonstrated neutrophil-rich urticaria, and the constellation of constitutional symptoms supported a systemic process. Bone marrow biopsy completed during the work up did reveal myelodysplastic syndrome (MDS). Urticaria can be seen in MDS, although rarely and typically associated with more

advanced disease and a poorer prognosis. Given the neutrophil-rich urticaria, diagnoses of Sweet and Schnitzler syndrome were considered, as both diseases can present as a persistent neutrophilic urticaria.

Testing

Laboratory abnormalities include: WBC 3.2, HgB 12.3, Plt 104, ESR 108, CRP 14.2mg/dL, ANA 1:160 speckled. Other labs found to be negative or within normal limits: PSA, HBV, HCV, EBV, lymphoma/CLL screen, Lyme EIA, CMP, B12, Folate, Ferritin, CPK, Urine Pr:Cr ratio, TSH, FT4, T-spot, C1-est inhibitor function, C3, C4, SPEP, IgG, IgA, IgM. Bone marrow biopsy demonstrated MDS with multilineage dysplasia, and a FISH probe for MDS was normal. Chest CT revealed pulmonary nodules which were larger in size at 6-month follow up, though PET imaging was reassuring; repeat CT and pulmonary follow up are planned.

Two skin biopsies were taken. The first demonstrated dense perivascular and interstitial inflammatory infiltrate with mononuclear cells, numerous neutrophils, and some eosinophils, involving mostly the lower dermis and the subcutaneous tissue. The second biopsy demonstrated neutrophilic dermatosis characterized by an intense superficial and deep perivascular and interstitial dermatitis composed of abundant neutrophils with conspicuous leukocytoclasia, and variable lymphocytes, histiocytes, and eosinophils.

Treatment

The patient had been started on prednisone after hospital discharge, with apparent improvement in the rash, though it is unclear if improvement was due to prednisone or waxing/waning of the process. During subsequent work up, he was treated with several agents including hydroxychloroquine and high-dose prednisone (nearly 1 mg/kg/day) for possible vasculitis, as well as omalizumab for possible chronic idiopathic urticaria. The patient has thus far shown no significant improvement with any of the above treatments. Most recently, potassium iodide was started as an alternative treatment for neutrophilic urticaria. Notably, treatment in the literature for urticaria associated with myelodysplastic syndrome as well as Sweet's syndrome is high-dose systemic steroids.

Patient Outcomes

While the patient initially improved while taking prednisone, this improvement was not sustained. The patient is currently being tapered off prednisone, and potassium iodide was started by dermatology as an alternative treatment for neutrophilic urticaria. He continues to be followed closely by allergy/immunology, dermatology, and rheumatology.

Lessons Learned

This case highlights the broad differential one should consider when evaluating a chronic urticarial rash. While the routine evaluation of chronic urticaria need not include extensive laboratory testing, in a case such as this in which the urticaria was not responding as expected to therapy and was associated with constitutional symptoms, systemic syndromes including but not limited to malignancy, autoimmune diseases, Schnitzler syndrome, Sweet syndrome, and infections should be considered. In this case, examination with more extensive testing including skin and bone marrow biopsy was warranted in pursuit of a unifying underlying diagnosis. In addition, caution must be exercised when designating a specific cause or diagnosis, as diagnostic anchoring can result in significant delays in obtaining a final diagnosis and treating the patient appropriately. This patient had been treated as an urticarial drug

reaction for many months without improvement in symptoms prior to the current workup and evaluation. In a complex case such as this, maintaining a broad differential and communication among specialists is essential.



Effectiveness of a desensitization protocol in hypersensitivity reactions caused by oxaliplatin

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Summary

Hypersensitivity reactions (HR) are unpredictable responses which cannot be explained by pharmacological action or toxicity due to drugs, but are caused by an immunological mechanism. Platinum salts are considered one of the groups most at risk for developing an HR. The incidence of oxaliplatin HR ranges between 12 and 15%, while only 0.5% to 2% of these reactions are severe. Due to the importance of the oxaliplatin treatment in this patient, the Oncology department requested desensitization to this drug as it was the only possible treatment capable of improving his long-term prognosis, despite the severity of the reaction. After a positive skin prick test at 1:10 dilution, a desensitization protocol was carried out in order to receive 273 mg of total dose. We used a three-bag protocol, took 5.66 hours and had no sign of a hypersensitivity reaction. Desensitization is the gradual reintroduction of small amounts of the causative drug of HR administered over prolonged periods until the total therapeutic dose is reached, thus allows its administration.

Patient Presentation

A 54-year-old male with diagnosis of left colon cancer in stage IIIB treated initially with left colectomy. Later he started adjuvant therapy with oxaliplatin but was changed to capecitabine due to cardiotoxicity. Invasion to the liver was detected during the chemotherapy treatment, so it was offered a regimen with oxaliplatin at 130mg/m² and capecitabine. After the first dose he had a type 3 severity score reaction with laryngospasm, foreign body sensation in the throat, paresthesia in the upper extremities and mandibular stiffness. Due to the importance of the drug his treatment, the Oncology department requested desensitization to oxaliplatin.

Diagnosis

Type 1 hypersensitivity reaction to oxaliplatin

Testing

As we had a respiratory adverse reaction to oxaliplatin, and the kind of reaction was most probably due to a type 1 hypersensitivity reaction, we realized a skin prick test to oxaliplatin at a 1:10 dilution. The skin test was positive, so we confirm our main diagnosis.

Treatment

A desensitization protocol was carried out in order to receive 273 mg of total dose in a three-bag protocol that last 5.66 hours.

Patient Outcomes

We didn't have any adverse reaction during the procedure and the next desensitization with the same protocol.

As the desensitization is the only treatment capable of create a temporal tolerance to a drug, but with the possibility of a severe allergic reaction, it must be only used in patients in which there are no better drug options. We recommend the use of more desensitization protocols in allergy department within more hospitals in these kind of patients.

Step	Solution	Infusion mL/h	Time (min)	Infused volumen (mL)	Infused dose (mg) per step	Cumulative dose (mg)
1	1	2.5	15	0.625	0.0075 mg	0.0075 mg
2	1	5	15	1.25	0.015 mg	0.0225 mg
3	1	10	15	2.5	0.03 mg	0.0525 mg
4	1	20	15	5	0.06 mg	0.1125 mg
5	2	5	15	1.25	0.1375 mg	0.25 mg
6	2	10	15	2.5	0.275 mg	0.525 mg
7	2	20	15	5	0.55 mg	1.075 mg
8	2	40	15	10	1.1 mg	2.175 mg
9	3	10	15	2.5	2.71 mg	4.885 mg
10	3	20	15	5	5.415 mg	10.3 mg
11	3	40	15	10	10.83 mg	21.13 m
12	3	80	174.4	232.5	251.8 mg	273 mg
Total dose: 273 mg						Total time= 5.66 h

Severe lymphopenia in patient with recent use of electronic vaping cigarette containing marijuana oil

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Summary

Patient is 29 year old male previously healthy, who was admitted for 1 week of fever, night sweats, and vomiting and diarrhea. He had used an electronic vaping cigarette containing marijuana oils 2 weeks prior. Chest CT revealed bilateral ground glass and reticular opacities. T-cells were checked due to concern for Pneumocystis pneumonia (PCP) and immunocompromised state. He was found to have severe T-cell lymphopenia with CD4 86, CD8 38. Infectious, malignant, and rheumatologic causes explored and ruled out. Bronchoscopy and trans-bronchial biopsy was consistent with acute inflammation. The patient improved on steroids and was diagnosed with vaping-associated lung disease. His severe T-cell lymphopenia resolved on repeat testing three weeks after discharge. Lymphopenia may be result of inflammation and the clinician should have a high index of suspicion when encountering patients with vaping-associated lung disease.

Patient Presentation

A 29 year old male presented to the hospital emergency room with fever, vomiting, diarrhea, and night sweats for 1 week as well as worsening cough. Fever would occur every night for one week and then would be resolved in the morning. In the emergency room he was hypoxic to 88% on pulse oximetry. He was not tachypneic. Lungs were clear to auscultation with no crackles or wheeze. He was placed on 2 liters of oxygen. A Chest CT was performed that showed bilateral ground glass and reticular opacities in lungs with lower lobe predominance.

He has no pertinent past medical history and was previously healthy with no hospitalizations. He has no family history of autoimmune disorders or immunodeficiency disorders. He lives with his wife and one child. He admits to vaping, most recently 2 weeks ago with tetrahydrocannabinol (THC). He denies intravenous drug use. He denies unexplained weight loss, sick contacts, recent international travel, or exposure to homeless shelters or jails.

Diagnosis

With fever, cough, absence of infectious source, ground glass opacities seen on imaging, as well as bronchoscopy results, suspicion was high for vaping-associated lung disease causing acute inflammation. This was a diagnosis of exclusion and infectious, rheumatologic, and malignant causes must be ruled out first. Infectious work up was extensive and unrevealing as mentioned above. Rheumatologic workup with elevated ESR to 91 and C-reactive protein to 366 but with negative ANA and auto-antibodies. Peripheral smear was reviewed by Hematology who saw toxic appearing neutrophils, otherwise there were no acute abnormalities. Peripheral flow cytometry was ordered however patient refused further testing.

Testing

As Chest CT was concerning for PCP pneumonia, which would indicate an immunocompromised status, T-cells were checked and significant for low CD4 of 86 and low CD8 of 38. Immunoglobulins were within

normal range. An extensive infectious work up was done which was positive for rhinovirus/enterovirus on a respiratory viral panel, non-reactive HIV with undetectable HIV viral load, EBV titers with evidence of past infection, negative CMV, negative Lyme, and negative Quantiferon Gold.

While he was admitted to the hospital, he underwent bronchoscopy and had a lung bronchoalveolar lavage done that showed diffusely erythematous airways but no significant secretions or endobronchial disease. Cultures were negative and cytopathology negative for malignancy. Grocott's methenamine silver (GMS) stain was negative for fungal elements. Transbronchial biopsy revealed acute inflammation, reactive type 2 pneumocyte hyperplasia, and focal intraalveolar fibrin.

Treatment

Patient was initially started on empiric antibiotics with Ceftriaxone and Azithromycin for presumed community acquired pneumonia but ultimately improved with intravenous methylprednisolone. Antibiotics were discontinued when no infectious source was identified. Due to his severe T-cell lymphopenia, he was started on trimethoprim-sulfamethoxazole for pneumocystis pneumonia prophylaxis.

Patient Outcomes

He continued to improve on steroid therapy and was ultimately discharged home, completing a two week steroid taper as an outpatient. Repeat testing was performed three weeks after discharge. T-cell subsets normalized with CD4 up to 533 and CD8 up to 417. ESR improved down to 10 and CRP was down to 0.11. A repeat Chest CT has been ordered but has not been completed yet at the time of his case report.

Lessons Learned

When patients are in a sustained inflammatory state it is possible that it can result in a severe lymphopenia such as in this patient. It is possible that his lymphopenia resulted from bone marrow suppression due to rhinovirus/enterovirus. However, it is also possible that it would be a result of inflammatory cytokines causing damage to hematopoietic stem and progenitor cells. Another possibility is that the severe inflammation caused sequestration of immune cells out of the vasculature and into the lung tissues. This case could serve as a model to explore inflammatory parameters in cases of vaping-associated lung disease.

As vaping is increasing in popularity in the United States, it is important to have a high index of suspicion for vaping as an etiology of disease for patients who present with fever, cough, vomiting, and diarrhea without other apparent cause. Cases of lipoid pneumonia due to the glycerin content in vaping fluids has been reported in the literature as an etiology of vaping-associated lung disease. Lipoid pneumonia occurs then as a result of a foreign body reaction to fat which can then result in an inflammatory response that destroys alveolar walls and interstitium.

There is a rising epidemic of patients with vaping-associated lung disease being reported recently; however, cases of lymphopenia in these patients have not yet been reported. In a case study reported on 5 patients who were diagnosed with electronic-cigarette induced acute lipoid pneumonia, all patients had a leukocytosis with neutrophilic predominance. Further investigation is necessary in order to give proper prophylaxis and anticipatory guidance.

Icatibant as a Novel Treatment for Severe Laryngeal Edema in a Patient with Features of Hypocomplementemic Urticarial Vasculitis

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Summary

A 42-year-old female with episodic lip and throat swelling was found to have markedly decreased C1q levels, verified on repeat testing. She was reported to have acquired angioedema and was able to successfully treat an episode of laryngeal edema with icatibant. She had a documented 10 year history of multiple reactions which had progressed from facial swelling to also involving swelling of her extremities and gastrointestinal symptoms in the last 2 years. On further questioning, her symptoms had worsened profoundly after the involuntary discontinuation of hydroxychloroquine, which she was prescribed for mixed connective tissue disease. She was also noted on questioning to have skin manifestation of urticaria which at times involved her palms and soles and was pruritic, painful, and burned. A presumed diagnosis of hypocomplementemic urticarial vasculitis syndrome (HUVS) was made.

Patient Presentation

The patient is a 42-year-old female who presented with recurrent episodes of worsening angioedema, multiple times involving the airway for which she had been given epinephrine in the past without relief of symptoms but had never required intubation. She had a history of undifferentiated connective tissue disorder diagnosed 8 years prior as well as an inflammatory pseudotumor removed from her lung 8 years ago. For her rheumatological disease, the patient was placed on hydroxychloroquine, but while stationed overseas she ran out of the medication and had trouble obtaining it, then was finally trialed off the medication. She noted the worsening and frequency of her angioedema occurred during the time period when this medication was discontinued. The patient had no family history of angioedema. On review of systems, the patient reported intermittent flares of urticaria on her arms, legs, palms, soles, and trunk which were pruritic, painful, and caused a burning sensation. They lasted 2-5 days and left hyperpigmentation marks. The patient had arthralgias, dyspnea, peripheral neuropathy, and ophthalmologic manifestations.

Diagnosis

The patient had a history of angioedema and atypical urticaria, with abnormal C1q testing. Her C1 esterase inhibitor levels and function were normal; so HUVS was suspected given her lab and clinical findings. She met both major and 2 of the minor criteria for HUVS (urticaria >6 months and low complement, with arthralgias and abdominal pain). She then underwent additional confirmatory testing which was pending.

Testing

This patient previously had a C1 esterase inhibitor functional level performed 10 and 8 years earlier, which were both normal. She also had multiple antibody panels performed via rheumatology for her underlying connective tissue disorder, with positive anti-nuclear antibody (ANA) 1:640 speckled, and positive antibodies to SS-A/Ro, ribonucleoprotein (RNP), rheumatoid factor, cyclic citrullinated peptide, and glycyl-tRNA synthetase (EJ) on testing.

Additional investigations were done 1 year prior to her presentation with another C1 esterase inhibitor functional level and C1 esterase inhibitor level with normal levels, and a complement C1q level was obtained at that time which was slightly below normal at 11.6 mg/dL. One year later when the patient returned with significantly worsening symptoms, these were repeated given that the C1q had been slightly low, and at that time the C1q was markedly depressed at 5.8 mg/dL. ESR was mildly elevated and CBC showed a microcytic anemia on multiple testing. Skin biopsy was not performed as she had no active skin lesions at the time of presentation.

Treatment

The patient was given a prescription for icatibant, a selective bradykinin B2 receptor antagonist, when it was felt she had acquired angioedema. She was instructed to use it in case of severe or life-threatening episode of laryngeal angioedema. She has utilized the subcutaneous injector on one occasion with immediate improvement in symptoms. The patient resumed hydroxychloroquine 200mg daily for the past 6 months, which is half her long-term previous dose from before her presumed HUVS diagnosis.

Patient Outcomes

The patient immediately responded to icatibant when she felt she needed it for airway swelling. She has continued to have several minor episodes of extremity swelling and urticarial rash which have been treated with diphenhydramine. Her case has been discussed with rheumatology.

Lessons Learned

Hypocomplementemic urticarial vasculitis syndrome is a rare autoimmune disorder which has specific clinical and serologic features, but some patients present with unusual manifestations. Laryngeal edema is a rare but recognized clinical expression of the disorder and may be confused for other angioedema or anaphylaxis episodes. The kallikrein-kinin system has been reported to be activated in vasculitis leading to the release of bradykinin, which may explain why this patient experienced relief with icatibant. To our knowledge, this is the first time icatibant has been reported as used in a patient with presumed HUVS for laryngeal edema with success. Icatibant has been used regularly in the management of patients with hereditary and acquired angioedema and has gained interest more recently for its successful role in the management of life-threatening angioedema in patients taking ACE inhibitors. Icatibant may have an effective place in managing challenging airway edema in other diseases.

Why interferon-gamma is still relevant in patients with chronic granulomatous disease

Author Justine M. Ade, MD

Training Program Mayo Clinic

Summary

An 18-year-old male with autosomal recessive chronic granulomatous disease status post failed sibling matched bone marrow transplant who was lost to follow up for over two years presents with cough for one week. The patient had reported poor compliance to interferon gamma but endorsed compliance with trimethoprim-sulfamethoxazole and itraconazole prophylaxis. Pulmonary function testing showed significantly decreased FEV1 of 56% and CT scan of his chest showed a large mass with surrounding micronodular infiltrate suggestive of worsening granulomatous disease with probable superimposed fungal pneumonia. He underwent rigid bronchoscopy with removal of the right lower lobe lesion which grew *Exophiala dermatitidis* and *Verruconis gallopava* species. Initial inpatient management included broad spectrum antimicrobials. Additionally, patient underwent surgical wedge resection of the right lower lobe which he tolerated well. Susceptibilities returned suggesting susceptibility to posaconazole with which he was discharged home on after a two-week hospital stay and is likely to continue for 9-12 months.

Patient Presentation

An 18-year-old male with autosomal recessive chronic granulomatous disease (AR-CGD, CYBA gene mutation) presents to the Allergy and Immunology clinic for follow up. Patient was lost to follow up over the last two years. He reported poor compliance with his interferon gamma due to the adverse effects, namely, it made him feel feverish. In addition, he stated he felt healthy and that he didn't enjoy taking the medication. He endorsed that he was taking his trimethoprim-sulfamethoxazole and itraconazole prophylaxis without issue. He also reported a cough for the past week.

Past Medical History: osteomyelitis (2003), wedge resection for pulmonary aspergillosis (2012), failed sibling matched bone marrow transplant (2012), asthma, history of a single generalized seizure (2009).

Social History: Patient's family is Spanish speaking, but the patient is bilingual. His medical visits are usually carried out with an interpreter. Patient stated school the year prior went well for him. He is entering the 11th grade. Denied alcohol and tobacco use.

Diagnosis

Given the findings on the patient's CT scan, his history of chronic granulomatous disease, his findings on bronchoscopy and preliminary cultures he was given a diagnosis of fungal pneumonia secondary to *Exophiala dermatitidis* and *Verruconis gallopava* species.

Testing

Ultimately pulmonary function testing was obtained given his history of asthma, prior *Aspergillus* infection, and presenting cough. Results were notable for FEV1 56%. This was significantly decreased from FEV1 of 74% on his last PFT 5 years prior. Patient was referred to pulmonology who followed him for asthma. He was noted to have bilaterally diminished breath sounds for which a CT of his chest was obtained. CT chest had findings of a large mass with surrounding micronodular infiltrate, septal

thickening of the right lower lobe and consolidation of the left lower lobe suggestive of worsening granulomatous disease with probable superimposed fungal pneumonia. He underwent rigid bronchoscopy with removal of the right lower lobe lesion which were sent for cultures that eventually returned growing *Exophiala dermatitidis* and *Verruconis gallopava* species.

Treatment

Patient underwent multispecialty evaluation during his hospital admission. With input from Infectious Disease and Surgery services, patient was initially treated with empiric antimicrobial therapy. This included vancomycin, cefepime, amphotericin B, and posaconazole. He subsequently underwent thoracoscopy which was complicated by dense adhesions. For this reason a thoracotomy was performed in which biopsies were obtained by wedge resection. Once susceptibilities returned, his antibiotic therapy was tailored to posaconazole. His interferon gamma was held given his acute infection and possibility of obscuring clinical response from adverse effects.

Patient Outcomes

At presentation and throughout the patient's hospitalization he was noted to be non-ill appearing and recovered from surgery without issue. He had objective measures of improvement including normalization of leukocytosis and decrease in CRP from 120 mg/L to 73 mg/L prior to discharge. He was discharged home on posaconazole with follow ups scheduled with Infectious Disease, Pulmonology, and Allergy and Immunology. At his follow up visits, he was noted to be doing well without evidence of fever. Surgical sites were healing well. Instructions for taking posaconazole had to be clarified with the patient at one point as he was taking 1 tablet of posaconazole three times a day as opposed to taking these at the same time. He will be re-starting his interferon gamma and his course of posaconazole, per Infectious Disease, is estimated to be weeks to months depending on his response. His progress will continue to be monitored during these follow up visits in addition to trending lab values.

Lessons Learned

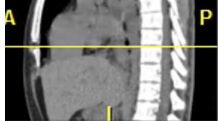
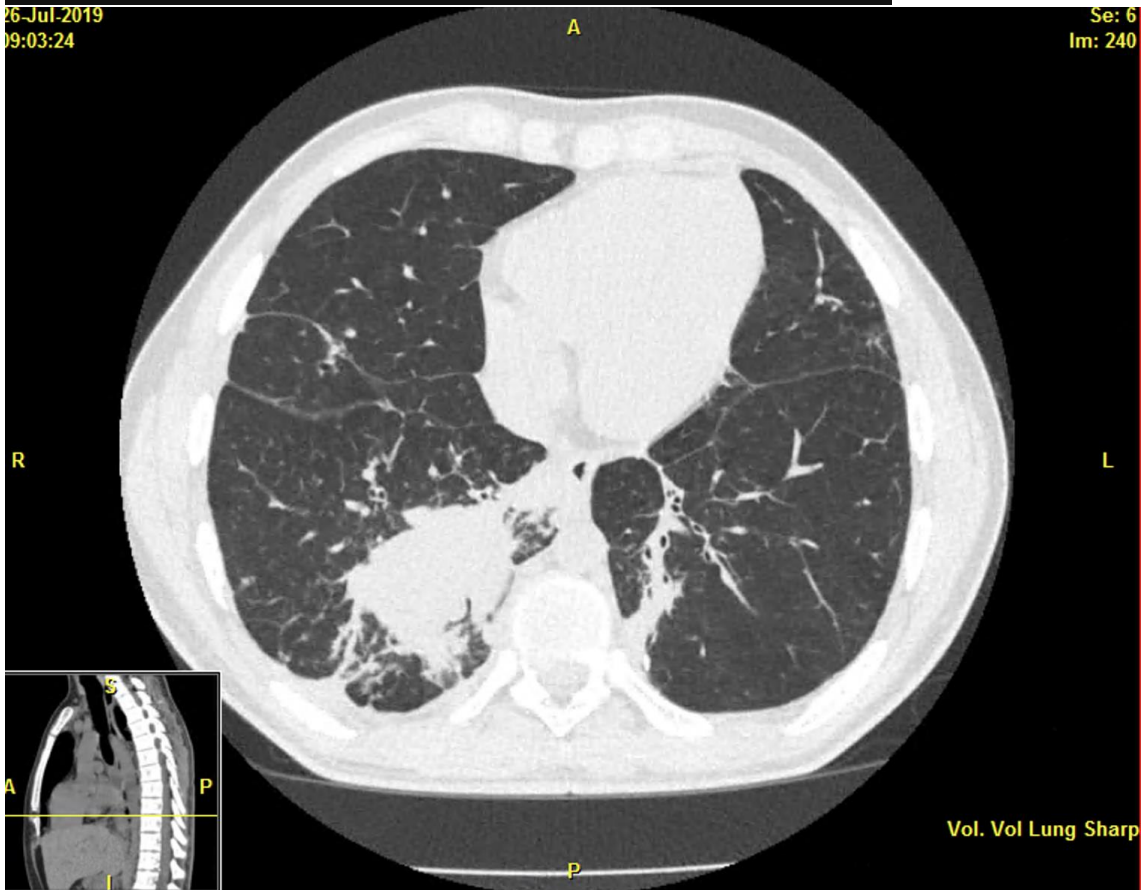
To our knowledge, this is the only case of fungal pneumonia caused by *Exophiala dermatitidis* and *Verruconis gallopava* in a patient with autosomal recessive chronic granulomatous disease. There exists one case report of *Exophiala dermatitidis* pneumonia in a CGD patient published in 1992. This patient was similarly managed with a prolonged course of fluconazole following surgical resection. In addition, there also exists one case report of *Verruconis gallopava* in a CGD patient in 2012 who was successfully treated with voriconazole. The co-existence of these two rare opportunistic fungal species leading to such a significant case of pneumonia in a patient with autosomal recessive chronic granulomatous disease, which is usually thought to be a more mild form of CGD, further illustrates the unique qualities of this case.

This case also highlights important lessons in CGD management. Early studies supporting the role of interferon gamma in the prevention of infection in CGD occurred before antifungal prophylaxis was widely used. However, this case implicates the critical role interferon-gamma prophylaxis can play in the management of patients with CGD. Additionally, this case echoes the growing concern for fungal resistance to traditional prophylactic therapies in chronic granulomatous disease with itraconazole. Lastly, this case emphasizes important challenges providers may face in managing adolescents with CGD. Given the mainstay of management in CGD includes regular use of prophylactic therapies, close follow up with monitoring of medication compliance is crucial in this age group.



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Atypical Biphasic Anaphylaxis to Radiocontrast Media in a Patient with Likely Underlying Mast Cell Disorder

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Training Program NYU Winthrop Hospital Internal Medicine Residency program, NYU Winthrop Hospital Allergy & Immunology Fellowship program

Summary

A 71 year old female presented with abdominal pain and underwent CT scan with IV radiocontrast.

Thirty minutes afterwards she developed generalized pruritus and erythema of the ears, nose and palms. She was agitated but without angioedema, nausea, lightheadedness or hypotension. She received diphenhydramine 50mg, methylprednisolone 125mg and lorazepam 1mg with resolution of symptoms. A tryptase level drawn during the reaction was 29.

Thirty-eight hours after the initial reaction, she developed labored breathing, urticaria and hypotension in absence of new medications or triggers. She received IM epinephrine 0.3mg twice, diphenhydramine 50mg, methylprednisolone 125mg and IV fluids. She was given vasopressors and intubated with significant laryngeal edema noted. A tryptase drawn during this reaction was 50.9. Vasopressors were weaned after 10hr and extubation occurred 1.5 days later.

A tryptase drawn 4 days later was 16.7. During a hospital visit 6mos later, a repeat baseline tryptase was 12.3.

Patient Presentation

The initial encounter with the patient occurred at the time of the late-phase (second) reaction. At that time, the tryptase from the index reaction was pending and she was intubated, sedated and on an epinephrine drip.

The patient has a medical history significant for diabetes mellitus, coronary artery disease, atrial fibrillation, and rheumatoid arthritis. The patient's family reported a prior episode of anaphylaxis approximately 3 years prior but did not know any pertinent details of the event, including the trigger or the range of symptoms she experienced.

Diagnosis

The patient's initial reaction was consistent with an anaphylactic reaction to radiocontrast media, with two organ systems involved (skin and central nervous system). The reaction 38 hours later was also consistent with anaphylaxis, involving the skin, respiratory, and cardiovascular systems. Once the elevated tryptase levels were available, the diagnosis of biphasic anaphylaxis was more certain. Several days after the resolution of these reactions, the patient's serum tryptase level of 16.7 remained elevated above the upper limit of normal for a baseline tryptase level of 11.4. Given the patient's previous episode of idiopathic anaphylaxis 3 years prior, a mast cell disorder was strongly considered. Unfortunately, the patient was not amenable to outpatient follow up for further evaluation and repeat tryptase level. To our knowledge, she has not had a bone marrow biopsy.

Testing

After the initial reaction to contrast media, a serum tryptase level was drawn and found to be significantly elevated at 29. This tryptase value combined with her findings of urticaria and agitation

suggest a diagnosis of anaphylaxis. After the second reaction 38 hours later, a repeat serum tryptase level was found to be further elevated at 50.9. This late-phase reaction and tryptase elevation in the absence of additional triggers or cofactors suggests a biphasic anaphylactic reaction. A baseline tryptase of 16.7 was obtained 4 days after the late phase response had completely resolved, suggesting an underlying mast cell disorder. The baseline tryptase elevation was confirmed on a second check 6 months later (12.3), but unfortunately the patient has been lost to follow-up.

Treatment

The patient's initial reaction was treated with IV diphenhydramine, IV methylprednisolone and IV lorazepam with resolution of symptoms. The late phase reaction was more severe and protracted, requiring epinephrine IM twice followed by an epinephrine drip in addition to IV fluids, diphenhydramine, and methylprednisolone. She was intubated for hemodynamic instability and airway protection. She was discharged with an epinephrine auto-injector, recommendation for avoidance of CT radiocontrast dyes and plan for follow-up to evaluate for an underlying mast cell disorder.

Patient Outcomes

The remainder of her hospital stay was uneventful. Her episode of anaphylaxis resolved and was stably discharged to her home. Unfortunately, the patient was not willing to return for outpatient follow up, but she denied any further anaphylactic episodes when follow up was obtained via phone.

Lessons Learned

Anaphylactic responses typically occur as singular episodes featuring urticarial and/or laryngeal edema with onset in minutes and peak/resolution within <8 hours. This case is a reminder that biphasic reactions occur unpredictably and can be more severe and or protracted than the index reaction. Additionally, a heightened level of awareness of the possibility of a biphasic reaction is required not just in the first 8 hours following an event, but likely in the following 2 days. All patients who experience anaphylaxis should be prescribed epinephrine to protect them in case such an event occurs. All patients who experience anaphylaxis with an associated elevated tryptase level should undergo repeat tryptase level testing to determine their baseline. When elevated, further evaluation for an underlying mast cell disorder is warranted.

An enigmatic case of HyperIgE levels

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Summary

This is the case of a 10 year old female referred from pulmonology to allergy subspecialty on account of "immeasurably" high IgE levels on a respiratory panel with a significant past medical history of allergic rhinitis, severe persistent asthma, severe atopic dermatitis constituting a background history of recurrent flares, complicated by Herpes simplex infection in infancy. Although elevated IgE levels are typically seen in atopic disease, the patient presented with coarse facial and dysmorphic features that created a diagnostic challenge. HyperIgE syndrome is a rare primary immunodeficiency syndrome¹, with an estimated incidence ranging from 1 in 500,000 to 1 in 100,000: Patients with this syndrome may have characteristic facial features and skeletal findings, recurrent infections (principally bacterial and Candida infections), dermatitis², skin abscess, pneumatocoeles¹. There are two forms; autosomal dominant and recessive¹, with significant variation in the constellation of symptoms and signs among individual patients².

Patient Presentation

HPI- 10 year old female with a pertinent history of "atopic march"; ascertained by perennial seasonal allergies involving: frequently itchy and watery eyes, nasal congestion since age 5 controlled with inhaled fluticasone, cetirizine and ketotifen eye drops; prior skin prick test done 4 years before presentation was suggestive of allergies to egg, peanuts, tree nuts and fish. Reaction to allergens involved vomiting, and throat irritation.

Patient was stepped up to severe persistent asthma status and diagnosed with associated exercise-induced bronchospasm; placed on albuterol prn and controller medications- mometasone furoate 200mg and singulair 5mg daily. Patient presented with a recent flare of diffuse eczema on face, trunk, neck, and extremities, severely itchy with superimposed crusting and weeping lesions and had been placed on triamcinolone ointment, tacrolimus for face and mupirocin cream by co-managing dermatology team with mild improvement. Patient had also developed an acute asthma exacerbation a month prior to presentation and was placed on oral prednisolone. There was no known history of recurrent pneumonias, otitis media or skin abscesses, snoring, somnolence during day, morning headaches or enuresis, easy bruising/thinning of skin, polyuria, polydipsia, polyphagia, previous pathological fractures. Patient was said to have shed baby teeth appropriately. Patient is premenarchal. Environmental hx: Patient lived in an apartment with no exposure to smoking, pets, mold, mice, carpets or roaches

Birth hx: Deficient as patient was adopted

Developmental Milestone: Patient has learning disability and was in a special Education 5th grade class.

Family hx: Unknown

Vitals were stable on presentation, with a significant BMI in the 97th percentile for age

Physical exam

General- Alert, slow processing noted on questions asked, Obese, with a broad nose, absent philtrum, coarse face: prominent forehead and deep set eyes, small hands and feet

Eyes- Eyelid dermatitis, periorbital hyperpigmentation with Dennie Morgan lines was noted

Ears- Normal pinna, Tympanic membrane normal bilaterally

Nose- Enlarged, pale inferior turbinates bilaterally
 Neck- No thyromegaly or cervical adenopathy noted
 Oral cavity- lips, mucosa, palate tongue, gums normal. prognathism and teeth crowding noted
 Lungs- Clear to auscultation bilaterally
 Cardiovascular- regular rate and rythm, S1, S2 no murmurs
 Abdomen- soft, non-tender, bowel sounds normoactive, no massess or organomegaly
 Neuro- grossly nonfocal
 MSK- no scoliosis, or deformities notes
 Skin- Diffuse Dry, scaly erythematous patches on arms, legs, trunk and face with overlying excoriation marks, lichenified plaques noted on both feet and ankle with superimposed weeping, honey crusted lesions. Pin-point hyperpigmented macules on upper chest.
 Genital- Tanner 1

Diagnosis

The patient is presently undergoing workup to rule out hyperIgE syndrome, However the differentials included-

1. HyperIgE syndrome due to the history of elevated IgE levels, recurrent severe eczema, coarse features and atopic disorders which can be seen in the autosomal recessive forms¹
2. Severe atopy- Due to patient's severe persistent asthma, severe allergic rhinitis and severe atopic dermatitis with food allergies which may explain high IgE levels
3. Fetal alcohol syndrome- Due to patient's history of learning disability, slow cognitive processing on exam, absent philtrium this diagnosis was considered, however there was deficient birth history and unknown history of maternal substance abuse in pregnancy.
4. Endocrine disorders- Patient is obese, with short stature (<10th percentile) , hence Cushing's disease/ Diabetes mellitus and hypothyroidism were considered; however chronic exogenous steroid use was ruled (last use of prednisolone was a short course as per history), her tanner stage was commensurate with her age, lab work brought in from referral showed- glucose-78, HbA1c- 5.4, TSH- 0.450 (CBC, CMP, Lipid panel done all within normal limits), patient had normal blood pressure and heart rate on presentation and in comparison to referral notes.

Testing

CBC was done to check for eosinophilia and other signs of immunodeficiency; wbc- 11.6, Hemoglobin- 9.8, HCT-32.2, RDW-17.5, MCV- 71.5, platelet count- 409 K/ul, Neutrophil- 53.4%, Lymphocytes- 34.9%, Eosinophils- 4.1%, Absolute neutrophil count- 6194.4 (normal); this was suggestive of iron deficiency anemia

A Food, Environmental (outdoor and indoor), and Tree Nut panel was done to determine IgE levels and possible environmental triggers, Invariably this confirmed that the patient had significant food and environmental allergies with total IgE level = 14,883H

Allergy Panel Nut mix: Peanut IgE >100.00 , sesame seed- 79.40 , HazelnutIgE-66.00, Coconut IgE- 88.30, Pecan nut IgE 79.10 , Cashew nut IgE- 77.30

Respiratory Allergy profile- pteronyssinus- 99.90 , Dermatophagoides farinae IgE >100.00 , cat danderIgE- 100.00, Dog dander-92.6, mouse urine protein- >100.00, cockroach-64.90,walnut tree-39.90, birch-30.40

Food panel- egg white- 41.80, codfish- >100.00, shrimp >100.00, walnut >100.00

Treatment

Patient was continued on the medications previously outlined. However, a referral to genetics was made for molecular testing to determine STAT 3 or DOCK8, TyK2 mutation or rule out other genetic diseases. Patient is yet to have this done. Since this was an initial visit, we had wanted to ascertain if there was an actual elevated IgE levels, future labs will involve ANA, CD4 counts, IgG subclasses, Immunoglobulins.

Patient Outcomes

Patient was scheduled to followup within 4 weeks of initial presentation

Lessons Learned

HyperIgE syndromes are relatively rare primary immunodeficiency syndromes characterized by recurrent severe staphylococcal abscesses of the skin, lungs and other sites with markedly elevated levels of serum IgE¹. The autosomal dominant type is caused by heterozygous mutations in the gene encoding STAT-3 that results in a negative effect on expression of STAT3 by the other non mutated gene¹. It is not clear exactly how the STAT-3 mutation causes all parts of the syndrome but it is thought that IL-17 deficiency leads to susceptible candida infection. In comparison, the autosomal recessive type involves mutations in DOCK8 on chromosome 9. DOCK8 is likely important for cell growth; these patients unlike the dominant type have severe atopic dermatitis, asthma, food allergies, anaphylaxis, recurrent skin viral infections, including severe herpes simplex, herpes zoster, molluscum contagiosum, and papillomavirus infections¹.

However, neurological problems like stroke, meningitis and aneurysms are prominent which this patient did not have. Patients with autosomal recessive type do not have pneumatoceles, history of fractures, or delayed shedding of baby teeth or unusual facies¹. However, most patients with hyperIgE will have eosinophilia and lymphopenia (patient did not have), low T-cell, serum IgM and variable IgG antibody responses¹ (yet to be tested).

A scoring system devised by the US National Institutes of Health (NIH) is available that can be used in patients with a family history of HIES². A score of 30 has a sensitivity of 87.5 percent and a specificity of 80.6 percent². The scoring system adjusts for age since some features are uncommon in infancy and early childhood. However, some young children and even some adults with HIES may not meet the scoring criteria². Thus, molecular screening should still be performed when there is a family history of HIES and the patient has some features suggestive of the disease, even if the score is <30. In this patient, a score of 30 (High serum IgE >2000 score 10, characteristic facies present-5, severe eczema-4, URI>6/year- 4, Serious infection (HSV infection)- 4 and increased nasal width >2SD-3). However, molecular testing is crucial to confirm diagnosis.

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Diagnostic Hesitancy: A Serious Case of Hives

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Summary

A 71-year-old man presented to his PCP with generalized urticaria for 6 weeks and was referred to allergy clinic for evaluation. While awaiting this appointment, we advised his PCP to check an SPEP, which revealed an m-spike. His PCP also obtained a PSA level, which was significantly elevated. We attempted to treat his urticaria with oral antihistamines and helped coordinate consultation with urology and oncology. In the interim, he was found to have eosinophilia, a very high tIgE level, and serologic evidence of Strongyloides. Treatment with ivermectin had no impact on his tIgE or urticaria. Oncologic evaluation for multiple myeloma was reassuring. Prostate biopsy and bone scan yielded a diagnosis of metastatic prostate cancer, for which he was started on androgen deprivation therapy. His urticaria subsequently resolved and was deemed secondary to prostate cancer. His eosinophilia remitted and his total IgE level fell as his PSA normalized and urticaria resolved.

Patient Presentation

A 71-year-old man with a personal history of almond allergy and treated hepatitis C cirrhosis presented with 6 weeks of diffuse urticaria. He suspected his hives were due to accidental almond ingestion. However, the urticaria persisted, with only mild improvement, despite his PCP treating with cetirizine 10 mg qday, ranitidine 150 mg bid, triamcinolone 0.5% cream, and briefly prednisone 40 mg qday. The patient had recently complained of urinary frequency and endorsed a ten-pound weight loss over a four-month period. His PCP obtained a PSA and, after initial discussion with allergy, an SPEP. His PSA was significantly elevated, and SPEP revealed an m-spike. Screening for colorectal cancer and hepatocellular carcinoma was up to date. He had a 50 pack-year smoking history and reported he had received appropriate lung cancer screening. His physical exam was notable for cachexia and urticarial lesions on his chest, back, and arms.

Diagnosis

His diagnosis was urticaria secondary to prostate cancer. There had been concern for a hematologic malignancy or myeloma due to an m-spike on SPEP, but he was determined to have MGUS by hematology/oncology after bone marrow biopsy. Urology diagnosed him with metastatic prostate cancer based on a prostate biopsy and bone scan, and he was then treated with androgen deprivation therapy. His urticaria completely resolved within 2-3 months of starting cancer treatment, and he remained symptom-free after stopping the antihistamines, which had only partially controlled his urticaria. Based on his diagnosis of prostate cancer and the resolution of urticaria after initiating treatment for cancer, his chronic urticaria was determined to be a paraneoplastic complication of prostate cancer.

Testing

His PSA was 103 ng/ml, which had been ordered due to lower urinary tract symptoms. SPEP was ordered due to ongoing urticaria and history of recent weight loss, and he was found to have an m-spike of 380 mg/dL. He also had elevated peripheral eosinophils at 500/uL and tIgE at 9895 IU/ml, so parasitic workup was done. His Strongyloides IgG antibody was positive. Based on the elevated PSA and m-spike,

there was concern that his urticaria could be secondary to malignancy. A workup for hematologic and prostate malignancies was initiated. He had no m-spike on UPEP and immunofixation was negative for monoclonal IgE or IgD. His serum kappa light chain was 120 mg/L, lambda light chain was 36 mg/L, and K/L ratio was 3.33, which were all elevated. His T-cell lymphoma profile was negative for aberrant t-cell population. His bone marrow biopsy revealed less than 10% clonal plasma cells, consistent with MGUS. Prostate biopsy showed adenocarcinoma, and a bone scan showed increased intensity suspicious for metastases at the thoracic spine, right iliac bone, and left sacroiliac joint.

Treatment

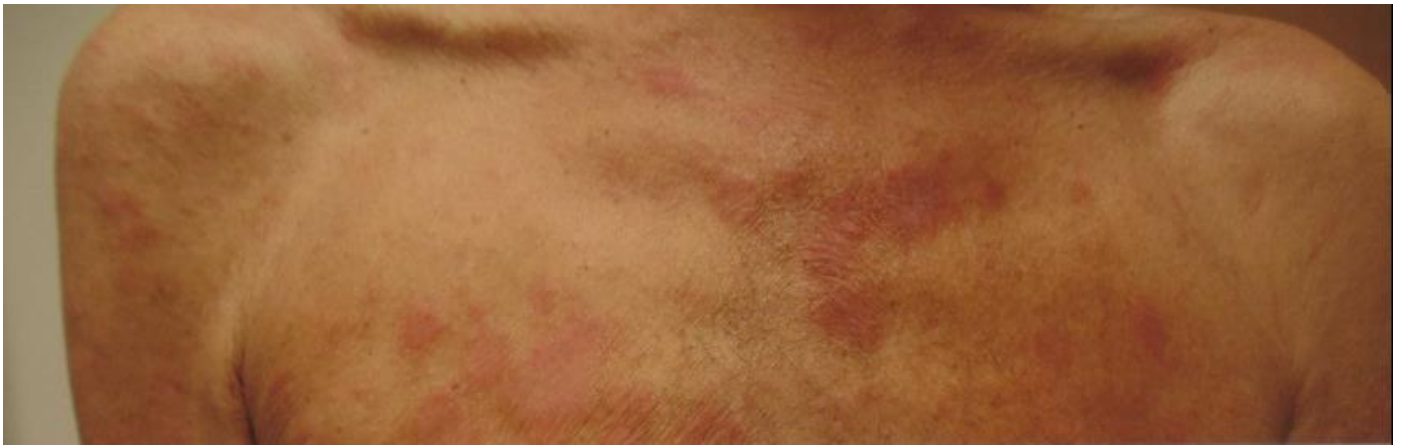
At his initial visit with allergy, cetirizine was increased to 20 mg bid to help improve symptoms while other specialists investigated probable malignancy. While it was unlikely *Strongyloides* was provoking his urticaria, we empirically treated him given the low risk of ivermectin coupled with the patient's eosinophilia and markedly high tIgE level. Ultimately, treatment of metastatic prostate cancer with the anti-androgen bicalutamide led to resolution of his urticaria, along with normalization of his PSA and peripheral eosinophil count. His tIgE level also decreased after starting this treatment.

Patient Outcomes

High dose cetirizine improved but did not resolve the patient's symptoms, and treatment for *Strongyloides* had no significant impact on either symptoms or laboratory values. His tIgE increased to 11,159 IU/ml and his peripheral eosinophil count decreased to 400/uL. Within 2-3 months of starting treatment for prostate cancer, his urticaria resolved. He was able to discontinue oral antihistamines without return of the urticaria. His PSA decreased to 1.63 ng/ml. Four months after initiating anti-androgen therapy, he remained free of urticaria, tIgE was 4,777 IU/ml, peripheral eosinophil count was 100 cells/uL, and his PSA had decreased further to 0.24 ng/ml.

Lessons Learned

While most cases of urticaria do not require a laboratory workup for an underlying etiology, it is important to take a good history and perform a chart review to help determine if further workup is warranted. Paraneoplastic urticaria is rare, and it is more commonly seen with hematologic malignancies or lung cancer. Urticaria secondary to prostate cancer has only been described in two prior case reports. One case described urticaria preceding a diagnosis of non-metastatic prostate cancer treated with radical prostatectomy. The second case described urticaria preceding a diagnosis of prostate cancer recurrence treated with androgen deprivation therapy. In both cases, the urticaria resolved after treating prostate cancer. A review of 26 patients in which urticaria preceded the diagnosis of malignancy found 23 patients (88%) experienced resolution of urticaria after treatment for cancer. Interestingly, this patient also had elevated tIgE and peripheral eosinophilia, neither of which resolved with empiric treatment for *Strongyloides*. It is known peripheral eosinophilia can be associated with many different types of cancer, but studies on elevated tIgE and cancer are conflicting. While one study showed elevated tIgE was not associated with an increased cancer risk and may even be protective against some cancers, another study of patients with head and neck cancer found these patients had elevated tIgE when compared to healthy controls. This case involved communication between four specialties: allergy/immunology, primary care, urology, and hematology/oncology. This communication was key in ruling out certain diagnoses and confirming the correct one.



When Mosquito Bite Allergy Requires Hematopoietic Stem Cell Transplant

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Training Program Children's Hospital Los Angeles Pediatrics Residency Program

Summary

A 5-year-old boy with history of nasal allergies and mild asthma presented with fevers to 104 degrees Fahrenheit, after which he developed severe local reactions to mosquito bites. Laboratory results were significant for increased NK-cells in the setting of extreme EBV viremia. The patient was diagnosed with EBV-associated NK-cell lymphoproliferative disease with hypersensitivity to mosquito bites. Chronic active EBV infection can progress to liver failure, hemophagocytic lymphohistiocytosis, organ dysfunction, or T-cell lymphomas. As curative therapy requires hematopoietic stem cell transplant (HSCT), the patient underwent HSCT with a 10/10 HLA matched sibling donor. His post-HSCT course was complicated by CMV viremia, mixed chimerism, and skin graft-versus-host disease. He is now 9 months post-HSCT. He has recovered from his complications and has returned to school.

Patient Presentation

A 5-year-old boy with history of nasal allergies and mild asthma presented with fever to 104 degrees Fahrenheit, exudative tonsillitis, oral sores, and moderate cervical lymphadenopathy. Rapid strep test was negative at that time. One month later, he developed severe local reactions to mosquito bites, each with >5 cm of erythema and induration and bullae which ulcerated after rupture. Mosquito bites were accompanied by fever to 104 degrees Fahrenheit for 4 days. Initially, he was diagnosed with periodic fever, adenitis, pharyngitis, and aphthous ulcers (PFAPA). Prednisone resulted in fever resolution within hours. Of note, mother is of European-Indonesian descent and dad is of European-African (Creole) descent. No other family members have had similar symptoms.

Diagnosis

Given extensive mosquito bite reactions with fever and NK-cell proliferation, diagnosis of EBV-associated NK-cell lymphoproliferative disease with hypersensitivity to mosquito bites (EBV-T/NK LPD-HMB) was made. Peripheral inflammatory cytokines, NK-cell dysfunction, and elevated serum IgE supported this diagnosis. This condition is rarely seen in the United States but has been described in East Asia. EBV infection of T- and/or NK- cells can lead to chronic active infection (CAEBV), which, if untreated, can progress to liver failure, hemophagocytic lymphohistiocytosis, organ dysfunction, or T-cell lymphomas.

Testing

Initial laboratory results were significant for normal CBC and differential, ESR elevated to 67mm/hr (normal <10), CRP elevated to 33mg/L (normal <3), IgE elevated to 12,093 kU/L (normal <307), with normal IgG, IgA, IgM levels. Epstein-Barr virus (EBV) quantitative PCR was elevated to >5,000,000 copies/mL.

Peripheral blood mononuclear cells were stained and sorted into populations of B-cells, T-cells and NK-cells. Lymphocyte subset analysis demonstrated percentages of CD3 (23%; 1538/mcL), CD4 (17%; 1109/mcL), CD8 (6%; 363/mcL), CD19 (9%; 587/mcL), and NK cells: CD6/56 (67%; 4435/mcL). After cell numbers were determined, the cells were lysed, and the number of EBV DNA copies per million cells

was determined using real time PCR. EBV was primarily in NK-cells (>5 million EBV DNA copies/million cells).

Treatment

Treatment options in the literature are typically multi-step, with the first step being immunochemotherapy (steroids, cyclosporine A, etoposide), second step being multi-drug chemotherapy, and third step being hematopoietic stem-cell transplantation (HSCT). The only curative treatment of this condition is allogeneic HSCT. Given the potential sequelae of CAEBV, HSCT was pursued. The patient received HSCT from a 10/10 HLA matched sibling donor, with initial complete reconstitution of donor derived B-cells, granulocytes, and NK-cells. His EBV viremia decreased by 2 logs.

Patient Outcomes

The patient's post-HSCT course was complicated by CMV viremia requiring anti-viral medications and hospitalization. He also had mixed chimerism requiring treatment with donor leukocyte infusion (DLI). After DLI, he developed grade 3 skin graft-versus-host disease requiring hospitalization and therapy with methylprednisolone, tacrolimus, and Ruxolitinib.

Of note, post-transplant EBV was identified primarily in B-cells (1,014 EBV DNA copies/million cells) compared to NK-cells pre-HSCT.

The patient is now 9 months post-HSCT. He has recovered from his initial symptoms and from the above complications. He has since returned to school.

Lessons Learned

Although rare, EBV-T/NK LPD should be suspected if patient presents with hypersensitivity to mosquito bites (HMB). It is important to sort lymphocytes to determine which cell types are infected. Clinicians should closely monitor HMB patients for possible sequelae of lymphoproliferative disease or hematologic malignancies.

As this condition may rapidly progress and has high mortality, curative allogeneic HSCT should be pursued as soon as possible.

A Hair-Raising Case of IVIG Use in a CVID Patient with Alopecia Universalis

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Summary

A 59-year-old female diagnosed with alopecia universalis for five years presents for immunologic evaluation due to thrombocytopenia, neutropenia, and low globulin level. Laboratory evaluation reveals a WBC count of 3500 cells/ul (3800-10,800), platelets of 130,000 cells/ul (140,000-400,000) and globulin of 1.7 g/dl (1.9-3.7). Lymphocyte subsets reveal CD3 count of 722 cells/ul (840-3060), CD4 of 602 cells/ul (490-1740), CD8 of 127 cells/ul (180-1170) and CD19 of 95 cells/ul (110-660). Quantitative immunoglobulins reveal an IgG of 484 mg/dl (694-1618), IgA of 117 mg/dl (81-416) and IgM of 14 mg/dl (48-271). IgG pneumococcal titers reveal 0/23 protective serotypes with no increase following vaccination with polysaccharide pneumococcal vaccine. Titers to tetanus and diphtheria are protective. She is diagnosed with CVID and IVIG replacement is initiated at 400 mg/kg/month. Following 6 months of treatment, the patient begins to notice return of eyelashes and eyebrows, and after 9 months, she experiences significant regrowth of scalp hair.

Patient Presentation

A 59-year-old female diagnosed with alopecia universalis for five years presents for immunologic evaluation due to thrombocytopenia, neutropenia, and low globulin levels. Her past medical history includes thyroid nodules with negative thyroid antibodies and joint pains with negative autoimmune serologies. She does not have a significant history of recurrent sinopulmonary infections. Her past surgical history includes tonsillectomy, adenoidectomy, and septoplasty. Social history is unremarkable without tobacco use. Family history is non-contributory without autoimmune disease or immune deficiency. She is not taking any medications associated with cytopenias or bone marrow suppression. Physical exam reveals alopecia universalis with absence of eyebrows and eyelashes, but no hepatosplenomegaly or lymphadenopathy.

Diagnosis

She is diagnosed with Common variable immune deficiency (CVID) with concomitant autoimmune alopecia universalis. The rationale for this diagnosis is evidence of hypogammaglobulinemia with poor antibody response to polysaccharide antigen. Her total loss of body hair, including eyebrows and eyelashes, is consistent with a diagnosis of alopecia universalis.

Testing

Laboratory evaluation reveals a WBC count of 3500 cells/ul (3800-10,800), platelets of 130,000 cells/ul (140,000-400,000) and globulin of 1.7 g/dl (1.9-3.7). Lymphocyte subsets reveal CD3 count of 722 cells/ul (840-3060), CD4 of 602 cells/ul (490-1740), CD8 of 127 cells/ul (180-1170) and CD19 of 95 cells/ul (110-660). Quantitative immunoglobulins reveal an IgG of 484 mg/dl (694-1618), IgA of 117 mg/dl (81-416) and IgM of 14 mg/dl (48-271). IgG pneumococcal titers show 0/23 protective serotypes with no increase following vaccination with polysaccharide pneumococcal vaccine. Titers to tetanus and diphtheria are protective. Chest radiograph performed one month prior to presentation is normal.

Treatment

IVIG replacement is initiated at 400 mg/kg/month. Despite absence of recurrent infections, she is started on treatment to prevent potentially severe future infections. IgG trough measured during treatment averages between 600-700 mg/dl.

Patient Outcomes

Following 6 months of treatment, the patient begins to notice return of eyelashes and eyebrows, and after 9 months, she experiences significant regrowth of scalp hair. After approximately 18 months of treatment, IVIG replacement is stopped for several months due to unforeseen circumstances, and patient again loses her scalp and body hair. When it is resumed, she notices complete hair regrowth within 6 months. It is maintained while she remains on treatment.

Lessons Learned

This is an unusual case of CVID initially presenting as alopecia universalis with significant regrowth of hair following 6 months of IVIG therapy at a typical replacement dose. Reversible alopecia universalis is a potential autoimmune complication in a subpopulation of CVID patients.

Review of the literature reveals that CVID is associated with autoimmune disease in about 20% of cases. Alopecia universalis (AU) has been found in 1.6% of patients with CVID [2]. One case in the literature describes significant hair regrowth in an 8-year-old with AU on IVIG after 2 months of treatment [2]. Prior to this, 3 cases reported no improvement of alopecia totalis in CVID patients placed on IVIG [4]. The proposed mechanism by which IVIG could be beneficial in the treatment of AU is related to modulation of IL-1, TNF, and IFN-gamma levels by peripheral blood mononuclear cells [2]. Elevated levels of TNF-alpha have been associated with alopecia areata, although use of specific TNF-alpha inhibitors has not been clearly effective [3].

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Two Cases of Kwashiorkor Due to Food Restriction from Unconfirmed Food Allergy

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Summary

We present two cases of edematous malnutrition (kwashiorkor) due to severe food restriction in response to an unconfirmed food allergy diagnosis.

Case 1: A 14-month-old with atopic dermatitis and multiple food allergies diagnosed by serum food specific IgE (sIgE) was admitted due to concern for weight loss, developmental regression, and diffuse edematous erythroderma. The patient was diagnosed with kwashiorkor and associated dermatosis. Her weight, rash, and behavior improved with skin care and nutrition and she was discharged with a plan for an outpatient oral food challenge (OFC).

Case 2: A 23-month-old with history of severe atopic dermatitis and food allergy diagnosed by sIgE was admitted for leg swelling, weight loss, and hypoalbuminemia with proteinuria. After institution of gradual nasogastric tube (NGT) refeeding, her swelling and abnormal laboratory values normalized, confirming a diagnosis of kwashiorkor. An outpatient OFC could not be performed due to oral aversion.

Patient Presentation

Case 1: A 14-month-old female with atopic dermatitis and multiple food sensitizations was admitted for weight loss, regression of developmental milestones, and worsening rash for 3 months. She had been using fewer words and appeared fatigued. She had a 1.6 kilogram (kg) weight loss (17.4% body weight) over the last three months. Physical exam revealed alopecia, mild lower extremity edema, and diffuse erythroderma.

At 10 months of age, she was diagnosed with food allergy to cow's milk, peanut, soy, wheat, egg, sesame, tree nuts, fish, and shellfish by sIgE. Parents reported no exposure to these foods before or after testing. Her diet was primarily breastmilk, rice milk, and vegetables. Her only reported allergic symptom was itching and parents did not note an urticarial reaction. Skin-prick testing (SPT) was negative for fish, shellfish, and wheat. She passed a soy OFC with plan to perform baked egg and baked milk OFC at the next visit, which did not occur prior to admission.

Case 2: A 23-month-old female with severe atopic dermatitis and multiple food sensitizations was admitted with a two-week history of leg swelling, diffuse dry skin, and fatigue. She had lost 0.9 kg (9.6% body weight) in three months. On examination, she was noted to have edema in her hands, legs, and feet as well as a peeling, dry, diffuse rash.

Seven months prior, she had sIgE testing to evaluate severe atopic dermatitis and reported pruritus without urticaria after milk and wheat consumption. Her sIgE was elevated to cow's milk, peanut, soy, wheat, and egg. Due to these results, parents strictly avoided these foods. The patient would only eat sweet potato, banana, and water and would spit out other solid foods.

Diagnosis

Case 1: Given the negative testing for underlying causes of failure to thrive, as well as improvement in the patient's weight and symptoms with proper nutrition, she was diagnosed with kwashiorkor and associated dermatosis.

Case 2: The initial findings of proteinuria were not replicated on retesting, and workup for malabsorption was negative, leading to a diagnosis of kwashiorkor with associated dermatosis.

Testing

Case 1: Initial testing was notable for severe protein-calorie malnutrition with an albumin of 1.4 g/dL (3.5-4.5 g/dL) as well as micronutrient deficiency with an iron of 10 mcg/dL (30-150 mcg/dL), vitamin B6 of 17.2 nmol/L (20.0-125.0 nmol/L), and zinc of 55.6 mcg/dL (60.0-120.0 mcg/dL). Stool studies for malabsorptive and infective processes were normal.

Case 2: Initial testing was concerning for nephrotic syndrome with an albumin of 1.9, urine protein of >499 mg/dL (<20 mg/dL), and 284 urine RBC/hpf. However, repeat urinalysis the next day was normal, suggesting the initial catheterization was traumatic. Under GI consultation, workup for malabsorptive processes was negative. An esophagogastroduodenoscopy was normal.

Treatment

Case 1: Oral refeeding was gradually instituted with soy formula, given her prior tolerance during in-clinic OFC. Her diffuse rash improved with proper nutrition and wet wraps with topical steroid treatment. With the consultation of a nutritionist, a plan was created for increasing table food intake as well as continuing supplementation with soy formula to meet macronutrient goals.

Case 2: Due to continued oral aversion, NGT refeeding was initiated with a hypoallergenic formula. Her diffuse rash improved with proper nutrition and wet wraps with topical steroid treatment. OFC with milk was attempted in hospital, but was stopped due to itching without urticaria.

Patient Outcomes

Case 1: The patient tolerated increasing amounts of soy formula and maintained adequate intake during the hospital stay. She began using more words and was more energetic. Due to parental preference, the patient continued to avoid wheat, fish, and shellfish during hospitalization despite negative prior SPT, but parents agreed to introduce them at home. She is scheduled in allergy clinic for an OFC to baked egg and baked milk.

Case 2: The patient gained weight on a stable feeding regimen in the hospital. Due to continued oral aversion, the patient was discharged home with NGT feedings and plan to reintroduce wheat and soy, given only mild elevation on sIgE. However, an OFC could not be performed due to food aversion so the child was referred to feeding therapy.

Lessons Learned

These cases describe severe morbidity and food aversion resulting from an uncertain food allergy diagnosis based solely on food sIgE. In each case, food sIgE panels performed to evaluate atopic dermatitis led to a restrictive elimination diet and resultant kwashiorkor. Evidence shows that in 50-90% of parent/patient reported food allergy, it is not confirmed by SPT, sIgE, or OFC. In a study of patients who had had a prior positive SPT or sIgE to a specific allergen, 89% were found to be tolerant to that allergen on OFC.

There have been numerous reported cases of alternative diets as treatment for perceived food allergy/atopic dermatitis leading to macronutrient and micronutrient deficiencies. Due to the possibility of long-term morbidity from elimination diets, medical therapy for atopic dermatitis should be optimized prior to food elimination, and food allergy should be assessed with OFC in children with no history of a type I hypersensitivity.

Complexity of Hypereosinophilia Evaluation in a Patient with Chronic Eosinophilic Pneumonia

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Summary

A 28 year old woman with past medical history of eosinophilic esophagitis presented with new onset symptoms of cough, wheezing and septal perforation. Two months prior to admission she was clinically diagnosed with asthma and treated with budesonide and albuterol. Due to worsening of symptoms she was admitted for treatment of CT scan documented pneumonia. Peripheral eosinophilia was noted but attributed to atopy. She was readmitted two weeks later with recurrence of respiratory symptoms with abnormal CT scan and persistent eosinophilia. Further work up for eosinophilia was performed investigating allergic, environmental, rheumatologic, infectious and malignant etiologies. A transbronchial lung biopsy showed an organizing pneumonia accompanied by eosinophils suggestive of chronic eosinophilic pneumonia (CEP). Despite the CEP diagnosis at discharge, the systemic symptoms and findings associated with her eosinophilia require further evaluation of eosinophilic granulomatosis with polyangiitis (EGPA) or hypereosinophilic syndrome (HES).

Patient Presentation

A 28 year old woman with past medical history of eosinophilic esophagitis, type 2 diabetes mellitus, obesity, anxiety, and depression admitted for recurrent pneumonia was noted to have peripheral eosinophilia of $1.87 - 2.28 \times 10^9/L$ within a one month period.

She was admitted for hypoxia, dyspnea and cough secondary to pneumonia, and started empirically on vancomycin, piperacillin-tazobactam, azithromycin, prednisone and albuterol after failing outpatient therapy. Her chest symptoms were treated as suspected asthma but had been poorly-controlled with inhaled budesonide and albuterol. At the time of consultation, her pulmonary symptoms had resolved on antibiotics and steroids but she remained admitted for management of creatinine elevation attributed to supratherapeutic vancomycin levels in the setting of dehydration. During the first admission, her eosinophilia was attributed to atopy due to an elevated total IgE of 5070 and elevated specific IgE to several grasses, trees, dog dander and cat urine. Her IgE to *Aspergillus fumigatus* was negative. She denied childhood asthma or eczema or any active allergic rhinitis symptoms. Although she had biopsy proven eosinophilic esophagitis diagnosed in 2008, her symptoms improved with PPI therapy and elimination diet, with repeat EGD showing resolution of eosinophilic inflammation. Her family history was non-contributory. Additional history includes recurrent epistaxis treated with embolization and complicated by recent nasal septal perforation. Allergy and Immunology was asked to help further determine a cause for her eosinophilia.

Diagnosis

A diagnosis of Chronic Eosinophilic Pneumonia was made by CT scan findings and pathology from a transbronchial biopsy.

A CT chest with contrast showed bilateral diffuse and centrilobular ground glass opacities and multiple borderline-enlarged mediastinal lymph nodes bilaterally. A bronchoalveolar lavage and left lower lobe

transbronchial biopsy showed histologic features of an organizing pneumonia with eosinophils within the alveolar septa and alveolar spaces, most consistent with (CEP).

However, ANCA is positive in only 30-60% of patients with EGPA. There are phases of the disease, which progress from prodromal to eosinophilic to vasculitis. 40% of patients present with pulmonary opacities and eosinophilia before vasculitis becomes evident. The transbronchial and septal biopsy that were negative do not rule out vasculitis. Ultimately, the “gold standard” is an open lung biopsy.

Testing

The differential diagnosis included hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA), chronic eosinophilic pneumonia (CEP), adult-onset eosinophilic asthma, hypersensitivity pneumonitis and malignancy such as Hodgkin’s lymphoma and CML.

HES was considered but tryptase, serum vitamin B12 and specific cytogenetics associated with HES, including the FIP1L1-PDGFR α fusion protein, PDGFR β , and FGFR1 were negative. Cytogenetics for CML, including BCR-ABL and JAK2 were negative. Her bone marrow showed eosinophilia (22%) but was otherwise normal. No cardiac involvement was found, as evidenced by a normal echocardiogram, EKG, and high-sensitivity troponin. Her hepatic work-up was only notable for a mildly elevated GGT and transaminases with normal total bilirubin.

Additional testing included a renal ultrasound negative for obstruction, a normal CT angiogram, negative ANCA, negative HIV1 and HIV2, and normal IgG, IgA, and IgM.

Parasitic evaluation was negative for giardia and cryptosporidium. She denied new medications or illicit drug use except for cigarettes and E-cigarettes. She had no skin findings or medication history consistent with a drug hypersensitivity reaction.

Treatment

The initial treatment for CEP, EGPA or HES is high-dose glucocorticoids. She was discharged home on 0.5 mg/kg/day of prednisone for four weeks with weaning to be determined at follow-up.

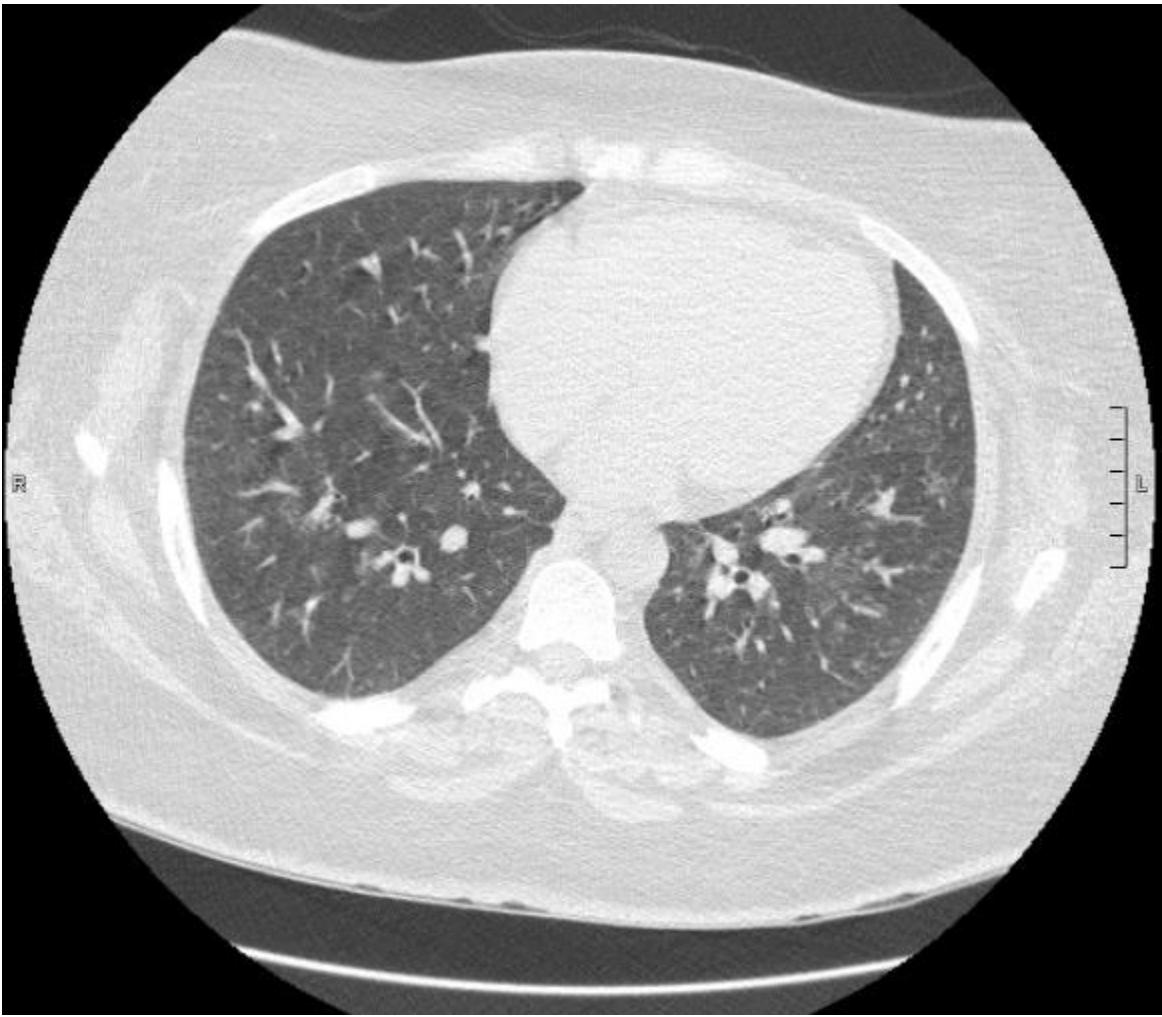
Patient Outcomes

In the two weeks since discharge, her symptoms and laboratory parameters have improved, with an eosinophil count of $0.82 \times 10^9/L$ and a Cr of 1.9. Weaning of prednisone with serial monitoring of eosinophils and follow-up pulmonary radiography will determine the next course of action.

Lessons Learned

It is not uncommon for eosinophilia to be attributed to underlying atopy. However, persistently elevated levels as high as $2.28 \times 10^9/L$ as was found in this patient warrant additional considerations.

While her working diagnosis is currently CEP, it can be seen in isolation or on a continuum with EGPA and HES. The negative ANCA and negative tissue biopsies for vasculitis should not stop further surveillance for these conditions. As initial laboratory evaluation for HES was negative, and idiopathic HES is a diagnosis of exclusion, continued consideration of EGPA is warranted. With long term steroid use prohibitive in a diabetic, she would be a candidate for newer biologic therapies such as mepolizumab.



Chlorhexidine: A Rare Cause of Perioperative Anaphylaxis

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Summary

A female with a cranial meningioma is scheduled for surgery. She develops hypotension, urticaria, bronchospasm and other symptoms of anaphylaxis soon after general anesthesia. Serum tryptase during anaphylaxis is 119 ng/ml (normal <11.4 ng/ml). Surgery is canceled with no cause identified. Chlorhexidine, midazolam, lidocaine, propofol, fentanyl, rocuronium, and furosemide were administered at induction of anesthesia. For the next surgical attempt, she is pretreated with diphenhydramine, ranitidine and the neuromuscular blocker is withheld. Again, she develops hypotension consistent with anaphylaxis and epinephrine is administered. She is referred for consultation. History indicates the night before the initial surgery she developed a cutaneous allergic reaction immediately after applying chlorhexidine body wash. It resolved by the next morning. Skin prick-puncture test to saline, latex and lidocaine are negative while histamine control and chlorhexidine are positive. Baseline serum tryptase is 6.4 ng/ml. The surgical team is instructed to avoid chlorhexidine and cranial surgery is successful.

Patient Presentation

A 48-year-old female is seen in clinic with a chief complaint of “anaphylaxis” prior to surgery for a cranial meningioma. Anaphylaxis, i.e., generalized urticaria, wheezing, and/or hypotension occurred during two surgical attempts, three weeks apart, immediately after induction and prior to surgery. Her past medical, social, family histories and review of symptoms are unremarkable or non-contributory. She has no history of prior drug, food or insect allergy, has no atopic diseases and is on no medications. She is seen four days after her second anaphylactic reaction.

She is a well-developed, well-nourished, cooperative female oriented to time, place and person with normal vital signs. The BMI is 31. She has mild erythema and lichenification of the skin on both wrists and the skin of the right neck, all sites of previous peripheral and central line insertions, areas which itched and she scratched for days. Pelvic, breast and rectal examination were not done. The rest of the physical examination is normal.

The exact etiology of her anaphylaxis was unknown following the initial history and physical examination. Once again, during the same visit, the attending physician went through a step by step narrative of these reactions and what she did in the 24 hours leading up to the first event. This in depth historical investigation revealed that the night before her first surgical attempt, she used chlorhexidine to cleanse her body. Immediately thereafter, she developed generalized urticaria, pruritus, and erythema which resolved prior to her surgical appointment.

The anesthesiologist for the case was contacted. It was discovered that during her first preop, central and peripheral insertion sites were cleaned with a chlorhexidine scrub. The patient also received the following medications: midazolam, lidocaine, propofol, fentanyl, dexamethasone, rocuronium, sevoflurane anesthesia, mannitol and furosemide. Twenty minutes after induction, she experienced tachycardia, hypotension, tongue swelling, diffuse urticaria and bronchospasm. She was treated with epinephrine, famotidine, methylprednisolone and stabilized. Serum tryptase during anaphylaxis was 119 ng/ml (normal <11.4 ng/ml).

Three weeks later, the patient was scheduled for repeat surgery and she decided not to bathe with chlorhexidine the night before. Once again, central and peripheral insertion sites were cleaned with a

chlorhexidine scrub. She was also given the following medications: diphenhydramine, ranitidine, midazolam, lidocaine, propofol, fentanyl, no neuromuscular blocker, sevoflurane anesthesia, and furosemide. Fifteen minutes after induction, she developed severe hypotension without any other signs or symptoms of anaphylaxis. She was treated with epinephrine, methylprednisolone, and phenylephrine, fluids and recovered.

Diagnosis

Chlorhexidine allergy was suggested by the history and confirmed by a prick-puncture skin test to chlorhexidine. The prick-puncture test resulted in a 8 x 6 mm wheal and a 12 x 10 mm flare within 15 minutes. Outpatient serum tryptase was 6.4 ng/ml (normal <11.4), eliminating mastocytosis as a possible diagnosis. Prick-puncture test to latex and lidocaine were negative compared to histamine and saline controls. The patient's history of a generalized cutaneous allergic reaction following exposure to chlorhexidine body wash and the anaphylactic reactions following the probable introduction of chlorhexidine by the venous route (peripheral and central line insertions) helped establish the diagnosis. These findings along with a positive percutaneous skin test lead to the conclusion, with near 100% certainty, that chlorhexidine is the culprit causing anaphylaxis.

Testing

Antibiotics and neuromuscular blockers are the two most common causes of perioperative anaphylaxis. An antibiotic was never prescribed and she was not given a neuromuscular blocking agent for the second surgical attempt. Latex is a common cause of perioperative anaphylaxis and some medical devices are made of latex. Caine drugs and their preservatives are rarely associated with systemic allergic reactions. Prick-puncture test helped to rule out suspect medications and identify the culprit. Her history of chlorhexidine body wash causing generalized urticaria, erythema and pruritus the night before the first surgery was the clue that led to the diagnosis. This was missed by the anesthesiologist and neurosurgeon, as well as by the allergy attending during the first of two interviews on the same day. Obtaining a detailed history is key to discovering the cause of perioperative anaphylaxis.

Treatment

The patient and surgical team were instructed to avoid chlorhexidine and chlorhexidine impregnated medical equipment prior to surgery. They were also instructed to avoid all unnecessary medications, especially those associated with perioperative anaphylaxis, i.e., antibiotics and neuromuscular blocking agents and be prepared to treat a potential systemic allergic reaction.

Patient Outcomes

Chlorhexidine was avoided and cranial surgery to remove the patient's meningioma was successful. The patient was shortly discharged home and is currently doing well.

Lessons Learned

Chlorhexidine is an antiseptic and disinfectant used in surgical and non-surgical settings. Many types of medical equipment are impregnated with chlorhexidine and the likelihood of a reaction increases if this solution is applied to an open wound. More reactions occur with alcohol based chlorhexidine solutions as compared to other solvents, and in this case isopropyl alcohol was used as the solvent, increasing the likelihood of a reaction.

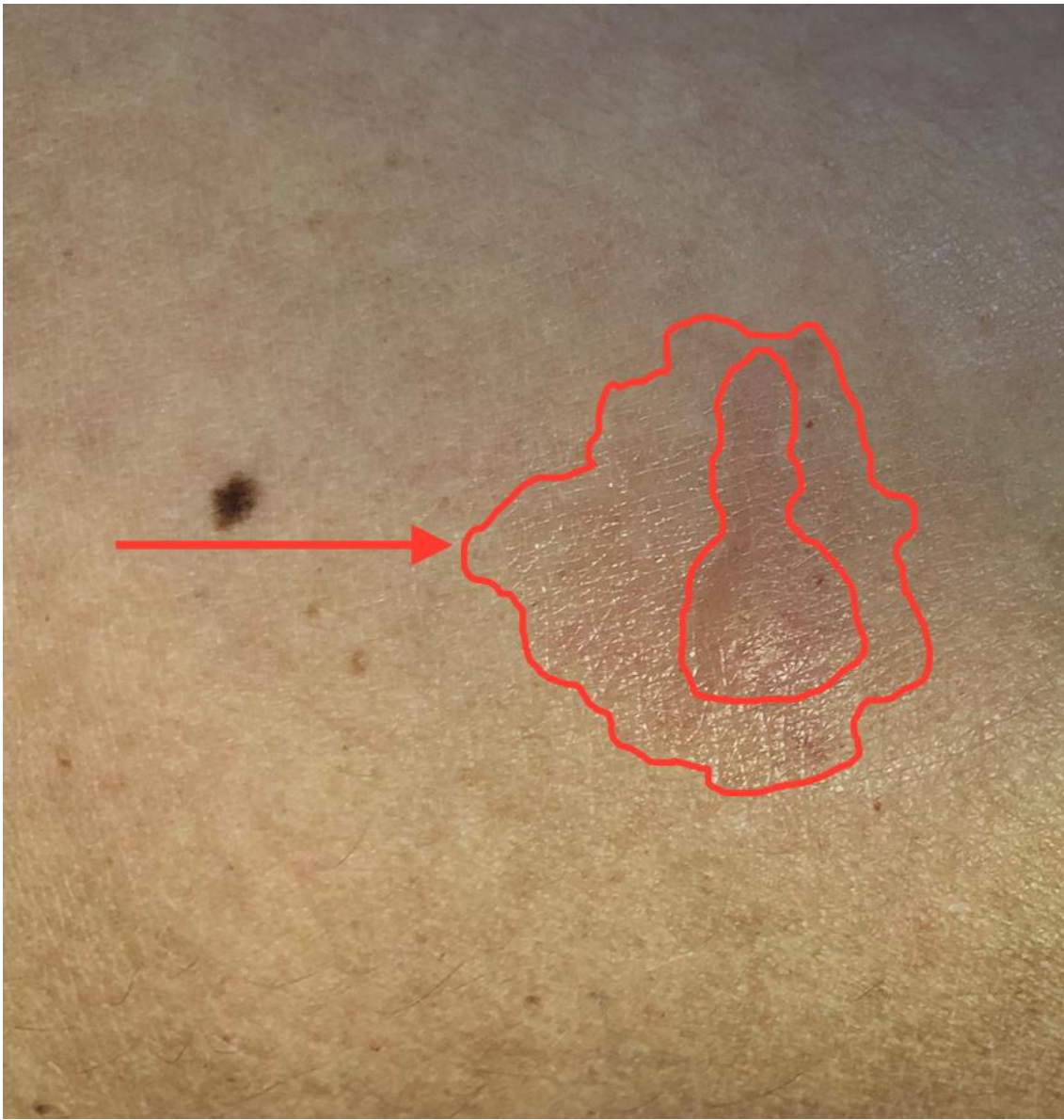
The safest management approach for a patient with this history is the definitive identification and complete avoidance of the causative agent. In summary, physicians should be aware that chlorhexidine is a rare and often unappreciated cause of perioperative anaphylaxis. A detailed and accurate history, coupled with appropriate prick-puncture skin test, played a key role in the discovery of the etiology of this patient's anaphylaxis.

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A case of probable immune-mediated *Mycoplasma Pneumoniae* Encephalitis.

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Summary

An 11-year-old female presented with a sore throat, fever, initially treated as viral pharyngitis. Then 5 days later she presented with altered mental status. Extensive encephalitis workup was performed with negative CSF PCR for multiple viral and bacterial etiologies, including an extensive panel for autoimmune encephalitis. The evaluation was remarkable only for positive serum IgM and IgG *Mycoplasma Pneumoniae*, despite negative PCR in CSF. Having a clinical picture compatible with immune-mediated encephalitis, *Mycoplasma Pneumoniae* was the only identifiable trigger. As described in recent reports, immune-mediated encephalitis can be secondary to *Mycoplasma Pneumoniae* infection, even with negative PCR for *Mycoplasma Pneumoniae* in CSF. This clinical picture is likely a result of immune-mediated cross-reactivity with galactocerebroside, which is a major glycolipid antigen in the myelinated neurons of both the peripheral and central nervous systems.

Patient Presentation

An 11-year-old female with an unremarkable past medical history presents on day of illness (DOI) 1, with a high fever at home 101.1 F, sore throat and pain with swallowing. Rapid strep test was negative and was discharged home with an initial diagnosis of viral pharyngitis with symptomatic treatment. On DOI 2, she was evaluated in another Urgent Care and tested negative for Rapid strep and Influenza and discharged home. On DOI 4, the patient continued with fever (103.1F), sore throat, frontal headache, and started with abdominal pain and vomiting. On DOI 5, she continued with fever 103F, headache, vomiting and started reporting blurred vision, pain, and stiffness in the neck, and photophobia. She was taken to the Emergency Department and CT of the head was performed with normal findings. She was empirically treated with ceftriaxone and vancomycin due to concern for meningitis. On DOI 6, the patient persisted with headache, vomiting, and new onset lethargy. On DOI 8, the mother reported ataxia, disorientation, decreased hand-eye coordination, and urinary incontinence. She was transferred to the PICU due to clinical deterioration with Glasgow Coma Scale (GSC) of 11 and bradycardia (HR in the 50s). GSC went down to 8, she was intubated and placed on mechanical ventilation. Acyclovir was added to her treatment. Magnetic Resonance (MRI) was performed with findings of rhombencephalitis. On DOI 9, lumbar puncture (LP) was performed with clear liquid, glucose 50mg/dL, protein 53mg/dL, WBC 34, Red Blood Cells 1, Polymerase chain reaction (PCR) performed in Cerebrospinal Fluid (CSF) and came negative for *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, Cytomegalovirus (CMV), Enterovirus, Herpes simplex virus 1 (HSV 1), HSV 2, Human herpesvirus 6, human parechovirus, Varicella zoster virus, *Cryptococcus neoformans/gattii*, Adenovirus and *Mycoplasma Pneumoniae*. Additionally, IgM and IgG in CSF Negative for West Nile Virus. N-methyl-D-Aspartate Receptor (NMDAR) Antibody IgG in CSF was negative. The final CSF culture was negative. On DOI 10, the patient was extubated with improved alertness and respiratory status. PCR was negative in serum for *Bartonella* and CMV. Serum serologies for West Nile Virus and *Bartonella henselae* were negative. She had normal C3, C4, IgA, IgM and IgG levels. Her blood IgM for *Mycoplasma Pneumoniae* was elevated at 4.93 (Negative ≤ 0.76 U/L). Extended blood autoimmune encephalitis panel was negative for the following Antibodies: NMDAR Ab, CASPR2 Ab IgG, LGI1 Ab IgG, AMPA Receptor Ab IgG, GABA-B Receptor Ab IgG, MOG Antibody IgG,

Aquaporin-4 Receptor Antibody, Voltage-Gated Potassium Channel Ab, Glutamic Acid Decarboxylase Antibody. On DOI 11, due to suspected autoimmune encephalitis high dose of methylprednisolone was started for 2 days and tapering for 10 days. On DOI 13, she had an improved neurological exam, was able to follow simple commands and write her first and last name. Due to the positive IgM and IgG for *Mycoplasma pneumoniae*, IV levofloxacin was started for 5 days, followed by 9 days orally to complete 14 days total course. On DOI 14, the patient was transferred from PICU to the pediatric ward. She was alert, oriented, good verbal response, able to sit up and out of bed with greater stability. On DOI 19, serum *Mycoplasma Pneumoniae* serologies were still elevated IgM 5.19, IgG 2.84 (Negative ≤ 0.09 U/L). On DOI 22, the patient was discharged, alert, oriented, answering questions, but walking with assistance. On DOI 47, the patient seen in follow up, with no symptoms of weakness, no gait instability, only with some word-finding difficulties. Blood *Mycoplasma Pneumoniae* antibody still elevated but trending down IgM 3.86 U/L and IgG 2.57 U/L. On DOI 71, the patient had a completely normal neurological exam.

Diagnosis

Probable immune-mediated encephalitis caused by *Mycoplasma Pneumoniae*. Extensive workup ruled out known infectious causes of encephalitis, and other significant causes of autoimmune encephalitis were also ruled out. The only clear evidence of acute infection was elevated IgM and IgG antibodies against *Mycoplasma Pneumoniae*, which has been recently reported as a cause of immune-mediated encephalitis, even despite having negative PCR in CSF for *Mycoplasma Pneumoniae*.

Testing

The main causes of infectious encephalitis were negative by CSF PCR: *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, CMV, Enterovirus, HSV 1, HSV 2, Human herpesvirus 6, human parechovirus, Varicella zoster virus, *Cryptococcus neoformans/gattii*, Adenovirus and *Mycoplasma pneumoniae*. Additionally, IgM and IgG in CSF negative for West Nile Virus and Anti- NMDAR Antibody IgG in CSF negative as well. The main causes autoimmune encephalitis due the following antibodies were negative: NMDAR Ab, CASPR2 Ab IgG, LGI1 Ab IgG, AMPA Receptor Ab IgG, GABA-B Receptor Ab IgG, MOG Antibody IgG, Aquaporin-4 Receptor Antibody, Voltage-Gated Potassium Channel Ab, Glutamic Acid Decarboxylase Antibody.

Serum PCR was negative for *Bartonella* and CMV. *Mycoplasma Pneumoniae* IgM and IgG were positive, which continued to be elevated 2 months later.

Treatment

High dose of methylprednisolone for 2 days and tapered over 10 days. Additionally, levofloxacin IV was started for 5 days, followed by 9 days orally to complete 14 days total course.

Patient Outcomes

The patient recovered completely by 2 months, with no neurological sequela.

Lessons Learned

Mycoplasma Infection can trigger immune-mediated encephalitis, even despite negative PCR in CSF. The mechanism is likely due to immune-mediated cross-reactivity to galactocerebroside found in myelinated neurons.

Lingual Tonsillectomy: A Novel Treatment Strategy In Adult Onset PFAPA Syndrome

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Summary

A 41-year-old gentleman was evaluated for periodic fevers occurring every 8 weeks. Each episode lasted 7-10 days with striking uvulitis alongside variable cervical lymphadenitis, pharyngitis and lower extremity rash. He had an unpredictable response to steroids and was intolerant of colchicine. Medical history was notable for childhood tonsillectomy for recurrent pharyngitis. Extensive laboratory work up revealed intermittent elevation of ESR/CRP only. CT neck and laryngoscopy confirmed adenoidal and lingual tonsillar hypertrophy. He underwent adenoidectomy and lingual tonsillectomy with sustained resolution of symptoms.

Patient Presentation

A 40 yr old male was referred to allergy and immunology for evaluation of recurrent fevers and uvulitis. Over the preceding 18 month period, he reported repeated episodes involving a combination of fever, pharyngitis and uvulitis. Fevers usually lasted 7-10 days and occurred every 6-8 weeks. They were noted to begin in the early afternoon and peak in the evening, usually reaching 102.5F. With antipyretic therapy, fever would break with only low grade fever by morning. Fever recurred by early afternoon. He had previously been treated with antibiotics and steroids, inducing temporary symptom resolution. Colchicine was trialed but stopped due to onset of a nodular skin rash of lower extremities with associated myalgia and arthralgia.

He had no other past medical history. His surgical history included a childhood tonsillectomy for recurrent pharyngitis, but without history of periodic fevers.

Family history was negative for auto inflammatory conditions, recurrent infection or immunodeficiency. Social history was notable for frequent travel to California and Arizona but no international travel. There were no sick contacts. He lives in Colorado and has two children aged 4 and 8. He works in construction.

Diagnosis

Given timeline of recurrent fever with discrete episodes every 4-8 weeks, a periodic fever syndrome was suspected. The episodic elevation of ESR and CRP with otherwise negative extensive infectious and rheumatologic work up was further supportive of this diagnosis. This patient had the cardinal features of PFAPA syndrome including periodic fever, pharyngitis/uvulitis and cervical adenitis in the absence of respiratory infection, with an asymptomatic period between episodes. Response to steroids, albeit unpredictable, was also supportive of this diagnosis. PFAPA presentation in adults is rare but also more variable than in younger children, with possible arthralgia and myalgia as seen in this case.

Testing

Extensive laboratory testing had been performed prior to our initial evaluation. This included periodic elevation of ESR/CRP. Complete blood count, comprehensive metabolic panel, serum protein electrophoresis, ferritin, anti nuclear antibody, rheumatoid factor and immunoglobulins were all

normal. Infectious work up including blood cultures, HIV, RPR, quantefreron gold and monospot testing were all negative. Rash biopsy showed panniculitis with granulomatous inflammation. A prior CT neck/chest/abdomen/pelvis was notable only for adenoid and lingual tonsillar hypertrophy with reactive upper jugular chain lymph nodes. ESR and CRP were repeated, with CRP elevation only. Repeat CT neck was performed, given most recent imaging was from 12 months prior. Repeat CT neck revealed scattered cervical adenopathy, increased from prior. Laryngoscopy was performed to evaluate for hypertrophy of tonsillar tissue. This confirmed adenoidal and lingual tonsillar hypertrophy.

Treatment

Glucocorticoids are the mainstay of treatment in PFAPA syndrome. Our patient had an incomplete response to steroids. He was intolerant of colchicine due to rash and myalgia. Therapeutic efficacy of tonsillectomy suggests a pivotal role of the tonsils in PFAPA pathogenesis. Given prominent hypertrophy of the remaining lymphoid tissue within Waldeyer's ring, lingual tonsillectomy and adenoidectomy was performed as an alternative therapeutic approach

Patient Outcomes

Patient had immediate improvement in his constitutional symptoms including fatigue, myalgia and arthralgia. Rash resolved completely. He has had sustained response to surgery with no recurrence of fever, uvulitis or cervical adenitis post operatively.

Lessons Learned

Previous small randomised controlled trials have demonstrated decreased frequency and severity of PFAPA related febrile episodes following tonsillectomy or adenotonsillectomy. This case highlights that hypertrophy of the remaining lymphoid structures within Waldeyer's ring may be associated with remote recurrence of PFAPA syndrome post tonsillectomy. Lingual tonsillectomy in adult onset PFAPA syndrome has not been reported previously. Intermittent glucocorticoid dosing remains the mainstay of therapy. However, surgical removal of remaining hypertrophied tonsillar tissue, including adenoidectomy and lingual tonsillectomy, is an alternative treatment strategy in select patients with PFAPA and may provide definitive resolution of symptoms.

A Rare Case of Systemic Contact Dermatitis Induced by NSAIDs

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Summary

Systemic contact dermatitis (SCD) is defined as a skin condition where a patient previously sensitized to an allergen via the cutaneous route subsequently reacts to a cross-reacting allergen via a systemic route. It can manifest as a skin eruption at the site of a previous contact dermatitis. Our case describes a patient who experienced contact dermatitis following topical Ketoprofen-containing cream with a reminiscent reaction after subsequently ingesting Ibuprofen. Contact dermatitis was subsequently confirmed after positive patch testing to the cream and its constituent components. This case describes the first instance of SCD caused by topical Ketoprofen and systemic Ibuprofen. It illustrates that NSAIDs can be a rare cause of SCD that can be diagnosed based on clinical history and confirmed based on patch testing.

Patient Presentation

Patient MS is a 42 year old female who initially presented in March, 2018 after developing a skin eruption on her ankle and elbow. Preceding the onset of these symptoms, the patient had been diagnosed with tennis elbow and Achilles tendonitis and had been prescribed a topical analgesic containing Ketoprofen (Multiprofen CC). After using this cream on her ankle and elbow for 1-2 days, she developed a red, vesicular, and desquamating eruption in the areas of application. She subsequently discontinued usage of her Multiprofen cream. Over the following two months, the patient ingested Ibuprofen on two occasions and Advil Cold and Sinus on one occasion. Each time she developed a similar vesicular eruption over her forearm 24-48 hours later, reminiscent of her reaction with the topical anti-inflammatory cream. She was able to tolerate Tylenol without adverse reaction. She did not use any other NSAIDs.

This patient had no prior occurrences of similar rashes. She has never had a skin reaction to metals or adhesives. She did have a childhood history of eczema. The patient is otherwise healthy and uses no other medications. She was not working at the time of her presentation. Family history was non-contributory.

Diagnosis

Patient MS was diagnosed with systemic contact dermatitis (SCD) to NSAIDs. SCD is defined as a skin condition where a patient previously sensitized to an allergen via the cutaneous route subsequently reacts to a cross-reacting allergen via a systemic route (oral, IV, IM or inhaled). It can manifest as a skin eruption at the site of a previous contact dermatitis. Although the exact mechanism leading to SCD has not yet been fully defined, it is likely mediated through a Type 4 (T-cell mediated) hypersensitivity reaction.

SCD was suspected in this patient given the similar vesicular skin eruptions resulting from topical ketoprofen-containing cream and systemic ibuprofen. Both of these NSAIDs are chemically related and belong to the family of propionic acid derivatives. Theoretically, this would increase the incidence of a cross-reacting allergen. It was initially unknown whether the first skin eruption was caused by ketoprofen itself or a constituent component of the topical cream. Thus, we elected to send the patient for patch testing to her anti-inflammatory cream as well as its constituent components. She had a 2+

reaction to Multiprofen cream. The other cream components were negative. This confirmed contact dermatitis to ketoprofen. Ibuprofen was felt to be responsible for systemic contact dermatitis based on the clinical history. It is currently unknown whether other NSAIDs will also trigger systemic contact dermatitis in this patient.

Testing

We sent the patient for patch testing as this is the only validated method of confirming T-cell mediated hypersensitivity, the suspected mechanism leading to SCD. Patch testing being positive to the cream and negative to its other components was critical to determining that Ketoprofen was responsible for the reaction. The patient had a 2+ reaction to Multiprofen cream. She did not react to other cream components including lidocaine and Amerchol L 101 (an emulsifier/emollient).

Treatment

At present, we have advised the patient to avoid all topical and systemic NSAIDs and to obtain a medical-alert bracelet indicating this. This advice was given as it is currently unclear which NSAIDs will lead to cross-reactions in the future.

In the future, we plan on performing patch testing to other individual NSAIDs such as Naproxen. If these are negative, graded oral challenges will be performed to assess for tolerability. An oral challenge to a COX-2 inhibitor such as Celebrex will also be performed in the future to ensure tolerability.

Patient Outcomes

Ms MS has continued all NSAID avoidance and has not had any recurrent episodes of skin rashes. She will return later this year for patch testing to other individual NSAIDs.

Lessons Learned

This case demonstrates the first reported case of systemic contact dermatitis caused by topical Ketoprofen and systemic Ibuprofen. Upon review of the literature, SCD has most commonly been described to metals (Mercury and Gold) and antimicrobials (neomycin, erythromycin and nystatin) as per a recent review on SCD (Aquino 2019). There has only been one published case of NSAID-mediated SCD. This case involved ingestion of Naproxen resulting in a delayed intertriginous eruption (Wolf et al, 2003).

Our case illustrates that NSAIDs can be a rare cause of SCD that can be diagnosed based on clinical history and confirmed based on patch testing.





Hypersensitivity to Paclitaxel in a patient with Laryngeal Cancer: Desensitization Protocol

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Training Program Allergy and Clinical Immunology

Summary

Laryngeal cancer is one of the causes of morbidity and mortality worldwide. It constitutes 1.1% of all cancers. Drug desensitization is a procedure by which the drug is administered during gradual dose increases. Although reactions to paclitaxel are often not mediated by IgE, they respond well to desensitization. These reactions commonly occur with the first or second infusion. It is a safe procedure and within pharmacoeconomics has similar costs of medical care compared to the administration of the drug in a conventional way.

The patient was consulted with the Allergy and Clinical Immunology service for presenting a systemic reaction with the first application of QT (Paclitaxel).

After performing skin tests (Intradermal) to paclitaxel, which was positive in 1:100 dilution, the desensitization protocol was performed with a total duration of 6.67 hours. During the performance, vital signs were constantly monitored, which remained stable throughout the procedure.

Patient Presentation

A 65-year-old female patient with a history of type 2 diabetes mellitus, arterial hypertension and laryngeal cancer (CA), which was diagnosed 6 months ago and identified the human papillomavirus as an etiologic agent. Tracheotomy was performed 6 months ago and radiotherapy was started completing 35 sessions. Subsequently, she began the first session of chemotherapy (QT) with Paclitaxel, 7 minutes after the start of the procedure, the patient presented with thoracolumbar pain, headache, facial erythroderma, palpitations and presyncope, dyspnea and hypoxemia (Sat O₂ 84%). Oxygen was supplied and administered Chlorpheniramine 8 mg, Hydrocortisone 200 mg IV, Adrenaline 0.5 mg IM.

Diagnosis

Hypersensitivity to Paclitaxel in a patient with Laryngeal Cancer

First session of chemotherapy (QT) with Paclitaxel: 7 minutes after the start of the procedure, the patient presented with thoracolumbar pain, headache, facial erythroderma, palpitations and presyncope, dyspnea and hypoxemia (Sat O₂ 84%)

Testing

After performing skin tests (Intradermal) to paclitaxel, which was positive in 1:100 dilution, the desensitization protocol was performed

Treatment

The desensitization protocol was performed with a total duration of 6.67 hours. During the performance, vital signs were constantly monitored, which remained stable throughout the procedure. It is a safe procedure and within pharmacoeconomics has similar costs of medical care compared to the administration of the drug in a conventional way

During the performance, vital signs were constantly monitored, which remained stable throughout the procedure

Paclitaxel is a first-line chemotherapeutic drug in the treatment of cancer as well as having a low cost, which represents a benefit for the patient and the country.

PROTOCOLO DE DESENSIBILIZACIÓN A PACLITAXEL DE 4 BOLSAS

[illegible]

Persistent Focal Epithelial Hyperplasia with elevated TNF α and T cell lymphopenia.

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Training Program Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

Summary

A six-year-old boy presented with numerous persistent oral lesions. He had multiple hypopigmented, papular lesions over the labial, lingual, and buccal mucosa. The lesions were not painful or pruritic. Based on clinical presentation he was diagnosed with Focal Epithelial Hyperplasia (FEH) also known as Heck's disease. He had significant facial dysmorphism with frontal bossing, micrognathia, and abnormal teeth. Basic immune evaluation showed normal cell counts and immunoglobulins. Cytokine/chemokine panel had significantly elevated TNF α to 84pg/mL (reference <22pg/mL). Genetic panel found 2 heterozygous variants of unknown significance (VUS). One year later TNF α level had normalized at <5pg/mL; however, CD4 and CD8 T cells were decreased for age to 421/uL and 170/uL, respectively. T cell functional assays were normal and T cell infecting viruses were checked with negative HIV, IgG positive and IgM negative HHV6. His oral lesions remained persistent throughout his course.

Patient Presentation

A six-year-old boy of Haitian descent with medical history significant only for one seizure and constipation was referred to our immunology clinic for numerous persistent oral lesions. He had numerous hypopigmented, raised, papular lesions over the labial, lingual, and buccal mucosa. These lesions had been present for over one year and were not painful or pruritic, and he had no difficulty eating. Since the initial presentation of symptoms, the lesions had quantitatively increased although some individual lesions had regressed. There was no history of frequent infections and no family history of immunodeficiency, miscarriage, stillbirth, consanguinity, or autoimmune disease. He displayed significant facial dysmorphism with frontal bossing, micrognathia, and abnormally shaped teeth including flattened and short central upper incisors and notched lower teeth.

Diagnosis

He was initially diagnosed with FEH based on clinical presentation and history. His dysmorphia and unremitting disease prompted further investigation into an underlying genetic cause for his symptoms and laboratory abnormalities; however, no genetic cause was found. Two heterozygous variants of unknown significance were discovered, although unlikely related to his disease process.

Testing

Initially, a basic immune evaluation was conducted including white blood cell count, neutrophils, lymphocytes, CD4 and CD8 T cells, B cells, NK cells, and immunoglobulin panel that were all normal for age. Cytokine/chemokine panel was drawn because prior studies in adults have shown that TNF α promotes Human Papillomavirus (HPV) and may influence the duration of infection. Cytokines including IFN γ , interleukin 2 receptor CD25, and interleukins 1 β , 2, 4, 5, 6, 8, 10, 12, 13, 17 were normal. TNF α was significantly elevated to 84pg/mL (reference <22pg/mL). Given dysmorphia and unremitting disease, genetic testing for immune deficiency was conducted with the Invitae Primary Immune Deficiency panel of 207 genes. Two heterozygous variants of unknown significance were present, but no

underlying genetic cause for his symptoms was found. Gene SLC7A7 is associated with autosomal recessive lysinuric protein intolerance. Our patient had heterozygous variant c.241C>T (p.Leu81Phe) that has not been reported with this disease. Gene VPS13B is associated with autosomal recessive Cohen syndrome. His heterozygous variant, c.9905C>T (p.Pro3302Leu) has not been reported with Cohen syndrome.

One year later, TNF α levels have normalized to <5pg/mL and IFN γ , interleukin 2 receptor CD25, and interleukins 1, 2, 4, 5, 6, 8, 10, 12, 13, 17 remained normal. Repeat cell counts showed low CD4 and CD8 T cells for age at 421/uL and 170/uL. Lymphocyte functional assays including mitogens and antigens were normal. T cell infecting viruses including HIV was negative and HHV6 showed IgG positive and IgM negative. HTLV is pending.

Treatment

FEH is a self limited and self-resolving disease with treatment generally not indicated unless lesions create a functional limitation. As the patient has been asymptomatic, we continue with close monitoring of the lesions clinically as well as laboratory monitoring of cell counts and cytokine levels given the previous abnormal results. FEH is associated with HPV serotypes 13 and 23, which are not included in the nine-valent HPV vaccination. Therefore, the vaccine was considered but not administered.

Patient Outcomes

He has remained asymptomatic throughout the course of the disease without frequent infections, although his oral lesions have been persistent and appear to increase in number.

Lessons Learned

FEH is a rare but benign infection of the mucosa that is caused by HPV. The mechanism of HPV persistence in FEH is not characterized, but it is likely due to increased viral persistence and an inability for the host immune response to successfully induce viral latency and containment. It has certain geographic predominance and is more common in Native Americans, South and Central Americans. Both innate and acquired immune responses are responsible for control of most HPV infections. Prior studies have shown that cell mediated T cell responses are critical for viral clearance and lesion regression and that elevated TNF α promotes HPV. The initial elevation of TNF α at diagnosis of our patient may have indicated increased susceptibility to FEH. This combined with T cell lymphopenia at follow up may also explain the persistence of disease. The fact that the TNF α level has normalized in our patient indicates that his chemokine levels may fluctuate cyclically or it may be an indication of impending disease improvement. Immunologic differences between individuals may significantly influence oral HPV clearance and the course of disease. Longitudinal monitoring of serum concentrations of cytokines and chemokines, as well as lymphocytes, may be useful as biomarkers in this disease.

Novel Hypomorphic RAG1 Pathogenic Variants Causing a Leaky SCID Phenotype in a 5-year-old Boy

Author Stephanie Nicole Vazquez

Training Program Memorial Healthcare System Joe DiMaggio Children's Hospital

Summary

5-year-old African American boy with history of prematurity, hypothyroidism, sickle cell trait and recurrent sinopulmonary and skin infections. Immune evaluation revealed severe pan-hypogammaglobulinemia. Lymphocyte subset showed significant depletion in CD19+ B-cells with normal T-cells and increased NK cell count. B-cell population analysis confirmed severely decreased absolute number of B-cells and %CD5+ B-cell population. Molecular testing revealed two variants of uncertain significance (VUS) in the RAG-1 gene (pGly393Val) and (pGly709Ala), confirmed to be in trans by parental genetic testing. Functional assays were pursued to analyze patient's T cell function by using flow cytometry. Patient's T-cells virtually lacked expressing Vα7.2 as well as favored Th1 and Tfh1. All evidences confirmed pathogenesis of hypomorphic RAG1 variants resulting in leaky SCID phenotype.

Patient Presentation

5-year-old African American boy with history of recurrent sinopulmonary and skin infections presented to our Pediatric Immunology and Allergy Clinic for evaluation of suspected primary immunodeficiency. His frequent infections began in infancy requiring treatment with oral antibiotics multiple times with only temporary resolution of symptoms. His past medical history included prematurity requiring 2-month stay in the NICU, hypothyroidism and sickle cell trait. There was no pertinent family history. Due to his recurrent sinus and skin infection his pediatrician referred him to an allergist who obtained an initial immune evaluation. Work up revealed severe pan-hypogammaglobulinemia, no functional antibodies to any vaccines and profound B-cell lymphopenia with normal T lymphocytes and elevated NK cells.

Diagnosis

Genetic sequencing of both parents revealed Trans complementation: father had RAG1 variant of c.1178G>T (p.Gly393Val) and mother had other RAG1 variant of c.2126G>C (p.Gly709Ala). The patient inherited each RAG1 variant: one from mother and the other from father suggesting two genomes containing different recessive mutations yielding a pathogenic RAG1 phenotype.

Flow cytometric analysis to quantify TCR-Vα7.2-expressing T lymphocytes revealed patient only had 0.5% T cells expressing Valpha 7.2 (Figure 1). Patients with RAG deficiency are severely impaired in their capacity to rearrange distal Valpha genes. Therefore, this test was a strong indicator to prove our patient's RAG-1 variants were pathogenic.

Further testing revealed patient's CD4 cells were skewed to Th1 as well as his Tfh cells were skewed to Tfh1 (Figure 2); a common finding in many cases with leaky phenotype.

A high proportion of his CD8 were CD57+ suggesting presence of cytotoxic activated CD8 (Figure 3), which are poised to express IFN-gamma. With the help of the NIH, we were able to confirm patient's diagnosis of leaky SCID caused by two novel hypomorphic RAG1 pathogenic variants.

Testing

His history of recurrent infections and initial laboratory results were indicative of a primary immunodeficiency. An expanded immune evaluation was obtained to corroborate previous findings. Testing included CBC with differential, Immunoglobulins (IgG, IgA, IgM, IgE), lymphocyte subset panel (T/B/NK differential), lymphocyte mitogen proliferation, total complement (CH50), vaccine titers, neutrophil oxidative burst assay and B cell population analysis. Initially, a humoral immune defect was on the top of our differential specifically X-linked Agammaglobulinemia. Genetic testing for BTK expression and a primary immunodeficiency (PID) panel was sent.

Results were consistent with previous findings of severe pan-hypogammaglobulinemia and profound B-cell lymphopenia with normal NK and T lymphocytes. Lymphocyte subset showed extreme decrease in CD19+ B-cells with normal T-cells and increased NK cells. B-cell analysis revealed severely decreased absolute number of B-cells and %CD5+ B-cells.

Total complement, neutrophil oxidative burst assay, lymphocyte mitogen and antigen panel were normal. DTap, Hib, Pneumococcal 23 serotypes, Measles and Mumps vaccine titers showed non-protective except for Anti-Rubella and Anti-Tetanus.

BTK expression was normal, but the PID panel revealed five specific variants of uncertain significance. Three of them were unlikely to play a role in his presentation, but there were two variants identified in the RAG1 gene (pGly393Val) and (pGly709Ala) that were highly suspicious. This sparked further investigation of possible novel RAG-1 mutations.

We consulted the National Institute of Health (NIH) for assistance in analyzing the patient's RAG-1 gene and T cell function. Serum samples of both parents were sent for gene sequencing of the two specific variants to evaluate mode of inheritance. A sample of the patient's serum was sent to the NIH for molecular analysis.

Treatment

Due to his severe hypogammaglobulinemia, patient receives monthly IVIG infusions with Gammagard SD. He is also on antibiotic prophylaxis with Trimethoprim-Sulfamethoxazole.

Patient Outcomes

Since starting treatment, patient's serum immunoglobulins have normalized and he has been infection free. He continues to follow up with Allergy and Immunology on a monthly basis. He has also been enrolled in an ongoing RAG deficiency research with the NIH conducted by Dr. Luigi Notarangelo. Future plans are to perform further molecular signatures of self-reactivity and analyze the bone marrow for blocks in B cell development that are characteristic of RAG.

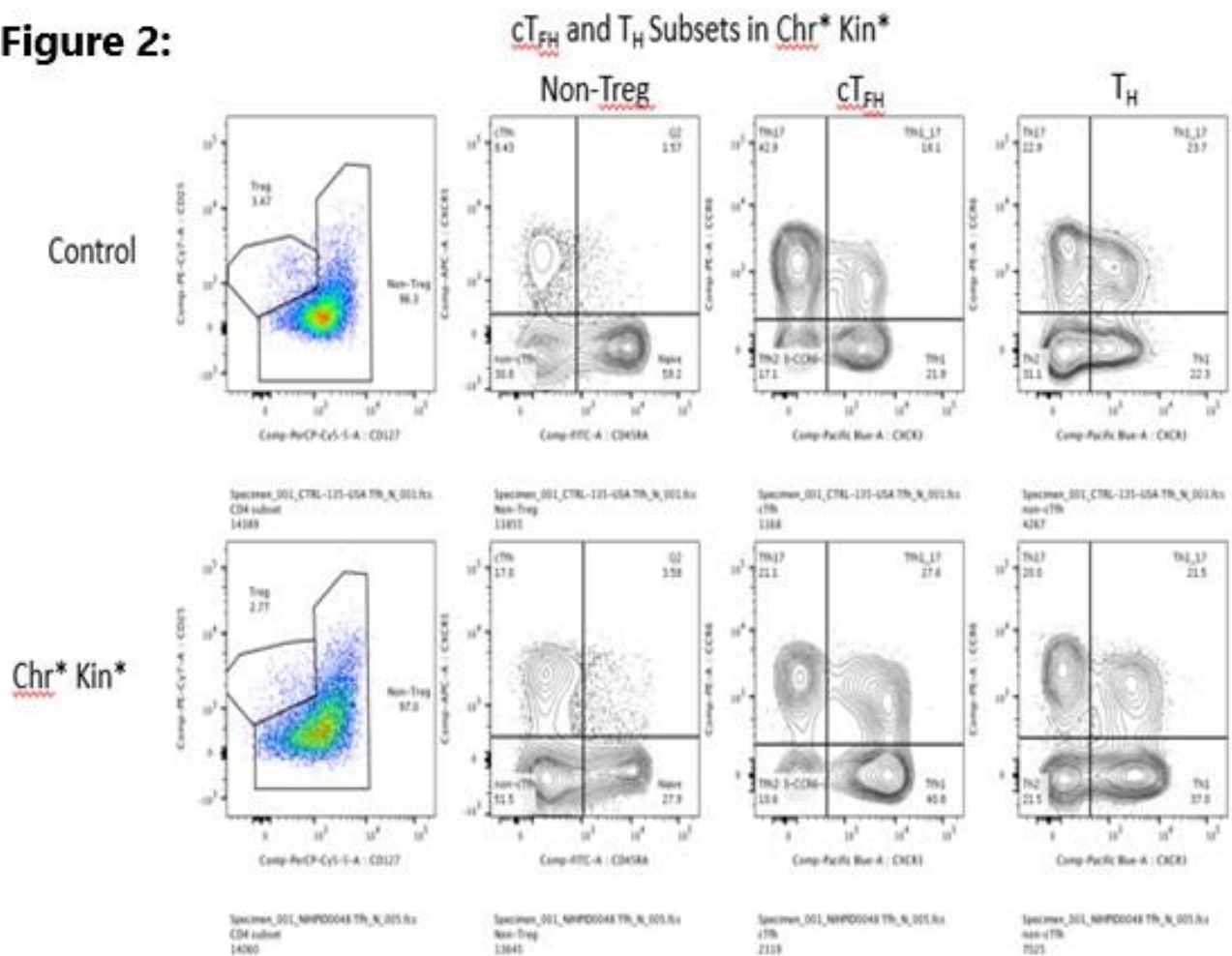
Lessons Learned

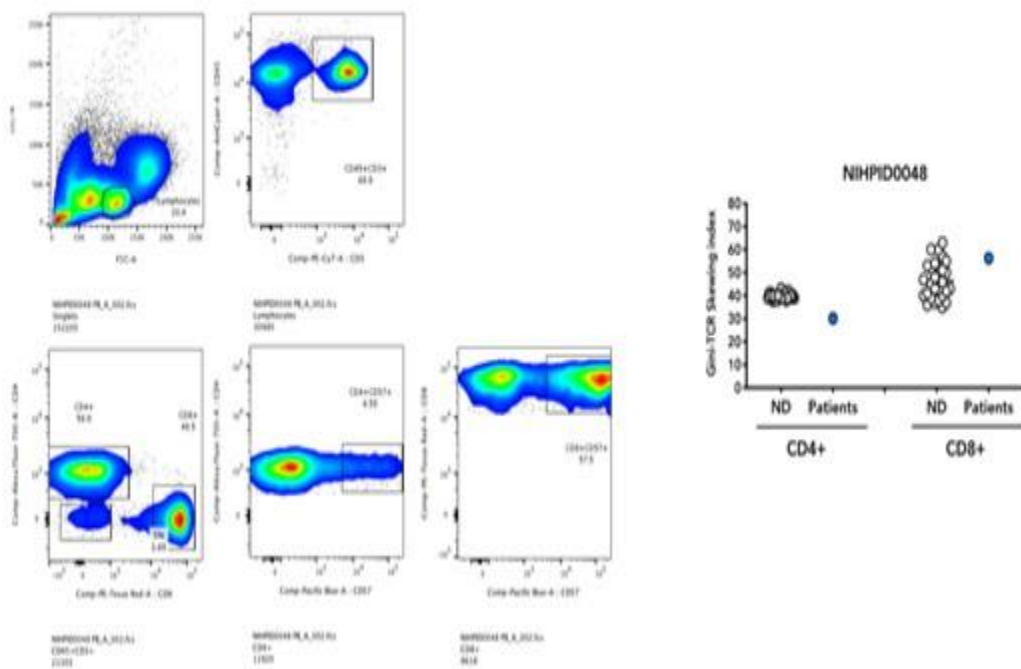
Severe combined immunodeficiency (SCID) is composed of multiple phenotypical diseases resulting in dysfunction of cell-mediated immunity and antibody deficiency due to disruption of lymphocyte differentiation. Multiple variants of a single gene have been associated with distinct SCID immunophenotypes. For this reason, uncertain variant mutations found in proteins involved in cytokine signaling, antigen presentation, V(D)J recombination, T-cell receptor (TCR) signaling and basic cellular function should trigger further testing.

Many defects in the V(D)J recombination mechanism are attributed to a RAG mutation resulting in profound T- and B-cell lymphopenia in the setting of normal NK function (T- B- NK+). Certain RAG mutations, often missense mutations, result in decreased RAG gene expression or partial dysfunction

which preserves some V(D)J recombination activity. These patients present with atypical type of SCID and the clinical severity is dependent on the level and function of RAG protein. These hypomorphic RAG mutations can result in a particular phenotype known as leaky SCID. This case demonstrates the importance of deeper investigation and questioning variants of uncertain significance (VUS). Functional analyses are becoming of vital importance to further clarify a VUS, especially when gene variants associated with primary immune deficiencies continue to emerge at a rapid pace as genetic testing is becoming more easily available in the field of immunology.

Figure 2:



cT_H and T_H Subsets in Chr* Kin*

Allergic reaction to metal implant without explantation

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Summary

We are presenting a case of a gentleman with a long history of metal dermatitis, who underwent a PFO closure with Amplatzer Atrial Septal Occluder, a device containing nitinol (an alloy of nickel and titanium). Soon afterwards, he started experiencing allergic symptoms of generalized pruritis intensifying in his palms, along with giant urticarial wheals on his trunk, arms and hands with angioedema in lips. Symptom management was difficult despite good compliance with antihistamines. He required 3 courses of steroids, including one intravenous. Patient is interesting because based on his initial symptoms, explantation of his atrial device seemed like the only option for him. However, as his symptoms settled down, an approach of watchful waiting was applied, to save him from high risks associated with open heart surgery. At 15 month follow up, patient reported significantly improved condition with mild intermittent urticaria. His message was, "Don't implant anything before testing!"

Patient Presentation

52 year old gentleman was evaluated in our allergy clinic, after he reported post-surgical allergy reactions. Patient had recently undergone PFO closure with an atrial septal occluder. Following the procedure, he experienced transient atrial fibrillation, which resolved. After 36 hours, he developed axillary swelling and lymphadenopathy associated with low grade fevers, which warranted an ED visit. He was reassured that this was likely reactive lymphadenopathy. Two weeks following the implant, our patient developed giant urticarial wheals on his trunk, arms and hands, especially problematic for him due to palmar pruritis. He presented to the ED again and was prescribed Prednisone and Benadryl with improvement. Patient had a remote adolescence history of metal dermatitis so he conducted an in-home metal challenge test, using rivets from his Levi jeans. Large wheals developed on his groin and trunk extending from the site of rivet. This was accompanied by severe itching of his hands and numbness and swelling of his lips. Patient was advised to seek allergy advice to determine whether medication or nickel in cardiac implant was the etiology of his severe urticaria, angioedema, and pruritus with intermittent heart palpitations and left axillary lymphadenopathy. His past medical history was significant for metal dermatitis in adolescence, characterized by intensely pruritic rash at the sites of metal contact. He was unable to wear any type of jewelry and with ear-piercing at age 18, his earlobe developed erythema and pruritus. He also reported gold metal reactions, inability to wear a watch and difficulties with his wedding ring. Family history was significant for mom and sister with allergies, grandfather and children with asthma.

Diagnosis

We initially suspected a nickel metal allergy, manifesting as allergic contact dermatitis. However, his blood tests and metal patch tests were negative for nickel, and positive to titanium and vanadium. His symptoms made sense in the light of his Titanium allergy, but he later also tested highly reactive, on LLT, to Nickel. So his final diagnosis was established as ALLERGIC METAL URTICARIA AND CONTACT DERMATITIS (TITANIUM, NICKEL, VANADIUM).

Testing

Testing was offered to evaluate a potential allergic reaction to ASO. His postoperative symptoms were consistent with both Type 1 and Type IV allergic reactions. Testing was designed to identify allergens involved. Metal patch testing was positive to titanium and vanadium and was negative to nickel. Serum and urine nickel testing was negative. Lymphocyte transformation testing (LTT) demonstrated high nickel reactivity. Using a nickel detection kit, we tested rivets of his Levi jeans, which were negative. We contacted Levi's Company confirming the rivets did not contain nickel but copper. We also contacted the manufacturer of his atrial septal device and found out it was made of titanium and nickel.–

Treatment

We initially prescribed fexofenadine and levocetirizine for his wheals and pruritis. Prednisone dose pack was provided to be used only for severe breakthrough symptoms of urticaria or angioedema. This was an interesting case because according to literature, once a metal allergy to an implant is identified, it is advised to explant the device. In this case however, our patient was doing well on fexofenadine once daily. He did have sporadic appearance of hives but they would settle down with levocetirizine. We considered explantation at one point but the cardiologist and the patient were concerned about risk of open heart surgery exceeding mild intermittent urticaria and so we took a watchful waiting approach. Time was of benefit as after 8 months there was further decrease in frequency of his symptoms. We waited for the device to endothelialize, with theory that he will become less symptomatic as this process occurs.

Patient Outcomes

On initial presentation, patient was experiencing severely debilitating allergic symptoms. He reported that his career had come to a halt due to his intermittent generalized pruritis and full body urticaria. This is why he was seriously considering explantation of his device. But then later, as time passed and his symptoms became well controlled, patient reported that he felt comfortable with the watchful waiting approach. He continued daily antihistamines and after 15 months, patient reported that he was successfully able to stay off of his fexofenadine. He was still having some sporadic allergic reactions, but they were manageable because symptoms were localized, much shorter in duration and never worse than a small itchy welt and would spontaneously disappear.

Lessons Learned

The lesson we learned was that sometimes taking the watchful waiting approach might be of most benefit to the patient. In our patient's case, he was initially set on getting the device explanted as soon as possible because his allergy symptoms were severely bothersome. His decision was also supported by the studies present in the literature. However, with time his symptoms decreased in frequency. With that reassurance, we were more comfortable to wait and watch his symptoms. At the 15 month follow up, our patient was happy with the decision of not explanting his device. When specifically asked what is the message he wishes to share with his story, he said, "Doctors should take reported metal allergies seriously. Do not implant anything before testing a patient first."



Autoimmune Progesterone Dermatitis Secondary to Etonogestrel Implantation

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Summary

A 23-year-old female patient presented with a chronic pruritic rash flaring five days prior to menses. Symptomatic onset began one month after etonogestrel implantation and persisted following removal. The rash concentrated on legs, face, and back, worsened with stress and sun exposure, and proved refractory to topical steroids. Associated symptoms included nausea, unintentional weight loss of 25 pounds within the past year, fatigue, and joint pain/stiffness. CBC, CMP, ESR, CRP, RF, ANCA, SPEP, LDH, C3, C4, and CH50 were within normal limits with negative Lyme/CCP/MPO/PR-3 antibodies. Progesterone prick and patch testing was notably positive with flaring of symptoms two days after testing, which was atypical from timing of usual flares. Desensitization was subsequently coordinated with the patient's gynecologist with a low-dose progesterone/estrogen contraceptive, which improved the rash. 17-OH progesterone and progesterone levels drawn after starting contraceptive have been low.

Patient Presentation

The patient is a 23-year-old G1P1 female with anxiety and depression who presented with "blistering acne" that flared with stress and consistently recurred five days prior to the onset of her menstrual cycle. She first noticed the rash following etonogestrel implantation three years prior to presentation. After removal of the implant one year later, symptoms persisted with rash concentrated on face, torso, and legs. She also noted painful, swollen MCP and PIP joints worsening in the morning and improving throughout the day. Stress and sun exposure exacerbated the rash, which proved refractory to topical steroids. Concurrent medications included methylphenidate and escitalopram. There was no history of atopy. Social history was positive for smoking (1 ppd for three years). Past medical history was otherwise unremarkable.

Diagnosis

The patient was presumptively diagnosed with autoimmune progesterone dermatitis given clinical history (manifestation following etonogestrel implantation, recurrence in conjunction with luteal phase of menstrual cycle) and laboratory findings (positive patch test and elevated serum progesterone).

Testing

Skin prick testing for food was performed upon patient's request and found to be unremarkable. A patch and prick test with progesterone was obtained given concern for rash occurring in conjunction with the luteal phase of the patient's menstrual cycle, which was positive and resulted in flaring of the rash. This, in turn, was unusual with regard to timing given the previous pattern of skin flares. Serum progesterone was also elevated at 83 during the luteal phase of the patient's menstrual cycle. CBC, ESR, CRP, CMP, ANCA with reflex, SPEP, LDH, C3, C4, and CH50 were found to be within normal limits.

Treatment

Given her acute symptoms, the patient was initiated on a steroid taper with dexamethasone and clobetasol along with dual antihistamine therapy with cetirizine and ranitidine. She was also started on desensitization via a low-dose progesterone/estrogen contraceptive in collaboration with her gynecologist. The patient was monitored closely for one hour following administration of the contraceptive, and her rash was found to worsen. 17-OH progesterone and progesterone levels were monitored following induction with the contraceptive, with the goal of having levels high enough to suppress endogenous progesterone production, yet low enough to avoid the recurrence of symptoms. The contraceptive dosage was titrated as tolerated pending symptoms and levels.

Patient Outcomes

The patient's rash has improved in appearance since the initiation of a low-dose progesterone/estrogen contraceptive, but still persists. She continues on antihistamine therapy with montelukast added to her medication regimen. Progesterone levels last obtained were noted to be low, and contraceptive dosing will be discussed with the patient's gynecologist at her upcoming clinic visit, although patient has had poor follow up. Referral to an academic institution is in process.

Lessons Learned

Autoimmune progesterone dermatitis is rare and difficult to diagnose due to both its variable presentation, from immediate to delayed reactions, and its lack of standard diagnosis criteria and testing. Patients may subsequently go undiagnosed for years. Even following diagnosis, treatment options such as desensitization are not standardized. Clinical suspicion is important for females with a cyclical rash and systemic symptoms. Symptomatic improvement may result from suppression of the progesterone surge during luteal phase by desensitization with progesterone. More research is needed for definitive treatment of symptoms.

Anaphylaxis x2 to the MMR Vaccine Mediated by IgE Hypersensitivity Reaction to Gelatin

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Training Program Wilford Hall Medical Center Allergy/Immunology Fellowship

Summary

Administration of the Measles-Mumps-Rubella (MMR) vaccination, or proof of this vaccination, is mandatory for new recruits in the military. MMR is a well-tolerated vaccination with rare reports of severe allergic reactions. It is estimated that a severe allergic reaction from any vaccination occurs at a rate of 1.3 per million doses of vaccines given (1), while rates of anaphylaxis to MMR are even lower (2). Reactions to the MMR vaccine are often caused by additive or residual vaccine components. In addition to MMR viral antigens, the vaccine also contains egg protein, neomycin, sorbitol, and gelatin (3). We report a case of anaphylaxis following MMR vaccination. Laboratory and skin testing results strongly suggest that this reaction was due to an IgE mediated hypersensitivity reaction to the gelatin component of the vaccine.

Patient Presentation

A 19-year-old male in the United States Air Force Basic Military Training program developed symptoms consistent with an anaphylactic reaction after receiving the MMR vaccine. During his in-processing, he was given an intramuscular (IM) penicillin injection 15 minutes prior to the MMR vaccine, but had no immediate symptoms at that time. About 2-3 minutes after getting the MMR vaccine, he developed onset of facial urticaria, periorbital swelling of both eyes with redness and itching, congestion, rhinorrhea, slight cough, and itchy throat. He was diagnosed with anaphylaxis and promptly treated with an epinephrine 0.3 mg intramuscular (IM) injection and 25 mg of diphenhydramine intravenously. He was subsequently taken to the ER where his symptoms continued to improve over a 6 hour observation period. He was discharged back to training on 50mg of prednisone daily for 5 days, 25mg of diphenhydramine every 8 hours as needed, and ranitidine 150 mg twice daily as needed. He was subsequently referred to us for further determination of the cause of his allergic reaction. At 6 years old, patient reports having a reaction to the varicella vaccine that resulted in some tightness of his throat, heaviness of his chest, and vomiting. Patient states he was monitored by his mom and symptoms gradually resolved on their own. He reports a suspected pork allergy, as he has immediate tightness in his chest after eating large amounts of pork. He also reports a suspected gelatin allergy, as he has immediate tightening in his throat after eating gummy bears, and develops hives on his face after using gelatin-containing face creams.

Diagnosis

History was consistent with possible IgE-mediated hypersensitivity to the MMR vaccine and/or the penicillin IM shot. PMH also concerning for possible allergy to gelatin and pork. Antibody titers to measles, mumps, and rubella were first obtained which showed patient was rubella immune and mumps immune, but still measles non-immune. Serum IgE testing was also obtained to gelatin and pork, which showed results positive for gelatin but negative for pork. Per Advisory Committee on Immunization Practices (ACIP) guidelines, patient still required one additional dose of the MMR vaccine as he was in a postsecondary institution with multiple close contacts (4). Patient was informed on the

risks and benefits of testing and administration of the MMR vaccine and he agreed to continue with the procedure.

Testing

Initial skin testing was found to be positive for the MMR vaccine with good positive and negative controls. However, per the “Adverse Reactions to Vaccines Practice Parameter 2012 Update”, the patient agreed to continue receiving the MMR vaccine in graduated doses at 15 minute intervals with a positive skin test. Per the practice parameter's graduated dosing protocol, he was first given a 0.05 ml injection of the vaccine at 1:10 dilution and was observed for 15 minutes without issues. He was then given a 0.05 mL injection of the vaccine at full strength, but protocol was stopped after the patient suddenly developed periorbital swelling of both eyes with redness and itching, congestion, and sneezing.

Treatment

Due to concern for anaphylaxis, the patient was given one dose of IM epinephrine 0.3mg, one dose of cetirizine 10 mg orally, and one dose of ranitidine 150 mg orally. 15-20 minutes later, he reported feeling better but continued to have mild left periorbital swelling, so an additional dose of cetirizine 10 mg was given with good response. He was observed for one hour then discharged home after complete resolution of his symptoms.

Patient Outcomes

The results of serology, skin testing, and challenge to the MMR vaccine showed that this patient's previous anaphylactic reaction was likely due to the vaccine and not the penicillin shot. Serum IgE testing further suggests that the reaction was due to an IgE mediated hypersensitivity reaction to the gelatin component in the vaccine. Discussed with patient that he would still require a 2nd dose of MMR in order to remain in the military. However, upon further investigation, he was able to locate prior immunization records documenting 2 previous MMR doses administered in childhood. As he now had 3 total documented doses of MMR, informed patient that no further doses of the vaccine were needed, even if subsequent MMR titers were found to be negative or equivocal. Discussed that a penicillin allergy could still not be ruled out as the cause of his first anaphylactic episode, but patient wished to return to training and pursue penicillin testing at his next duty station.

Lessons Learned

The MMR vaccine is generally well tolerated and reports of anaphylaxis to this vaccine are rare. IgE mediated reactions to MMR are often caused by additives or residual vaccine components. We report a case of anaphylaxis to the MMR vaccine in a new military recruit with confirmed IgE sensitivity to gelatin. Further skin testing and challenge to the vaccine suggests that his anaphylactic reactions were due to the hydrolyzed gelatin component. This case illustrates the importance of obtaining proper history and immunization records prior to administration of vaccines.

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High “Profilin” Case

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Summary

This case describes a 27-year old female with past medical history of allergic rhinitis who is avoiding walnuts, hazelnuts, almonds, apple, peach, nectarine, apricot, plum, kiwi, strawberry, mango, pineapple, cherry, soy, parsley, cilantro, potato, carrot, and tomato due to itchy mouth, emesis, and urticaria upon ingestion. There was high suspicion that she had a profilin allergy and she was instructed to completely avoid these foods. She is currently receiving immunotherapy for pollen and mold, with which she has noticed mild improvement in her allergic rhinitis symptoms.

Patient Presentation

Patient is a 27-year-old female with a past medical history of allergic rhinitis who presents to allergy clinic for evaluation. She is avoiding a long list of foods including walnuts, hazelnuts, almonds, apple, peach, nectarine, apricot, plum, kiwi, strawberry, mango, pineapple, cherry, soy, parsley, cilantro, potato, carrot, and tomato. She reports being diagnosed with Oral Allergy Syndrome 10 years ago when she ate an apple, and developed itching and swelling of her lips and tongue within 5 minutes of ingestion. Since that encounter, she has intermittently eaten apples (both cooked and raw) with associated oral symptoms, but has also had associated urticaria and emesis within an hour of ingestion. She has similar systemic symptoms with the foods listed above. She has an epinephrine auto-injector, but has never needed to use it. Patient is a non-smoker with no pertinent family history.

Diagnosis

Patient’s sensitivity to birch noted on her skin testing, allergic rhinitis, and clinical local reaction (itchy mouth and throat) to apple, cherry, peach, plum, nectarine, apricot, kiwi, carrot, parsley, soy, almond, and hazelnut is consistent with pollen food syndrome. The broad array of fruits and vegetables was concerning for an allergy to profilin.

Testing

Skin testing was performed which was positive for birch mix, hickory mix, dock/sorrel, and almond and negative for cashew, walnut, pecan, hazelnut, apple, carrot, strawberry, tomato, and soy. Her blood testing was positive for alternaria, cat, dog, oak, pecan hickory, walnut, and white ash. Blood testing was negative for Bermuda grass, timothy grasses and ragweed. Tryptase was also negative.

Treatment

Given the severity of this patient’s pollen food syndrome, complete avoidance of walnuts, hazelnuts, almonds, apple, peach, nectarine, apricot, plum, kiwi, strawberry, mango, pineapple, cherry, soy, dill, cilantro, potato, carrot, and tomato was recommended. She was instructed to keep an epinephrine auto-injector at all times to use in case of a severe reaction.

Patient Outcomes

With regard to her allergic rhinitis, the patient is currently receiving immunotherapy to mold, grasses, and trees with some improvement in her rhinitis symptoms.

Lessons Learned

Profilins are panallergens made of small proteins in the cytoplasm of eukaryotic cells that affect cell shape and function. They have been identified in trees, grass and weed pollens as well as many fruits and vegetables, including hazelnuts, almonds, apple, cherry, peach, pear, plum, strawberry, asparagus, banana, bell pepper, potato, tomato, carrot, celery, parsley, lychee, mango, watermelon, garden pea, peanut, soybean, pineapple, and walnut. This is a unique case that highlights a patient with a systemic reaction to numerous profilin containing fruits and vegetables. In clinical situations such as this, complete avoidance of the food is recommended and patients should be prescribed an epinephrine auto-injector to use in the event of a severe anaphylactic reaction.

Neutrophil recovery after intravenous immunoglobulins in a pediatric patient with B cell-ALL during maintenance chemotherapy

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Summary

We present a 9-year-old boy with B cell-Acute Lymphoblastic Leukemia (B-ALL) in remission, on maintenance chemotherapy, who presented with fever, severe neutropenia and anemia despite chemotherapy being on hold for two weeks. His initial work up included antineutrophil antibody which was negative and bone marrow biopsy showed trilineage hematopoiesis, due to concern for relapse. He was found to have a direct antiglobulin test positive for C3, but negative for IgG and negative indirect antiglobulin test, suggesting the presence of IgM antibodies to red blood cells, concerning for an autoimmune process. Due to concern for an autoimmune process resulting in neutropenia and anemia, high dose intravenous immunoglobulins (IVIG) was given for 3 days. He also received one unit of packed red blood cells due to decreasing hemoglobin to 6.8 g/dL. On third day of IVIG therapy, patient was found to have rising fevers, and IVIG was stopped. The next day, patient was afebrile and absolute neutrophil count (ANC) recovered to 1200.

Patient Presentation

We present a 9-year-old boy with B-ALL in remission, who presents with persistent neutropenia and acute anemia while receiving cycle 1 of maintenance chemotherapy. He presented to clinic for scheduled chemotherapy, but the absolute neutrophil count (ANC) was 400. It was thought to be secondary to a viral infection, due to oral lesions, thus chemotherapy was held. Patient returned to clinic 2 weeks later for follow up. At presentation to clinic he was febrile and had persistent neutropenia with an ANC of 100, though he was otherwise asymptomatic and hemodynamically stable. Patient was admitted for intravenous antibiotics due to fever and neutropenia and a bone marrow biopsy to rule out relapsed leukemia due to persistent neutropenia and worsening anemia.

Diagnosis

The differential for neutropenia coupled with anemia but no thrombocytopenia included disease processes that affected neutrophils and anemia. A bone marrow biopsy was performed due to concern for relapse of his hematologic malignancy, but the biopsy preliminarily showed no infiltrative process. There was concern that the neutropenia was possible due to the patient's chemotherapy, but the chemotherapy had been on hold for more than 2 weeks and his reticulocyte count was high suggesting bone marrow recovery. Since he was febrile on admission, infection was considered as a cause of his neutropenia and anemia; thus, a respiratory viral panel was sent out, as well as labs for CMV, EBV, Parvovirus, and TB. Blood cultures were also collected. Given his anemia, direct and indirect Coombs tests were performed to look for antibodies to red blood cells, and total bilirubin and LDH labs were collected to look for evidence of hemolysis. Given his positive direct Coombs test, there was concern for an autoimmune process that could also be affecting his neutrophil count, and thus anti-neutrophil antibody laboratory studies were also ordered.

Testing

The patient had neutropenia, anemia, but no thrombocytopenia. A bone marrow biopsy was performed due to concern for relapse, but no infiltrative process was found, and he appeared to be having bone marrow recovery with a good reticulocyte count. Lab studies obtained to determine if the patient had an infection were found to be negative, except for EBV, to which he had IgG but not IgM antibodies. Blood cultures were also negative. Thus, there was no known infection to suggest bone marrow suppression secondary to infection. Given a positive direct Coombs test, there was evidence of antibodies to red blood cells, suggesting diseases such as autoimmune hemolytic anemia (AIHA). However, his total bilirubin and LDH labs were normal, which suggested there was not a significant amount of hemolysis occurring. A direct Coombs test does not necessarily indicate that there were antibodies to RBCs resulting in hemolysis, and a positive C3 result suggested that the antibodies present were probably IgM. Thus, AIHA was less likely. Given the profound neutropenia, there was also concern for an autoimmune process targeting neutrophils, such as autoimmune neutropenia. However, antibodies to neutrophils were not detected. But, given that anti-neutrophil antibodies are known to be difficult to detect, autoimmune neutropenia could not be ruled out. Thus, since autoimmune neutropenia could not be ruled out and no other process leading to neutropenia could be identified, the decision was made to start treatment with intravenous immunoglobulin (IVIG). Immunoglobulin levels were obtained prior to starting IVIg, including for IgA, which were found to be within normal limits.

Treatment

A literature search revealed a small number of studies describing the use of high-dose IVIG for the treatment of autoimmune neutropenia (Bussel et al., 1983; Bux, Behrens, Jaeger, & Welte, 1998; Hilgartner & Bussel, 1987). The usual dose was 1-3 grams/kg given over 2 to 5 days. Other treatment options for autoimmune neutropenia include Granulocyte-Colony Stimulating Factor (G-CSF) and steroids. The reports showed success with IVIG alone, so our patient was started on a dose of 2g/kg spaced over 3 days. The option of starting G-CSF was also presented to the primary team but was not given as there was no evidence of failure of production causing neutropenia. Immunoglobulin levels were obtained prior to starting IVIG, and after IgA levels were found to be normal, IVIG was started.

Patient Outcomes

Our patient was started on 20g of IVIG per day for three days. He tolerated the IVIG well for the first two days. Incidentally, on day 2 of his IVIG treatment, his hemoglobin dropped to 6.8 and he was tachycardic to 128, so he was given 1 unit of packed RBCs. On the third day of IVIG therapy, he was found to have rising fevers, and IVIG was stopped. The next day, he was afebrile throughout the day and his ANC was found to have recovered to 1200, so he was discharged home. His neutrophil counts continued to increase and he was able to resume maintenance chemotherapy. He was been able to maintain the improved blood cell counts for the next 3 months.

Lessons Learned

Our patient presented with profound neutropenia coupled with anemia. He was being treated with chemotherapy for B-ALL, but his chemotherapy had been on hold for more than 2 weeks when he developed the profound neutropenia and fever. There was no evidence of a process affecting his bone marrow, and no viral or bacterial infection was identified despite presenting with fever. He did have a positive direct Coombs test suggesting an autoimmune process. While no anti-neutrophil antibodies were detected, an autoimmune neutropenia remained at the top of the differential. Given his age, it

was not the typical presentation for autoimmune neutropenia, which generally presents early in life (5-15 months) (Farruggia et al., 2015). Autoimmune neutropenia can be associated with infection or other autoimmune diseases; potentially immune dysregulation related to the leukemia or chemotherapy triggered the production of anti-neutrophil antibodies. We found that our patient's absolute neutrophil count recovered rapidly with 3 days of high-dose IVIG at a dose of 2g/kg over 3 days. Thus high-dose IVIG therapy can be used to treat profound neutropenia when other causes of neutropenia are ruled out and an autoimmune process is suspected.

Allergy to beer: not everything is due to LTP

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Summary

Beer is an alcoholic drink widely consumed all over the world. Several cases of contact urticaria induced by beer have been described. However, cases of severe reactions after beer ingestion are becoming more frequent.

The main ingredients of beer used for the brewing process are barley, malt, hops, brewers yeast and water. The protein composition of malt, which is obtained from germinated and heated roasted barley, and beer changes during the beer production process, which includes malting, mashing, boiling, fermentation and filtering. In most cases, allergy has been associated with hypersensitivity to the nonspecific lipid transfer protein (LTP), a heat-and pepsin-resistant plant pan-allergen, although allergy to specific proteins in cereals has been described in the literature.

We present a case of allergy to beer due to a different protein than the well-known LTP.

Patient Presentation

18-year-old female, born in Madrid, who suffered pharynx, ocular, lingual and otic itching associated with lip angioedema a few minutes after drinking a small sip of beer. It was the first time she had ever tasted an alcoholic beverage. The patient referred oral itching after the ingestion of cookies with traces of barley. She tolerated other cereals such as wheat, corn and rye.

Diagnosis

Allergy to Beer in a patient sensitized to the Protein Z4 or Serpin, contained in barley

Testing

Molecular study was performed for the detection of specific IgE (ImmunoCAP System FEIA, ThermoFisher Scientific AB, Uppsala, Sweden), with negative results for all the components included (Art v3, Ara h9 (nsLTP), Cor a8, Pru p3, Ber e1, peanut storage proteins (Ara h1, Ara h2, Ara h3), phl p12, Bet v1, barley, peanut, hazelnut, almond, chestnut, pistachio, pine nut, walnut, seeds.

Due to the negative results of ImmunoCAP, we performed Skin prick-test to the commercial battery of cereals (which include wheat, barley, oats, soybeans, rice, grass pea, rye and corn) (Laboratorios LETI, Madrid, Spain), with positive result for barley and corn.

We also did Prick-prick with barley and chose different beers to perform prick-prick: common barley malt beer (Pilsner Urquell), toasted barley malt beer (Oharas), wheat and barley malt beer (St Bernardus Wit), gluten-free barley beer (Mahou); with positive results for all of them.

Given the negative result for LTP allergy and in order to identify the protein involved in the reaction, the beer extract was analyzed by SDS-PAGE Immunoblotting under reducing conditions (with 2-mercaptoethanol), detecting IgE-binding band of 45 kDa in the extract, which would correspond to a Protein Z4 or Serpin, as previously described.

Treatment

It was indicated to avoid the ingestion of any beer and food containing barley. The patient was allowed to continue ingesting the rest of the cereals, including wheat and corn, as she tolerated them. Antihistamines, steroids and autoinjector of adrenaline were prescribed in case of reaction

Patient Outcomes

We indicated to avoid any beer, including gluten-free. Gluten-free beer is achieved through an enzymatic process that uses endoproteases during the fermentation stage, which are able to remove the remaining gluten from the beer without compromising other properties of the product. That is to say, keeping barley among its components. On the other hand, we also prohibited the drinking of wheat beer as in most cases those labeled as wheat beer have a percentage of barley among its ingredients. Following these recommendations the patient didn't have any further reactions.

Lessons Learned

Beer has been implicated as the causative agent of contact urticaria and severe IgE-mediated anaphylaxis. Most cases of beer allergy reported so far have been associated with hypersensitivity to the 9 kDa non-specific lipid transfer protein (LTP). Garcia-Casado et al have characterized another beer allergen of 45kDa named as Protein Z4 or Serpin.

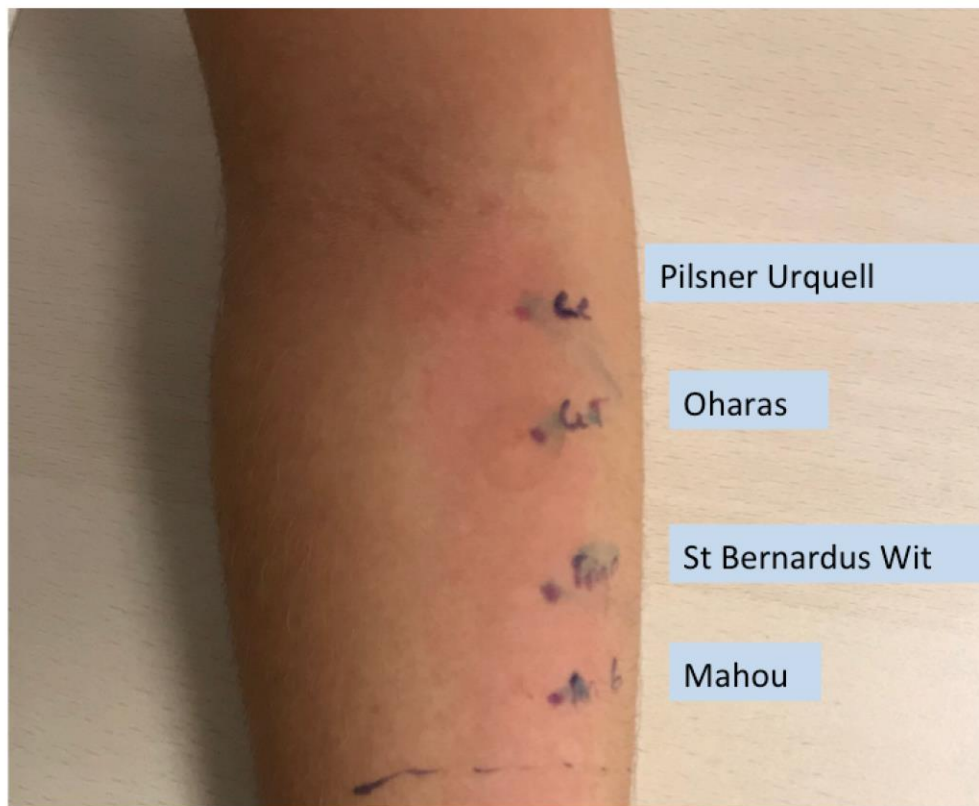
These two beer allergens have been considered as the main barley proteins that could survive the malting and brewing processes and thus become the major components of the beer protein fraction. Protein Z4 can also be found in wheat.

In our case, we present a patient with a clear history of allergy reaction after the consumption of beer. The negative results of the ImmunoCAP to barley and LTP encouraged us to perform the skin tests and the SDS Page Immunoblotting to identify the specific proteins that caused the reaction. The result of our study allowed us to indicate the most appropriate treatment and to evaluate the cross-reactivity with other cereals.

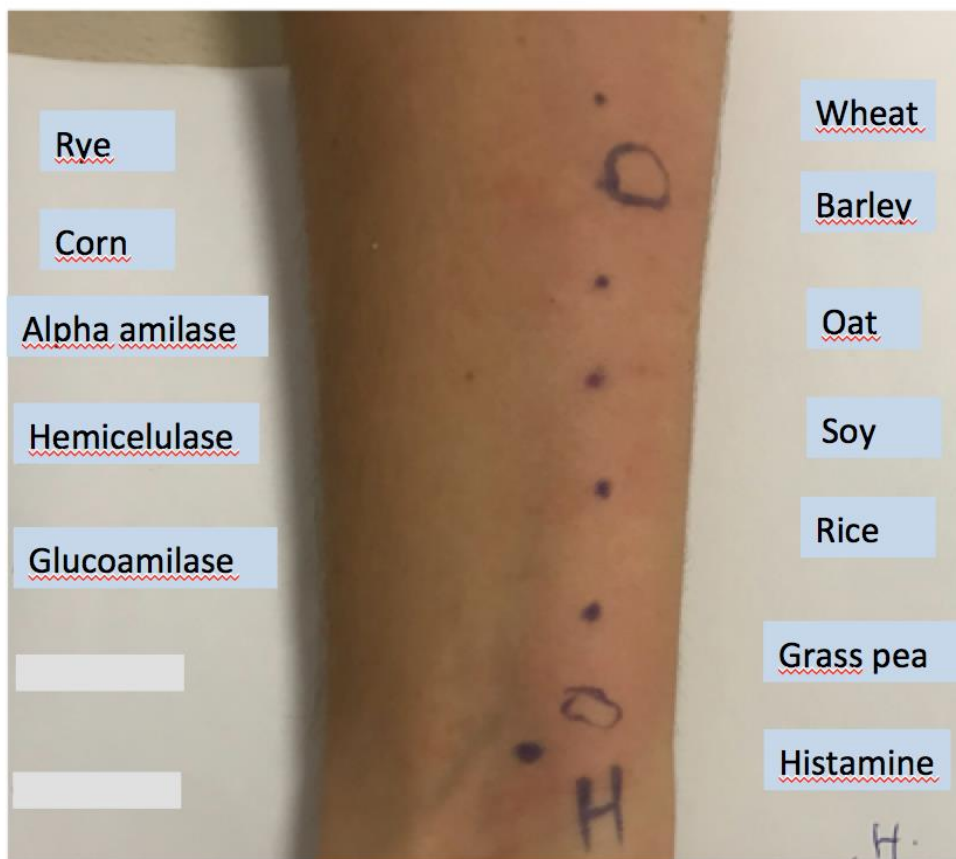
This patient only reported symptoms with barley and tolerated wheat. This fact would indicate that the cross reactivity between the Protein Z4 of barley and wheat might be low. Nevertheless, the cross reactivity should be verified in a wider spectrum of cases.

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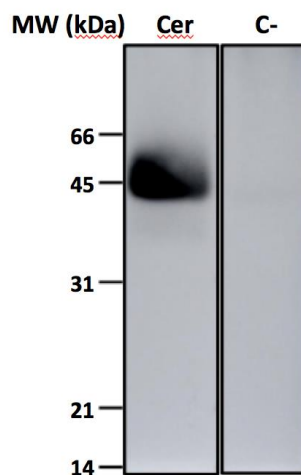
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Prick prick test with the different beers (in order): common barley malt beer (*Pilsner Urquell*), toasted barley malt beer (*Oharas*), wheat and barley malt beer (*St Bernardus Wit*), gluten-free barley beer (*Mahou*):



Skin prick tests with commercial battery for cereals (in order, from right to left) : wheat, barley, oat, soy, rice, grass pea, rye, corn, alpha amilase, hemicelulase, glucoamilase



SDS-Page Immunoblotting of the beer extract.

1-. Patient's serum allergic to beer.

2-. Negative control serum (non-atopic).

Lymphocytic variant hypereosinophilic syndrome with systemic mastocytosis

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Summary

A 59-year-old man incidentally found to have peripheral hypereosinophilia (absolute eosinophil count $7.4 \times 10^9/L$) later developed fatigue and rash. Bone marrow biopsy identified hypercellular bone marrow with dense aggregates of mast cells with aberrant CD25 expression consistent with a diagnosis of systemic mastocytosis. He was initially treated with hydroxyurea without improvement and received midostaurin and frequent prednisone tapers over a one-year period. Repeat bone marrow biopsy showed reduced mast cell aggregates with ongoing hypereosinophilia. Further workup for eosinophilia at that time demonstrated T cell receptor clonality suggestive of a T cell neoplasm and lymphocytic variant hypereosinophilic syndrome. He was treated with methotrexate and mepolizumab while tapering off midostaurin. This case highlights an individual with eosinophilia associated systemic mastocytosis who upon treatment for mastocytosis was found to have persistent hypereosinophilia with evidence of a clonal T cell population suggestive of a lymphocytic variant HES.

Patient Presentation

A 59-year-old man presented to our Allergy/Immunology (A/I) clinic with intermittent rash and persistent fatigue in the setting of recent diagnosis of systemic mastocytosis and peripheral eosinophilia. Seventeen months prior to this visit, the patient was asymptomatic, but during a routine health examination by his primary care provider (PCP), a complete blood count (CBC) with differential was performed that demonstrated a white blood cell count of $12.2 \times 10^9/L$, 60% eosinophils with absolute eosinophil count (AEC) of $7.4 \times 10^9/L$. Hemoglobin was 15.1 g/dl, and platelet count $210 \times 10^9/L$. He was referred to oncology clinic and initially managed expectantly.

Fifteen months prior to A/I evaluation, he reported persistent fatigue and periodic appearance of cutaneous lesions including erythematous nodules on his palms, and ecchymoses on his distal fingertips. Repeat CBC showed an AEC of $6.4 \times 10^9/L$. Skin biopsies were consistent with spongiotic dermatitis. Bone marrow aspiration and biopsy revealed hypercellular bone marrow (>90%) and a mast cell neoplasm with dense aggregates of mast cells with aberrant CD25 expression and marked eosinophilia. Cytogenetics showed 46, XY. FISH showed no deletion of CHIC2/LNX, no rearrangement of PDGFRA, PDGFRB, or FGFR1 and no BCR-ABL1 gene fusion. Tryptase was not measured. He was diagnosed with systemic mastocytosis since he met one major WHO criterion (multifocal dense infiltrates of mast cells in bone marrow) and one minor WHO criterion (mast cells in bone marrow with aberrant expression of CD25).

Hydroxyurea was initiated without symptom improvement. Fourteen months prior to A/I evaluation, because of concern for underlying myeloid neoplasm, midostaurin was initiated along with frequent prednisone tapers. Symptoms improved but did not resolve. AEC decreased to $0.3 \times 10^9/L$. However, hemoglobin was elevated at 17.2 g/dL. Episodic numbness, tingling, and erythema of the hands and finger tips plus diffuse joint pain persisted. Five months prior to A/I evaluation, repeat skin biopsy showed 26 mast cells in one high power field, dermal edema, and perivascular lymphohistiocytic infiltrate but no findings consistent with cutaneous mastocytosis. Omalizumab was initiated at 150mg every 28 days and discontinued after three months with little effect on fatigue, rash, and arthralgias.

Three months prior to A/I evaluation, Hematology/Oncology at our hospital performed additional testing. Serum tryptase was elevated at 38.7 ng/ml, but blood was negative for KIT Asp816Val mutation. Strongyloides antibody, obtained to workup eosinophilia, was negative. Lymphocyte subset analysis showed mildly decreased absolute number of CD19 positive cells at 95 cells/ μ l (reference range 105 – 920 cells/ μ l), but normal absolute numbers of CD3, CD4, CD8, and CD16/56 positive cells. A myeloid mutation panel sent on whole blood was negative for mutations in 21 genes including FLT3, KIT, and NRAS. Repeat bone marrow biopsy performed 1 month prior to A/I evaluation and 14 months after the initial biopsy demonstrated normocellular bone marrow (50%), tri-lineage hematopoiesis and eosinophilia. Mast cell aggregates were not identified. There was no significant dyspoiesis. Bone marrow was negative for KIT Asp816Val mutation. Peripheral AEC was $1.0 \times 10^9/L$. During A/I evaluation, the patient described persistent fatigue preventing him from working full time. He reported worsening dyspnea on exertion despite prednisone 20 mg daily tapered down from 60 mg over one month prior to A/I evaluation. The non-pruritic cutaneous lesions persisted. There was no wheezing or cough, no fevers, night sweats, or weight loss and no chest pain, orthopnea, dysphagia, or abdominal pain. Physical examination was notable for erythroderma of face and chest without dermatographism or urticaria pigmentosa.

Diagnosis

T-cell receptor clonality assay revealed a clonal T-cell receptor gamma gene rearrangement suggestive of a lymphoid neoplasm likely of T-cell lineage. This test, plus the patient's initial bone marrow biopsy showing mast cell aggregates with aberrant CD25 staining along with marked eosinophilia, supported a diagnosis of systemic mastocytosis with concomitant LV-HES.

Testing

The patient presented with a working diagnosis of hypereosinophilic syndrome (HES) in the setting of systemic mastocytosis with the assumption that systemic mastocytosis was driving the eosinophilia. Yet, eosinophilia, cutaneous and systemic symptoms persisted despite therapies directed against systemic mastocytosis. A/I evaluation involved repeat CBC with differential showing elevated HCT of 18.2 g/dL concerning for polycythemia, persistent eosinophilia, with AEC of $0.6 \times 10^9/L$, tryptase of 28.5 ng/ml, and total IgE of 163 IU/ml. Since workup for myeloid HES was negative, we sent blood for a T-cell receptor clonality assay to assess for lymphocytic variant HES (LV-HES). To evaluate for possible end organ damage related to persistent eosinophilia, we assessed troponin I which was normal at <0.034 , BUN, creatinine, and alkaline phosphatase and transaminases which were all normal. Results of pulmonary function testing are pending.

Treatment

With co-management from Hematology/Oncology, the patient was continued on midostaurin for systemic mastocytosis. Omalizumab was discontinued as it was ineffective in treating the patient's cutaneous symptoms, fatigue, and arthralgias. Therapeutic phlebotomy was initiated for probable polycythemia. With the identification of a clonal T-cell population alongside persistent eosinophilia, treatment focused on finding effective steroid sparing regimens to control LV-HES and monitoring for progression to a more aggressive T-cell neoplasm. The patient was started on weekly methotrexate. After 2 months on methotrexate, anti-IL-5 therapy with mepolizumab 300mg subcutaneously every four

weeks was started. One month after mepolizumab began, midostaurin was discontinued due to concerns that it was contributing to the patient's fatigue.

Patient Outcomes

Prior to initiation of the above treatment regimen, the patient had persistent arthralgia and fatigue. With steroid tapered from prednisone 20mg daily to 10mg daily, eosinophils rose from $0.6 \times 10^9/L$ to $1.0 \times 10^9/L$. After initiating methotrexate, eosinophils dropped to $0.8 \times 10^9/L$. With the addition of mepolizumab, symptoms stabilized and AEC normalized. Further laboratory and symptomatic evaluation is ongoing.

Lessons Learned

We describe a case of systemic mastocytosis with associated eosinophilia later found to be LV-HES with an associated clonal T-cell population. LV-HES associated with systemic mastocytosis are not widely reported in the literature. A case of sub-diagnostic systemic mastocytosis was described in a patient with LV-HES, with a clonal T-cell population and the absence of KIT gene mutation in mast cells (Jain P, et al. Blood Res 2017;52:71-73). Our presentation illustrates the importance of periodic reassessment of the etiology of eosinophilia, particularly if laboratory abnormalities and symptoms persist despite treatment of the condition thought to be driving the eosinophilia. Furthermore, we present a treatment plan for LV-HES with concurrent systemic mastocytosis using mepolizumab.

Immune dysfunction in a patient with albinism

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Summary

This patient is a 6-year-old female with a history of recurrent urinary tract infections, autoimmune hemolytic anemia recalcitrant to multiple therapies, and oculocutaneous albinism who presents with persistent hypogammaglobulinemia requiring monthly intravenous immunoglobulin replacement. Her immune evaluation was consistent with an isolated impairment of B cell differentiation and defective IgG production. Whole exome sequencing did not find a specific cause for this patient's combined medical presentation other than a homozygous variant of unknown clinical significance in the OCA2 gene. Oculocutaneous albinism may occur as non-syndromic forms as well as syndromic forms. Syndromic forms include Hermansky-Pudlak, Chediak-Higashi and Griscelli syndromes, which are mainly characterized by defects in granulocytes, cytotoxic T cells and natural killer cells, respectively. An association between OCA2 variants and an isolated immune dysfunction of B cell differentiation has not been previously described in the literature, and may represent a new subset of humoral immunodeficiency.

Patient Presentation

This is a 6-year-old female with a history of autoimmune hemolytic anemia (AIHA), horizontal nystagmus, oculocutaneous albinism, and unspecified hypogammaglobulinemia with low Immunoglobulin G (IgG). Her autoimmune hemolytic anemia had been recalcitrant to multiple therapies including Sirolimus, Rituximab, Bortezomib, 6-mercaptopurine, methotrexate, and steroids. She underwent a splenectomy two years prior to presentation, after which she was started on Penicillin prophylaxis. Her last crisis of AIHA was 2 weeks prior to her initial visit to our clinic for which she received a transfusion of packed red blood cells, intravenous immunoglobulin (IVIG), and steroids. She also has a history of recurrent urinary tract infections, with two episodes of Klebsiella urosepsis and urolithiasis. Urolithiasis was attributed to hypocitraturia for which she is on citrate therapy.

On exam, vital signs were within normal limits for age. She was in the 24th percentile for height, 39th percentile for weight, with a BMI of 15.8 kg/m². Physical exam was significant for albinism with pale skin, light brown iris and light brown hair, all of which were markedly hypopigmented compared to her family members. She also had horizontal nystagmus.

She presented to immunology clinic for evaluation of persistently low IgG levels. Her low IgG levels were initially attributed to effects of Rituximab and Bortezomib therapy which she had received previously for AIHA. However, at the time of our evaluation it had been two years since she had last received these therapies and this was no longer a plausible explanation.

This patient is a product of a consanguineous union (parents are first cousins). She has a sister who is 3 years older and is healthy. She has a sibling who died at 1 day of life from an unknown cause. Her father has a history of nephrolithiasis of unclear composition. There is no family history of autoimmunity or albinism.

Diagnosis

In summary, our evaluation showed impaired B cell differentiation and defective immunoglobulin production correlating with a clinical picture of severe recurrent infections and autoimmune disorders.

This is consistent with a primary humoral immunodeficiency. In addition, whole genome sequencing revealed a homozygous variant of unknown clinical significance in OCA2, which does explain her pale skin, hair and nystagmus. This is the first report of an association between this variant and AIHA, hypogammaglobulinemia, or nephrolithiasis.

Testing

A history of frequent infections and persistently low levels of IgG requiring frequent immunoglobulin replacement prompted evaluation for causes of immunodeficiency. Complete blood count revealed leukocytosis (21,600/uL), mild thrombocytosis (595,000/uL) with elevated absolute neutrophils (9,020/uL), lymphocytes (10,590/uL), and monocytes (1,610/uL). Evaluation of antibody titers were complicated by recent administration of intravenous immunoglobulin. A complete immune evaluation was obtained to screen for primary immunodeficiencies. Results revealed low IgG (total IgG 349 mg/dL), normal IgA (167 mg/dL), normal IgM (47 mg/dL). She had elevated absolute T cell subsets (CD3+ 8,330/uL, CD4+ 4,633/uL, CD8+ 3,487/uL, HLA-DR 4,131/uL), elevated total B cells (CD19+ 3,864/uL), increased naïve B cells, decreased memory B cells and decreased isotype switched memory B cells (IgM-/IgD-). She had normal Natural Killer (NK) cell function, normal neutrophil oxidative burst, normal complement, and normal mannose-binding lectin. Lymphocyte antigen panel demonstrated low-normal responses to tetanus and candida. Lymphocyte mitogen responses were normal to phytohemagglutinin (PHA), and Pokeweed (PW), and low to Concanavalin A (ConA).

Given the borderline elevated IgA, elevated T cells, AIHA and history of splenomegaly, evaluation for Autoimmune Lymphoproliferative Syndrome (ALPS) was obtained. ALPS panel as well as soluble Fas ligand were negative. Th17, IL17A+, and CCR6+CD45RA- were normal. Foxp3 protein expression assay showed decreased percentage of T-reg cells (2.4% of CD4 cells) with normal Foxp3 expression, and normal absolute numbers of T-regs and Foxp3+ cells. CT of the chest, abdomen, and pelvis were obtained to rule out presence of acute or chronic infections or malignancy. There was no evidence of bronchiectasis or chronic lung disease. Abdominal CT did reveal cortical thinning and scarring from prior infection of the right kidney as well as a non-obstructing lower pole calyceal calcification on the right. Earlier results obtained from an outside institution 3 years prior included transmembrane activator and CAML interactor (TACI) sequencing for common variable immunodeficiency disorder (CVID), which was negative. Electron microscopy (EM) and array comparative genomic hybridization (CGH) for Hermansky Pudlak syndrome was also negative. Whole exome sequencing did not reveal a specific cause for this patient's combined medical presentation other than a homozygous variant of unknown clinical significance in the OCA2 (oculocutaneous albinism 2) gene. Each parent is a carrier of the variant, c.2020C>G.

Throughout our evaluation, our patient displayed poor linear growth even after discontinuation of steroid therapy, fatigue, and constipation. Labs revealed elevated TSH (37 IU/mL), and normal free T4 (1.19 ng/dL). Repeat tests confirmed true hypothyroidism with low free T4 (0.74 ng/dL) and elevated anti-thyroglobulin antibodies (1,106 IU/mL). She was started on Synthroid and is currently being followed by pediatric endocrinology with improvement of her symptoms.

Treatment

Our patient was started on adequate doses of IVIG infusions roughly every 2 months with a trough level goal of 1,000 mg/dL. Once targeted IgG levels were achieved, she was transitioned to subcutaneous immunoglobulin every 14 days. She continues with penicillin prophylaxis secondary to her splenectomy, and was started on mycophenolate mofetil therapy for AIHA. She is now up to date with all her vaccines.

Patient Outcomes

Since optimizing therapy for our patient's hypogammaglobulinemia with adequate titer surveillance and optimal dosing of immunoglobulin replacement, she has been stable without recurrence of UTIs or other infections. Together with adequate therapies for AIHA and autoimmune hypothyroidism she has had improved growth and stamina.

Lessons Learned

This case presents a unique association of a primary humoral immunodeficiency and albinism which has not been previously described in the literature. Hypopigmentation disorders known to be associated with immunodeficiency include Hermansky-Pudlak, Chediak-Higashi and Griscelli syndrome, however, these mainly involve defects in granulocytes, cytotoxic T cells and NK cell function. Interestingly, our patient displays an isolated defect in immunoglobulin production and possibly function, with normal granulocytes, T cell and NK cells. Mutations in the OCA2 gene are known to cause oculocutaneous albinism (OCA) as an autosomal recessive trait. The OCA2 protein is found in a large proportion of melanocytes and is located on the melanosome membrane, likely acting as a tyrosine transporter. The homozygous c.2020C>G OCA2 variant has been reported as manifesting with typical features of OCA with hypopigmentation of the eyes, hair, and skin. Patients presenting with OCA and recurrent infections should be screened for immunoglobulin levels and defects in humoral immunity as this may represent a new subset of humoral immunodeficiency.

Isosulfan Blue Dye: An Emerging Cause of Perioperative Anaphylaxis

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Summary

Perioperative anaphylaxis remains a clinical challenge due to multiple agents being administered within close proximity. Most common causes include, but are not limited to, neuromuscular blockade agents, antibiotics and chlorhexidine. We present two cases with perioperative anaphylaxis due to isosulfan blue dye during mastectomy for breast cancer. Patients presented with refractory hypotension within 15 minutes of isosulfan blue dye and nuclear isotope infusion. They were evaluated with skin testing for all the medications used, except for the nuclear isotopes. Both patients tested positive for isosulfan blue dye. Patient 1 was also positive for midazolam. Subsequently, patients successfully underwent mastectomy with avoidance of agents they tested positive for, use of methylene blue instead of isosulfan blue dye and premedication. These cases highlight the importance of considering every agent as a possible culprit in allergic reactions and expanding skin testing to include as many of the suspected drugs as possible.

Patient Presentation

We present two patients who developed perioperative anaphylaxis during bilateral mastectomy for breast cancer. Patient 1 is a 51-year-old female who received midazolam, fentanyl, lidocaine, propofol and rocuronium for anesthesia induction. 5 minutes later she was given isosulfan blue dye and nuclear medicine isotope for sentinel lymph node biopsy. 19 minutes after receiving induction she developed severe hypotension and tachycardia requiring vasopressors. Patient did not have prior history of general anesthesia, but she had undergone multiple dental procedures and an esophagogastroduodenoscopy without any adverse events. Patient 2 was given cefazolin, midazolam, rocuronium, propofol and fentanyl which 5 minutes later were followed by isosulfan blue dye, Technetium-99m sulfur colloid and a second dose of rocuronium. Ten minutes later she developed facial swelling, increased pulmonary pressures and hypotension requiring vasopressors. She had previously undergone general anesthesia multiple times without any adverse reactions.

Diagnosis

Both patients were diagnosed with and evaluated for perioperative anaphylaxis due to their presentation and clinical findings.

Testing

Both patients underwent skin testing for the agents that were used during their procedures, except for the nuclear medicine isotopes. Patient 1 was also skin tested for penicillin and cephalosporins. Patient 1 was positive for isosulfan blue dye and midazolam, whereas patient 2 was only positive for isosulfan blue dye. Both patients were also evaluated for latex allergy with negative results. Local anesthetic skin testing and challenges were negative. Tryptase or histamine levels from the reaction were not available, but their basal tryptase levels were within normal limits.

Treatment

Surgical and anesthesia teams for both patients were provided with a premedication regimen consisting of prednisone and diphenhydramine. Drugs that can cause direct mast cell degranulation were recommended to be infused slowly. In light of the skin test results, both teams were recommended to use alternative agents for isosulfan blue dye and nuclear medicine isotopes. For patient 1, avoidance of midazolam was also recommended.

Patient Outcomes

Both patients underwent bilateral mastectomy and reconstruction following the above described recommendations with uneventful anesthesia.

Lessons Learned

Perioperative anaphylaxis cases are challenging due to multiple agents being infused in close proximity. Most common causes include antibiotics, neuromuscular-blocking agents and chlorhexidine. Our cases highlight the importance of considering not just these common causes but every agent as a possible culprit in allergic reactions and expanding skin testing to include as many of the suspected drugs as possible. Mast cell degranulation markers are helpful in definitive diagnosis of perioperative anaphylaxis and efforts in raising awareness of this in other medical specialties is important.





The Case of the Swollen Face: An Unknown Variant of Angioedema in SLE

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Summary

C1 Inhibitor deficiency can be either hereditary or acquired (C1INH-AAE), with the hereditary form (HAE Types 1 or 2) being significantly more common. The acquired form of C1 Inhibitor deficiency has been recognized as related to lymphoproliferative disorders, or from the presence of auto-antibodies to C1-Inhibitor. We have identified and present a possibly new variant of acquired angioedema associated with autoimmune disorders like SLE.

Patient Presentation

A 73 y/o F patient with a past medical history significant for HTN, SLE associated with lupus nephritis, who presented to the hospital with lip and facial swelling found to have laryngeal swelling requiring intubation after presentation. The patient had presented with similar complaints 2 years and 3 years previous to this admission and was initially labeled as hereditary angioedema. The primary team consulted our allergy/immunology service for advice regarding monitoring and medication management in this patient with angioedema. We evaluated the patient in the inpatient setting and then followed up in the outpatient clinic for additional investigations. At the time of consultation, the patient had received C1 esterase replacement 1500 units. We had reviewed her current and previous episodes as below: 2016- Patient presented with airway angioedema that required a tracheostomy. Due to this being her first episode, patient was thought to be having angioedema related to her ACEI, hence her ACEI was discontinued. She also received steroids and antihistamines without any C1 esterase inhibitor replacement.

2017- Angioedema started with right sided facial swelling that progressed to lip edema and with laryngoscopy that showed evidence of airway edema but with patency.

2019 (current episode) - Angioedema was involving lip, face, and laryngeal area requiring intubation. On review of the patient's family history, the patient suggested there may be some family history of similar episodes, however, this could not be confirmed.

Diagnosis

Hereditary angioedema (HAE) is a rare disorder that is a result of C1 esterase inhibitor protein deficiency (85 percent of the cases Type I) or malfunction (15 percent of cases type II). Typically, it is considered when there is a history of recurrent episodes of laryngeal edema/angioedema without evidence of urticaria. Often there is family history of angioedema but it may occur spontaneously. There may also be a history of abdominal pain/vomiting. Patients with a low C4, family history of angioedema with a low C1 inhibitor protein level is likely to be HAE type 1, whereas those with impaired C1 function represent type 2 HAE. If there is no family history, late age at presentation, and C1q being low, then acquired angioedema is considered more likely. If C4 is low and C1 inhibitor protein is normal or elevated with normal function then other non-HAE causes of C4 consumption are considered.

In our patient, the diagnosis was difficult due to the initial presentation in 2016 of low normal C4, low C1 esterase inhibitor with normal function, and normal C1q a profile that does not clearly fit into any of the well-established categories. The 2017 and 2019 episode had a low C4 with just below normal C1 antigen

levels and normal C1 function. A literature review revealed a single report of a new type of acquired C1 inhibitor deficiency thought to be associated with systemic lupus erythematosus¹. This description of a series of 3 patients with SLE showing evidence of angioedema without significant SLE activity at the time of the disease, and a positive effect of steroids, fits well with our patient. However, in this report, there was also evidence of C3 and C4 consumption which was only slightly seen in our patient with the C4 level being low but the C3 levels being normal. This makes our patient unique and suggests that there may be a varying degree of complement consumption in this possibly new variant of acquired angioedema in SLE.

Testing

Please refer to TABLE 1 for a review of the patient's labs from the 3 episodes.

Other workup was negative for Cardiolipin antibodies (IgA, IgM, and IgG), DRVVT, and a double stranded DNA antibody) during the 2019 episode.

Treatment

In 2019, the patient was given terbutaline 0.25 mg x 1, methylprednisolone 125 mg x 1, diphenhydramine 50 mg x 1, famotidine 20 mg x 1, dexamethasone 8 mg x 1, and C1 esterase inhibitor injection 1500 units. Initially there was no distinctive diagnosis of acquired angioedema due to the lack of serological testing, hence the patient was initially treated with C1 esterase inhibitor replacement. Patient was also placed on steroids along with anti-histamine therapy by the primary team, which had been continued given the thought that histaminergic angioedema may still be in the differential. Patient was given the recommendation by our team to plan to get a bradykinin receptor antagonist for acute management should she have any further acute episodes of angioedema.

Patient Outcomes

After intubation and initial treatment, the patient was continued on dexamethasone 8 mg q8h during the hospital course and eventually was extubated on day 4 of admission. She was discharged on a steroid taper of prednisone 60 mg/day for 5 days and then reduced 10 mg every 5 days. On outpatient follow up, the patient was advised to complete the prednisone taper and provided a prescription for icatibant (bradykinin receptor antagonist) to use for acute attacks. She was advised to avoid ACE inhibitors and NSAIDs. Laboratory studies were repeated approximately 2 weeks after the episode and we maintained close outpatient follow up. Labs 2 weeks after 2019 reveal reduced C1 antigen and function with normal C4 levels.

Lessons Learned

We believe that our adult female patient with slightly low C4, low C1 esterase inhibitor levels, and without any clinical or biologic evidence of lupus activity represents an under reported subset of acquired angioedema. We refer to a previously published report of 3 patients with SLE that suggests this possibly new variant related to complement consumption, but the patient we present possibly sheds a new light on the pathophysiology related to this variant. This case elucidates the importance of recognizing and identifying an uncommon variety of C1INH-AAE in SLE patients for timely, cost-effective, and potentially life-saving management.

TABLE 1	2 Weeks After Episode	2019 (after replacement)	2019 (before replacement)	2017 (after replacement)	2016 (no replacement)
C3 (normal 81-157 mg/dL)		138.2	115		
C4 (normal 13-39 mg/dL)	15	19.43	1.65	5	14
C1 INH Level (normal 21-39 mg/dL)	8	20		20	11
C1 INH Function (normal >68 percent)	50	81		90	71
C1q (normal 5.0-8.6 mg/dL)	7.6			6.5	6.5

NOD2 Mutation in a Pediatric Patient Presenting With Recurrent Infections

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Summary

An 8-year-old male presented with a 3-year history of recurrent respiratory infections, dermatitis resistant to topical steroids, oral candidiasis, *Helicobacter pylori* antral gastritis resistant to multiple antimicrobials, *Clostridium difficile* enteritis and non-typhoid *Salmonella* gastroenteritis with subsequent bacteremia. Immunologic work up was overall normal except for persistent eosinophilia, elevated IgE, and suboptimal pneumococcal antibody titers, which improved after receiving Pneumovax-23. Based on his significant infection history despite a relatively normal immunologic evaluation, genetic testing was performed and revealed the presence of a heterozygous nucleotide-binding oligomerization domain containing 2 (NOD2) mutation, with known association to Crohn's Disease. Recent literature has described the association of NOD2 mutations with enteropathy and autoimmune manifestations in patients with Common Variable Immunodeficiency (CVID). In addition, NOD2-associated autoinflammatory disease (NAID) is an emerging entity. Our patient is unique in that he presented with recurrent infections which, despite having normal immunoglobulin levels, improved significantly on intravenous immunoglobulin (IVIG).

Co-Authors:

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Patient Presentation

The patient initially presented to the immunology clinic at 5 years of age after being hospitalized for *Salmonella* bacteremia. Prior to admission, he presented to his pediatrician's office with a 1-month history of intermittent fevers, vomiting and non-bloody diarrhea. A stool culture obtained at that time was positive to *Clostridium difficile*, *Salmonella* and astrovirus. His gastrointestinal symptoms improved with metronidazole, however he remained febrile and was subsequently found to have non-typhoid *Salmonella* bacteremia. After resolution of his acute illness, he developed *Helicobacter pylori* that was resistant to multiple courses of antibiotics. Evaluation for inflammatory bowel disease was negative. Additional infectious history included multiple upper respiratory infections, ear infections, episodes of cellulitis, and oral candidiasis. He also had previously been evaluated by a pulmonologist for a chronic productive cough and had a normal bronchoscopy, CT scan, and sweat test.

Upon presentation to our clinic, the patient's physical exam was normal except for a non-specific localized dermatitis on his arms. Initial immunologic work up revealed an absolute eosinophil count of 725K/uL, normal lymphocyte subpopulations, normal total IgG (650 mg/dL), IgA (163 mg/dL), and IgM (89 mg/dL), and elevated IgE (2779 IUg/dL). Vaccine titers were protective to *Haemophilus influenza* type B, Tetanus and Diphtheria. Vaccine titers to *Streptococcus pneumoniae* were protective to 2/14 serotypes which improved to 14/14 serotypes after administration of Pneumovax-23. Lymphocyte proliferation studies revealed absent responses to candida and tetanus toxoid with normal responses to mitogens. Allergy testing to indoor and outdoor inhalants was negative.

Diagnosis

Molecular diagnosis revealed the presence of a heterozygous NOD2 mutation, asn852ser. Experimental studies have shown that while the missense change does not interfere with normal membrane localization, it impairs MDP-induced NF- κ B activation.

Testing

Genetic testing was performed to help elucidate an underlying cause for the patient's atypical pattern of infections via an Invitae® Primary Immunodeficiency Panel.

Treatment

Based on the frequency and severity of infections in our patient, he was started on intravenous immunoglobulin replacement (400mg/kg/month).

Patient Outcomes

After being placed on immunoglobulin replacement over the past eighteen months, our patient has had a significant decrease in the frequency and severity of infections. He has only required antibiotics twice by his pediatrician (impetigo and inguinal lymphadenitis). He also developed molluscum contagiosum which self-resolved. He has not developed any atypical or severe infections and has remained asymptomatic from a gastrointestinal standpoint. Of note, the patient has developed a right sensorineural hearing loss from unknown etiology. We recently attempted to do a trial off of IVIG, but it was restarted due to recurrence of respiratory infections, chronic cough, malaise, and fatigue.

Lessons Learned

The NOD2 gene is mapped to chromosome 16q 12-21, and 128 NOD2 variants have been reported to date [1]. As part of the innate immune system, NOD2 acts as a cytosolic pathogen recognition protein to activate the cell or induce apoptosis [2]. Despite the previously recognized associations between NOD2 mutations, Crohn's disease, and NAID, there are few reports describing this mutation among patients presenting solely with recurrent infections. Disease-associated NOD2 variants may predispose patients to intestinal inflammation and subsequent infections, but further studies are needed to elucidate this pathway and to evaluate the possible role of NOD2 in extraintestinal infections. In addition to this unique presentation which led to the discovery of a NOD2 mutation, our case highlights the significant benefit that immunoglobulin replacement may have in patients without a clearly defined humoral immunodeficiency.