Infant with Idiopathic Congenital T-cell Lymphopenia, Ulcerated Rash, and Multiorgan Cystic Changes of the Lung and Biliary Tree

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Summary
The T-cell receptor excision circles (TREC) assay evaluates for Severe Combined Immunodeficiency (SCID) by detecting low or absent naive T-cells on the newborn screen. This assay can also identify non-SCID infants with T-cell lymphopenia allowing for initiation of prophylactic, lifesaving treatments. We present the case of an infant with the following clinical triad: idiopathic congenital T-cell lymphopenia, widespread ulcerated rash, and multiorgan cystic changes of the lung parenchyma and biliary tree. The TREC count was undetectable. Lymphocyte subset revealed low T-cells and NK-cells. B-cell phenotyping showed no switched memory cells. Mitogen proliferation assay was normal. Infectious workup was negative. Whole exome sequencing showed six variants of unknown significance. He was treated with IVIG and prophylaxis for opportunistic infections. His lymphopenia, rash, and cystic changes all improved. This case depicts a favorable clinical course of a rare disease process that has never been described in the literature to our knowledge.

Patient Presentation
A 34-week male infant was born with a diffuse ulcerated rash of the torso, trunk, extremities, palms, and soles. Immediately after birth he had respiratory distress. Pregnancy was complicated by prolonged rupture of membranes and meconium stained fluid. There was no prenatal history of infections. There was no family history of immunodeficiencies.

Diagnosis
The infant had absent TRECs with ALC of less than 500 x10^6/L, but his mitogen proliferation assay was normal, so he did not meet the criteria for SCID. His WES was unyielding, and he had no evidence of phenotypic dysmorphisms that were consistent with other T-cell lymphopenia associated diseases. Testing was negative for infectious or congenital causes to explain his clinical picture.

Testing
Newborn screen showed absent TRECs. Repeat screen one week later and at 37 weeks corrected age showed continued absent TRECs. Absolute Lymphocyte Count (ALC) was 340 x10^6/L. Flow cytometry showed low T-cells and NK-cells (see photo 1). B-Cell phenotyping showed no switched memory CD19+CD27+IGD- at 0.00% (normal reference range 0.1 - 1.9%) and low transitional B-cells CD19+CD24++CD38++ at 0.4% (normal reference range 8.3 - 15.8%). T-cell mitogen proliferation assay was normal. Max proliferation of PWM as % CD3 was 34.4%. Max proliferation of PHA as % CD3 was 75.1 %. Initial immunoglobulins were IgG-262 mg/DL, IgA-7 mg/DL, IgM<30 mg/DL, and IgE<2 mg/DL. No thymus was visualized on imaging, however the CD4 Recent Thymic Emigrants (RTE) test was 91.7
cells/mcL which is suggestive of thymic tissue present. Skin biopsy was nonspecific with no evidence of infection, and CD1a staining was normal to rule out Langerhans Cell Histiocytosis (LCH). Imaging showed bilateral cystic lung disease (see photo 2), hepatosplenomegaly, and choledochal cyst. Infectious work up was negative for bacterial, viral, and fungal infections from respiratory aspirate, CSF, urine, blood, and skin. Additional screening was negative for TORCH infections (Toxoplasmosis, Syphilis, Varicella, Parvovirus, Rubella, Cytomegalovirus, Herpes Simplex Virus), Epstein-Barr virus, Human Immunodeficiency Virus, Pneumocystis jiroveci pneumonia, Legionella, Adenovirus, Enterovirus, Human Herpesvirus 6, Hepatitis B, and Hepatitis C. Karyotype was normal. Pulmonary Fibrosis and Surfactant Dysfunction Disorders genetic sequencing panel was negative. Genetic testing of the primary immunodeficiency panel showed six variants of unknown significance (VUS) that include: AP3B1 c.1868C>T (p.Ser623Phe) heterozygous, CD79A c.371G>A (p.Arg124His) heterozygous, IFNGR2 c.308C>T (p.Ala103Val) heterozygous, LYST c.2438G>A (p.Arg813Gln) heterozygous, PTPRC c.1441A>G (p.Lys481Glu) heterozygous, and TMC8 c.25T>C (p.Ser9Pro) heterozygous. Whole exome sequencing (WES) showed the same six VUS.

**Treatment**

Due to his ulcerative rash and respiratory failure, after birth he was started on broad spectrum antimicrobials. His regimen was changed to prophylaxis for opportunistic infections including Acyclovir, Bactrim, and Fluconazole after the initial infectious work up was negative and he continued to demonstrate profound lymphopenia. He was started on IVIG at one week of life due to his hypogammaglobulinemia and lack of B cell Memory Cells, and continued infusions every three to four weeks. Respiratory support was weaned from mechanical ventilation to high flow nasal cannula (HFNC) and eventually nasal cannula (NC) support. Intermittent IV steroids were administered for his cystic lung disease, without clear associated response.

**Patient Outcomes**

He remained in the hospital for six months. His widespread rash improved. He was without infection for the duration of his time except for a urinary tract infection with coagulase-negative staphylococcus. His lymphopenia gradually improved. He was discharged from the hospital at six months on IVIG, antibacterial, anti-viral, and anti-fungal prophylaxis. At his one month follow up he was breathing on room air. His ALC was 4802 x106/L with increased T-cells and NK-cells (see photo 1). Immunoglobulins were IgG-618 mg/DL, IgA-7 mg/DL, and IgM-17 mg/DL, while maintained on IVIG infusions. B-cell phenotyping showed increased switched memory cells CD19+CD27+IGD- at 0.3%. Cystic degeneration of both the lung parenchyma (see photo 3) and biliary tree improved significantly. He remained without infection; hence his anti-bacterial, anti-viral, and anti-fungal prophylaxis were discontinued.

**Lessons Learned**

Early identification of this patient’s lymphopenia based upon the TREC assay allowed for perinatal treatment with prophylactic anti-microbials and IVIG. This treatment may have prevented respiratory infections while the cystic degeneration of his lungs was allowed to heal. Even though clinical testing did not reveal an underlying etiology and testing showed no signs of infection, we hypothesize that there could have been an undetectable intrauterine infection that resulted in the observed lymphopenia and cystic changes. This is the first report of an infant with the following clinical triad: idiopathic congenital T-cell lymphopenia, widespread ulcerated rash, and multiorgan cystic changes of the lung parenchyma and biliary tree with no underlying known genetic mutation to explain his presentation. This case depicts
a favorable clinical course of a rare disease process that has never been described in the literature to our knowledge.
Cytarabine Toxic Erythema of Chemotherapy in a Pediatric Patient

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Summary
A 10-year-old Hispanic male with newly diagnosed acute myeloid leukemia developed worsening rash within one week of starting induction chemotherapy with cytarabine, daunorubicin, and etoposide, along with multiple new drugs including antibiotic, antiepileptic, and antipsychotic agents. Despite removal of likely offending agents, rash persisted and worsened, developing into large edematous purpuric plaques on the face, trunk, and extremities with sparing of the skin folds. This progressed to bullous eruptions, desquamation, and resolution. The patient’s course is consistent with toxic erythema of chemotherapy (TEC) secondary to cytarabine, which to our knowledge has not been reported in the pediatric population.

Patient Presentation
A 10-year-old male was admitted for new diagnosis acute myeloid leukemia following presentation with ear drainage, fatigue, and weight loss. He was started on induction chemotherapy with cytarabine, daunorubicin, and etoposide. He also received cefepime and vancomycin for neutropenic fever and was started on trimethoprim-sulfamethazole for pneumocystis prophylaxis. Other new medications included levetiracetam and olanzapine.

Patient developed a non-pruritic, blanching, erythematous macular rash on his face, chest, and bilateral upper and lower extremities 5 days after initiating cytarabine (and 6 days after initiating all new medications). The rash was circumscribed in the face and neck (most prominent on the mandible bilaterally, photo 1), diffuse on his trunk and extremities, and sparing of the palms and soles. He had no mucosal involvement and negative nikolsky sign. Laboratory work up, including chemistry, LFTs, and CRP were within normal limits; the patient was severely pancytopenic with no eosinophilia. Given the necessity of his therapies and limited nature of the rash, the patient was initially continued on his medications and managed with cetirizine and topical steroids.

Over the course of the next two weeks, the rash worsened with development of raised, confluent purpuric papules along with edema throughout his face, trunk, and extremities, with continued sparing of the skin folds and palms and soles (photos 2 and 3). These were non-painful and non-pruritic. He continued to have no mucosal involvement. He had completed cytarabine, daunorubicin, and etoposide by day 8 of the rash. Cefepime, vancomycin, and olanzapine were stopped as possible offending agents. By the third week of onset, the patient developed widespread desquamation. New bullous eruptions occurred on the medial and intertriginous areas of the hands and lateral aspects of the feet. Complete resolution occurred by four weeks.

Diagnosis
His presentation, clinical course, and morphology of rash was consistent with toxic erythema of chemotherapy (TEC) to cytarabine, an uncommon limited skin reaction that has been reported in the adult population. Differential diagnosis also included atypical drug reaction with eosinophilia and systemic symptoms (DRESS), delayed hypersensitivity drug reaction, and Steven Johnson Syndrome/Toxic Epidermal Necrolysis. Regarding DRESS, the timing of the initiation of new medications and the onset of rash were not consistent. He did have transaminitis and pleural effusion during his
course, but this was attributed to his oncological therapy and fluid resuscitation. Furthermore, his regiSCAR score was 1, inconsistent with DRESS.

**Testing**
The patient had skin biopsy performed, which displayed focal vacuolar interface of the basal epidermal layer, occasional epidermal neutrophils, superficial perivascular lymphocytic infiltrate with rare eosinophils, and dermal edema and extravasation of erythrocytes. The findings were non-specific and suggestive of drug exanthema.

Laboratory studies including CBC and differential, chemistry, liver function tests, inflammatory markers, and HHV6, EBV, and CMV was performed due to concern for atypical DRESS. CBC showed pancytopenia and the remainder of the lab work was normal other than transiently elevated AST and ALT (in the range expected with induction chemotherapy).

**Treatment**
2 weeks after onset, he was started on methylprednisolone 1mg/kg, which was transitioned to oral steroids and tapered over the course of 30 days. He remained on cetirizine and topical steroids.

**Patient Outcomes**
The rash was responsive to steroid therapy and improved. There was complete resolution within one month.

There was recurrence in the second cycle of induction immediately upon completion of a 7-day course of cytarabine. The patient experienced erythema and desquamation of the hands and feet; the course was limited and was managed with topical steroids.

**Lessons Learned**
Cutaneous manifestations of cytarabine are common, but presentation as a papular purpuric eruption or violaceous erythema is rare.

Cases of TEC secondary to cytarabine have been sparsely reported in the adult population. In a case series performed by Ruben et al, the rash presents an average of 8.6 days after initiation of cytarabine, but can occur upon completion of chemotherapy as well (1). The rash morphologically has been described as beginning as erythematous papules that evolve into purpuric papules originating on the upper and lower extremities, chest, and axilla (1). Common areas of involvement are the abdomen and lower extremities, upper extremities, chest, back and affinity for the groin, axilla, skin folds, neck, bilateral ears, hairline, and scalp (1). The rash resolves with desquamation, which occurs approximately 15 to 30 days after onset (1). It should be noted that while our patient had involvement of the mandible and neck, he had sparing of the skin folds, which is uncommon for TEC. The histopathology findings tend to be variable and non-specific, but lymphocytic infiltration is common (1). Of a sample size of 16 patients, half (8) had received cytarabine previously, with 4 having documented prior cutaneous manifestations. Among a small sample size (n=4), half of patients (2) who received subsequent courses of cytarabine experienced recurrence (1). The etiology of TEC is unknown but the variability of exposure and recurrence suggests against an immunological process.

Despite its prominent presentation, TEC is self-limiting and benign without systemic manifestations. It can be mistaken for more severe reactions, leading to unnecessary investigations and interventions, including discontinuation of critical therapies. Cytarabine should not be stopped, nor should the development of a TEC rash preclude subsequent treatment. In our patient, recurrence of the rash was
successfully managed with topical steroids. In summary, we hope that this case will raise the awareness of TEC in patients treated with cytarabine that develop similar cutaneous findings. To our knowledge, this patient’s case is the first reported incident of TEC secondary to cytarabine in the pediatric population.

Cyclosporine is effective in a patient with severe, chronic spontaneous urticaria, refractory to antihistamines and omalizumab

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Summary
Many patients with chronic spontaneous urticaria (CU) have symptom resolution with antihistamine monotherapy. Patients who remain symptomatic require step-up therapy. Omalizumab is now most commonly chosen because of its favorable side-effect profile. Here we report a case to illustrate the clinical effectiveness of cyclosporine over omalizumab. Our patient is an adolescent female, with refractory CU and angioedema. She had a fleeting response to antihistamines, so we initiated omalizumab. Because she showed suboptimal response on maximal omalizumab dosing (300mg, every 2 weeks), we started cyclosporine. She had full, sustained resolution of CU symptoms, within one week, without any noted adverse effects. This case suggests that cyclosporine should be considered early in some children with CU who require step-up therapy.

Patient Presentation
Our patient is a seventeen-year-old female who developed sudden, diffuse urticaria, which started on her buttocks and extended to her abdomen, legs, arms and face. Lesions were raised, erythematous, pruritic, and continued for twenty-four hours before resolution. She presented to an outside allergy clinic, was diagnosed with acute urticaria and started cetirizine. Her symptoms resolved for one week, then returned. These episodes initially happened weekly, but progressed to daily over the next two months. Symptoms also increased in severity, to include eyelid, lip, and ear swelling, diffuse myalgia and joint pains. Her allergist diagnosed CU, added daily ranitidine, and referred her to dermatology. Dermatology evaluation was reassuring, with normal CBC, CMP, ESR, UA. HIV antigen/antibody, hepatitis B surface antigen and surface antibody, and hepatitis C antibody testing were negative. Her skin biopsy showed urticaria pigmentosa. She started fexofenadine and topical corticosteroids. Days later, she presented to the emergency department for urticaria, angioedema, and sensation of throat swelling. She received an epinephrine injection, which resolved her angioedema. Despite maximal antihistamine therapy, she continued to have daily urticaria and angioedema. Dermatology initiated an oral course of prednisone, which resulted in some symptom reduction. Her allergist added montelukast and referred her to rheumatology. Rheumatology evaluation showed no abnormalities in CBC, LFTs, ESR, CRP, urinalysis, lymphocyte enumeration, C-ANCA, P-ANCA, atypical pANCA, C3, C4, CH50, C1Q binding, or C1 esterase inhibitor function. Due to low hepatitis B titer, they obtained additional vaccine titers. She maintained adequate titers to all vaccines except for S. pneumoniae, diphtheria, and tetanus. These findings prompted a referral to our immunology clinic. Upon presentation, she continued to have daily episodes of urticaria and angioedema despite taking cetirizine 10mg BID, fexofenadine 180mg BID, ranitidine 150mg BID, monteleukast 10mg qHS, prednisone 30mg BID and topical corticosteroids. Our patient had no prior urticarial episodes, no food or environmental allergies and no asthma. She received all age-appropriate immunizations. Family history is remarkable for mother with allergic rhinitis, sister with atopic dermatitis and allergic rhinitis, father with an adverse reaction to sulfa antibiotics. There is no family history of CU or autoimmune disease.
Diagnosis
We agreed with prior diagnosis of CU, given the presence urticaria and associated angioedema episodes, occurring at least several times per week for three months. Extensive work-up including infectious and autoimmune evaluation, had not identified an underlying cause, classifying it as spontaneous CU.

Testing
Former evaluations did not reveal an underlying etiology for her CU. Our laboratory evaluation was also unrevealing, with negative EBV and CMV DNA PCRs. Immunoglobulins (IgG, IgA, IgM, IgE) and tryptase were within normal limits, and IgE antibody (anti-IgE IgG) was not detected. ANA, TSH, free T4, C3, and C4 were normal.

Treatment
Following practice parameters, we considered step-up therapy and chose omalizumab 300mg, given its demonstrated utility and side-effect profile. She received four doses at four week intervals with moderate symptom improvement. However, she had recurrent exacerbations with each attempt to wean systemic corticosteroids. By increasing the frequency of omaluzimab to every two weeks, we were able to wean her steroids off. However, she continued to experience symptom breakthrough, during stressful events or illness. Due to suboptimal response to maximum omalizumab therapy, we initiated cyclosporine therapy (2.8mg/kg/day, divided BID). Baseline blood pressure and screening labs were obtained prior to starting cyclosporine.

Patient Outcomes
Her urticarial lesions faded significantly, within three days of starting cyclosporine, and her skin was clear by day seven. Moreover, she had no further angioedema, myalgia or joint pain. She was able to sleep through the night and attend school. After two weeks without breakthrough, we spaced omaluzimab to every four weeks. Our patient has remained symptom-free on omaluzimab and cyclosporine.

Lessons Learned
Our case suggests that some patients with refractory CU will have better clinical improvement with cyclosporine than omalizumab. This suggests there may be a subset of patients where cyclosporine should be considered early, perhaps even prior to omalizumab. Cyclosporine is associated with hypertension and nephrotoxicity, and thus requires laboratory monitoring. However, low dose cyclosporine, as used for CU, is generally well tolerated. Some patients report GI symptoms while on therapy, which resolve by decreasing the medication dose.

Systemic CU symptoms (most commonly joint paint, headache, GI issues) correlate with more severe disease and the need for therapy escalation. Studies have shown an association between systemic symptoms, disease severity, and autoantibodies to IgE FceRI or IgE5,6. One study showed a correlation between higher chronic urticaria index and responsiveness to cyclosporine7, suggesting that this may be a better step-up therapy than omalizumab in this patient subset. Other studies demonstrate that elevated IgE predicts good clinical response to omalizumab8. Our patient had low IgE (7kU/L), suggesting omalizumab may not be the best initial step-up treatment.
Overall, this case demonstrates a need to consider starting cyclosporine before omalizumab, when stepping up therapy in adolescent patients with severe CU, systemic symptoms, and low IgE. Clinicians should always balance potential medication benefits and harms, and initiate the best medication as early as possible. Further studies are needed to elucidate which patients may benefit from early introduction of omalizumab vs. cyclosporine as step-up therapy for refractory CU.

References
CMV encephalitis following subdural hematoma in the setting of Good syndrome

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Summary
Good syndrome is a primary immunodeficiency characterized by low immunoglobulin levels with reduced or absent B cells and associated thymoma. We present a case of an 81-year-old woman with a history of Good syndrome, complicated by recurrent skin and sinopulmonary infections, status post thymectomy and on immunoglobulin replacement, who presented to the emergency department (ED) with a right subdural hematoma. Her hospital course was complicated by persistent fluid re-accumulation in the subdural space requiring multiple surgical evacuations. Subsequent subdural membrane biopsy revealed the presence of cytomegalovirus (CMV) via immunohistochemical staining. Quantitative real-time PCR on peripheral blood confirmed a high CMV viral load. The patient’s neurologic status improved significantly after treatment with IV ganciclovir. She remains on oral valganciclovir suppressive therapy indefinitely.

Patient Presentation
An 81-year-old woman with a history of Good syndrome, complicated by recurrent skin and sinopulmonary infections, status post thymectomy and on immunoglobulin replacement, presented to the ED with a one-week history of constant diffuse headache. The patient had been in her usual state of health until one week prior to presentation, when she started experiencing generalized headaches which worsened over the course of the week. The patient denied associated fevers, chills, neck stiffness, visual changes, paresthesia, vertigo or motor weakness. Her only other symptoms had been fatigue and mild urinary urgency and frequency which occurred 11 days prior to presentation. The patient was diagnosed with thymoma five years prior to this episode following a 7-day history of productive cough and associated fever, chills and myalgia leading to chest x-ray showing a left lower lobe pneumonia and a mediastinal mass. Chest CT showed a lobulated soft tissue mass in the anterior mediastinum which was confirmed to be a thymoma following median sternotomy, thymectomy, and surgical pathology evaluation. The patient was diagnosed with Good syndrome following multiple hospital admissions for intravenous antibiotics to treat Achromobacter xylosoxidan bacteremia and cellulitis. The patient’s Achromobacter bacteremia was complicated by recurrent empyema requiring VATS and decortication. These episodes prompted an evaluation for primary humoral immune deficiency which revealed undetectable immunoglobulin (Ig)A, IgM, and IgE and low IgG (89 mg/dL), undetectable tetanus antibody titers, and a frequency of CD19+ cells of <1% with an undetectable absolute CD19+ cell count. Her past medical history was also significant for vitiligo, achalasia, hypertension, cataracts, untreated CMV esophageal ulcer, Candida esophagitis and onychomycosis. Medications included weekly subcutaneous immunoglobulin replacement therapy which had significantly reduced her infectious burden until this recent presentation to the ED. Physical examination revealed elevated blood pressure to 189/86 and intact neurologic function. CT head without contrast showed a right frontal and temporal subdural hematoma causing mass effect with 11mm of right-to-left midline shift (Photo 1). The patient underwent emergent evacuation of the hematoma. Her post-operative course was complicated by persistent and recurrent fluid accumulation in the subdural space requiring repeat evacuations. The
drained accumulations were non-bloody. Two weeks after the initial subdural hematoma drainage, the patient underwent subdural membrane biopsy in conjunction with fluid drainage. Immunohistochemical stain for CMV was positive. Due to fluctuating neurological status and inability to protect her airway, the patient was intubated. Allergy/Immunology was consulted for further recommendations.

**Diagnosis**
The re-accumulation of subdural fluid was attributed to inflammatory edema in the setting of persistent CMV encephalitis. The explanation of how CMV reached the central nervous system (CNS) was initially unclear. CMV retinitis has been described in patients with Good syndrome (Sen HN et al., 2005; Popiela M et al., 2009; Mateo-Montoya A et al., 2010). Because of concern that the patient developed CMV retinitis that spread to the CNS, Ophthalmology was consulted. A fundoscopic exam was normal, thereby ruling out CMV retinitis and avoiding the need for intravitreal anti-viral therapy. Thus, our working diagnosis was that untreated CMV esophagitis led to CMV viremia, seeding the CNS in the setting of the initial subdural hematoma.

**Testing**
CMV infection has been reported as an infectious complication of Good syndrome (Tarr PE et al., Medicine, 2001). This patient’s history was notable for untreated CMV esophagitis, diagnosed by immunohistochemical staining of an esophageal biopsy in 2017. A peripheral blood quantitative CMV PCR revealed viremia with a viral load of 160,438 IU/ml. Since anti-viral immunity typically involves cell mediated immune responses, flow cytometry, cytotoxic T-lymphocyte (CTL) functional assay, NK cell functional assay, and mitogen-stimulation proliferation studies were obtained to assess for NK and T-cell defects. Lymphocyte flow cytometry panel showed CD4+ T cell lymphopenia with an absolute CD4 count of 285 and CD19+ cell frequency of <1%. CTL and NK cell functional assays were normal. Mitogen studies also indicated adequate response to phytohemagglutinin (PHA).

**Treatment**
In consultation with Infectious Disease, we considered several treatment options including continued immunoglobulin replacement therapy and (1) intravenous (IV) anti-viral medication alone, (2) IV anti-viral medication plus CMV-specific IgG replacement, (3) IV anti-viral medication plus intrathecal CMV-specific IgG replacement. After weighing the risks and benefits of each treatment option, including the potential for thrombosis and significant intracranial fluid shifts with the introduction of intrathecal CMV-specific IgG in the setting of subdural fluid accumulation and brain edema, we opted for treatment with IV ganciclovir alone.

**Patient Outcomes**
Initial improvement in the patient’s neurological status was noted after 10 days of IV ganciclovir. The patient responded well to six weeks of IV ganciclovir; her mental status significantly improved over next 4 weeks. After 6 weeks of treatment, a repeat CMV PCR revealed a near 1000-fold decrease in viral load to 171 IU/ml. The patient subsequently transitioned to treatment dose oral valganciclovir for an additional 10 weeks. She remains on CMV prophylaxis with oral valganciclovir indefinitely, with dosing adjustments made based on her viral load which is followed every 3 weeks. The current viral load goal is 235 IU/ml. She also remains on subcutaneous immunoglobulin replacement therapy.
Lessons Learned

Recurrent sinopulmonary infections, particularly due to encapsulated organisms, are the most common type of infection seen in Good syndrome. The disease is also associated with autoimmune conditions such as myasthenia gravis, pure red cell aplasia, pernicious anemia, type I diabetes, and immune thrombocytopenic purpura (ITP). Good syndrome can be complicated by CMV infection, including CMV esophagitis, retinitis, and encephalitis (Kelleher et al., 2003 Tarr et al., 2001 and Assi et al., 2002). Notably, CMV infection can occur with mild CD4 T cell lymphopenia and normal cytotoxic T-cell and NK-cell responses and has even been documented in the presence of normal CD4+ T cell counts and normal T cell proliferative responses to PHA stimulation (Tarr et al., 2001).

It remains unclear why Good syndrome is frequently complicated by CMV infection. One possible explanation, supported by in vitro experiments by Matangkasombut et al., 2016 is that while the percentage of CMV-specific T cells in Good syndrome patients increases appropriately during active CMV infection with high CMV viral load, T-cell ability to produce IFN-gamma is reduced compared to T cells harvested during quiescence and low CMV viral load. This case illustrates that opportunistic infections, like CMV, traditionally associated with marked T-cell deficiencies, can occur in Good syndrome even in the setting of adequate T-cell numbers and functionality. Clinicians must be vigilant in aggressively treating CMV infection in Good syndrome patients. Moreover, clinicians should have a high suspicion for CMV encephalitis in the setting of altered mental status in a Good syndrome patient.
A child with poorly controlled asthma despite daily use of inhaled corticosteroids: How and when NOT to use the spacer.

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Summary
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It is well known that many patients use suboptimal inhaler technique. We report an unusual case of misuse of an AeroChamber in a child with poorly-controlled asthma despite treatment with budesonide inhaler.

A 7-year-old boy with a diagnosis of uncontrolled asthma presented to the National Jewish Health Pediatric Day Program. He was on daily inhaled corticosteroid, budesonide inhalation powder, with excellent adherence. Upon further questioning, he was using his budesonide inhalation powder by placing the Pulmicort Flexhaler into the AeroChamber opening (depicted below). Budesonide inhalation powder was discontinued. ICS-LABA MDI therapy (mometasone-formoterol) was started, and he was taught proper indications for an AeroChamber. His exercise tolerance and spirometry improved significantly as seen in daily spirometry for 8 weekdays. FEV1 gradually improved from 80% predicted to 112% predicted. His FEV1/FVC also improved from 71 to 88.

Patient Presentation
The child’s daily activities were highly restricted due to frequent episodes of exercise-induced dyspnea, and he had almost nightly asthma symptoms. These persistent asthma symptoms occurred despite excellent adherence with supervised daily budesonide as his controller therapy, 2 puffs once daily. Upon further questioning, mom mentioned that she was prescribed an AeroChamber for use with the budesonide inhalation powder and she “complied” with the instructions by placing the Pulmicort Flexhaler into the AeroChamber opening as depicted in the attached image below.

Diagnosis
Poorly controlled asthma due to inappropriate use of inhaler technique (inappropriate use of an AeroChamber).

Testing
His initial spirometry demonstrated airway obstruction with an FEV1 percent predicted of 80% and an FEV1/FVC of 71. His FEV1 reversed by 19% with bronchodilator treatment.

Treatment
Budesonide inhalation powder was discontinued. He was prescribed ICS-LABA MDI therapy (mometasone-formoterol) and taught proper indications and technique for use of his AeroChamber.

Patient Outcomes
Two days after ICS-LABA treatment was initiated, he passed an exercise challenge without any decrease in lung function. Daily spirometry was obtained for 8 weekdays after ICS-LABA treatment was initiated.
His FEV1 gradually improved from 80% predicted to 112% predicted. His FEV1/FVC also improved from 71 to 88.

Prior to initiating ICS-LABA therapy, he had had extremely low exercise tolerance and was home bound, mostly playing video games and watching videos on the cell phone. He spoke in short sentences only when necessary as he easily developed shortness of breath by talking. Within a week of initiating ICS-LABA therapy, he started to actively play outside, spending minimal time for sedentary activities at home. He also started to talk remarkably more to the point that his mom was bothered by his excessive talking throughout the day.

**Lessons Learned**

Spacer use is highly encouraged with aerosolized inhaler treatment for asthma. It optimizes coordination and lung deposition by slowing down the aerosol, and filters out larger aerosol particles reducing oropharyngeal impaction and gastrointestinal absorption. However, some health care professionals may not be aware that AeroChambers should not be used for powdered inhalers. Also, parents may be confused when they are prescribed different types of inhalers resulting in medications being used improperly. In this case, the confusion may have been heightened since the Pulmicort Flexhaler fits the AeroChamber aperture. It is important that health care professionals review proper inhaler technique with their patients and are aware of the different types of inhaler delivery devices to prevent misuse of the AeroChamber for powdered inhalers.
Severe refractory chronic urticaria and angioedema treated with rituximab

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Summary
This is the case of a 45 year-old female with severe chronic urticaria and angioedema, refractory to high-dose antihistamines, leukotriene receptor antagonist, cyclosporine, dapsone, and omalizumab. After an extensive workup, her urticaria and angioedema was determined to be most likely autoimmune in etiology, given mild hypogammaglobulinemia and a low complement component 4 (C4). She was therefore tried on rituximab, and had moderate improvement in her symptoms, which she is still receiving for maintenance therapy. Additionally, her lip swelling has been managed with as needed icatibant. This is an interesting case of rituximab used as maintenance therapy for chronic urticaria and angioedema.

Patient Presentation
A 45 year-old female with a past medical history of mild intermittent asthma, chronic arthralgias, migraines, and three years of chronic urticaria and angioedema presented with severe refractory urticaria and angioedema. She had been previously treated with high-dose antihistamines, leukotriene antagonist, cyclosporine, dapsone, ketotifen, and frequent high dose oral steroids. Her symptoms started three years prior to the current presentation, with diffuse hives, lip swelling, as well as intermittent throat tightness. Her hives occurred approximately every other day and were sporadic, resolving on their own after a few hours. She had lip swelling five to six times per month, and it would usually respond to large doses of antihistamines and oral steroids. Along with the lip swelling, she would sometimes also get throat tightness. On one occasion, she was intubated after receiving two injections of epinephrine, antihistamines, steroids, and C1 esterase inhibitor. She was not on ACE inhibitors or NSAIDs. She also had no identifiable food triggers.

Diagnosis
She was diagnosed with chronic urticaria and angioedema secondary to an autoimmune etiology. This was determined given her diffuse arthralgias, mild hypogammaglobulinemia, low C4, and lack of identifiable food triggers. It seemed that she had two underlying etiologies of her angioedema: first, histamine-mediated when it was present with concomitant urticaria, and second, bradykinin-mediated when it occurred alone. This was consistent with the frequent lack of response of her angioedema to epinephrine or high dose antihistamines. She had low C4, but normal C1 esterase inhibitor level and function, so hereditary or acquired angioedema were unlikely diagnoses.

Testing
When she had first presented, she underwent a full evaluation for food allergies, autoimmune causes, and hereditary and acquired angioedema. A panel looking for IgE mediated food allergies was negative. A total IgE was less than 2. Her baseline tryptase was 3. She had an IgG between 537 and 673 (normal 694 to 1618). Her IgA was normal and IgM slightly elevated at 263. She had protective antibody titers to tetanus and strep pneumoniae vaccines. Complement component 4 was slightly low at 14. Her C1 inhibitor level and function were normal. She also had normal ESR, ANA, and chronic urticaria (CU) index. To further evaluate for urticarial vasculitis, a skin biopsy was performed, which was consistent
with urticaria with “sparse diffuse interstitial infiltrate which includes scattered eosinophils and neutrophils. No vasculitis seen.” Next, she was worked up for idiopathic anaphylaxis, mast cell disorders, and underlying malignancies with 24 hour urine collections for prostaglandin D2, metanephrines, and bone marrow biopsy, which were all unrevealing.

**Treatment**
She was first placed on high dose antihistamines, a leukotriene receptor antagonist, and cyclosporine, which did not have much benefit. Due to hypogammaglobulinemia (IgG 694), intravenous immunoglobulin (IVIG) was tried, which led to post-infusion nausea, vomiting, and an increase in her urticaria. She was also placed on omalizumab for a brief period of time, given its primary indication in chronic urticaria, which did not reduce her symptoms or decrease the number of days she took off from work. Finally, she was placed on rituximab infusions, first receiving four weekly doses of 1000 mg. The rationale behind trying rituximab was based on its immunomodulatory effect in a patient with signs of immune dysregulation. She was maintained on montelukast and high dose antihistamines. Additionally, for her lip swelling, she was prescribed icatibant as needed for acute attacks, since the swelling was often refractory to antihistamines and epinephrine.

**Patient Outcomes**
Her urticaria and angioedema moderately improved, measured as a decrease in her number of days off from work, after the four initial rituximab infusions. Her cyclosporine was stopped about six months later but unfortunately, she had recurrence of her symptoms so it was restarted. She was eventually also taken off omalizumab after receiving about five injections due to ineffectiveness. She is currently maintained on rituximab 1000 mg infusions, two weeks apart, every six months, cyclosporine 150 mg twice a day in between rituximab infusions, cetirizine twice per day, montelukast daily, hydroxyzine daily, and ranitidine twice per day, with overall improvement in her symptoms from when she first presented. For acute angioedema attacks, she uses icatibant, which has been working well for her.

**Lessons Learned**
First, autoimmune causes of chronic urticaria and angioedema may not be easy to diagnose. In this patient, she had chronic arthralgias and a somewhat low C4, as well as no other apparent etiologies of her urticaria and angioedema. Since it was thought to be autoimmune, we tried immune modulatory therapies such as cyclosporine and rituximab, the latter of which seemed to help the most. Second, it is interesting that her angioedema did not respond to epinephrine at times, but did respond to icatibant, which is a selective bradykinin b2 receptor antagonist. This is evidence for the fact that in patients without hereditary angioedema, icatibant may still be effective.
Laronidase desensitization in a fluid-sensitive young child with Hurler syndrome post stem cell transplant

Author Stephanie Ann Kubala, MD
Training Program National Institutes of Health

Summary
Mucopolysaccharidosis type I (MPSI), Hurler syndrome, is a neuronopathic lysosomal storage disorder causing intralysosomal accumulation of glycosaminoglycans. Multiple organs, including liver, heart, brain, skeletal, lymphoid organs, and soft tissues can be affected. Hematopoietic Stem Cell Transplant (HSCT) is the standard of care for children with severe MPS1. Intravenous enzyme replacement therapy (ERT) with laronidase is typically used prior to transplant and allows some children who would otherwise be ineligible for HSCT to tolerate conditioning and transplant. We describe a case of anaphylaxis to laronidase in a 15 month-old boy 18 days post-HSCT with prior tolerance of laronidase and our successful adaptation of prior desensitization protocols to accommodate lower fluid volumes and allow for continued ERT. We aim to highlight the risk of ERT hypersensitivity and reaction during immune modulation and flexibility in providing therapeutic desensitization based on a patient’s unique qualities.

Patient Presentation
We were consulted on a 15 month-old boy due to concern for an anaphylactic reaction to his weekly laronidase infusion 18 days post unrelated umbilical cord transplant (UCBT). He was diagnosed with severe MPS1 at the age of 13 months, was initiated on ERT at 14 months, and had previously successfully tolerated 10 laronidase infusions with diphenhydramine and acetaminophen premedication. During his 11th ERT infusion, the patient developed angioedema, flushing, emesis, hypotension, tachycardia, and oxygen desaturation to 88%. He was treated with intramuscular epinephrine with rapid improvement in symptoms and vital signs, and he returned to baseline within 15 minutes. He received diphenhydramine, hydrocortisone, and ranitidine over the next 24 hours to prevent a biphasic reaction. The patient received platelets 4-5 hours prior to ERT infusion. In addition, the line may have been flushed during the infusion, which may have temporarily increased the infusion rate.

Diagnosis
His reaction was consistent with a Type 1 hypersensitivity because it was immediate, involved multiple organ systems (skin, GI, cardiovascular, and respiratory), and responded to epinephrine. However, non-immunologic anaphylaxis could not be ruled out as it was possible that he received a faster rate of the enzyme during the line change/flush, which could have precipitated non-immunologic anaphylaxis. Inconsistent with non-immunologic reaction is the fact that laronidase is an uncommon cause of non-immunologic anaphylaxis, unlike opiates, NSAIDs, vancomycin, chemotherapeutic agents, biologics, and radiocontrast media. Unfortunately, tryptase was not drawn within 2 hours of the event, so we were unable to confirm if his symptoms were due to true mast cell release.

Testing
At the request of the manufacturer (Genzyme; Cambridge, MA, USA), the Genetics team sent tryptase, C3, C4, total IgE, and anti-laronidase IgG and IgE to Genzyme about 24 hours after his reaction. Total IgG
was also sent. Mature tryptase was negative, but his total tryptase was elevated at 18 ng/mL (normal 1-11.4 ng/mL). Anti-laronidase IgE antibodies were detectable (6.29 kU/L (normal <0.35 kU/L)) and C3 and total IgE were elevated (159 mg/dL and 1572 IU/mL, respectively). IgG was normal at 534 IU/mL. Additionally, although he was awaiting engraftment (absolute neutrophil count of 0 K/mL), his absolute lymphocyte count (ALC) was within normal limits at 150 K/mL.

**Treatment**

Given that we were unable to distinguish between immunologic and non-immunologic anaphylaxis, and his relatively fragile status post-HSCT, we determined the safest option would be to initiate a weekly desensitization protocol. Due to his concurrent fluid sensitivity, a previously described desensitization protocol (total infusion volume ~300ml) was inappropriate for this young patient. Therefore, we adapted the protocol described by Rosenberg et al., 2016 and created a 3 bag, 12-step protocol resulting in a final infusion volume of 133ml (100ml of enzyme infusion and 33ml of carrier fluid given when infusion is less than 10ml/hr), given over 6.8 hours. He received methylprednisone, diphenhydramine, acetaminophen, ranitidine, and cetirizine before infusion. We advised resending tryptase levels within 1-4 hours if he were to develop a repeat reaction.

**Patient Outcomes**

Using the above described desensitization protocol, he was able to tolerate continued weekly ERT infusions. Unfortunately, he developed primary engraftment failure secondary to rejection of the initial UCBT. He recently underwent an additional matched unrelated donor transplant and was engrafting 16-days post-transplant. Per our Genetics colleagues, he will continue weekly ERT infusions of laronidase until normal endogenous production is noted, most likely around 3 months post-engraftment.

**Lessons Learned**

This case illustrates that anaphylactic reactions are unexpected, yet possible after bone marrow eradication and prior to HSCT engraftment. Our patient had an ALC of 150 K/mL and an elevated total IgE with normal IgG. Therefore, it is possible he had residual plasma cells producing laronidase-specific IgE that bound to mast cells within the tissues which were activated by the drug, or the drug complexed to an unknown molecule. These cells may have been masked and/or regulated by other cells that were depleted, allowing expansion of these enzyme-reactive cells within the bone marrow niche to produce enough antibody to have a clinical effect.

The utility of the anti-laronidase IgG and IgE in determining the cause of his episode is unclear; Genzyme reports that 99/102 (97%) of patients in clinical trials developed laronidase IgG. Post-marketing, ~1% of patients experienced severe infusion/allergic reactions and tested positive for laronidase IgE. Some of these patients have discontinued treatment and others have been successfully re-challenged, but data are unclear how re-challenge was performed. Whether these IgG/IgE antibodies are neutralizing, inhibitory, and/or able to trigger mast cell or basophil activation is unknown.

As mentioned above, there are two previous case reports of patients (an 11 year-old girl and a 11 month-old boy) with hypersensitivity to laronidase that describe successful desensitization protocols. We describe the use of a desensitization protocol in a 15 month-old boy with Hurler syndrome who developed anaphylaxis to laronidase shortly after a cord blood transplant. This patient represents at least the second successful use of this adapted lower volume protocol for smaller, fluid sensitive patients and could be considered in similar cases of hypersensitivity to continue enzyme safely during HSCT awaiting engraftment rather than discontinuation of ERT.
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Total infusion=100ml
Anaphylactic reaction to topical bacitracin.

Author Sevdenur Keskin MD, M Razi Rafeeq MD
Training Program The University of Toledo Pediatrics Residency

Summary
A 58-year-old female presented to allergy/immunology office practice for evaluation of a recent episode of anaphylaxis. Four weeks prior to her visit, she was treated at a hospital emergency department (ED) with generalized hives, hypotension, respiratory difficulty and gastrointestinal symptoms which occurred minutes after application of Neo-Polycin Ophthalmic Ointment (Neomycin, Polymyxin B and Bacitracin) to an open wound on her forearm.

Skin prick testing was performed using serial dilutions of Neo-Polycin and the three individual antimicrobial components in white petrolatum. Skin prick tests were positive to Neo-Polycin and bacitracin. Neomycin and polymyxin B skin prick tests were negative. Appropriate responses were noted to controls (histamine, saline and petrolatum). Skin prick tests to both Neo-Polycin and bacitracin in full strength were negative in 3 healthy controls.

We report a case of anaphylactic reaction to bacitracin with confirmed IgE-mediated hypersensitivity. Bacitracin, a commonly used over-the-counter topical antibacterial agent, can rarely cause anaphylaxis.

Patient Presentation
A 58-year-old Caucasian female was referred to Allergy clinic for further work up after having had an anaphylactic reaction. She applied Neo-Polycin ophthalmic ointment to an open wound on her left arm. After few minutes of application, she developed hives, angioedema, eye, throat and tongue swelling. She had chest tightness, difficulty in breathing, nausea and emesis episode. She felt faint and laid on a chair. EMS was called and upon arrival she was given IM epinephrine in thigh with IM Benadryl and supplemental oxygen. She was transferred to hospital ED where she was given IV fluids, oxygen supplementation, Pepcid and Solu-Medrol. She was fully conscious at arrival and was feeling better within 45 min. She was discharged home after 4 hours of observation with Epinephrine autoinjectors, oral antihistamines, prednisone and was referred to allergy/immunology office practice for consultation and evaluation.

Patient has allergic rhinitis and does not have any history of asthma, allergic reactions or anaphylaxis to any drugs, latex, foods or topical antibiotics. Her vitals were normal and her exam was unremarkable except eczema patches on both upper and lower extremities with superimposed skin infection.

Diagnosis
Patient’s clinical presentation at the time of event and her skin prick test results confirmed a diagnosis of IgE mediated bacitracin hypersensitivity which resulted in a recent anaphylactic episode.

Testing
Patient underwent skin-prick testing for inhalant allergens and was positive for tree pollens and negative for other inhalant allergens. Her serum tryptase while she was asymptomatic was within normal levels. Her serum IgE was normal at 53 IU/ml. Her CBC was unremarkable and vitamin-D level was normal.
Skin prick testing was performed using serial dilutions of Neo-Polycin and the three individual antimicrobial medication constituents in white petrolatum. Skin prick tests were negative to Neo-Polycin at 1:1,000 but positive at 1:100 and 1:10 dilutions. Skin prick tests were positive to bacitracin at 1:1,000 and 1:100 dilutions. Neomycin and polymyxin B skin prick tests were negative at 1:1,000, 1:100 and 1:10 dilutions. Appropriate responses to controls (histamine, saline and petrolatum) were noted. Skin prick tests to both Neo-Polycin and bacitracin in full strength were negative in 3 healthy controls.

**Treatment**
Patient was instructed to avoid bacitracin and prescribed epinephrine auto injector-two pack and liquid oral antihistamine to keep on hand.

**Patient Outcomes**
Patient had a follow up in the clinic and did well after discharge. She did not have any episode of anaphylaxis or allergic reaction with complete avoidance of topical antibiotics.

**Lessons Learned**
Bacitracin is a wildly used over-the-counter topical antibacterial medication to treat and prevent skin infections after minor burns or abrasions. It is also used for ophthalmic infections, as well as wound prophylaxis and irrigations during surgical procedures. Bacitracin and neomycin are known to cause an allergic contact dermatitis but IgE mediated reactions with bacitracin is extremely rare. There have been rare case reports in perioperative anaphylaxis and severe anaphylaxis were associated with bacitracin usage. Given the fact that bacitracin is commonly used as a single or combination topical antimicrobial, it is very important to be aware of bacitracin’s this rare but this potentially life-threatening adverse effect. Especially its usage on broken skin can cause increase systemic absorption with elevated serum levels which may result in anaphylaxis such as exemplified in our patient.
Effectiveness of a desensitization protocol in hypersensitivity reactions caused by paclitaxel

Author Rodrigo De la Cruz-Cruz
Training Program FIT allergy and immunology

Summary
Paclitaxel is a widely used antineoplastic drug. Hypersensitivity reactions to taxanes (HR) are unpredictable responses which cannot be explained by pharmacological action or toxicity due to drugs, but are caused by an immunological mechanism. Slower infusion rates and premedication have decreased its incidence, but despite this intervention, HR are still common.

Patient Presentation
A 48-year-old female with diagnosis of ovarian cancer in stage IC 4 years prior to our intervention, treated previously with hystero-oophorectomy, then started adjuvant therapy with paclitaxel. During her first paclitaxel dose, she had an HR with intense lumbar pain, dyspnea, hypertension and anxiety, anaphylaxis is diagnosed, so she was administered oxygen, hydrocortisone and an intramuscular 0.5mg epinephrine as a single dose.
As this drug was the best possible treatment capable of improving her long-term prognosis and therefore, essential for her treatment, the oncology department requested desensitization to paclitaxel, despite the severity of the reaction. The diagnosis of an HR to paclitaxel was confirmed with a negative skin prick test at 1:10 dilution and a positive intradermal allergy test positive at 1:100 dilution. Then a desensitization protocol was carried out in order to receive the total dose. We used a four-bag protocol with no sign of a hypersensitivity reaction.

Diagnosis
The diagnosis of an HR to paclitaxel was our first differential diagnosis because of her respiratory, cardiovascular and digestive symptoms.

Testing
At first we made an skin prick test at 1:10 dilution which was negative, then we made an intradermal allergy test at 1:100 dilution which was positive, thus confirming our diagnosis.

Treatment
A desensitization protocol was carried out in order to receive the total dose of 300mg. We used a four-bag protocol with no sign of a hypersensitivity reaction.

Patient Outcomes
During the procedure, no signs of hypersensitivity reaction happened.

Lessons Learned
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 allowing its safe administration.
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Total dose: 300 mg  
Total time = 6.67 h
Rapid trimethoprim/sulfamethoxazole desensitization in a patient with a history of hypersensitivity reaction

Author Rodrigo De la Cruz-Cruz
Training Program FIT allergy and immunology

Summary
A 42 year-old female diagnosed with HIV in 2013 and allergy to trimethoprim/sulfamethoxazole, characterized by pruritic erythematous-based hives after receiving a treatment for acute gastroenteritis. She refers visiting the ophthalmologist, who encountered signs of chorioretinitis secondary to a Toxoplasma gondii infection. She received treatment with trimethoprim/sulfamethoxazole, which required attention by our service. The desensitization protocol proceed without anomalies and she kept the treatment with the above-mentioned antibiotic.

Patient Presentation
A 42 year-old female diagnosed with HIV in 2013 and allergy to trimethoprim/sulfamethoxazole, characterized by pruritic erythematous-based hives after receiving a treatment for acute gastroenteritis. She refers visiting the ophthalmologist, who encountered signs of chorioretinitis secondary to a Toxoplasma gondii infection which needed this drug treatment.

Diagnosis
Because of the dermatologic signs, hives and pruritus, our first differential diagnosis was a type 1 hypersensibity reaction to the drug.

Testing
We made a trimethoprim/sulfamethoxazole skin prick test an 1:10 dilution

Treatment
We made an oral desensitization protocol of trimethoprim/sulfamethoxazole in 4 dilutions for a total dose of 160/800 mg over 3 hours 15 minutes.

Patient Outcomes
We didn’t have any signs of a new hipersensitivity reaction during the procedure.

Lessons Learned
Adverse reactions secondary to sulfonamides vary from mild episodes as urticaria and erythema multiforme to severe episodes as anaphylaxis. The desensitization process consists of medicine administration in progressively higher doses at intervals between 15 to 30 minutes. The trimethoprim/sulfamethoxazole desensitization schemes show to be an effective method, therefore is alternative of treatment. This work exposes two cases of allergic reactions to trimethoprim/sulfamethoxazole in patients who responded satisfactorily to desensitization schemes.
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Desensitization Protocol For Hypersensitivity To Paclitaxel In Patient With Recurrent Cancer, A Safe And Effective Method

Author Gehnssy Karolina Rocha Silva
Training Program FIT in allergy and clinical immunology

Summary
Introduction: Use of chemotherapy compounds in clinical practice is increasing, leading to a rise in the incidence of hypersensitivity reactions. Taxanes are agents that lead to cell death by preventing mitosis. These chemotherapeutic agents cause hypersensitivity reactions, which develop more frequently in the first or second cycle of chemotherapy.
Case: A 39-year-old woman, with type 2 diabetes mellitus, cervical cancer, received chemotherapy, radiotherapy and brachytherapy management that ended in June 2017. In July 2019 diagnosis of bladder and peritoneum recurrence. She begins her condition in the first cycle of chemotherapy with paclitaxel, she has bronchospasm with desaturation at 76%, is administered steroid and resolves. She subsequently presents lumbar pain, erythema, rash, epigastralgia, nausea and syncope and is referred to our service. Positive intradermal test (1:10). A desensitization protocol is performed in 16 steps, completing without adverse events. The desensitization protocols allow to continue with the treatment causing the hypersensitivity reaction.

Patient Presentation
A 39-year-old woman, with type 2 diabetes mellitus since 2006, diagnosed with stage IIB cervical cancer on March 9, 2017, received chemotherapy, radiotherapy and brachytherapy management that ended in June 2017. In March 2018, proctitis and colitis were diagnosed. post-radiation, a colostomy is performed on November 2018. In July 2019, a bladder biopsy is shown with a positive result for squamous carcinoma, a diagnosis of bladder and peritoneum recurrence is made without known drug allergies. She begins her condition in the first cycle of chemotherapy with paclitaxel, with premedication with dexamethasone, chlorphenamine and ranitidine, she has bronchospasm with desaturation at 76%, is administered steroid and resolves. She subsequently presents lumbar pain, erythema, rash, epigastralgia, nausea and syncope and is referred to our service.

Diagnosis
Due to the symptoms presented in the first cycle of chemotherapy, a type I hypersensitivity reaction was considered Diagnosis: hypersensitivity to paclitaxel

Testing
Skin test was performed: prick test is performed to paclitaxel that is reported negative, positive intradermal test (1:10).

Treatment
A 4-bag desensitization protocol is performed in 16 steps (table 1), completing in 6 hours 40 minutes without adverse events at a total dose of 300 mg.
Patient Outcomes
Intradermic test was carried out that positive results and confirmed diagnosis of hipersensivity type I, desensitization protocol could be performed without eventualities.

Lessons Learned
The desensitization protocols allow to continue with the treatment causing the hypersensitivity reaction, being an appropriate option for the patient to continue with first line of treatment and thereby improving the prognosis and quality of life. There are promising results in desensitization protocols.

<table>
<thead>
<tr>
<th>Step</th>
<th>Solution</th>
<th>Infusion mL/h</th>
<th>Time (min)</th>
<th>Volume infused (mL)</th>
<th>Percentage infused</th>
<th>Dose infused (mg) per step</th>
<th>Cumulative dose (mg)</th>
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<td>5</td>
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<td>16</td>
<td>4</td>
<td>80</td>
<td>174.4</td>
<td>232.5</td>
<td>92.2% (8% c/ 15 min)</td>
<td>276.68</td>
<td>300 mg</td>
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</tbody>
</table>

Total time = 6.67 h
Hypersensitivity to aspirin in a pregnant patient with preeclampsia: Desensitization Protocol

Author Argentina Rodriguez Casas
Training Program FIT in allergy and immunology

Summary
Low doses of aspirin as prevention of preeclampsia (PE) have been examined extensively, but the prescription indication, timing of treatment initiation and dose vary widely between different studies and guidelines. Case: A 36-year-old female patient, with a 14-week gestation pregnancy, gestational diabetes, grade II obesity and preeclampsia, was indicated 150 mg daily of aspirin. Five hours after taking aspirin, the patient develops pruritus in the forearm and later presents pruritic maculopapular rash. Desensitization was initiated and she was premedicated 1 hour prior. During the administration, vital signs were constantly monitored, which remained stable during the procedure. Aspirin reduces the risk of premature preeclampsia, but not of term preeclampsia, and only when it starts at ≤ 16 weeks gestation at a daily dose of ≥100 mg. Aspirin desensitization followed by daily aspirin therapy is an important treatment option, and its efficacy has been validated in multiple research studies.

Patient Presentation
A 36-year-old female patient, with a 14-week gestation pregnancy, gestational diabetes, grade II obesity and preeclampsia, diagnosed in the maternal fetal consultation 7 days prior, was indicated 150 mg daily of aspirin. Five hours after taking aspirin, the patient develops pruritus in the forearm and later presents pruritic maculopapular rash, located in both upper limbs, of sudden onset while she was asleep. The patient suspended the administration of aspirin and the skin lesions lasted 4 days. She was evaluated by the endocrinology service for control of gestational diabetes and referred to our allergy and clinical immunology service for presenting a type IV adverse reaction to medication (aspirin). Desensitization was initiated and she was premedicated 1 hour prior with montelukast 10 mg single dose and chlorphenamine 10 mg single dose. The desensitization protocol was performed with a duration of 4 hours. During the administration, vital signs were constantly monitored, which remained stable during the procedure.

Diagnosis
As this patient has dermatologic signs of an acute disease after the administration of aspirin, our first differential diagnosis was a type IV hypersensitivity reaction, a maculopapular rash.

Testing
Interrogation and elaboration of a complete medical history: pathological history, risk factors, evolution and current state of the disease, clinical manifestations and time of evolution of skin lesions compatible with type IV hypersensitivity reactions.

Treatment
We made a desensitization to oral aspirin in 3 dilutions, in a time of 4 hours.
Patient Outcomes
Our patient had no signs of a new hypersensitivity reaction during the procedure

Lessons Learned
Drug desensitization is an option for our patients that only has the only therapeutic option and that in the future may reduce the risk of complications from preeclampsia where our patient and his product will benefit.

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<thead>
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<th>3 Syringe</th>
<th>Volume (mL) per syringe</th>
<th>Dilution</th>
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<tr>
<td>Solution A</td>
<td>10</td>
<td>1:100</td>
</tr>
<tr>
<td>Solution B</td>
<td>10</td>
<td>1:10</td>
</tr>
<tr>
<td>Solution C</td>
<td>1 tablets</td>
<td>1:1</td>
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</table>

Total doses: 150 mg Total time: 4 hours

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<tr>
<th>Steps</th>
<th>Solution</th>
<th>Time (min)</th>
<th>Solution volume (ml)</th>
<th>Medication dose</th>
<th>Cumulative dose</th>
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<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>30</td>
<td>1 ml</td>
<td>1 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>60</td>
<td>2 ml</td>
<td>2 mg</td>
<td>3 mg</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>90</td>
<td>5 ml</td>
<td>5 mg</td>
<td>8 mg</td>
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<tr>
<td>4</td>
<td>B</td>
<td>120</td>
<td>1 ml</td>
<td>10 mg</td>
<td>18 mg</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>150</td>
<td>2 ml</td>
<td>20 mg</td>
<td>38 mg</td>
</tr>
<tr>
<td>6</td>
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<td>C</td>
<td>240</td>
<td>1.5 tab</td>
<td>150 mg</td>
<td>308 mg</td>
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Rare Case of an Eczema Mimic

Author Elizabeth K. George, M.D., M.P.H.
Training Program National Jewish Health Adult Allergy Immunology Program

Summary
An 85-year-old female presented to our allergy clinic for evaluation of an eczematous skin rash thought to be due to a systemic drug or possible new skin allergy. The patient, who has no prior history of atopic disease or eczema, developed a highly pruritic, non-painful rash roughly 1.5 years ago. The rash initially was localized to the dorsum of her hands, and spread to include her extremities, trunk and back. Laboratory evaluation revealed mild leukocytosis and peripheral eosinophilia. Skin biopsies were performed in clinic which were sent for hematoxylin and eosin (H&E) staining and direct immunofluorescence (DIF) which showed acanthotic epithelium and eosinophilic spongiosis with linear deposition of C3 respectively. Immunoserologic workup revealed increased autoantibodies against the basement membrane zone detected by ELISA revealing the diagnosis of non-bulbous pemphigoid. The patient was initiated on a prolonged oral steroid taper with improvement of her skin findings.

Patient Presentation
An 85-year-old female with a medical history of mild dementia, diastolic heart failure, mitral regurgitation, atrial fibrillation, and hypertension presented to our allergy clinic for evaluation of an eczematous skin rash thought to be due to a systemic drug or possible new skin allergy. The patient, who has no prior history of atopic disease or eczema, developed a pruritic, non-painful rash roughly 1.5 years ago. The rash initially was localized to the bilateral dorsum of her hands, but over the following year, it spread to include her arms, legs, trunk, chest, and back. She describes the rash as extremely pruritic, but not worse at nighttime compared to daytime. Although not present currently, she describes the occurrence of small, firm, fluid-filled vesicles. After scratching, these vesicles will leak a clear, golden colored fluid. There is no mucosal involvement, and it spares the palmar and plantar skin. No aggravating factors were identified. Warm water is helpful with pruritis, and the topical steroids have been mildly effective in treatment. Otherwise, there were no clear alleviating factors. She denies any new medications, including NSAIDs or courses of antibiotics. Her medications have been mostly unchanged for months to years prior the rash onset, and included aspirin, digoxin, apixaban, enalapril, metoprolol, ezetimibe, and paroxetine. She denies any new cosmetic products, soap, shampoo, or lotions nor does she dye her hair. She also does not have any new pets in the home. Her primary care physician, believing it was likely a drug rash, discontinued her metoprolol medication, as it was believed to be possibly causative, but the rash continued to worsen.

She had previously seen a dermatologist, who diagnosed her with eczema, and initiated treatment with a high dose topical corticosteroid (betamethasone 0.05% topical ointment) and fexofenadine 180 mg twice daily for itching. The rash was widespread and the topical ointment was completely used after 2 days. The steroid cream was mild effective. The anti-histamine has seemed to make little difference with the pruritis.

Her review of systems was positive for occasional nighttime fevers, but she denies chills, or night sweats. She has had ~15 lbs unexpected weight loss, which the family attributes to a lack of appetite. She denies fatigue or other systemic symptoms.
Diagnosis
The diagnosis we reached was non-bulbous pemphigoid. Non-bulbous pemphigoid (NBP) is an autoimmune disease, and lesser recognized phenotype of bullous pemphigoid. It is characterized by autoantibody deposition at the epithelial basement membrane zone which frequently affects elderly adults. The heterogenous skin presentation can result in difficulty in diagnosis given it does not classically presents with tense subepithelial blisters. The diagnosis was based on skin biopsies which revealed linear C3 deposition on immunofluorescence and subsequent immunoserologic workup which was positive for autoantibodies that target the structural proteins in the basement membrane.

Testing
A complete blood count was remarkable for mild leukocytosis (11,300 cells/uL) and peripheral eosinophilia (800 cells/uL, 7.3%). A comprehensive metabolic panel was mostly unremarkable except a mildly elevated total bilirubin (1.9 mg/dL). A high sensitivity CRP was elevated at 2.9 mg/L. Sedimentation rate was normal at 14 mm/h.

Two 5 mm skin biopsies were performed. One biopsy was sent for histology hematoxylin and eosin (H&E) staining and the other for direct immunofluorescence (DIF). The H&E slide reveals acanthotic epithelium and eosinophilic spongiosis. The DIF revealed deposition of C3 without a deposition of IgG identified. Immunoserologic workup revealed increased autoantibodies against the non-collagenous 16A domain of BP180 (NC16A) and BP230 detected by ELISA.

Treatment
Prednisone was initiated at 40 mg PO daily (0.60 mg/kg) with the plan to taper and add on high dose topical corticosteroids once the rash was more manageable. The data to support the efficacy of glucocorticoid-sparing agents in nonbullous (and bullous) pemphigoid are limited. Expert recommendations are to obtain control with steroids and then consider starting a steroid-sparing agent, such as azathioprine, mycophenolate and methotrexate, just prior to the start of glucocorticoid taper. However, caution and careful consideration of the risks versus benefits of pursuing these agents was advised in the elderly population.

Patient Outcomes
The patient reported a marked improvement in symptoms after 4 weeks of prednisone (See Picture 3). Screening for malignancy in the context of unexpected weight loss and newly diagnosed NBP included CT scans of the chest, abdomen and pelvis, which were unremarkable. The plan is to continue to taper her steroids as tolerated.

Lessons Learned
In elderly patients presenting with a diffuse, severely pruritic rash, accompanied peripheral blood eosinophilia and demonstrating eosinophilic spongiosis on H&E skin biopsies, are most often diagnosed diseases with eczema or a drug rash. It is common practice to treat these patients with topical or systemic steroids without further testing. There were several atypical characteristics in this individual that were concerning, including the patient’s age, weight loss, persistence and severity of her skin lesions, refractory nature to first line therapy, and the description of tense or hard, fluid-filled vesicles which was not visualized on exam.

Diagnosis of NBP is based on detection of skin-bound IgG or complement C3 in linear deposition along basement membrane zone by DIF, by circulating antibodies by indirect immunofluorescence, or both.
Interestingly, histopathology is often non-specific and thus the diagnosis can not be excluded by histopathology alone. This highlights the importance in utilizing DIF during skin biopsy. In reviewing the available literature regarding this disease process, a study by Lamberts et. al. report an overall standardized mortality ratio of 8.6 and 1-, 2-, and 3-year all-cause mortality in NBP were 14%, 34%, and 46% respectively in a study of 69 participants diagnosed with nonbullous pemphigoid. In comparison to the more classic phenotype of bullous pemphigoid, NBP mortality rates are increased. In a meta-analysis performed by Atzmony et al, there was a significant association between hematologic malignancies and bullous pemphigoid with an odds ratio of 2.6 [95% CI, 2.08-3.24]. Thus, it will be important to continue to monitor for development of malignancy as it may present at a later date. Unfortunately, our patient did have a prolonged disease exposure prior to diagnosis of NBP. A diagnosis of nonbullous pemphigoid should be included in the differential for a generalized pruritic rash, particularly in the elderly population.
Persistent Hypogammaglobulinemia after Chemotherapy and Rituximab Despite B Lymphocyte Recovery

Author Mohga Behairy, DO, Leigh Ann Kerns, MD
Training Program Cleveland Clinic Children’s Hospital

Summary
This is a three year old boy with a history of Burkitt’s leukemia treated with several rounds of chemotherapy with Rituximab who subsequently developed hypogammaglobulinemia and was treated with intravenous immunoglobulin (IVIG) followed by subcutaneous immunoglobulin (Hizentra). His hypogammaglobulinemia persisted in spite of normalization of B lymphocytes.

Patient Presentation
This is a previously healthy male diagnosed with Burkitt’s leukemia at eight months of age. He was treated per COG ANHL 1131/C3 chemotherapy protocol with Rituximab for six months and subsequently went into clinical remission. Immunoglobulin levels at the time of diagnosis were within normal limits for his age: IgG 361 mg/dL, IgA 10 mg/dL, and IgM 13 mg/dL. He was started on IVIG with the initiation of chemotherapy and his immunoglobulins remained normal throughout his treatment. IVIG was stopped at the end of chemotherapy. Two months after completion of chemotherapy, he developed significant hypogammaglobulinemia with an IgG drop from 448 mg/dL to 208 mg/dL, an IgA drop from 10 mg/dL to <7 mg/dL, and an IgM drop from 13 mg/dL to <4 mg/dL. Flow cytometry showed a diminished CD19+ B cell count of 2 cells/μL. He was restarted on monthly IVIG infusions at 6 grams per month to treat presumed Rituximab induced hypogammaglobulinemia. After four rounds of IVIG, his CD19+ B cell count normalized to 1316 cells/μL, his IgM increased to 39 mg/dL, his IgA increased to 29 mg/dL, and his IgG only reached 419 mg/dL despite four months of immunoglobulin replacement. It was thought that he had recovery of his B cells so IVIG was held. After several months off IVIG, his IgG dropped to 111 mg/dL and his IgA dropped to <7 mg/dL despite CD19+ B cells remaining normal at 2420 cells/μL. Additionally, he did not show adequate vaccination titer response after receiving tetanus, diphtheria and pneumococcal vaccinations. A genetic panel was performed and did not reveal a primary immunodeficiency. He was started on 7 grams of monthly IVIG then transitioned to 3 grams of weekly Hizentra. On this regimen, he has maintained normal B cell counts (last at 1198 cells/μL), normal IgG (last at 1040 mg/dL), normal IgM (last at 180 mg/dL), but persistently low IgA at <7 mg/dL.

Diagnosis
The diagnosis in this case remains unclear. Initially, his hypogammaglobulinemia was attributed to anti-CD20 Rituximab therapy. However, given normalization of B lymphocytes with persistent hypogammaglobulinemia, other causes are more likely. It is possible that his persistent hypogammaglobulinemia is a result of other chemotherapeutic agents. A significant underlying immune deficiency has not been ruled out.

Testing
Patient had regular testing of immunoglobulins and lymphocyte function to monitor therapy (see attached table 1 as photo 1).
A humoral immunity panel was done showed that he did not have adequate vaccine titers after leukemia treatment in spite of previously receiving tetanus, diphtheria, and pneumococcal vaccination. A genetic panel was done including a large series of genetic mutations linked to several known primary immunodeficiencies. He had three variations of uncertain significance detected on his genetic testing, but testing was negative for known pathologic variants of the tested immunodeficiencies.

Treatment
He was initially treated with monthly IVIG infusions of 6 grams per infusion. This was later increased to 7 grams per infusion. He was then transitioned to 3 grams of weekly Hizentra subcutaneous infusions.

Patient Outcomes
With normalization of his B cell counts and improved IgG levels, a trial of IgG supplementation may be considered in the next 1-2 years.

Lessons Learned
Rituximab is an anti-CD20 monoclonal antibody that depletes CD20-expressing B cells in lymphoid tissue and circulation [1]. For that reason, it is often associated with hypogammaglobulinemia [1]. In most cases, there is repletion of B cells and in turn restoration of immunoglobulins within one year after completion of Rituximab. What is interesting about this patient is the persistence of hypogammaglobulinemia for more than 2 years after chemotherapy with Rituximab despite full recovery of B lymphocyte counts. There is literature on patients with leukemia treated with chemotherapy who develop persistent humoral dysfunction and hypogammaglobulinemia that can take years to resolve [2, 3, 4]. This may be the explanation behind this patient’s persistent hypogammaglobulinemia. Additionally, an underlying immune problem is still a consideration; however, a definitive cause has not been determined.

References
<table>
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<tr>
<th>Timeline</th>
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<th>IgA</th>
<th>IgM</th>
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<td>9 months post chemo</td>
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<td>97</td>
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Infliximab and its Utility in Granulomatous Dermatitis in CVID

Author Paul Faybusovich
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Summary
This is a 37-year-old Caucasian gentleman with a history of Common Variable Immune Deficiency (CVID) on replacement subcutaneous immunoglobulin and biopsy confirmed recurrent granulomatous dermatitis with disfiguring skin scarring. He initially failed all oral treatments for his skin manifestations and so was started on Infliximab at varying doses. Due to intermittent neutropenia and episodes of esophagitis intermittent cessation of Infliximab was required. This would result in exacerbations of his granulomas and hence was restarted on Infliximab. He had multiple skin grafts with adequate results and eventual cessation of Infliximab but shortly after developed listeria gastroenteritis leading to meningitis but had an uneventful recovery. To prevent relapse, he was continued on chronic oral steroids to prevent any further exacerbations of his chronic granulomatous dermatitis which has been successful but if the need arises will plan on restarting Infliximab at a lower dose.

Patient Presentation
A 37-year-old Caucasian gentleman with a past medical history of Common Variable Immune Deficiency (CVID), recurrent granulomatous dermatitis, and a history of chronic lower extremity ulcers initially presented with multiple ulcerations. He was initially diagnosed with CVID in 2009 and suspected granulomatous dermatitis at an outside facility in 2000 with progression of ulcerations leading to disfigured scarring. After failed treatment with corticosteroids, Etanercept, Plaquenil, Methotrexate and Doxycycline alternative treatment was started with Infliximab with improvement of his condition. He had unforeseen complications of neutropenia requiring discontinuation of Infliximab. This resulted in exacerbations of his disease so Infliximab was restarted intermittently with close observation of his absolute neutrophil count. He later on developed an episode of dysphagia and had an EGD performed showing a laryngeal abscess without granulomatous inflammation, but positive for candida and HSV type 1 and 2. His treatment was continued at our facility where infliximab was continued accordingly. At that time his skin ulcerations gradually stabilized and he had multiple skin grafts performed so it was decided to discontinue infliximab in April of 2019.

Diagnosis
The patient already had a known diagnosis of CVID based on previous records with a subtherapeutic IgG level. He was also diagnosed with disfiguring granulomatous dermatitis formerly via skin biopsy on 1/19/15 at an outside facility and had multiple other skin biopsies at our facility between 2018-2019 showing fibrosing dermatitis, stasis dermatitis, dermal fibrosis and lymphohistiocytic inflammation accordingly.

Testing
The initial testing performed for CVID included immunoglobulin levels IgG, IgM, IgA, as well as vaccine titer to tetanus and pneumococcal. These were already performed and hence the patient being on immunoglobulin replacement prior to initiating care at our facility. Interval IgG levels were checked to ensure adequate levels and rule out infection. A neutrophil oxidative burst assay was also performed at an outside facility in 2015 to rule out a secondary immune dysfunction such as chronic granulomatous
disease and this was also found to be normal. Multiple EGD’s were also performed for dysphagia which was negative for granulomatous inflammation but positive for fungal overgrowth and HSV which were treated accordingly.

**Treatment**
Due to the patient history of CVID the patient was continued on his subcutaneous immunoglobulin every 2 weeks and adjusted accordingly to maintain a therapeutic IgG level. He was followed by infectious disease and treated with a 21 day course of IV ampicillin for listeria meningitis. For his candida esophagitis he was put on 1 week of fluconazole then Mycelex troches 5 times a day for prophylaxis. He was also given acyclovir orally for 1 week for HSV esophagitis. No further prophylactic medication was recommended otherwise.

**Patient Outcomes**
Since our visit he unfortunately did develop listeria gastroenteritis which progressed to enteritis with the presumption that it may have been due to his chronic Infliximab use causing immunosuppression. He recovered uneventfully, though his skin ulcerations began to flare up and required multiple debridement’s and hospital admissions on 2 separate occasions, one on which he received a skin graft. As a result, the patient was put on Methotrexate and chronic oral steroids, but was unable to tolerate Methotrexate so as a result it was discontinued and prednisone dose was increased to compensate for this issue. The goal now is to slowly taper his prednisone by 1mg every 2 weeks so he would not be steroid dependent as well as to prevent him from having any recurrent granuloma flare ups. If he were to have a recurrence when trying to taper steroids then we would have to consider restarting Infliximab with benefits and risks being carefully weighed and having close observation so complications such as meningitis do not reoccur.

**Lessons Learned**
This case shows how CVID may come with a myriad of complications. The skin manifestations in our patient became debilitating. Initially he failed oral therapies but responded well to Infliximab and had either regression or stasis of existing lesions. This was seen in previous papers “Infliximab for Treatment of Granulomatous Disease in Patients with Common Variable Immunodeficiency” published in the Journal of Immunology in 2014. Another paper titled “Granulomatous Disease in CVID: Retrospective Analysis of Clinical Characteristics and Treatment Efficacy in a Cohort of 59 Patient” in the Journal Clinical Immunology published in 2013 also strengthened the argument of Infliximab use in granuloma development in CVID. However, with infliximab use comes risks. These risks are further amplified in a patient who is already immunocompromised with his known history of CVID thus its use must be cautiously weight on its risk vs benefits. He contracted listeria meningitis but thankfully recovered without complications. The question now is knowing we had an event like this, if in the future an opportunity presented itself in a similar fashion would we repeat the same course of action?
Aeroallergen immunotherapy in the treatment of refractory phlyctenular conjunctivitis

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Summary
Our patient is a child with allergic conjunctivitis presenting with a one year history of noninfectious phlyctenular conjunctivitis refractory to multiple medications. Untreated, this condition may lead to corneal perforation and scarring. Indicated by a history of allergic conjunctivitis, she began aeroallergen immunotherapy (AIT). Within months there was a significant decrease in the size of the phlyctenule accompanied by periods of symptom resolution. The lesion showed intermittent improvement with AIT treatments and was exacerbated by her environmental exposures. Phlyctenular conjunctivitis is considered a Type IV cell-mediated reaction to an infectious antigen. Our case challenges this, suggesting a potential mechanism of IgE mediated Type I hypersensitivity reaction to environmental allergens. We believe this is the first reported case of allergy injections improving refractory phlyctenular conjunctivitis.

Patient Presentation
A ten-year-old Caucasian girl was referred by her primary care physician with the chief complaint of “bump on eye”. The left sided nodule was first observed in October of 2017 after she played in a pile of fallen leaves. Her mom first attributed this to a foreign body, attempting to wash it out, but found none. Her initial diagnosis by her primary care physician was pterygium. However, the ocular nodule persisted for months, prompting a visit to a pediatric ophthalmologist with the subsequent diagnosis of phlyctenular conjunctivitis. Over the next year, she received artificial tears, ocular antihistamine, antibiotics, NSAID drops, ocular steroids and a baby shampoo eye wash. These treatments were administered multiple times a day. At one point she was prescribed nine eye drops per day, requiring frequent visits to the school nurse. None of these medications eliminated the nodule. Some improvement resulted from administration of steroid eye drops; however, these were discontinued due to increased intraocular pressure.

Her past medical history was significant for history of seasonal allergies characterized by itchy/watery eyes since the age of five, treated with cetirizine and ocular ketotifen. There was no history of foreign travel, eye infection, corneal abrasion, excessive rubbing, chemical exposure, or foreign body in the eye. She had no infectious complications such as recurrent sinusitis or otitis media, and she had not experienced any lower airway symptoms such as asthma, cough or wheezing. Her family history includes mother with allergic rhinitis and father with asthma.
She presented on a regimen of loratadine 10 mg daily, artificial tear drops twice daily, ocular azelastine twice daily, and ocular NSAID drops three times daily.

On exam, her right eye was normal with white conjunctiva and sclera. Her left eye displayed a phlyctenular nodule at 9:00 measuring 2 mm by 2 mm with erythematous margins. (Photo 1)

Diagnosis
Our patient was diagnosed with allergen-mediated phlyctenular conjunctivitis.
Testing
Skin testing to environmental allergens was positive for trees, grass, weed, dust mite, cat, dog and mold.

Treatment
She received AIT in addition to ocular medications prescribed by her ophthalmologist. Allergy injections were administered biweekly during the summer and winter, and up to once weekly during the spring and fall when her environmental triggers peaked.

Patient Outcomes
Substantial relief of her eye symptoms occurred with AIT. At her most recent follow up appointment, the patient and her mother report a reduction in symptoms proportional to the timing of her allergy injections. Within a day of receiving maintenance dose AIT, the phlyctenule became smaller, less erythematous, and flat (Photo 2). At its best, the nodule was not visible, usually corresponding with low environmental triggers and allergy injection administration within the past week. Two or more weeks after receiving AIT, the nodule returned; red and visibly raised. During times of high environmental triggers, these symptoms reemerge more quickly, sometimes within as little as a week, requiring weekly injection intervals. The patient and her mother are grateful to see that she is responding to treatment and are hopeful that this benefit will continue.

Lessons Learned
This case offers a new approach to the treatment of a potentially severe disorder. Phlyctenular conjunctivitis is considered a Type IV hypersensitivity reaction to infectious antigens, most often treated with antibiotics and steroid eye drops. Our case complicates this understanding of the etiology of phlyctenular conjunctivitis with evidence of a Type I hypersensitivity reaction to environmental triggers causing this condition. Furthermore, AIT shows dosage-timing dependent relief of symptomatic phlyctenular conjunctivitis refractory to antibiotic and steroid therapy.

Our patient was unique with exposure to environmental allergens inducing a phlyctenule which was controlled with AIT. Aeroallergens have not been cited as triggers to this condition and to our knowledge, never treated with AIT. Literature review produced one case report describing two pediatric patients with phlyctenular conjunctivitis refractory to steroid and antibiotic treatment, indicating 0.03% Tacrolimus ointment as an effective treatment. Tacrolimus is an immunosuppressant drug used for immunosuppression in transplant recipients as well as refractory eczema, further supporting our case for a phlyctenular conjunctivitis etiology independent of infectious agents and secondary to an allergic hypersensitivity. No cases of phlyctenular conjunctivitis treated with AIT have been reported. In summary, this case demonstrates the importance of identifying environmental allergens in refractory phlyctenular conjunctivitis and the benefits of AIT.
Tolerance of baked egg products in pediatric patient with food protein-induced enterocolitis syndrome to unbaked egg

**Author** Dr. Taylor Lin MD  
**Training Program** University of Colorado, Pediatric Allergy & Immunology

**Summary**
An 8 month old male with mild eczema was evaluated for possible egg allergy prior to any egg ingestion. Skin prick testing was positive for egg white sensitization and a food challenge was recommended to confirm a diagnosis of egg allergy. Between 8 and 12 months of age he was tolerating small amounts of baked egg in multiple forms (muffins, cupcakes). At 12 months of age the patient developed food protein-induced enterocolitis syndrome after ingestion of 18.5 g of unbaked egg during the challenge without IgE-mediated symptoms. The current FPIES guideline states patients with FPIES to egg should avoid egg in all forms. Other than three case reports and one retrospective review, there is a lack of evidence-based research and pathophysiologic understanding of FPIES to direct the clinician regarding introduction of baked egg in the setting of FPIES to egg.

**Patient Presentation**
The patient is an ex-term 8 month old male with full sister with IgE-mediated egg allergy presenting with a concern regarding egg allergy. At this time he had not yet eaten any egg (baked or unbaked), but given sister's history the family was concerned about the risk of having an egg allergy. He was tolerating other foods including cow milk based formula, peanut butter, oatmeal, quinoa, salmon, fruits, and vegetables. He has mild eczema that was adequately treated with intermittent low dose topical steroid. Family history is notable for sister with mild eczema and IgE-mediated egg allergy which she outgrew by age 3. After this first evaluation and prior to the food challenge, the patient tried and was tolerating baked egg containing products including King Hawaiian rolls daily (0.5 g egg protein), half of a large muffin weekly (0.5 g egg protein), cookies two to three times weekly (0.2 g egg protein), and cupcakes monthly (0.5 g egg protein). For reference, 1 egg contains about 8 grams of protein.

**Diagnosis**
Initial skin prick testing to egg white was positive for sensitization (4mm mean wheal diameter) with negative saline control and positive histamine control (3mm mean wheal diameter). It was recommended to return for food challenge to unbaked egg using scrambled egg which was performed at 12 months of age. Baseline assessment at time of challenge showed that he was well, afebrile, and asymptomatic. He was given scrambled egg in increasing doses 20 minutes apart (1g, 2.5g, 5g, and 10g) which he initially tolerated well. 15 minutes after his 10 g dose he vomited and developed pallor, for which he was given 2.5 mg of cetirizine. 45 minutes later he vomited again and was given 0.15 mg IM epinephrine. He remained active but was fussy. 5 minutes after epinephrine he vomited for a third time and then napped. 2 hours after epinephrine dose (3 hours his last egg ingestion) he woke up and vomited a fourth time and had loose stool. He was given 1.3 mg ondansetron and did not have any further vomiting for the 2.5 hours he was monitored his last emesis. He was well appearing and tolerating solids and liquids. No intravenous fluids were required for resuscitation. During the challenge he did not develop any hives, angioedema, cough, or nasal congestion. He did not have any further episodes of emesis or loose stools after returning home.
Testing
The patient was diagnosed with acute food protein-induced enterocolitis syndrome to egg using the clinical criteria as outlined in the international consensus guidelines of FPIES: vomiting 1-4 hours after ingestion of suspect food in the absence of classic IgE-mediated skin or respiratory symptoms, with marked pallor, diarrhea in 24 hours, and lethargy with suspected reaction (1).

Treatment
Given our patient’s tolerance of small quantities of baked egg (~0.5 g daily) and lack of clear evidence regarding counseling on baked egg avoidance in FPIES when it is currently being tolerated, we permitted him to continue eating those foods he tolerated in the same quantities. It was recommended he avoid any new baked egg containing foods and all unbaked egg. It was discouraged to eat the current baked egg product in greater quantities.

Patient Outcomes
Upon follow up, the patient continued to tolerate the same baked egg containing products at a similar frequency and quantity without any FPIES reactions. He had also not had any accidental unbaked egg exposures.

Lessons Learned
The current of understanding of the pathophysiology of FPIES is that it is a non-IgE-mediated food allergy and therefore the alteration of protein conformation should theoretically not change the likelihood of FPIES reaction (2). The international consensus guidelines recommend avoidance of baked and unbaked egg in patients with FPIES, but this is a conservative approach in the setting of lacking studies evaluating tolerance to egg proteins in baked products in children with FPIES (1). A case study by Caubet et al. reported the intolerance of baked egg products in a 7 month old male with FPIES to egg and Mehr et al. found 4/5 children with egg FPIES reacted to baked egg (3,5). Miceli Sopo et al. in a retrospective multicenter review found 3/27 children with egg FPIES tolerate baked egg prior to unbaked egg (4). In our case, the child only reacted to unbaked egg. Our patient may not have developed FPIES to baked egg due to low ingestion doses (~0.5 g egg protein at a time) and reacted during challenge due to higher protein doses (~2.9 g of egg protein). Many different threshold doses for inciting an FPIES reaction have been reported and there is no identified reliable threshold dose (1,4). If his tolerance is not dose dependent, then he may have a phenotype of FPIES with mechanism where specific IgE may play a role. This phenotype has been postulated by Miceli Sopo (2). This would be supported by his positive skin prick testing to egg. A more thorough understanding of FPIES pathophysiology and the role, if any, of IgE in FPIES could help clinicians understand better if baked egg could be tolerated in certain patients with FPIES. As previously highlighted by Nowak et al., evaluation of baked egg tolerance is a future need in our understanding of FPIES and our case provides support of its tolerance in at least a subset of patients.

Turn Down the Heat in a Cajun with Colchicine

Author Aimee Sutherland, MD
Training Program Tulane University

Summary
Mr. D is a 33 year-old Cajun man who presents with a 20 year history of recurrent fevers. Fevers developed every two weeks with temperatures ranging from 101 to as high as 105 degrees Fahrenheit. Additional symptoms included myalgias, malaise and headache. Surgical history is notable for an exploratory laparotomy as a child that was unrevealing. The patient had no family history of autoimmune or rheumatologic disease. On physical examination, patient afebrile, with stable vital signs. Physical exam was without lymphadenopathy, aphthous ulcers, pharyngitis, and rashes. Labs revealed an elevated IgG4; patient otherwise had a negative infectious, malignancy, and rheumatologic workup while inpatient and was referred to Allergy and Immunology for further evaluation as an outpatient. In clinic, patient was initiated on colchicine 0.6mg orally twice daily. A periodic fever syndrome panel was ordered. On follow up, patient had remained afebrile for two months since starting the colchicine. The periodic fever syndrome panel came back negative.

Patient Presentation
The patient is a 33 year-old Cajun man who presented to allergy and immunology clinic for evaluation of recurrent fevers that patient began experiencing at the age of ten. Patient reported fevers of approximately 101 degrees Fahrenheit occurring every 2 weeks with temperatures reaching as high as 105 degrees Fahrenheit occurring twice a year requiring hospitalization. Work-up during hospitalizations were ultimately negative for any source. Fevers would last for approximately 3-4 days and resolve without further intervention. Additional symptoms included intermittent abdominal pain, otherwise, patient denied rashes, aphthous ulcers, serositis, pharyngitis, adenitis, rashes, arthralgias, cough, shortness of breath, nausea, vomiting, diarrhea, dysuria, weight loss, and night sweats. The only other medical problems included allergies. Family history was negative for any autoimmune diseases and no other family members experienced similar fevers and symptoms. Surgical history was remarkable for a negative exploratory laparotomy as a child due to fevers and abdominal pain.

Diagnosis
The patient likely has a variant of periodic fever syndrome of unknown origin as genetic testing with the periodic fever syndrome panel often yields negative results. Familial mediterranean fever syndrome is also a possibility based on clinical criteria of fever with abdominal pain, favorable response to colchicine, age of onset, spontaneous remission of fever with symptom-free interval between fevers, and a negative exploratory laparotomy.

Testing
Laboratory testing in this patient included a normal ESR, CRP, and ferritin. The patient had an elevated IgG4 level, but other immunoglobulins were within normal limits. Rheumatologic work up included a negative anti-DNA antibody, anti-nuclear antibody, rheumatoid factor. Infectious work up was negative for brucella, Q-Fever, histoplasma, blastomycosis, aspergillus. Patient had negative exploratory laparotomy during childhood.
**Treatment**
Patient was started on colchicine 0.6mg twice daily. The decision to start colchicine was based on the liklihood of the patient having a periodic fever syndrome of unknown origin versus familial mediterranean fever syndrome.

**Patient Outcomes**
Patient has remained afebrile after two months of empiric therapy with colchicine and without further complications.

**Lessons Learned**
Fever is a common symptom with basic workup often yielding probable source of infection. Rarely does a patient develop persistent fevers without an identifiable source. Auto-inflammatory etiologies should be considered in patients in which malignancy, autoimmune disorders and unusual infections have been ruled out. Symptom patterns and risk factors, such as family history, patient ethnicity, and symptoms may aid the clinician in diagnosing a particular periodic fever syndrome. The diagnosis can be challenging due to variations in genetic mutations and inheritance patterns, likely seen in the patient discussed in the case.
While diagnosis can be made clinically, the use of genetic testing allows for confirmatory testing in patients with an ambiguous presentation. However, despite advances in diagnostics, a large proportion of patients have negative genetic testing. In such patients, empiric treatment with either glucocorticoids, colchicine, or interleukin-1 antagonists may support the diagnosis of a periodic fever syndrome.
Periodic Fever syndromes patients are at increased risk for secondary complications if not started on appropriate therapy. Such complications include amyloidosis, small bowel obstruction and infertility. Empiric treatment is of importance as it can prevent such complications. Further, development of secondary complications could potentially further muddle the diagnostic picture in a patient with recurrent fevers.
HLH secondary to HSV viremia in a Pregnant Adolescent Female

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Summary
We report the case of a 15 year old pregnant female with HSV-2 viremia, acute liver failure, and hemophagocytic lymphohistiocytosis (HLH). Her severe presentation is concerning for primary immune defects. HLH is associated with several immune defects and immune dysregulation. Genetic evaluation yielded two variants of unknown significance. Both were dismissed as not relevant to her presentation. Other immunodiagnostic evaluation did not reveal any abnormalities. Most recent evaluation has shown resolved HLH and disseminated HSV with acyclovir monotherapy. This case highlights the rare presentation of HLH in pregnancy precipitated by HSV-2 infection in an otherwise healthy female.

Patient Presentation
A previously healthy 15-year-old primigravida, at 13 weeks gestation, presented with low-grade fevers, nausea, and emesis. She also endorsed chills, decreased oral intake, and urinary frequency. She was diagnosed one week prior with influenza and treated with Tamiflu. She had a previous history of ear and sinus infections. Birth and family history were unremarkable. Physical examination revealed diffuse abdominal tenderness and hepatomegaly. Initial laboratory evaluation revealed hepatitis (ALT 591 U/L, AST 893 U/L) and leukopenia (3.6 1000/uL). Over the next 7 days, transaminases further increased (AST 5,233 U/L, ALT 1,783 U/L) and she developed hepatic encephalopathy with liver synthetic dysfunction consistent with acute liver failure (PT 23.5 sec, INR 1.9, albumin 1.9 gm/dL). She remained febrile and developed anemia (Hb 8.2 g/dL). Infectious workup revealed EBV(1419 copies/ml) and HSV-2 viremia (>100,000 copies/ml). The patient was further diagnosed with HLH based on the following clinical criteria: splenomegaly, fever, hypofibrinogenemia (160 mg/dL), elevated ferritin (>40,000 ng/ml), and hemophagocytosis within the bone marrow. Soluble IL-2 R and NK cell function were not assessed prior to treatment.

Diagnosis
She was found to have disseminated EBV and HSV-2 viremia that led to acute liver failure and HLH diagnosed based on Histocyte Society HLH-2004 criteria with fever, splenomegaly, hypofibrinogenemia, elevated ferritin, and hemophagocytosis in bone marrow [2]. No primary or other genetic cause of HLH were determined. HLH in this patient is thought to be caused by a dysregulated response to HSV-2 likely due to immune alterations that take place in pregnancy.

Testing
Immune evaluation for primary causes of HLH were conducted as the clinical picture could not differentiate between primary (familial) or secondary HLH (acquired) [1]. Evaluation revealed normal XIAP expression, perforin/granzyme B expression, normal NK cell function (post treatment). Sequencing of (ADA, AP3B1, BLOC1S6, BTK, CD27, CD70, IL2RA, IL2RG, ITK, LYST, MAGT1, MEFV, MVK, NCRC4, NLRP3, PNP, PRF1, RAB27A, SH2D1A, SLC7A7, STX11, STXBP2, TNFRSF1A, UNC13D, WAS, XIAP) did not reveal a diagnosis. Further genetic analysis revealed 2 heterozygous variants of unknown significance: FERMT3 associated with leukocyte adhesion deficiency type 3 and RORC associated with chronic mucocutaneous candidiasis.
Treatment
There are no current guidelines for treatment of HLH in pregnancy. The goal of treatment in secondary HLH is to subdue the hyper inflammatory process driving the over activation of the immune system [1]. This is done by treating the inciting process but sometimes requires additional immunosuppressants due to the extent of immune over activation. In this case, the decision to treat with IV acyclovir was made after consultation and discussion with the Primary team, Infectious Disease, Hematology, High Risk Obstetrics, and our Immunology team as HSV was thought to be underlying trigger. Single therapy was continued due to down trending ferritin, reduction in fevers, and improvements in coagulopathy. Liver function tests normalized and HSV PCR gradually became undetectable as patient was treated with IV acyclovir. IV Acyclovir continued for 31 days and was transitioned to oral valacyclovir PO for suppressive therapy.

Patient Outcomes
Immune evaluation consistent with HLH that has since resolved. Patient continues to have close follow-up with High Risk Obstetrics, Infectious Disease, and Immunology. Since the last evaluation, patient briefly stopped valacyclovir for approximately 2 weeks and had an outbreak of genital herpes that did not lead to viremia. She restarted the medications and the genital herpes resolved. There continues to be discussion on length of treatment of the HSV between Infectious disease and Immunology teams.

Lessons Learned
Due to the rarity of HLH in pregnancy, there are no guidelines and the pathophysiology is widely unknown. This case describes the earliest infectious triggered HLH presentation in pregnancy. The presence of HLH in the setting of any severe infection in a healthy individual suggests an underlying immune deficiency that warrants further investigation by an immunologist [1]. In pregnancy, the severity of HSV-2 infection increases with each trimester due to decreasing cell mediated immunity throughout the course of pregnancy [3]. In our patient with previous history of recurrent infection developed HLH in the first trimester, suggesting an underlying immune defect. Extensive review of the literature revealed only 3 other case reports of HLH in pregnancy secondary to HSV-2, all of which occurred in the third trimester[ 4,5,6]. Treatment has included immune suppression along with appropriate anti-virals. [4,5,6,]. Our patient did not require immunosuppression to clear the virus which could suggest the relatively more intact cell mediated response once the anti-viral was given killing off the trigger of HLH.

Authors: Sullivan S, Liu M, Murphy M, Shapiro D, Leiding JW

References
A rare case of terminal complement deficiency

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Summary
We present a 44-year-old male with a history of ulcerative colitis and myositis who was referred to our Immunology clinic with low CH50 and personal history of meningitis. Immunological investigations revealed a terminal complement (C5 and C8) deficiency. Subsequently, he was appropriately immunized and prophylactic antibiotic treatment was recommended. Genetic testing for complement deficiency is currently pending. Terminal complement deficiency is rare and robust evidence regarding specific management protocols are lacking. This case demonstrates the importance and recognition of complement deficiency in a patient with complex comorbidities and emphasizes the need for ongoing research regarding this rare condition.

Patient Presentation
A 44-year-old Caucasian man was referred to our Clinical Immunology and Allergy clinic for a low CH50 level (<14u/mL; normal 42-95). He has a past medical history significant for ulcerative colitis diagnosed at age 24. He had an inflammatory myositis flare 2 years prior and during his initial workup, was incidentally found to have a low CH50. Infectious history was pertinent for meningitis at age 21 requiring two weeks of hospitalization and intravenous antibiotics. The causative organism was not identified. He had an episode of C. difficile at age 44, but otherwise did not have recurrent sinopulmonary infections, opportunistic infections, further invasive infections such as sepsis or osteomyelitis. No history of skin abscesses, deep-seated infections, thrush, or disseminated viral infections.
His family history was significant for meningitis occurring in both his brother and sister. His father had a history of colitis. There was no other history of myopathy, known genetic conditions, or malignancies. No consanguinity.
The patient has allergic rhinitis but no atopic dermatitis, or asthma.
The patient currently is married with 3 children and is a lifelong non-smoker.
His physical exam on initial assessment was unremarkable. No dysmorphic features. Head and neck examination were normal with tonsillar tissue present and a normal oropharynx. Cervical lymph nodes were palpated, but were small and mobile. He had a normal cardiac exam. The patient had good air entry bilaterally with no wheeze or crackles. No atopic dermatitis. No hepatosplenomegaly.

Diagnosis
Based on the personal history of meningitis and family history of meningitis, with investigations demonstrating low C8 and C5 levels, this patient was diagnosed with a terminal complement deficiency.

Testing
Given the low CH50 and a history of invasive meningitis, a primary immunodeficiency was suspected and specifically, terminal complement deficiency was highest on our differential.
An immunodeficiency workup was performed. CBC showed a hemoglobin of 159g/L (130-175), leukocyte count of 6.2 (4.0-10.0), platelets 174 (150-400) and a normal differential with normal neutrophil and lymphocyte counts.
Immunoglobulin levels were normal with IgG of 7.2g/L (7.0-16.0), IgA 1.4g/L (0.7-4.0) and IgM 0.6g/L (0.4-2.3).
Lymphocyte immunophenotyping demonstrated normal CD 19 cells (B cells), NK cells, CD3+CD4+ T cells. His cytotoxic CD8+ T cells were slightly reduced at 0.242 (0.249-0.953).
The patient’s CH50 was repeated and was again <14u/mL.
C3 was normal at 1.02g/L (0.90-1.80) and C4 normal at 0.23g/L (0.10-0.40).
With CH50 level being undetectable and early C3 and C4 complement levels being normal, we highly suspected a terminal complement pathway deficiency (C5-C9) affecting the membrane attack complex, which would make this individual at an increased risk to invasive Neisseria species.
Ultimately, specific complement results demonstrated a low C5 level at 48g/L (55-113) and low C8 level at 13g/L (49-106).

**Treatment**
Based on the diagnosis, we recommended the patient be vaccinated to N. meningitidis. Vaccinations to S. pneumoniae and H. influenzae were recommended as well.
Prophylactic antibiotic therapy was suggested when ongoing gastrointestinal symptoms improved. The patient’s history of uncontrolled ulcerative colitis, a history of C. difficile infection, and a lack of further significant infections resulted in a complex and individualized management plan, when considering prophylactic antibiotic initiation.
Proper hygiene recommendations and safety measures for individuals with primary immunodeficiency were reviewed.

**Patient Outcomes**
The patient was successfully vaccinated to N. meningitidis, S. pneumoniae and H. influenzae and has had no significant infections on follow up. Genetic testing is pending to identify the gene(s) involved to explain this patient’s terminal complement deficiency and possibly associated co-morbid conditions.

**Lessons Learned**
This case illustrated the importance of developing a clinical approach to patients with suspected primary immunodeficiency, as well as the appropriate workup and management for a patient with a terminal complement deficiency. Terminal complement deficiencies although rare, have been reported in the literature with mutations in C8 beta subunit being the predominant cause in Caucasian populations (1).
Terminal complement deficiency is generally not associated with autoimmune conditions such as lupus, and C8 deficiency has not been associated with the development of myopathy (2). We elected to perform genetic testing for further insight into this rare case, particularly considering the patient’s co-morbid conditions. We hope this case will contribute to an area of Immunology where robust evidence and management strategies are lacking.

**Reference**
A Child with Chronic Granulomatous Disease and Immune Thrombocytopenic Purpura

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Summary
A child with chronic granulomatous disease and a history of severe necrotizing fungal pneumonia was seen initially in clinic several days after beginning antibiotics for a bronchiectasis exacerbation. Her exam was positive for diffuse erythematous macules scattered over her trunk and abdomen. Her laboratory workup revealed a significantly depressed platelet count and positive anti-platelet antibody testing. She was admitted to the hospital where she was treated with steroids and IVIG. Over the next seven days her rash showed significant evidence of improvement and her platelet count normalized.

Patient Presentation
An 8-year-old girl with autosomal recessive chronic granulomatous disease (CGD) and a history of necrotizing fungal pneumonia secondary to Fulvifomes inermis was treated with amoxicillin/clavulanate for a bronchiectasis exacerbation. When seen on day 7 of illness and day 5 of antibiotics she was noted to have violaceous and erythematous macules scattered over her trunk and abdomen. An adverse drug reaction was suspected and her antibiotic was discontinued.

Diagnosis
Our patient was diagnosed with immune thrombocytopenic purpura based off of clinical exam findings of a violaceous rash with evidence of macules and petechia on exam with a significantly depressed platelet count.

Testing
The diagnosis of immune thrombocytopenic purpura was further supported by a positive titer to anti-platelet antibody to glycoprotein IIb/IIIa. Inciting etiologies, namely respiratory viral testing and testing for mycoplasma were negative.

Treatment
Our patient was treated with prednisolone 2 mg/kg and 2 g/kg of IVIG.

Patient Outcomes
After these interventions her platelet count rose to 32 K/uL and a week later where her platelet count was 169 K/uL while on a prednisone taper.

Lessons Learned
This patient’s case highlights three important learning points that are germane to the pathophysiology of CGD.

Our patient’s CGD was diagnosed at 5 years of age when she presented with a primarily right sided necrotizing pneumonia. Dihydrorhodamine was diagnostic and we have been unable to obtain gene studies due to lack of insurance authorization. She presented previously with lymphadenitis that was
diagnosed as cat scratch disease and CGD was not entertained. Open lung biopsy revealed that the lungs were diffusely scarred and firm on palpation with poor inflation. Her lung biopsy demonstrated only extensive granulomatous tissue without evidence of lung parenchyma. Her bronchoalveolar lavage fluid grew Fulvifomes inermis, a wood fungus which is generally not considered pathogenic in immunocompetent hosts. However, cases of cutaneous infections and lower respiratory tract infections have been described in patients with CGD. This organism caused a bilateral necrotizing lung process which resulted in pneumatoceles, bronchiectasis, and a temporary supplemental oxygen requirement. Interestingly, despite her severe lung disease she was able to wean off oxygen within 6 months and her imaging studies revealed significant improvement in her cystic disease within 1 year. An intact oxidative burst is thought to be important in tissue repair, however, our patient was able to recover from her illness despite her neutrophil defect. This suggests that repair mechanisms exist in the lungs that are not dependent upon the proper functioning of neutrophils.

It is also important that although autoimmune disease is often diagnosed in patients with CGD, ITP is rarely reported. Systemic lupus erythematosus, inflammatory bowel disease, and rheumatoid arthritis have been well described, but the literature is scant regarding ITP in CGD. Factors contributing to autoimmune disease include the activation of the immune system from chronic infection and inflammation and poor clearing of debris. Additional studies are needed to determine if chronic immunomodulatory therapy with gamma interferon may be beneficial in reducing the risk of ITP and other immune disease in CGD.
Coronary Artery Vasospasm as a Unique Presentation of Aspirin-Exacerbated Respiratory Disease with Hypereosinophilia

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Summary
A 33-year-old female with a past medical history of asthma, sinusitis, nasal polyposis and aspirin sensitivity presented with chest pain secondary to coronary vasospasms requiring near-continuous IV nitroglycerin. The patient was found to have hypereosinophilia in addition to a significantly elevated urine LTE4. Out of concern for eosinophilia-mediated coronary vasospasm in the setting of aspirin-exacerbated respiratory disease, the patient was initiated on high-dose dexamethasone. Eosinophils were undetectable shortly after initiating dexamethasone. The patient was then able to be transitioned to an oral anti-anginal medication regimen, and she was discharged on a four week taper of dexamethasone. The patient was re-evaluated one month after hospitalization, and she was able to resume her daily routine with no restrictions.

Patient Presentation
A 33-year-old female with a past medical history notable for severe coronary vasospasm of the LAD and RCA complicated by cardiomyopathy with reduced ejection fraction (30-35%), asthma, sinusitis, and nasal polyposis presented to our institution for further evaluation and management of severe coronary vasospasms. In terms of her sinus disease and nasal polyposis, she underwent nasal polypectomy two years ago, and pathology was consistent with allergic type inflammatory polyps with prominent eosinophils. Additionally, at that time she was told she had an allergy to NSAIDs after she experienced shortness of breath shortly after taking either aspirin or ibuprofen. The patient was in her usual state of health until one week prior to referral to our institution. At that time, she was in the shower and began experiencing an intense, squeezing chest pain, which radiated to her arms, jaw, and neck. She had never experienced a pain like this before, and she was ultimately driven to the emergency department by her husband. She underwent cardiac catheterization where coronary vasospasms were visualized in real time. At that point she received intracoronary nitroglycerin, and her coronary arteries dilated immediately, resulting in complete resolution of her chest pain. Repeat angiogram after administration of intracoronary nitroglycerin revealed normal coronaries without atherosclerotic disease. In addition to heart catheterization, outside hospital evaluation was notable for hypereosinophilia (absolute eosinophil count 3290/mm^3), echocardiogram revealing an ejection fraction (EF) of 35%, and an ESR of 32. Unfortunately, she had experienced multiple episodes of chest pain as she was trialed on oral anti-anginal medications. Due to her severe vasospasms requiring IV medications that could not be de-escalated in the setting of her reduced EF, she was transferred to our institution’s coronary critical care unit for further evaluation and management recommendations.

Diagnosis
The patient was diagnosed with eosinophilia-associated coronary vasospasm with secondary cardiomyopathy, as she continued to demonstrate hypereosinophilia and cardiac dysfunction. Autoimmune, vasculitic, or mast-cell related etiologies were unlikely given her normal laboratory studies addressing these specific concerns. Her elevated urine LTE4 and past medical history of NSAID
sensitivity, bronchospasm, sinus disease, nasal polyposis were consistent with aspirin-exacerbated respiratory disease (AERD). Thereby, her eosinophilia was likely associated with her history of AERD.

**Testing**
Upon arrival to the coronary critical care unit, the patient was hemodynamically stable, maintaining normal oxygen saturations on room air. She arrived with a nitroglycerin drip in place. Due to her hypereosinophilia and cardiac issues, eosinophil-related cardiac disease was a concern. Further evaluation was notable for continued hypereosinophilia (absolute eosinophil count 1770/mm$^3$), urine LTE4 elevated to 2,958 pg/mg (ref ≤ 104), and unremarkable C3, C4, ANCA, ANA, and extractable nuclear antigen panel. Tryptase was normal at 4.2 ng/ml. Repeat TTE revealed an EF of 43% and inferoseptal wall motion abnormalities with moderate mitral regurgitation. There was no intracardiac mass or thrombus.

**Treatment**
The patient was initiated on a diltiazem drip nearly continuously for the first four days. Nitroglycerin drip was utilized intermittently for the first seven days. She was trialed on a number of oral medications for anginal/endothelial benefit including isosorbide mononitrate, nifedipine, diltiazem, cilostazol, atorvastatin, clopidogrel and vitamin E. With concern for an underlying eosinophilic etiology, the patient was started on high dose dexamethasone. The patient’s eosinophil count normalized shortly after the initiation of dexamethasone.

**Patient Outcomes**
Following one week of high dose dexamethasone, the patient’s anti-anginal medications were able to be converted to a purely oral regimen and the patient was discharged to home with a four week steroid taper in addition to multiple anti-anginal medications.

**Lessons Learned**
Aspirin-exacerbated respiratory disease (AERD), also known as Samter’s Triad, consists of asthma, sinus disease with recurrent nasal polyps and sensitivity to aspirin and NSAIDs$^1$. AERD leads to respiratory symptoms by causing an increase in pro-inflammatory leukotrienes and a decrease in anti-inflammatory prostaglandins$^1,2$. More specifically, aspirin diverts arachidonic acid metabolites to the lipoxygenase pathway$^1,2$. This also leads to a decrease in the levels of prostaglandin E2, the anti-inflammatory prostaglandin, along with an increase in the synthesis of cysteinyl leukotrienes which cause increased bronchial inflammation$^1,2$. Interestingly, this can be associated with a number of conditions, including coronary vasospasm.

AERD is an uncommon association with coronary vasospasm, although the frequency of this association is unknown$^3$. This vasospasm is thought to be an eosinophil associated vasospasm, which may be why typical anti-anginal medications do not provide much relief for a number of these patients$^3$. Rather, eosinophil-suppressing steroid treatment is key to proper treatment$^3$. Therefore, identifying AERD as part of the patient’s history and physical is crucial to guiding anti-anginal therapy. While this patient did experience relief with typical anti-anginal medications, she was only able to be discontinued from her IV nitroglycerin infusion seven days after initiation of a high dose steroid regimen. Of note, her eosinophils were undetectable at the time of discharge. She has since followed up as an outpatient at which time she was not restricted in her daily activities.
Hypersensitivity to Trimetropim / sulfamethoxazole (T/S) in a patient with liver transplantation: Desensitization protocol

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Summary
More than 7% of the population may be affected by an adverse drug reaction. Desensitization is the induction of a temporary state of clinical tolerance to a compound responsible for a drug hypersensitivity reaction. Pneumocystis jiroveci infection causes severe lung infections in transplant patients in the first 3 to 6 months post-transplant. However, with the use of prophylaxis in the first 6 months of T/S, the incidence of this infection decreases considerably. The desensitization process consists in administering the medication involved in progressively increasing doses, with 15 minute intervals. The ultra-fast desensitization protocol was performed with a total duration of 3 hours. During the performance, vital signs were constantly monitored, which remained stable. Medication administration was started 24 hours after the end of the protocol, with good tolerance.

Patient Presentation
A 62-year-old male patient, with a personal pathological history of type 2 diabetes mellitus, in addition to liver cirrhosis and esophageal varices of 10 years of evolution, which required hospitalizations on multiple occasions. He presented urticaria at 50 years of age, post-ingestion of trimetropin / sulfamethoxazole (T/S). On this occasion he entered the University Hospital "Dr. José Eleuterio González" with a liver transplant surgical plan. The liver transplant was performed. At 5 days post-transplant, the patient merited initiating prophylactic treatment with T/S, so the first dose was prescribed and administered, secondary to the administration of the drug he presented again with hives.

Diagnosis
Hypersensitivity to Trimetropim / sulfamethoxazole (T/S)

Testing
No skin test was performed

Treatment
Pneumocystis jiroveci infection causes severe lung infections in transplant patients in the first 3 to 6 months post-transplant. However, with the use of prophylaxis in the first 6 months of T/S, the incidence of this infection decreases. The ultra-fast desensitization protocol was performed with a total duration of 3 hours.

Patient Outcomes
Medication administration was started 24 hours after the end of the protocol, with good tolerance.
Lessons Learned
The use of trimetopin sulfamethoxazole as part of the prophylactic treatment in our patient was possible, after successful desensitization to this drug, which represents positive results for the patient, since it is low cost and first line of treatment.
Regan C. Pyle et al. reported the largest case series of successful outpatient graded administration of TMP-SMX with both 1-day and >1-day protocols, which have shown to be safe and well tolerated in patients without HIV and with a history of sulfonamide ADR.
Unmasking Kabuki syndrome: a 7-year-old girl with a history of otitis media, hypogammaglobulinemia and autoimmune cytopenias.

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Summary
Kabuki syndrome (KS) is a rare disorder characterized by distinct facial features, postnatal growth deficiency, mild-to-moderate intellectual disability, various skeletal and visceral abnormalities and immune dysregulation. KS is caused by pathogenic variants in two known genes, KMT2D (histone-lysine N-methyltransferase 2D) and KDM6A (lysine-specific demethylase 6A), which function as epigenetic modulators, through histone modification, in the course of embryogenesis and in several biological processes. Although not completely understood, it is postulated that this epigenetic dysregulation has downstream effects resulting in varying presentations of immunodeficiency and autoimmunity. We report a 7-year-old female with history of recurrent acute otitis media, hypogammaglobulinemia and autoimmunity diagnosed with Kabuki syndrome.

Patient Presentation
Our patient is a 7-year-old girl with a complex medical history including repaired congenital heart disease, hypotonia, global developmental delay, hypogammaglobulinemia and Evan’s syndrome who presented to our institution for immune evaluation.
In brief, during her infant and early toddler years, she was noted to have hypotonia and global developmental delay requiring supportive services including physical and speech therapies. She also had previous surgery for velopharyngeal insufficiency, and placement of tympanostomy tubes for recurrent acute otitis media.
At the age of 5, she presented with extensive bruising and isolated profound thrombocytopenia. She was diagnosed with immune thrombocytopenia (ITP) which was treated with a total of two doses of intravenous immunoglobulin (IVIG) with an initial positive response. However, in the ensuing months, she had recurrent oscillating severe thrombocytopenia despite being asymptomatic. She was subsequently diagnosed with Evan’s syndrome when she developed autoimmune neutropenia; her hemoglobin level remained normal despite a positive direct antiglobulin test and elevated reticulocyte count which suggested autoimmune hemolysis. She had a history of extensive genetic testing which included chromosomal microarray negative for DiGeorge syndrome, genetic testing for neurodevelopmental disorders which showed several variants of uncertain significance that did not fit when clinically correlated, and finally genetic testing for autoimmune lymphoproliferative syndrome which was negative.
At the age of 7, when she presented to our institution, her physical examination included dysmorphic facies described as long palpebral fissures bilaterally, broad nasal bridge with a flattened nasal tip and widely spaced teeth. She was also noted to have short stature, splenomegaly, mild global hypotonia and intellectual disability. This array of findings in the context of her complex past medical history of recurrent ear infections, hypogammaglobulinemia and autoimmunity raised our suspicion for Kabuki syndrome.
**Diagnosis**
The heterozygous pathogenic variant, c.5891C>T, causes a premature translational stop signal in exon 26. This leads to a loss-of-function of the KMT2D gene resulting in autosomal dominant Kabuki syndrome.

**Testing**
The count and distribution of her T-, B-, and NK-cell subsets were normal for age. She demonstrated suboptimal protection to Streptococcus pneumoniae with adequate antibody titers to only 6 of 23 serotypes. Her quantitative immunoglobulins included a low IgG at 480 mg/dL (normal range: 667 to 1179 mg/dL), low IgA 33 mg/dL (normal range: 79 to 169 mg/dL) and normal IgM 58 mg/dL (normal range: 40 to 90 mg/dL). Ultimately, genetic testing for KS revealed one pathogenic heterozygous variant, c.5677C>T, (p.Gln1893*) and one heterozygous variant of uncertain significance, c.5891C>T (p.Pro1964Leu), in the KMT2D gene.

**Treatment**
Fortunately, despite her hypogammaglobulinemia, she has not experienced recurrent infections since the placement of tympanostomy tubes. Nonetheless, from an immunologic standpoint, she will require continued surveillance of complete blood counts and immunoglobulin levels. If she develops frequent or severe infections, she may benefit from booster vaccinations, prophylactic antibiotics, and/or IVIG replacement therapy. Further doses of IVIG or other immunomodulating agents may be required if she becomes clinically symptomatic due to her autoimmune cytopenias.

**Patient Outcomes**
Arriving at the correct diagnosis has profound implications for her long-term management and outcome. Early evaluation and intervention from an immunodeficiency perspective can help prevent recurrent infections that may otherwise lead to consequences such as bronchiectasis or interstitial lung disease. Overall, KS patients have a predilection for development of inflammatory or autoimmune disorders, gastrointestinal problems and even malignancies, so any new signs or symptoms will need to be addressed and monitored closely over time.

**Lessons Learned**
KS is a rare multisystemic genetic disorder with an estimated prevalence of 1/32,000 people. It is characterized by distinctive facial features, short stature, intellectual disability, skeletal and visceral abnormalities in addition to immune dysregulation. KS is due to pathogenic variants in KMT2D (autosomal dominant inheritance) and KDM6A (X-linked inheritance) which encode for proteins involved in the COMPASS complex. The COMPASS complex helps with transcription of the AID complex involved in somatic hypermutation and class-switch recombination. It is hypothesized that epigenetic modulations in KMT2D and KDM6A may cause dysfunction in this process leading to immunodeficiency. The COMPASS complex is also involved in regulation of FOXP3, a key gene involved in differentiation of naïve CD4+ T cells into T-regulatory cells; thus, pathogenic variants in KMT2D and KDM6A may epigenetically modify FOXP3 function resulting in faults in T-cell tolerance which manifest as autoimmunity.

The immunopathology seen in KS is heterogeneous, but can include increased susceptibility to infections, reduced serum immunoglobulin levels and/or autoimmune conditions such as ITP, autoimmune hemolytic anemia, thyroiditis and vitiligo. The prevalence of immunodeficiency and
Autoimmunity increases with age. A previous study by Margot et al. showed that 18% of children versus 35% of adults manifested hypogammaglobulinemia and only 6% of children versus 26% of adults manifested autoimmune disease. It is also known that these comorbid autoimmune conditions have a more severe chronic or relapsing course in KS patients compared to the general population. Thus, periodic examination of immune health can allow for early diagnosis, timely intervention and reduction in long-term consequences.

Overall, KS patients often display a unique physical phenotype that may heighten clinical suspicion for this diagnosis. However, clinicians should be aware that there is high interindividual variability in the immunological phenotype on a wide spectrum from asymptomatic to immunodeficiency or autoimmunity, or both. Once KS is diagnosed, prompt referral to an immunologist may help improve long-term outcomes for these patients.
Snailed it! The Mysterious Case of Contact Dermatitis.

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**Summary**  
Allergic contact dermatitis (ACD) is a T-cell mediated inflammatory response caused by exposure to an allergen in previously sensitized individual. Approximately 20% of adult individuals experience ACD, most commonly affecting women between 20-55 years of age. ACD typically presents as a localized eruption in areas of allergen exposure. Generalized reactions are much less frequently reported. Here we present a unique case of erythroderma resulting from a presumed contact allergy to a “Snail Slime” face mask, applied overnight to the patient’s face and body.

**Patient Presentation**  
A 49-year-old female with no past medical history, presented with a widespread erythematous pruritic maculopapular rash associated with facial and bilateral hand swelling for five days. Initially, the rash began on her palms and forearms and spread to her arms, neck, face, trunk, back, and lower extremities legs. She was unable to take her rings off her hands given the extent of swelling. She reported fever to 102.5F and no relief of symptoms with Benadryl. She denied a history of dermatologic disease, asthma, allergic rhinitis, or known allergies. No new insect, outdoor, workplace, lotions, detergent or food exposures. She denied recent travels, recent tampon or pad exposures. No recent sexual activity. She did recently start using intranasal methamphetamine 2-3 weeks prior, last use was the day after the rash onset. Upon further questioning, she reported using “Snail Slime” face mask the night before the rash developed, and on several other occasions in the past month, without reactions. She applied the sheet mask to her face and spread the remaining liquid across her body.  
On admission, she was febrile to 102.5F and tachycardic to 119. Physical exam demonstrated a generalized, blanching erythematous maculopapular rash involving the palms and sparing the soles of the feet with small islands of uninvolved skin between coalescing rash. The palmar surfaces were raised and hyperkeratotic. The fingers, palms, neck, face, and lips were notably edematous, and the skin felt taught and warm to touch. The oral mucosa was uninvolved.

**Diagnosis**  
ACD is a T-cell mediated delayed-type IV hypersensitivity reaction caused by exposure to an allergen in previously sensitized individuals. Sensitization typically takes 10-14 days and depends on several factors including frequency and duration of exposure, site of application, amount of product applied, and integrity of the skin. Re-exposure to the allergen following this sensitization phase results in dermatitis.

**Testing**  
Laboratory tests revealed LDH 415, CRP 41.9, ESR 45, procalcitonin <0.5, WBC 9.8. On Day 2, LDH increased to 636. Absolute eosinophil and IgE levels were within the normal range. Viral panel, HIV, and RPR were negative.

**Treatment**  
Given concern for ACD, she was started on IV methylprednisolone 60mg TID, IV Benadryl 50mg TID and Triamcinolone 0.1% cream BID on affected areas. She was discharged on a Prednisone 60mg two-week
taper with instructions to continue applying triamcinolone 0.1% cream twice daily. She was referred to an allergist for patch testing.

**Patient Outcomes**
Our patient was discharged following successful treatment with systemic and topical corticosteroids and was unfortunately lost to follow-up before patch-testing could be performed to confirm snail slime extract allergy and test for other potential allergens including fragrances and essential oils which are occasionally contained within facemasks.

**Lessons Learned**
This case demonstrated that careful history is imperative in the practice of allergy/immunology given that patients may not report allergic reactions to products that are used regularly. Our patient did not report that she used the snail mask until further interrogation on the next day of admission. She believed that it would be impossible to react to a product that was not new to her. Allergic contact dermatitis requires sensitization phase before onset, which is a critical piece of information to gather for definitive diagnosis. No prior cases of snail mask or slime allergies have been reported, therefore we did not have a significant amount of data to compare too.
“Shift in Food Culture exposing Novel Food Allergies: Buchanania ianzan – Exposed”

Author Megha Vashist
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Summary
With the shift in food culture from producer based to consumer based there has been a focus on clean, diverse, and authentic foods leading to the incorporation of more exotic foods. Allergies to foods such as milk, tree nut, peanuts, etc. are widely known and it is rare to go to a restaurant that doesn't accommodate to these restrictions or have alternatives. Surprisingly, not much is known about allergies to exotic foods. In this case, we discuss the first case of allergy to buchanania ianzan (BI) seed, otherwise known as charoli- an almond flavored tree nut native to India used predominantly in Indian dishes. In regards to this, we will discuss a 6 year old boy who developed nasal itching, rhinorrhea, and vomiting after consumption of nutmeg and charoli. Presence of an allergen mediated IgE reaction was confirmed with a positive result to charoli skin prick and puddle test. Little is known about charoli allergy and with the ongoing changes in food trends, it is important to be cognizant of allergies and cross-reactivity to novel foods.

Patient Presentation
A 6 year old boy, well known to the pediatric allergy clinic for allergy to tree nuts, peanuts, sesame and non-baked egg, presented with complaints of rhinorrhea, nasal itching, and vomiting after ingestion of a dish containing nutmeg and charoli. He was treated at home with Benadryl resulting in resolution of symptoms.

Diagnosis
Based on symptoms and results of testing, the diagnosis of charoli allergy was made.

Testing
In order to confirm diagnosis, skin testing using charoli and nutmeg extracts were performed. Histamine 10mg/mL was used as a positive control and saline 0.9% was used as the negative control resulting in a 9mm wheal and no wheal respectively. Prick-to-prick technique and puddle test were performed for both charoli and nutmeg. Prick-to-prick testing involving a prick to food of interest followed by an intradermal skin prick resulted in a 13mm wheal to charoli and 0mm wheal to nutmeg. Puddle-prick test, in which a drop of extract made of charoli and nutmeg were placed on the skin followed by a prick through the drop into the skin resulted in a 42mm wheal to charoli and 0mm wheal to nutmeg. Based on symptoms and results of testing, the diagnosis of charoli allergy was made and patient was instructed to refrain from charoli and dishes containing charoli along in addition to counseling on proper Epi Pen usage that the patient already had.

Treatment
The patient was instructed to refrain from charoli and dishes containing charoli. In addition, further counseling on proper Epi Pen usage was provided.
Patient Outcomes
The patient adhered to the given recommendations and remained asymptomatic.

Lessons Learned
Given the increasing prevalence of food allergies and popularity of food trends leading to incorporation of exotic foods, it is important to be aware of new food allergies. Tree nuts have been widely known to cause allergy – amongst these tree nuts is charoli, used commonly in Indian dishes. Due to its high protein content (~22%), the oil extracted from the nut has been used in place of almond and olive oil. In a study conducted by Kumar. S, et. Al. allergenic potential of BI was demonstrated via identification of several prominent IgE binding proteins in sera of mice sensitized with BI crude protein extract and in patients with positive skin prick test to BI. Furthermore, high levels of specific IgE, IgG, Th1/Th2 cytokines, histamine, prostaglandin D2, cysteinyl leukotriene, and mast cell expansion in spleen, liver, and intestine as well as up-regulation of CD4 + T cells, CD 8+ T and B cells, mouse mast cell protease-1, thymic stromal lymphopoietin, and transcription factors actively involved in systemic reactions in food allergy were found in BI sensitized mice. Immunoblotting revealed cross reactivity of IgE binding proteins in crude extract of cashew, pistachio, and peanuts in sensitized mice. Additionally, clinical symptoms such as puffiness around eyes and mouth, diarrhea, increased respiratory rate, wheezing, labored respiration, perioral cyanosis, and a death were observed in BI sensitized mice after intraperitoneal injection of BI crude protein extract. These findings demonstrate the importance of being cognizant of food allergy to novel foods, especially in individuals with documented food allergy.
Cyclophosphamide desensitization in a pediatric patient with Ewing’s sarcoma

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Summary
Patient is a 13-year-old female with history of Ewing’s sarcoma of the right pubic ramus who is receiving chemotherapy per protocol AEWS0031. This includes alternating cycles of cyclophosphamide/vincristine/doxorubicin and ifosfamide/etoposide every two weeks. During cycle one, she developed facial swelling, flushing and pruritus along with eye burning and peri-oral numbness/tingling 30 minutes into cyclophosphamide infusion. She tolerated cycle two with ifosfamide/etoposide although she was pretreated with dexamethasone and diphenhydramine. During cycle three, she again developed lip swelling and tingling 25 minutes into cyclophosphamide despite pretreatment with dexamethasone and diphenhydramine. Allergy/Immunology was consulted prior to the next cycle given concern for immediate hypersensitivity reaction to cyclophosphamide and its requirement for future chemotherapy. Decision was made to forgo skin testing because desensitization would be performed regardless of result given convincing clinical picture. Therefore, a 12 step desensitization protocol was developed and patient was able to tolerate cyclophosphamide without further issue.

Patient Presentation
Patient is a 13-year-old previously healthy female with history of Ewing’s sarcoma of the right pubic ramus who is receiving chemotherapy per protocol AEWS0031. Her therapy plan includes alternating cycles of cyclophosphamide/vincristine/doxorubicin and ifosfamide/etoposide every two weeks. She also receives mesna prior to ifosfamide and cyclophosphamide infusion in addition to four and eight hours later. During cycle one, she developed facial swelling, flushing and pruritus along with eye burning and peri-oral numbness/tingling 30 minutes into cyclophosphamide infusion. Infusion was stopped and she received a dose of diphenhydramine which helped resolve symptoms; however, same symptoms returned after restarting cyclophosphamide infusion so it was discontinued early. Decision was made by primary team to pretreat her next cycle of ifosfamide/etoposide with dexamethasone and diphenhydramine since ifosfamide has a similar chemical structure to cyclophosphamide. She tolerated this infusion without issue. During cycle three, she again developed lip swelling and tingling 25 minutes into cyclophosphamide despite pretreatment with dexamethasone and diphenhydramine. She was given a dose of cetirizine and infusion was stopped early. She was able to tolerate cycle four of ifosfamide /etoposide again with pretreatment.

Diagnosis
Allergy/Immunology was consulted prior to her fifth cycle with cyclophosphamide. There was initial question by the primary team if she was having a hypersensitivity reaction to the cyclophosphamide or mesna. However, her symptoms occurred within 30 minutes of both cyclophosphamide infusions and she was able to tolerate mesna during her other cycles with ifosfamide. Therefore, we suspect that she has an IgE mediated hypersensitivity reaction to cyclophosphamide.

Testing
Skin testing would have been an option but we had enough clinical data to suspect cyclophosphamide as the source of her symptoms. Lastly, cyclophosphamide is broken down into a number of metabolites...
and it is possible that individuals may have an IgE mediated reaction to one of the metabolites. In this case, skin testing would be negative to cyclophosphamide itself which may be falsely reassuring as metabolites are not easily available for skin testing.

**Treatment**

A 12 step desensitization protocol for cyclophosphamide was developed with the help of pharmacy and oncology. Given that our institution did not have a standardized cyclophosphamide desensitization protocol, it was adapted from Castells’ 12 step protocol for rapid drug desensitization to chemotherapeutic drugs. Prior to the start of desensitization, she was pretreated with dexamethasone, diphenhydramine and ranitidine. Three concentrations of the cyclophosphamide were then prepared: 0.1 mg/ml, 1 mg/ml and 10 mg/ml. Steps one through four used the 0.1 mg/ml concentration and administered doses of 0.0384 mg, 0.0768 mg, 0.192 mg and 0.384 mg increasing every 15 minutes. Steps five through eight used the 1 mg/ml concentration and administered doses of 0.96 mg, 1.92 mg, 3.84 mg and 7.68 mg increasing every 15 minutes. Steps nine through eleven used the 10 mg/ml concentration and administered doses of 19.2 mg, 38.4 mg and 76.8 mg increasing every 15 minutes. The last step included the same concentration administered over 174 minutes for a dose of 1770.5 mg. Her full dose was 1920 mg. The desensitization was performed in our day medicine unit with 1:1 nursing and vitals taken at the end of each step. Total time for the desensitization protocol was 5 hours and 39 minutes.

**Patient Outcomes**

She underwent the cyclophosphamide desensitization without any adverse events. The plan will be to continue her current chemotherapy protocol and perform desensitization each time she requires cyclophosphamide.

**Lessons Learned**

Chemotherapy agents have many associated adverse drug reactions. The most important lesson from this case is to recognize potential anaphylaxis as one of those reactions. However, it can be especially difficult to determine the culprit when multiple agents are used in conjunction. For this case, the patient had already undergone four cycles of chemotherapy so we had enough clinical data to recognize cyclophosphamide as the likely cause. In other instances, it may be helpful to perform skin testing. Yet, this may not always be reliable. In a case report by Rosas-Vargas et al., a 13-year-old boy skin tested negative to cyclophosphamide twice despite having a hypersensitivity reaction requiring desensitization. Patients may actually be sensitive to one of the metabolites of cyclophosphamide so additional skin testing to its metabolites may also be necessary. Lastly, we have shown successful desensitization in a pediatric patient who required continued use of cyclophosphamide using a 12 step rapid drug desensitization protocol.

References:


Case of an infant with FPIES triggered by egg developing IgE mediated egg allergy

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Summary
This is a case of a 7-month-old male infant with moderate eczema found to have negative skin prick testing (SPT) to egg and subsequent food protein induced enterocolitis syndrome (FPIES) triggered by egg. Infant developed profound repetitive vomiting two hours after ingestion. Infant was also diagnosed with concurrent soy triggered FPIES. 11 months after the initial FPIES reaction to egg, egg reintroduction was attempted and the infant developed hives within 10 minutes of ingestion, however, without any vomiting or diarrhea. At a subsequent follow-up visit, repeat SPT and serum specific IgE testing were largely positive for egg, thus demonstrating a conversion between non-IgE mediated and IgE mediated allergies. While atypical FPIES is better described for cow’s milk, there is limited data with other food triggers such as egg.

Patient Presentation
Patient is a 7-month-old male, with history of moderate eczema, who presented to Allergy/Immunology clinic for concern for food allergies. Infant was exclusively breastfed until 5 months of age, without any maternal dietary restrictions. Initial consultation was due to a localized immediate flat red rash appearing after skin contact to hummus and peanuts. SPT was performed for sesame seed, garlic, peanut, and egg, all of which were negative. Thus, the reactions to hummus and peanuts were thought to be irritant reactions rather than true allergies. Egg and peanut introduction was recommended. However, 2 hours after egg ingestion at home, infant started repeatedly vomiting, at least 10 times in small-medium amounts. Thereafter, he was noted to be lethargic, prompting evaluation at an emergency department (ED). Eventually he returned to baseline without requiring intravenous fluid resuscitation. In discussion with allergy, the clinical picture was consistent with FPIES and diet was restricted of egg, rice and oats.

10 days later, a similar reaction was appreciated after tofu ingestion, however clinical picture complicated by sick contact. FPIES triggered by soy was confirmed with repeat introduction of tofu couple weeks later.
At 12 months of age rice and oat were successfully introduced to the patient without issue. At 17 months of age, 11 months since his initial reaction to eggs, egg were rechallenged at home. He initially tolerated baked egg. However after several bites of French toast, within 10 minutes, he developed a red, itchy rash consistent with hives on his face and neck as well as eye swelling. He was treated with Benadryl and symptoms resolved within 1 hour. This was consistent with an IgE mediated reaction.

Diagnosis
Given the clinical history, timeframe and character of symptoms with resolution of symptoms by food avoidance) and negative initial SPT, this infant was diagnosed with FPIES triggered by egg and soy. After avoiding egg for 11 months from the last reaction, egg was rechallenged. However, clinical symptoms, along with SPT and serum IgE testing, were consistent with the development of an IgE mediated egg
allergy. Therefore, this child demonstrates an atypical FPIES picture with a possible component of phenotype conversion.

Testing
The diagnosis of FPIES is clinical. Oral food challenges can be confirmatory, however, given the suggestive clinical history with initial SPT was negative for egg, this was not indicated in our case. Serum specific IgE testing was not indicated. 11 months after the reaction, prior to reintroduction, testing was not repeated.

With the subsequent reaction to the reintroduction of eggs and concern for IgE mediated allergy, repeat SPT for egg was performed and was largely positive (12 mm wheal) along with serum specific IgE testing, showing ovomucoid IgE at 5.78 kU/L and egg white IgE at 11.50 kU/L. This demonstrated the development of an IgE mediated egg allergy in an infant who initially presented with clear diagnosis of egg induced FPIES and initial negative SPT for egg.

Treatment
The mainstay of therapy for acute FPIES reactions includes rehydration and antiemetics, both which this infant received with each acute episode. No antihistamines or epinephrine was given as it is not indicated. Outside of acute reactions, the treatment for FPIES is to avoid known and most common food triggers.

Most cases of FPIES resolve as the child grows older, being completely gone by 3-4 years of age. Although there are no clear guidelines, introduction of common trigger foods is recommended at 12 months of age with trigger rechallenges to occur 12-18 months after initial reaction. In our case, rice and oats were introduced at 12 months of age with good tolerance. Eggs were reintroduced after waiting 11 months. Although there were no symptoms consistent with an FPIES reaction upon rechallenge, the patient demonstrated an IgE mediated allergy to egg, despite initial testing being negative. Thus, egg continued to be restricted from the diet and was to be followed over time. An epinephrine auto-injector was prescribed to the patient.

Patient Outcomes
Prognosis for FPIES is very good with most children outgrowing the allergy by 3-4 years of age. Thus, by avoiding the food triggers, soy and egg, this infant did not have any further episodes of FPIES and was able to regain weight after slow reintroduction of wheat, rice, oats, peanuts, legumes, and other foods. By 17 months of age and waiting 11 months since the initial reaction, the infant did not have any FPIES like reaction upon reintroduction of egg. However, what is interesting about this case is that this child subsequently developed an IgE mediated reaction to egg after this period of avoidance; thus, demonstrating a possible conversion of phenotypes between non-IgE mediated and IgE mediated reactions.

Lessons Learned
Here we present a novel conversion of an egg FPIES, a non-IgE, Th2 cell mediated food allergy, into an IgE mediated phenotype. There have been studies by Caubet, et al discussing the complex relationship of FPIES and IgE mediated allergies. There is scant data about foods, in particular egg, transitioning between non-IgE and IgE mediated food allergy phenotypes. Caubet et al, demonstrate a similar transition of milk FPIES to an IgE mediated phenotype. They describe their experience of 160 patients with FPIES and found that 24% had evidence of IgE sensitization to the FPIES-inducing food and 10% of
patients with cow’s milk induced FPIES developed IgE mediated allergy to cow’s milk secondarily. Others such as, Miceli Sopo et al and Barni et al describe infants with either cow’s milk or egg IgE mediated allergy, with subsequent negative SPT testing and resolution of clinical symptoms but development of FPIES during OFCs; thus, suggesting conversion of one allergic phenotype to another particularly to the same food. There have also been cases demonstrating conversion between two allergic phenotypes after food removal for treatment of atopic diseases such as eosinophilic esophagitis and atopic dermatitis. Thus, these studies demonstrate that there may be a mixed process at play as we see in atypical FPIES. Better understanding of the interplay and pathophysiology of T cell mediated and IgE mediated food allergies is needed. Our case adds to the growing discussion on this complex relationship by further demonstrating the conversion between allergic phenotypes and the importance of getting initial baseline as well as follow up SPT IgE testing for patients presenting with FPIES prior to reintroduction.

Works Cited
A premature infant with CHARGE Syndrome and partial thymic aplasia

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Summary
This patient is a premature male infant with numerous anatomic anomalies including bilateral colobomas, congenital heart defects, intrauterine growth restriction, micropenis (<1.3cm), aplasia of the semicircular canals, stenosis of external auditory canals, and bilateral choanal atresia consistent with CHARGE syndrome. Based on findings of profound T-cell immunodeficiency, the patient may represent the “complete DiGeorge” subtype of patients with CHARGE syndrome previously described in the literature.

Patient Presentation
The patient was born prematurely at 30 weeks and 5 days gestational age. Shortly after birth, he developed respiratory distress and hemodynamic instability requiring intubation and several minutes of CPR. Prostaglandin was started due to concern for borderline left heart structures and possible coarctation on fetal ultrasound. Postnatal echo revealed VSD, ASD, moderately sized PDA, and mild aortic isthmus/left ventricular outflow tract hypoplasia. Severe pulmonary hypertension was later identified secondary to premature lung disease with superimposed edema. When a nasogastric tube was unable to be passed, CT of the sinuses revealed mid-face hypoplasia and bilateral choanal atresia. Genetic testing subsequently confirmed CHARGE syndrome. At two weeks of life, the patient developed increased respiratory requirements and was found to have E. coli tracheitis, which was treated with antibiotics. Two weeks later, the patient was found to have purulent material in the lungs during bronchoscopy, and cultures later demonstrated Staphylococcus epidermidis tracheitis/pneumonia. Following a newborn screen demonstrating low TRECs, the patient was found to have profound T cell lymphopenia secondary to likely thymic maldevelopment. Lymphocyte subset analysis was notable for markedly low T cells, intact B and NK cell lines, and normal quantitative immunoglobulins (see Table 1). He was started on monthly immunoglobulin therapy.

Diagnosis
The patient satisfied criteria for a diagnosis of CHARGE syndrome based on both clinical findings (coloboma, heart defects, atresia of choanae, retardation of growth, genital underdevelopment, and ear abnormalities) and genetic testing demonstrating a new mutation in the CHD7 gene. From an immunologic perspective, the patient meets criteria for partial athymia, including very low levels of naive T cells (< 50/mm3 CD3+ T cells co-expressing CD45RA and CD62L) and very low levels of TRECS (TRECS< 100 per 100k T cells). Repeat qualitative immunoglobulins demonstrated low IgG, suggesting the absence of T-cell driven B cell activation.

Testing
While initial patient management focused on respiratory and cardiac stabilization (as well as endocrine workup due to finding of micropenis at birth, which was reassuring for normal gonadal, adrenal, and thyroid axes), the finding of low TREC levels on newborn screen prompted further immunologic investigation. Initial lymphocyte subset analyses demonstrated low levels of T-cells concerning for SCID, 22q11 deletion, prematurity, or other lymphocyte deficiency. Repeat lymphocyte subsets were performed with
CD45RA/RO cells to differentiate the infant’s production of naive T cells from circulating maternal T cells, which demonstrated congenital immune deficiency. Genetic testing with an immunodeficiency gene panel revealed a stop codon (pathogenic variant) in CHD7 c.4318C>T p.Gln1440*, confirming the diagnosis of CHARGE syndrome with likely associated immunodeficiency. Monthly lymphocyte subset analysis is ongoing, as T-cell number may improve with age, as is sometimes seen in 22q11.2 deletion syndromes.

**Treatment**

As a syndrome with multisystem involvement, the treatment of this patient with CHARGE syndrome complicated by T cell lymphopenia required a multifactorial approach. To address his craniofacial anomalies, the infant underwent surgical repair of his choanal atresia at approximately 2 months of life. Following two failed attempts at medical PDA closure with Indocin and Tylenol, catheter device closure of the PDA was also performed at this time. Given his profound T cell immunodeficiency, basic management of SCID was followed including no live vaccines, CMV negative and irradiated blood products (when required), indefinite anti-fungal and pneumocystis pneumonia prophylaxis, and monthly immunoglobulin replacement, given the risk for hypogammaglobulinemia/impaired B cell function in the absence of functioning T cells. The patient required decolonization for MSSA and broad spectrum antibiotic treatment for both E. coli tracheitis and S. epidermidis tracheitis.

**Patient Outcomes**

This patient’s condition remains guarded. Due to impairment in thymic development resulting in impaired functional T cell production, thymus transplant rather than hematopoietic stem cell transplant is considered the most suitable definitive therapy in this condition, as bone marrow reconstitution via bone marrow transplant or infusion of peripherally harvested lymphocytes has poorer outcomes (ie. higher risk for death and graft failure). Unfortunately only two institutions worldwide offer this therapy, Duke University and Great Ormand Street (UK). This case is currently being discussed with the thymic transplantation team at Duke to evaluate potential future options.

**Lessons Learned**

The spectrum of immunodeficiency in CHARGE syndrome is still incompletely understood, and can range from asymptomatic derangements in absolute T-cell numbers to life-threatening severe combined immunodeficiency (SCID), referred to as the “complete DiGeorge” subtype (Wong et al. EJHG 2015; Mehr S et al. AJMG 2017). This latter subtype, thought to correlate with thymic maldevelopment, involves stem cells that are produced in normal numbers but cannot undergo thymic education and maturation. As many as 80% of patients with CHARGE syndrome in cross-sectional studies have been found to have decreased or absent T-cells, with a majority also demonstrating insufficient B cell responses and recurrent infections (Wong et al. EJHG 2015). In the present case, while our patient does not have total absence of T-cells consistent with complete thymic aplasia, his significant reductions in T-cells with associated B-function impairment (in addition to recurrent infections) strongly argue for a partial thymic aplasia. Importantly, there is a growing awareness that the immune dysfunction in CHARGE may contribute to the morbidity and mortality of the syndrome (Jyonouchi et al. Pediatrics 2009), and that the overlap between CHARGE and other multiple congenital anomaly (MCA) syndromes may reflect the shared molecular pathways of CHD7 and other genes (e.g. TBX1, JAGGED1, FGFR1), particularly due to the recognized role of CHD7 in thymic development. A better understanding of the
immune dysfunction in CHARGE is critical both for optimal treatment of affected individuals, and to enrich our understanding of immune regulation overall.

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Atypical course of Idiopathic CD4 Lymphocytopenia

Author Prudhvi Regula, MD; Harry A Lee, MD, FAAAAI
Training Program UAB Montgomery Internal Medicine residency program

Summary
Idiopathic CD4 lymphocytopenia is a rare condition characterized by persistent CD4 lymphocytopenia in the absence of HIV infection or other causes of immunodeficiency. Usually, patients are diagnosed after they present with an opportunistic infection and need antibiotic prophylaxis for the prevention of opportunistic infections. We report a case of ICL who was diagnosed during the evaluation of chronic fatigue without any opportunistic infections at the time of diagnosis. Even though the patient chose not to take prophylaxis, she remained asymptomatic without opportunistic infections during close follow-up appointments.

Patient Presentation
The patient is a 44-year-old caucasian female with allergic rhinitis who was referred for evaluation of low CD4 count which was detected during a thorough workup for chronic fatigue and chronic generalized pruritus from her primary physician office. She had a remote history of fungal skin infection which was not seen at the time of presentation. During her childhood, she had a few episodes of sinus infections. The patient was not exposed to immunosuppressant medications or steroids in the past.

Diagnosis
A diagnosis of ICL was made after excluding HIV infection, viral infections, autoimmune conditions, hematological malignancies, and other immunodeficiency conditions.

Testing
Laboratory testing confirmed a low absolute count CD4 count of 85 cells/mm³. She was HIV negative. Laboratory testing was repeated after 4 months which showed persistent CD4 lymphocytopenia (100 cells/mm³) with a negative HIV. Viral infections like parvo B19, HSV-6, EBV were ruled out. No mycobacterial infections or autoimmune conditions were detected. No evidence of hematological malignancy was found (but a bone marrow biopsy was not performed). Testing for other immunodeficiencies including complement levels and functioning were within normal limits.

Treatment
Antibiotic prophylaxis with trimethoprim-sulfamethoxazole for Pneumocystis jirovecii pneumonia was planned, but the patient was reluctant to use as she had a significant skin rash and itching with TMP-SMX before. Alternative antibiotics were discussed with the patient and she refused to take medications as she was not having an infection. The patient was educated about the risk of developing opportunistic infections with several possible infectious agents and she still wanted to watch without antibiotics.

Patient Outcomes
The patient was closely followed-up for opportunistic infections for more than 4 years and has not developed any so far. Her CD4 count on multiple occasions continued to remain low (less than 100 cells/mm³) along with a negative HIV test.
Lessons Learned

ICL is defined by persistent lymphocytopenia in the absence of HIV infection or other causes of immunodeficiency. CD4 counts should be less than 300 cells per cubic millimeter or less than 20% of total lymphocytes on separate occasions, usually two to three months apart. ICL is a rare condition, first described in 1992, found worldwide and has no gender predilection. The pathogenesis is unknown and unclear. Clinical manifestations range from asymptomatic patients with isolated laboratory finding to life-threatening opportunistic infections. Common opportunistic infectious agents include candida, cryptococcus, human papillomavirus, varicella-zoster virus and mycobacteria, Pneumocystis jirovecii. ICL is a diagnosis of exclusion. HIV infection, congenital immunodeficiencies, malignancies, and exogenous causes of immune dysfunction must be excluded. The prognosis is variable and depends largely on the severity of the clinical presentation, with most severe infections occurring at diagnosis or soon thereafter. In most patients, CD4 values remain stable rather than progressing to the very low levels seen in untreated HIV infection. There are no treatment guidelines established for this condition. The main treatment modality is the prevention of opportunistic infections and treatment of infection if they occur. Some studies say that same prophylaxis guidelines for HIV can be followed for ICL.

This patient described above had no opportunistic infections at the time of presentation. She was diagnosed during a thorough evaluation of her chronic fatigue. Even though the patient was not on antibiotic prophylaxis, she remained asymptomatic for several years after initial diagnosis and has not developed opportunistic infections during close follow-up appointments. Her CD4 count was very low (<100 cells/mm³) on most follow-up visits. This suggests that there could possibly be other factors that influence the development of opportunistic infections in these patients apart from a low CD4 count. It also implicates that the degree of CD4 lymphocytopenia may not correlate with the severity of the disease.

Selective IgA deficiency - a rare presentation of the most common immunodeficiency

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Summary
IgA deficiency is the most common primary immunodeficiency syndromes. Most patients have no clinical symptoms. We describe a patient with a history of significant bacterial infections found to have selective IgA deficiency. A 65-year-old female with a history of postpartum intracerebral hemorrhage complicated by a brain abscess and subsequent intractable epilepsy presented with recurrent bacterial infections. The patient reported multiple hospitalizations for status epilepticus requiring treatment with Phenytoin and Phenobarbital. Immunoglobulin levels were notable for an IgA of 9, IgG of 685, and IgM of 88. Two years after immunoglobulin levels were tested, she developed bacterial parotitis, osteomyelitis of the lumbar spine, osteomyelitis of the foot, repeated clostridium difficile infections, recurrent sinusitis, and chronic onychomycosis over a ten-year period. On day of presentation to clinic, immunoglobulin levels revealed an undetectable IgA, IgG of 847, IgM of 82 and poor pneumococcal vaccine response. IgG supplementation was initiated to reduce further infections.

Patient Presentation
Our patient is a 65-year-old female who presented to clinic for an immunodeficiency work-up. She had a history of eczema and indoor allergies. She described a long history of recurrent bacterial infections beginning after giving birth to her first child in 1992. Her pregnancy was complicated by an intracerebral hemorrhage requiring a craniotomy and shortly after she developed a brain abscess. She was treated with IV antibiotics for two months. She subsequently developed cerebral calcifications leading to intractable epilepsy requiring two additional craniotomies and multiple hospitalizations to treat status epilepticus. As a result, various anticonvulsants were used, most frequently Phenytoin and Phenobarbital. As her seizure frequency increased, she began developing severe bacterial infections. Over a ten-year period, she reported a bacterial parotid gland infection, osteomyelitis of the lumbar spine, osteomyelitis of her fourth digit of her left foot, three clostridium difficile infections, and chronic onychomycosis. She reported recurrent sinus infections since childhood. Family history included a son with recurrent sinus infections and pneumonia. She denied anaphylaxis after receiving blood products, autoimmune diseases or malignancy. Last administration of Phenytoin was over 5 years ago. Phenobarbital remained the primary anticonvulsant for her epilepsy dating back to 1992.

Diagnosis
Upon initial evaluation, our suspicions were high for selective IgA deficiency progression to common variable immunodeficiency. To our surprise, immunoglobulin G levels were normal. Severe bacterial infections are rare in selective IgA deficiencies as other immune defense systems help compensate for the deficiency including non-circulating IgM and neutrophils. Literature describes select IgA deficiencies with abnormal antibody responses to antigens.
Testing
Two years prior to the development of her parotid gland infection, immunoglobulin levels were obtained revealing an IgA of 9, IgG of 685, and IgM of 88. We repeated her immunoglobulin levels and found an undetectable IgA, IgG of 847, and IgM of 82. Flow cytometry showed normal B-cell and T-cell count. She had a normal response to protein antigen tetanus toxoid and diphtheria toxoid. She had an inappropriate polysaccharide antigen response to the pneumococcal vaccine.

Treatment
Due to the patients decreased response to polysaccharide antigens, a trial of IV immunoglobulin G replacement was initiated.

Patient Outcomes
Unfortunately, treatment was delayed due to the national shortage of IV immunoglobulin G. Treatment is scheduled to begin next month. Since her initial evaluation, she remains clinically stable.

Lessons Learned
It is unclear whether the patient had a primary selective IgA deficiency prior to her initiation of Phenytoin or if her IgA levels declined as a result of treatment with Phenytoin. Persistent undetectable levels of IgA after discontinuation of Phenytoin, suggests a primary immunodeficiency. Limited treatment options exist for IgA deficiency as IgA cannot be safely replaced or augmented. Antibiotics remain the gold standard for therapy. This case highlights the clinical usefulness of vaccine response in patients with severe infections with normal IgG levels. Impairment in this response provides an indication for the use of IV immunoglobulin G thus limiting the use of antibiotics and preventing further harmful infections.
Aspirin desensitization for aspirin-exacerbated respiratory disease; Aspirin for the chemoprevention of colorectal adenomas

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Training Program Montefiore Medical Center

Summary
We present a 68 year old female with aspirin exacerbated respiratory disease (AERD); aspirin hypersensitivity, chronic rhinosinusitis with nasal polyps and severe persistent asthma, and a history of recurrent colonic adenomatous polyps who since the age of 23, had been found to have a great number of tubular adenomas. Multiple colonoscopies throughout the years identified at least 21 adenomatous colon polyps. Colon resection was considered. Genetic testing for hereditary colorectal cancer was done.
Given her concomitant 5-year history of AERD, aspirin desensitization had been offered to the patient for nasal polyp prevention and asthma control. She eventually underwent aspirin desensitization and to date, she remains on a regular dose aspirin (325mg) with noted benefits in her upper and lower airway disease.
Less expected, however, was the beneficial role aspirin would also have in the prevention of colorectal adenomas. Earlier this year, 3 years after being desensitized to aspirin, our patient had her first negative surveillance colonoscopy.

Patient Presentation
Our patient is a 68 year old female with history of chronic rhinosinusitis with multiple surgeries for nasal polyps, severe persistent asthma and history of recurrent colonic adenomatous polyps who was referred to our clinic for aspirin desensitization for management of her upper and lower airway symptoms. Throughout her life, she had undergone numerous colonoscopies with findings of multiple, large tubular adenomas to the point that colon resection was considered and discussed with patient. Little is known regarding our patient’s family history as she is adopted. She did, however, undergo genetic testing which ruled out genetic or hereditary polyposis syndrome. She was a former smoker who quit smoking after battling with multiple bouts of sinusitis and had considered aspirin desensitization for many years for improvement of this. Further motivation came upon learning aspirin’s role in colorectal cancer chemoprevention. Aspirin desensitization and continued use improved her upper and lower airway disease with the added benefit of serving a role as a chemopreventive agent in this patient with increased propensity to colonic polyp formation.

Diagnosis
Testing for our patient included multiple pulmonary function testing, nasal endoscopies and clinical evaluation which taken together, describe her as a subset of asthmatic patients with severe respiratory symptoms exacerbated by aspirin or NSAID exposure.

Testing
Testing for our patient included multiple pulmonary function testing, nasal endoscopies and clinical evaluation which taken together, describe her as a subset of asthmatic patients with severe respiratory symptoms exacerbated by aspirin or NSAID exposure.
Treatment
Aspirin desensitization followed by daily aspirin use. Aspirin desensitization is associated with significant reduction in both upper and lower airway symptoms, improvement in the sense of smell, decreased number of sinus infections, retardation of nasal polyp regrowth.

Patient Outcomes
In 2016, our patient started aspirin desensitization and till date she remains on regular dose aspirin (325 mg daily). Biologics including mepolizumab and benralizumab were tried but were not well tolerated given side effects. She has noted improvement with her nasal symptoms and asthma with her daily aspirin dose. In addition, surveillance colonoscopy done earlier this year (3 years after her last colonoscopy) showed no evidence of polyps for the first time. She is now planned for a surveillance colonoscopy in 2024.

Lessons Learned
Aspirin desensitization can be beneficial in some patients with aspirin-exacerbated respiratory disease (AERD). Well known is the benefit of patients with AERD and concomitant coronary artery disease who require daily aspirin. Another example of AERD patients that could benefit from aspirin desensitization are patients with rheumatological disorders (i.e. arthritis) or chronic pain syndrome. Here, we present a patient with AERD who has benefited from aspirin desensitization not only for improvement of her upper and lower airway symptoms, but also for use of aspirin as chemoprevention in colorectal neoplasia.
Heterogeneous Expression of CD40 Ligand: An Atypical Presentation of Hyper IgM Syndrome

Author Nicole Canon MD, Brian Modena MD
Training Program National Jewish Health/University of Colorado

Summary
A 45-year-old male presented to our institution with a previous diagnosis of Combined Variable Immune Deficiency (CVID) on Intravenous Immunoglobulin (IVIG) therapy, sarcoidosis, prostate carcinoma, orbital melanoma, multiple squamous cell carcinomas of the skin, splenomegaly status-post splenectomy, autoimmune hemolytic anemia (AIHA), and a propensity for severe bacterial as well as viral infections. Further evaluation revealed a low IgA, unremarkable IgG on IVIG, and normal IgM with CD40 ligand (CD40L) deficiency concerning for HyperIgM (HIGM) syndrome. Although the disease has been attributed to an X-linked inheritance pattern for CD40L deficiency, it has rarely manifested in a heterozygous population of CD40L deficient cells. We present an atypical presentation of HIGM in the setting of a heterogeneous expression of CD40L deficient cells.

Patient Presentation
A 45-year-old male with sarcoidosis, prostate carcinoma, orbital melanoma, recurrent squamous cell carcinoma of the skin, splenomegaly status-post splenectomy, AIHA, and recurrent infections presented for re-evaluation of previously diagnosed CVID. As a child, he had recurrent upper respiratory viral infections. By 1996, he was hospitalized for AIHA that required treatment with steroids. He did well until 2007 when he was hospitalized for nine months in the setting of severe Haemophilus influenzae pneumonia where he spent 3 months intubated with subsequent tracheostomy. On 2009, he had streptococcal meningitis and by 2015, he had 5 ICU admissions for pneumonias that led to intubations. Due to recurrent sepsis, he was initiated on IVIG for suspected CVID and had no recurrent episodes of sepsis. On 2017, he developed a ‘blood disorder’ that led to hospitalizations secondary to bleeding within his lungs and urinary tract. It was unknown if he had disseminated intravascular coagulation vs immune thrombocytopenic purpura vs ANCA-vasculitis but he had profound thrombocytopenia that resolved with steroids. Despite being on IVIG, he had ongoing recurrent sinus infections which occurred every 2 weeks which prompted his re-evaluation. He has no family history of consanguinity or immunodeficiency. He had no developmental delay, interstitial lung disease, brain lesions, or gastrointestinal disease. His father worked for a uranium plant until he was 6 years old.

Diagnosis
Given his multiple malignancies, AIHA, and immune deficiency with normal IgM populations, we suspected HIGM. Flow cytometry revealed his T cells were CD40L deficient although there was heterozygous expression among the cells tested. Although less likely, we have to consider CTLA-4 deficiency however he lacks intestinal involvement. Within HIGM, we cannot rule out subtypes that present similarly to X-linked HIGM such as CD40 gene deficiency in HIGM type 3. Given lack of opportunistic infections, activation-induced cytidine deaminase deficiency (AID) in HIGM Type 2 or uracil-DNA glycoslase (UNG) deficiency in HIGM Type 5 is still a possibility. Finally, with his low IgG and IgA, bronchiectasis, AIHA, history of cancers, and predisposition to recurrent infections, we still cannot rule out CVID with autoimmune features although this is a diagnosis of exclusion. Furthermore, the
presence of CD40L deficient cells and his infections with encapsulated organisms is more consistent with X-linked HIGM.

**Testing**

CBC with differential revealed no cytopenias. CMP showed no transaminitis or hypoalbuminemia. Quantitative immunoglobulin levels showed a low IgA, normal IgG in the setting of IVIG replacement, and normal IgM. Flow cytometry to CD40L revealed a heterozygous population of CD40L deficient cells. Memory B cell populations were normal. Bone marrow biopsy showed no blasts or abnormal cell populations. Lymph node biopsy demonstrated non-caseating granulomas without lymphoma. CT scan showed mid/lower lung bronchiectasis and multi-station lymphadenopathy with parenchymal septal thickening with perilymphatic nodularity. Testing for CD40L binding capacity and genetic mutations in the CD40 as well as CD40L genes are still pending.

**Treatment**

The patient remained on IVIG and was started on azithromycin by pulmonology to prevent recurrent lung infections. We are awaiting his genetic testing to verify the diagnosis of CD40L deficiency. Given that IVIG doesn’t protect against opportunistic infections in X-linked or CD40L deficient HIGM, we plan to start prophylactic azithromycin and trimethoprim- cotrimoxazole to protect against cryptosporidium and pneumocystis pneumonia respectively. He may be a future candidate for allogeneic hematopoietic stem cell transplantation for definitive treatment.

**Patient Outcomes**

While on IVIG, he had no major or opportunistic infections but continues to have chronic sinus infections which occur roughly every two weeks. Previously, he had lymphocytosis with 11,000 cells/L with no evidence of blasts peripherally. Given this lab finding and his multiple malignancies, we referred him to his oncologist for further evaluation and monitoring. He will follow with us for further management of his immune deficiency.

**Lessons Learned**

HIGM is a heterogeneous disorder characterized by recurrent infections, autoimmune disease, and a predisposition to malignancy. Approximately 70% of patients have X-linked HIGM which involves the CD40L gene located on the X-chromosome which encodes for CD40L. Due to its variation, deficiencies can stem from underproduction of CD40L or lack of the functional form of the protein. When this occurs, the interaction between CD40 in B cells and CD40L in T cells cannot occur leading to the inhibition of B-cell antibody isotype class switching. Thus, patients with HIGM have normal or elevated IgM with low levels of IgE, IgA, and IgG. Of note, Jhamnani et al reported that 7-23% of patients with CD40L deficiency may have detectable CD40L expression but dysfunctional proteins. Hence, a CD40L binding capacity assay should be performed before excluding HIGM. Furthermore, our population showed overall decreased levels of CD40L with varied expression of CD40L among the T cells in our patient. One hypothesis, although unlikely, is that the patient had two genetic codes (i.e. a chimera). Another possibility is that the CD40L is mutated and dysfunctional. In this scenario, incomplete binding of the antibody used for flow cytometry could have contributed to our findings. Finally, we cannot rule out a lab error and will repeat his flow cytometry to verify our test results. HIGM and CVID’s similar clinical presentation as well as laboratory findings can lead to misdiagnosis. Thus, we must keep in mind
that CVID is a diagnosis of exclusion. HIGM can be suspected based on clinical history but ultimately, mutation analysis should be used for definitive confirmation to allow for early targeted therapy.
Chest discomfort with allergic reaction – when it is more than wheezing and respiratory distress

Author Chirs Brooks
Training Program University of Minnesota

Summary
A 57 year old female with history of atopy, nasal polyps, and sinusitis presents with anaphylaxis after being given moxifloxacin. In addition to receiving standard treatment for anaphylaxis, she complains of chest discomfort and as part of her workup an electrocardiogram was performed, which showed evidence of possible acute coronary syndrome. She was eventually diagnosed with Kounis syndrome, which is acute coronary syndrome with the release of inflammatory mediators that causes coronary artery spasm.

Patient Presentation
The patient is a 57-year-old female with a past medical history notable for rheumatoid arthritis treated with leflunomide and etanercept; moderate to severe cough variant asthma treated with inhaled budesonide, fluticasone furoate, and vilanterol; allergic and non-allergic rhinitis treated with fexofenadine and fluticasone nasal spray; rashes following multiple drugs (sulfa, penicillin, and cefuroxime); venom allergy; chronic rhinosinusitis requiring left maxillary and ethmoid sinus surgery with continuous sinus symptoms over the previous 4-5 months; five past left nasal polypectomies; past tobacco use; and depression treated with citalopram and bupropion who initially presented to the emergency department with acute onset of throat and chest tightness and wheezing; dyspnea; blurry vision; lip swelling; pruritis of the upper palate; and itching, redness, and burning of her hands 40 minutes after an initial dose of moxifloxacin and prednisone for acute bacterial sinusitis. Two weeks prior to presentation she was prescribed doxycycline for a sinus infection. After a 1-week course of doxycycline without improvement she was started on a 1-week course of levofloxacin. After continued lack of improvement she had a head CT which found right paranasal sinus air fluid levels and then she was prescribed a 21-day course of moxifloxacin and prednisone. On initial exam she was noted to have urticaria of the face, swelling of the lips, minimal swelling of the tongue, and redness of the posterior oropharynx; stridor and wheezing; and urticaria on the abdomen, back and proximal thighs. She was given 0.5 mg of IM epinephrine, 50 mg of IV diphenhydramine, 20 mg of IV famotidine, 125 mg of IV methylprednisolone, and 0.5 mL of 2.25% racemic nebulized epinephrine. An additional 0.5 mg of IM epinephrine was given 10 minutes after the first dose. An electrocardiogram was obtained due to her chest tightness which found a septal infarct of undetermined age. She also had a marked ST abnormality and possible inferior subendocardial injury. With her respiratory distress despite multiple doses of IM epinephrine and racemic nebulized epinephrine and abnormal ECG, she was intubated for airway protection. No posterior oropharyngeal or vocal cord edema was noted during intubation. She had several episodes of unsustained ventricular tachycardia, with the longest being a five-beat run. She had a four-beat run of supraventricular tachycardia. She had some atrial arrhythmias and premature ventricular contractions as well. She did not require any antiarrhythmic agents. A follow up ECG one hour later showed continued evidence of septal infarct with Q waves in V1 and V2. Her troponins remained negative. She was extubated about 16 hours later and post extubation had no dyspnea, stridor, or wheezing. After 24 hours of IV methylprednisolone she was transitioned to 40 mg of oral
prednisolone daily. Echocardiogram was performed which found mid and basal septal and anteroseptal hypokinesis. A nuclear stress test shows a fixed anterior, anteroseptal and apical defect. She had no history of myocardial infarction, angina pectoris, or arrhythmia, although she did describe atypical chest discomfort for several months. At follow up from the hospital several days later, she was recommended to see allergy/immunology and a CT coronary angiogram was set up as an outpatient. She was discharged on 12.5 mg of metoprolol twice per day, aspirin 81 mg daily, and atorvastatin 20 mg daily, as well as a week total of oral steroids. She followed up in allergy/immunology clinic approximately seven months after her initial ED presentation.

**Diagnosis**
Kounis syndrome – concurrence of acute coronary syndrome with any mast cell mediated allergy, hypersensitivity, anaphylactic, or anaphylactoid insult. The release of inflammatory mediators including histamine, neutral proteases, arachidonic acid products, platelet activating factor and a variety of cytokines and chemokines are increased in blood and have been incriminated to induce coronary artery spasm and/or atheromatous plaque erosion or rupture.

**Testing**
Follow up electrocardiogram 9 months later was normal. With normalization of cardiac function and ruling out alternative diagnosis, Kounis syndrome was mainly a clinical diagnosis.

**Treatment**
Avoidance of future release of inflammatory mediators, both by avoidance of triggers that may elicit an allergic response as well as improved control of her underlying allergic pathologies including both rhinitis and asthma. Currently the patient is on montelukast 10 mg per day, fexofenadine 180 mg daily, and ranitidine 150 mg twice per day.

**Patient Outcomes**
Follow up electrocardiogram 9 months after the initial ED visit was normal.

**Lessons Learned**
Chest pain that is experienced during anaphylaxis may not be only due to only wheezing and respiratory difficulty, but may be due to true cardiac pathology. If the patient complains of chest pain, the clinician should ask about symptoms suggestive of acute cardiac pathology and a low threshold to obtain an electrocardiogram should be set.
Management of ADA-SCID Patient with Revcovi (elapegademase-lvlr) During Pregnancy

Author: Sofia Edwards-Salmon, MD
Training Program: Emory Pediatrics Residency Program

Summary
This is the first reported case of management of an ADA-SCID patient with Revcovi (elapegademase-lvlr) during pregnancy. A 31yo female with ADA-SCID presented to our urban academic clinic for management of her third pregnancy. Her first pregnancy (while receiving pegademase bovine (peg-ADA) enzyme replacement) resulted in a healthy baby girl while her second pregnancy was ectopic. During the patient’s third pregnancy, it was necessary to transition Adagen to Revcovi (PEGylated recombinant adenosine deaminase (rADA) enzyme) due to manufacturing issues. At 25 weeks gestation, Revcovi was started through a specialty pharmacy. Laboratory assessment was performed regularly per Revcovi transition guidelines. Similar to her first pregnancy, she required immunoglobulin replacement in her third trimester due to decreasing serum IgG levels. Otherwise, laboratory parameters including plasma ADA levels, deoxyadenosine nucleotide (dAXP) levels, and lymphocyte subsets remained stable. She delivered a healthy baby boy at 37 weeks gestation with no complications.

Patient Presentation
The patient was a 31 yo G3PO111 AA female who presented to clinic for management of her ADA-SCID during her third pregnancy. She had a successful first pregnancy while on Adagen 4 years prior to presentation for this pregnancy. Her second pregnancy was ectopic. She was first diagnosed with ADA-SCID at age 3. She has been on enzyme replacement therapy Adagen since age 4-5. She was on IVIG until she was 11 years old and did not require it again until the third trimester of her first and third pregnancy.

Diagnosis
Patient had been previously diagnosed with ADA-SCID at age 3.

Testing
There is scarce literature on ADA-SCID patients and pregnancy. Our patient had successfully carried out her first pregnancy with Adagen. There was no reported literature on treatment of ADA-SCID patients during pregnancy with Revcovi but the transition from Adagen to Revcovi was necessary due to Adagen manufacturing issues. Transition was made following Revcovi transition guidelines. She was given intramuscular injections two times per week. She was monitored with frequent visits and laboratory checks throughout her pregnancy. In her third trimester, she needed IVIG supplementation three weeks prior to delivery. She continued to get IVIG treatment monthly for the next 2 months.

Treatment
During this patient’s third pregnancy, it was necessary to transition Adagen to Revcovi (PEGylated recombinant adenosine deaminase (rADA) enzyme) due to manufacturing issues. Patient was continued on Adagen until 25 weeks gestation, when Revcovi was started. Laboratory assessment was performed regularly per Revcovi transition guidelines. Similar to her first pregnancy, she required immunoglobulin
replacement in her third trimester due to decreasing serum IgG levels. Otherwise, laboratory parameters including plasma ADA levels, deoxyadenosine nucleotide (dAXP) levels, and lymphocyte subsets remained stable. She continued to get IVIG treatment monthly for the next 2 months after delivery.

**Patient Outcomes**
She delivered a healthy baby boy at 37 weeks via induced vaginal delivery without complication and incurred no infectious episodes while pregnant. Baby had a normal complete blood cell count and SCID newborn screening via T-cell receptor excision circle (TREC) assay. They were discharged home within 48 hours. Patient remains on twice weekly Revcovi. IVIG treatments were stopped 2 months after delivery because of how well the patient was doing. She and her baby remain healthy to this day.

**Lessons Learned**
Adenosine deaminase(ADA)-deficient severe combined immunodeficiency (SCID) (ADA-SCID) accounts for approximately 15% of SCID cases and few reports exist regarding its management during pregnancy. There was one case report found which involved a pregnant patient with SCID titled “Successful Pregnancy in a Patient With Severe Combined Immunodeficiency Syndrome Treated With Bone Marrow Transplantation” by Shrivastava, Arora, Simpson, and Wing. In this article, a woman with SCID who had been treated with bone marrow transplant in childhood and successfully carried out a pregnancy despite alloimmunization of Rh (D) during pregnancy. The article was published in 2008 in the Obstetrics & Gynecology journal. Other than this article little was found on the matter of pregnancy and SCID and no reports were found on management of ADA-SCID pregnancies with enzyme replacement therapy. Management of ADA-SCID pregnancies while on recombinant peg-ADA replacement is valuable to clinical immunologists in order to optimize care as no current guidelines nor reports upon literature review currently exist.
Atypical Complete DiGeorge Anomaly Found on SCID Newborn Screening

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Summary
Patient was born at 34 weeks, infant of diabetic mother with preeclampsia, with positive newborn screen (NBS) for severe combined immunodeficiency (SCID) and T-cell Receptor Excision Circles (TRECs) of zero. Hospital course complicated by athymia, vertebral anomaly, erythroderma, eosinophilia, lymphadenopathy, and both transient hypoparathyroidism and hypocalcemia at birth. Atypical in the lack of cardiac defects and negative genetic testing. Mitogen studies showed decrease in T cell proliferative responses to phytohemagglutinin. T-cell Receptor (TCR) V-beta repertoire analysis showed oligoclonal T cells. Lymphocyte enumeration panel demonstrated a lack of naive T cells. Patient was diagnosed as atypical complete DiGeorge anomaly (cDGA) with Omenn syndrome-like phenotype given clinical presentation and diagnostic testing. Patient was initiated on immunosuppressive treatment while awaiting thymus transplantation.

Patient Presentation
Patient was born at 34 weeks to 28-year-old gravida 4 para 2 female with history of pregnancy-induced hypertension and insulin-dependent gestational diabetes. Delivered via repeat cesarean section due to maternal presentation with preeclampsia. Prenatal care significant for group B streptococcus positive urine culture, otherwise unremarkable. Was transferred to our hospital due to newborn screen presumptive positive for SCID and TREC value of zero. Upon admission, patient found to have patent foramen ovale, mild bilateral hydronephrosis, two vessel cord, vertebral anomalies, erythroderma, absent thymus, as well as transient hypocalcemia and hypoparathyroidism. Chest x-ray showed vertebral segmentation anomaly from T4 to T10 and hemivertebrae deformity of T9. On exam, patient had erythematous, peeling skin of all extremities, seborrheic dermatitis of the scalp, and lymphadenopathy of bilateral axilla and groin.

Diagnosis
Initial testing included a confirmatory complete blood count and lymphocyte immunotyping, as patient presentation was concerning for SCID or a related disorder. Given hypocalcemia and absent thymus on chest x-ray, microarray was sent as well as flow cytometry that showed low T cells (99% mature, 1% immature). Lymphocyte enumeration panel showed significantly decreased CD3, CD4, CD8 T cells. Low levels of naive T cell and TRECs of zero were consistent with athymia. Patient confirmed to have eosinophilia, low T cells, and skewing of the T cell compartment to almost all mature T cells. Immunoglobulin testing showed increased immunoglobulin E levels. TCR V-beta repertoire indicated oligoclonal T cell expansion. Patient tested negative for maternal engraftment that may also cause oligoclonal expansion of autoreactive T cells. High resolution chromosomes, microarray, and primary immunodeficiency panel returned negative, which ruled out typical DiGeorge syndrome. Skin biopsy to test fibroblasts for radiation sensitivity was negative, thus dismissing DNA repair disorders that may also cause T and B cell immunodeficiencies.
Testing
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Treatment
After diagnosis was made, patient was started on immunoglobulin replacement. Patient received brief calcium supplementation for transient hypocalcemia. After studies were obtained to assess clonality, steroids were initiated to lower the lymphocyte count and help with the rapid expansion of lymphocytes. T cell levels were closely monitored with immunosuppressive therapy, including both steroids and cyclosporine. Given immunosuppression, patient was started on fungal prophylaxis with fluconazole and pneumocystis pneumonia prophylaxis with bactrim. Patient was placed on waiting list for thymus transplant with the goal of normalization of host T cell development and function after transplantation.

Patient Outcomes
Patient was discharged home on cyclosporine and a steroid regimen, but briefly readmitted for elevated blood urea nitrogen, creatinine, and cyclosporine levels on routine bloodwork. Levels drawn corresponded with acute kidney injury secondary to dehydration and toxicity from cyclosporine. Patient was taken off cyclosporine and started on mycophenolate. Rash mildly improved on topical tacrolimus and hydrocortisone. Alemtuzumab was started for erythroderma resistant to oral and topical glucocorticoids, as well as topical tacrolimus. Patient was trialed on subcutaneous Alemtuzumab that was tolerated well. At this time, patient’s treatment regimen includes oral steroids, mycophenolate, subcutaneous immunoglobulin, bactrim, fluconazole, as well as topical hydrocortisone and tacrolimus. Patient is making stable progress in regard to development and weight gain while awaiting thymic transplant.

Lessons Learned
This case further elucidates pathophysiology, potential risk factors, and importance of newborn screening for severe combined immunodeficiency (SCID). This case demonstrates how NBS for SCID may increase early diagnosis, which is crucial given the heterogeneity of clinical presentations. Through early identification of these patients we can not only anticipate clinical course, but also the appropriate short and long-term treatment. An association between adverse prenatal determinants and developing atypical CDGA may exist, but the mechanism is unknown. Furthermore, there is the question of etiology and time of clinical onset of the associated Omenn syndrome-like phenotype as our case presented at birth compared to later presentations. This case illustrates areas of vital research that may lead to
reclassification without the DiGeorge moniker and may distinguish this condition as a separate entity. The articles “A Case of Atypical, Complete DiGeorge Syndrome without 22q11 Mutation” and “Complete DiGeorge syndrome: Development of rash, lymphadenopathy, and oligoclonal T cells in 5 cases” were both reviewed in preparing this case.
Lanadelumab in the treatment of acquired angioedema, a case series

Author Tonia S. Afshan, MD MPH and Theodore Kelbel, MD
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Summary
Acquired angioedema is a rare but serious disease. Primary management options involve treatment of underlying causes and controlling acute episodes of angioedema. There is no FDA-approved long-term prophylactic therapy for patients who experience unpredictable, debilitating, and/or life-threatening attacks of angioedema. Lanadelumab, previously approved to treat hereditary angioedema, has not been studied in the treatment of acquired angioedema but offers a logical therapeutic target given similar pathophysiology between the two diseases. Two patients, ages 67 and 87, with acquired angioedema who were previously managed with icatibant for acute symptoms, were started on lanadelumab to prevent episodes of angioedema. Over the following 9 months to present neither patient has had episodes of angioedema. At 6 months of therapy, both patients transitioned to once monthly dosing and have remained without episodes to date. To the best of our knowledge, this is the first case series describing treatment of acquired angioedema with lanadelumab.

Patient Presentation
Patient 1: The patient is a 67-year-old male who was seen for recurrent episodes of abdominal pain that began around age 65. During two of these episodes, the patient underwent CT imaging of his abdomen, which showed edema of various parts of the gastrointestinal tract along with ascites, suggesting angioedema as the etiology. His abdominal attacks were occurring approximately every 2 weeks, and were described as abdominal pain that would build and intensify over the course of a day and cause abdominal distension and debilitation. These episodes were described to last 24-48 hours. The patient also reported episodes of edema of his hands with vibration, such as after using a lawn mower, and with cold exposure. These episodes were reported to last 12-24 hours. The patient's medical history included MGUS and he followed with Oncology for this, but he had no other underlying lymphoproliferative, malignant, or autoimmune findings. He did not have any family history of angioedema.
Patient 2: The patient is an 87-year-old male who was initially seen for recurrent episodes of orofacial angioedema and episodes of abdominal pain and bloating that began around age 85. He had two episodes of facial swelling separated by several months, neither of which responded to anti-histamines or steroids and lasted 48-72 hours. Additionally, during two of the abdominal episodes, this patient also underwent CT imaging of his abdomen, which showed edema and bowel wall thickening, that later resolved on subsequent imaging. The patient was previously thought to have an underlying appendiceal malignancy, which was ultimately unfounded on pathology. He also underwent diagnostics and evaluation for Waldenstrom macroglobulinemia, which was negative. To date, the patient has not been found to have an underlying lymphoproliferative, malignant, or autoimmune process. He did not have any family history of angioedema.

Diagnosis
Given both patients' histories of episodes of angioedema starting at ages 65 and 85 respectively, lack of response to steroids and anti-histamines, response to and control of acute symptoms with icatibant, and laboratory testing (discussed below), we felt strongly that acquired angioedema was the diagnosis.
Additionally, given the older ages at which symptoms began, laboratory testing, and negative family histories, we did not feel that the diagnosis of hereditary angioedema was supported.

**Testing**
Laboratory studies including C4 level, C1q level, and C1NH antigenic level and function were obtained for both patients. The results below are consistent with a diagnosis of acquired angioedema with C1NH deficiency. Although the second patient’s C1q level was technically normal, it was just outside the reference range to be considered low; furthermore, it was been discussed that this level and the quantitative level of C1 esterase inhibitor may be normal in some cases of acquired angioedema. These results combined with the patients’ histories and other factors discussed above further cemented the diagnosis.

Patient 1: Laboratory studies showed low C4 level (<2), low C1q level (<5), and low C1 esterase inhibitor, both quantitatively and functionally (5, <10 respectively).

Patient 2: Laboratory studies showed low C4 level (<2), just normal C1q level (14 with lower limit of normal being 12), and low C1 esterase inhibitor, both quantitatively and functionally (13, <10 respectively).

**Treatment**
Both patients were initially prescribed epinephrine auto-injectors and icatibant for acute symptom episodes, and it was recommended that they receive bertinert prior to any procedures requiring intubation. Ultimately, both patients were started on Lanadelumab for long-term prophylaxis for angioedema episodes.

**Patient Outcomes**
Both patients were started on lanadelumab and over the following 11 months to present have had no episodes of angioedema. At 6 months of therapy, both patients transitioned to once monthly dosing and have continued without episodes to date.

**Lessons Learned**
Lanadelumab was successfully used to prevent episodes of angioedema in two patients diagnosed with acquired angioedema during 11 months of therapy. To the best of our knowledge, this is the first case series describing treatment of acquired angioedema with lanadelumab. Although not yet FDA-approved for treatment of acquired angioedema, further research is warranted given the success of this drug in the two patients presented in this case series.
Omalizumab Use with Positive Results In a Pediatric Patient Less than 6 Years Old

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Summary
This is a case of a 5 year old male with poorly-controlled severe asthma with allergic precipitates and concomitant sinusitis despite maximum inhaled and oral medication regimen. Omalizumab was initiated with goals of symptom relief, decreased oral steroid courses, and decreased exacerbations requiring emergency visits. Significant improvement was noted after initiation of regular omalizumab injections.

Patient Presentation
A 5 year old male initially presented for seasonal allergies, chronic recurrent sinusitis, and poorly controlled severe asthma. Prior to start of therapy, his IgE level was 338 U/mL and environmental skin testing was positive to multiple environmental allergens including dust mite, cockroach, weeds, and trees. He had failed treatment with inhaled corticosteroids + long acting beta agonists, and leukotriene receptor antagonists, experiencing monthly exacerbations requiring emergency department visits and prednisone courses.

Diagnosis
Diagnosis of severe persistent asthma was established prior to initiation of omalizumab.

Testing
Strategies for investigating included monitoring number of oral prednisone courses, number of emergency room visits, and family's subjective reporting of symptom burden.

Treatment
He had failed treatment with inhaled corticosteroids + long acting beta agonists, and leukotriene receptor antagonists, experiencing monthly exacerbations requiring emergency department visits and prednisone courses. Given his treatment failure, subcutaneous omalizumab 225 mg every 4 weeks was initiated.

Patient Outcomes
Since initiation of omalizumab, the patient’s symptoms significantly improved and he has not required hospital visits or systemic steroids for exacerbations. Mother reports greatly reduced rescue medication use and improvement in exercise tolerance.

Lessons Learned
Pediatric patients less than <6 years of age with uncontrolled allergic asthma may benefit from omalizumab. Studies are needed in this population to assess efficacy and safety of omalizumab.
Human-Metapneumovirus Induced Incomplete Stevens-Johnson Syndrome

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Training Program University of Chicago Medical Center

Summary
Incomplete Stevens-Johnson syndrome (SJS) is a rare variation of SJS where skin lesions may be absent, and most often present as extrapulmonary manifestations of Mycoplasma pneumoniae infection. This is an atypical case of a patient who developed incomplete SJS from human-metapneumovirus. A 25-year-old male presented with worsening intraoral blisters in the setting of cough, sore throat, and fever. The blisters had started after his second dose of guaifenesin-dextromethorphan, which was a new medication. He was intubated for airway protection. The initial leading diagnosis was drug hypersensitivity reaction. However, during admission he continued to have oral lesions and developed painful conjunctivitis and dysuria. He had no cutaneous lesions or major laboratory abnormalities. A broad infectious workup returned positive for human-metapneumovirus on respiratory viral panel (RVP). Given painful oral mucositis, conjunctivitis, urethritis, and lack of skin involvement, the most likely diagnosis is human-metapneumovirus induced incomplete SJS.

Patient Presentation
A 25-year-old male presented to the emergency department (ED) with worsening oral blisters over 3 days. Patient reported 1 week of cough, sore throat, and congestion. His oral blisters had started after his second dose of guaifenesin-dextromethorphan, which was a new medication for him. He also reported a one time fever to 38.9 degrees celsius at home and painful swallowing. Prior to his ED presentation he had visited urgent care, where he had a herpes swab that came back negative. Patient had no significant medical history. He was not taking regular medications. He reported seasonal allergies worse in the spring for which he used intranasal corticosteroids but denied any food or drug allergies, as well as history of asthma or eczema. Family history was unremarkable. In the ED, vitals were within normal limits with temperature 37.6, blood pressure 145/80, pulse 90, oxygen saturation 99% on room air. Physical examination was notable for lip swelling, mucopurulent mucosal surface of the upper lip that was sloughing off, and diffuse blistering lesions of the buccal mucosa. The posterior oropharynx was edematous with small blisters. He had no skin lesions. Fiberoptic laryngoscope by otolaryngology showed posterior oropharyngeal edema and he was intubated for airway protection.

Diagnosis
Initially, the leading differential was drug hypersensitivity reaction to guaifenesin-dextromethorphan given the timing of oral blisters. SJS was an important diagnosis to consider given viral URI symptoms, fevers, and mucosal lesions with sloughing, however the lack of classic cutaneous lesions made this less likely initially. Infection including HSV, bacterial mucositis, and erosive oral candidiasis were considered, but oral swabs returned negative. Oral lichen planus and mucous membrane pemphigoid were considered but were less likely given acute onset of symptoms.

He improved with IV dexamethasone, famotidine, and diphenhydramine, and was extubated within two days, perhaps making drug hypersensitivity more likely. However, his hospital course took a turn. When
he was ready to transition out of the intensive care unit, he acutely developed bilateral conjunctival
redness and pain as well as dysuria. Urinalysis with culture was performed without evidence of
infection.

The original differentials were revisited given the course of events. To summarize, patient had painful
oral mucositis, conjunctivitis, urethritis, and lack of skin involvement in the setting of viral prodrome,
which is characteristic of incomplete SJS.

**Testing**
Infectious etiologies were investigated given his intraoral findings and fevers at home. Oral lesions were
swabbed for HSV, VZV, candida, gonorrhea, chlamydia, bacteria, and fungus. HIV was sent as acute HIV
can present with painful mucocutaneous ulcerations, and to investigate for evidence of
immunodeficiency. Syphilis was checked as secondary infections may present with oral mucous patches.
These studies came back normal. RVP was obtained given his viral upper respiratory symptoms and
returned positive for human-metapneumovirus.
Basic labs including complete blood count, metabolic panel, ESR, and CRP were unremarkable and
without evidence of infection. Blood cultures showed no growth. Chest radiograph was obtained given
history of cough and fevers, which showed no acute process.

**Treatment**
He was started on IV dexamethasone, famotidine, and diphenhydramine due to oropharyngeal swelling
as well as concern for hypersensitivity reaction to his new medication. Antibiotics, antifungals, and
antivirals were considered but deferred given lack of infectious signs on labs. Supportive care with IV
hydration, magic mouthwash, and analgesia continued.

**Patient Outcomes**
The patient was extubated and moved to the general floor within 2 days of admission where supportive
care continued, and he was discharged home within a week. He did not develop any infectious
complications of incomplete SJS. He followed-up in allergy and immunology clinic in 2 weeks where he
reported overall improvement, but residual cough and pain in his cheeks. His diagnosis of incomplete
SJS was discussed in detail. Nonetheless, he was advised to avoid guaifenesin-dextromethorphan and an
epinephrine auto-injector was prescribed.

**Lessons Learned**
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are conditions characterized by
severe mucocutaneous reactions of the skin and involvement of the ocular, oral, and genital mucous
membranes. They are most often precipitated by drugs and infections. Incomplete SJS is a rare variation
of SJS where the classic skin lesions may be absent and has now been well-documented as an extra-
pulmonary manifestation of Mycoplasma pneumoniae infection. This patient had incomplete SJS
secondary to human-metapneumovirus and had delayed conjunctival and urogenital manifestations
that made the diagnosis challenging. Awareness that SJS may have a wide spectrum of clinical presentations
and etiologies will help clinicians avoid diagnostic delays from atypical presentations.
There have been case reports of rare infectious etiologies of SJS/TEN. One review of children with
recurrent episodes of SJS by Olson et al. reports positive testing for human metapneumovirus,
Chlamydophila pneumoniae, parainfluenza virus type 2, and rhinovirus. Other reported causes include
HSV and CMV. Drugs most commonly implicated in SJS/TEN include allopurinol, antiepileptics, and sulfonamides. SJS/TEN secondary to guaifenesin-dextromethorphan has yet not been reported. The treatment of SJS remains supportive with fluids, analgesia, and close monitoring of electrolytes and signs of infectious complications. Antibiotics should be used in cases secondary to Mycoplasma pneumoniae. Systemic corticosteroid therapy is controversial as the risk of sepsis may increase, but some studies have shown benefit if given within 24-48 hours of symptom onset.
Two cases of immunodeficiency associated to Chromosome 18 p deletion and Ring Chromosome 18

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Summary
We report two patients with chromosome 18 abnormalities associated with recurrent respiratory infections and sepsis who were later found to be associated with immunodeficiency. Patient 1 is a 27-year-old male with Chromosome 18p deletion and cardiac malformation, who was found to have low CD4 and low IgM levels. Patient 2 is a 6-year-old female with Ring Chromosome 18 with atrial septal defect, hypothyroidism, and cleft palate who had lymphopenia and low immunoglobulin levels.

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Patient Presentation
Patient 1 is a 27-year-old male with Chromosome 18 p deletion, global developmental delay, repaired Tetralogy of Fallot, and atrioventricular block. He was born in Cuba, and while his perinatal history is unknown, he has a history of multiple hospitalizations due to surgical interventions and infections. Patient established care at our hospital at age 10. Since then, he has had recurrent respiratory infections and sepsis with associated low IgM levels (38 mg/dL). He was found to have a low CD4 T-cell percentage (27.5%) with a normal absolute count (479 cells/µL). Follow up immune workup revealed normal IgG and IgA levels, with a persistent decreased IgM level (35 mg/dL). He has been stable with no recent infections requiring hospitalizations, and was recently diagnosed with hypothyroidism and started on replacement treatment.

Patient 2 is a 6-year-old female with Ring chromosome 18, agenesis of corpus callosum, hypothyroidism, cleft palate, atrial septal defect, asthma, food allergy and eczema. She had a prolonged NICU stay with recurrent staphylococcal skin infection and recurrent respiratory infections. Her initial immune evaluation when she was 6 months old revealed lymphopenia with decreased B-cell and T-cell counts [CD4+/CD3+ 33% (685 cells/µL), CD8+/CD3+ 42% (868 cells/µL), CD19+ 14% (307 cells/µL)] with undetectable IgA levels (<8 mg/dL) and decreased IgM levels (30 mg/dL). She received a single dose of Intravenous gamma globulin at 500 mg/kg which was followed by clinical improvement. The most recent follow up revealed normal lymphocyte subsets and normal IgM (56 mg/dL). She has required hospitalizations over the last year due to pneumonia and central line infection, which resulted in ICU admissions.

Diagnosis
Patient 1 has Chromosome 18 p deletion, global developmental delay, repaired Tetralogy of Fallot, and atrioventricular block. His recurrent respiratory infections and sepsis episodes are associated low IgM levels (38 mg/dL) and a low CD4 T-cell percentage (27.5%) with a normal absolute count (479 cells/µL). Patient 2 has Ring chromosome 18, agenesis of corpus callosum, hypothyroidism, cleft palate, atrial septal defect, asthma, food allergy and eczema. Her recurrent staphylococcal skin infections and recurrent respiratory infections are associated with lymphopenia with decreased B-cell and T-cell
counts [CD4+/CD3+ 33% (685 cells/µL), CD8+/CD3+ 42% (868 cells/µL), CD19+ 14% (307 cells/µL)] with undetectable IgA levels (<8 mg/dL) and decreased IgM levels (30 mg/dL).

**Testing**
Patient 1 had low IgM levels (38 mg/dL) associated with his episodes of sepsis and recurrent respiratory infections. He was found to have a low CD4 T-cell percentage (27.5%) with a normal absolute count (479 cells/µL). Follow up immune workup revealed normal IgG and IgA levels, with a persistent decreased IgM level (35 mg/dL).
Patient 2 had lymphopenia with decreased B-cell and T-cell counts [CD4+/CD3+ 33% (685 cells/µL), CD8+/CD3+ 42% (868 cells/µL), CD19+ 14% (307 cells/µL)] with undetectable IgA levels (<8 mg/dL) and decreased IgM levels (30 mg/dL) during her initial immune work up when she was 6 months old. The most recent follow up revealed normal lymphocyte subsets and normal IgM (56 mg/dL).

**Treatment**
Patient 1 is not on any antibiotic prophylaxis or antibody replacement therapy at this moment.
Patient 2 had improvement in her recurrent respiratory and skin infection after intravenous immune globulin infusion.

**Patient Outcomes**
Patient 1 has been stable with no recent infections requiring hospitalizations.
Patient 2 has required hospitalizations over the last year due to pneumonia and central line infection, which resulted in ICU admissions.

**Lessons Learned**
Patients with Chromosome 18 p deletion and Ring Chromosome 18 may have an associated immunodeficiency. We recommend consideration of an immune work up for patients with mutations affecting the chromosome 18. Timely evaluation at the time of initial diagnosis and close follow up over time may benefit these patients and potentially decrease life-threatening infections.
Pulmonary Sclerosing Hemangioma in a Young Adult with Coexisting 22q11.2 deletion, Evans Syndrome and CVID with MALT1 variant

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Summary
Common Variable Immune Deficiency (CVID) is known to be associated with increased incidence of hematologic malignancy while tumors like lymphoma and hepatoblastoma have been reported in 22q11deletion syndrome. Pulmonary sclerosing hemangioma (pneumocytoma) is a rare benign tumor of epithelial origin, typically described in women over 50 years of age. It has not been previously reported in 22q11del syndrome or CVID or Evans. We report a case of young adult with coexisting 22q11 deletion, Evans syndrome, CVID with novel MALT1 variant who presented with a suspicious pulmonary nodule which lead to the diagnosis of pulmonary sclerosing hemangioma.

Patient Presentation
Our patient is a 21- year-old young adult with CVID, 22q11 deletion syndrome, Evans syndrome and EBV-associated lymphoproliferation. He initially presented to our center at 4 years of age with easy bruising and recurrent epistaxis. He was also noted to be developmentally delayed. His CBC revealed pancytopenia with hemoglobin 8.4g/dl (11.2-14.4), white blood cell count 2.3K/mm3 (4.1-11.3) with absolute neutrophil count of 100/mm3 (normal>1500/mm3) and platelets of 109K/mm3(130-450). He underwent extensive hematologic evaluation for malignancy upon which his chest X- ray and CT scan showed absence of normal thymic tissue. His bone marrow biopsy did not show malignancy. Immunologic evaluation revealed a normal IgG 935mg/dl (463-1447), IgA 220mg/dl (23-209), IgM 103mg/dl (43-214) and IgE 15IU/ml (1-87). He had low CD3 cell count of 675/mm3 (1072-3890) and low CD4 count of 333/mm3 (562-2692). A positive direct antiglobin test was suggestive of autoimmune cytopenias and he was diagnosed with Evans syndrome. Due to low T cell counts a FISH probe was performed and was positive for 22q11.2 deletion. The parental genetic testing also revealed 22q11.2 deletion for his mother as well. For the management of Evans syndrome, patient has needed many course of oral steroids, IVIG, rituximab and mycophenolate mofetil for episodes of cytopenias and is currently on daily oral prednisone 10mg every morning. For low CD3 and CD4 T cell counts he was started on trimethoprim/sulfamethoxazole prophylaxis. His most recent mitogen culture continues to show low response. At 5 years of age his IgG was 463 mg/dl (633-1535). Antibody responses to 14 pneumococcal serotypes were notably low. He was subsequently started on IVIG replacement at 400mg/kg monthly and remains on the same. At the age of 14 years he presented with significant splenomegaly as well as lymphadenopathy. PET scan revealed multiple FDG avid enlarged lymph nodes in the neck and supraclavicular region. Lymph node biopsy was suspicious of small focus of lymphoma which was treated with 4 cycles of rituximab and repeat PET scan in the same year was negative. At the age of 18 years he was admitted for nausea, fatigue, early satiety and night sweats. PET scan showed increased mediastinal and retroperitoneal lymphadenopathy and increased FDG-avidity in previously noted lymph nodes. Extensive work up was done and was significant for a positive EBV PCR
and a diagnosis of EBV associated lymphoproliferation was made. Repeat PET scan showed improvement. His lymphoproliferative disease is monitored closely with yearly chest CT scans. At 15 years of age his chest CT revealed a small pulmonary nodule in left lower lobe. This mass was noted to increase in size over the years with most recent measurement of 3.5 x 3.5 x 3.7 cm at 21 years of age. At baseline, the patient denied chest pain but according to his aunt who is the legal guardian the patient was described to be in poor physical shape and noted to become short of breath after going up and down 2 flights of stairs. Increasing pulmonary nodule size with symptoms was concerning and patient underwent further evaluation.

**Diagnosis**

Pulmonary sclerosing hemangioma is a rare benign tumor of epithelial origin, typically described in women over 50 years of age. Due to its rarity, the symptoms and natural course of the tumor are not well understood. Cough, dyspnea, chest pain, fever or more commonly, asymptomatic lesions have been described in case reports. Genetic testing revealed a pathogenic variant in TBX1 and variants of uncertain significance in MALT1 and CSF2RA. TBX1 gene is associated with autosomal dominant DiGeorge/Velocardiofacial syndrome and is one of the commonly deleted genes in the recurrent 22q11.2 microdeletion. MALT1 gene is associated with autosomal recessive combined immunodeficiency of impaired T cell responses and poor antibody responses which could potentially fit our patient’s immunological profile. However, the clinical significance of this variant is uncertain at this time as MALT1 deficiency is autosomal recessive, so single variant is unlikely to be sufficient as a single explanation for his disease. The presence of variant of uncertain significance was also identified in CSF2RA gene. This gene is associated with X-linked primary pulmonary alveolar proteinosis (PAP). Patients with PAP present with dyspnea with striking chest imaging abnormalities of ground grass opacification crossed by heavy septal lines; which are not seen in our patient. The clinical significance of this variant is also uncertain at this time as PAP is autosomal recessive, so single variant is unlikely to be sufficient as a single explanation for the disease.

**Testing**

A CT guided biopsy of the pulmonary nodule and histopathology confirmed the diagnosis of pulmonary sclerosing hemangioma. Genetic testing revealed a pathogenic variant in TBX1 and variants in MALT1 and CSF2RA.

**Treatment**

Robotic/open left lower lobectomy for surgical excision of benign sclerosing hemangioma was performed by cardiothoracic surgeons.

**Patient Outcomes**

On post-op follow up patient reported that his breathing has improved since the surgical resection. He continues to closely follow up with multiple subspecialties involved in his care.

**Lessons Learned**

Although malignancy is a concern in a young adult with CVID and 22q11 deletion presenting with lung nodule, this case presents a rare benign tumor that should be considered in the differential diagnosis.
We believe this is the first reported case of primary sclerosing hemangioma (pneumocytoma) in a patient who has coexisting 22q11.2 deletion, Evans syndrome and CVID with MALT1 variant.
Immediate allergic reaction followed by successful desensitization to ursodiol

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Summary
Ursodiol or ursodeoxycholic acid (UDCA) is the mainstay treatment for primary biliary cirrhosis (PBC). Infrequent adverse effects of UDCA include pruritus, diarrhea and weight gain, but hypersensitivity to UDCA has not been reported. Herein we describe a patient with PBC who developed an immediate allergic reaction to UDCA. A new UDCA desensitization protocol was developed and the patient successfully completed the protocol. Following desensitization, she initially experienced subjective pruritus each time after taking UDCA. It was attributed to medication side effect and she agreed to continue taking UDCA. One month after desensitization, her pruritus resolved and she continued to tolerate UDCA.

Patient Presentation
At the time of her PBC diagnosis, our 59-year-old patient started on UDCA 500mg twice daily. On Day 4 of therapy, she developed full body hives, chest tightness and dyspnea within one hour of ingestion. These symptoms self-resolved in an hour. Subsequently she lowered UDCA dose to 250mg twice daily at the recommendation of her hepatologist. On day 2 of re-exposure, she developed similar but more severe symptoms within an hour of ingestion. These symptoms self-resolved in a few hours. UDCA was discontinued by her hepatologist and she was referred to the allergy clinic for possible UDCA allergy.

Diagnosis
IgE-mediated reaction to UDCA

Testing
There is no validated skin prick testing to or available IgE measurement for UDCA. The history was very clear, so a provocation test to UDCA was not done. The diagnosis was made based on the detailed clinical history.

Treatment
Given the ongoing need for UDCA, a desensitization protocol to UDCA was developed. The patient was successfully desensitized to UDCA in the intensive care unit and has remained on UDCA 500mg twice daily.

Patient Outcomes
Following desensitization, patient initially experienced recurrent pruritus each time after taking UDCA. A careful evaluation in the clinic did not raise any concerns for an allergic reaction and pruritus was attributed to medication side effect. After a discussion with the patient, she agreed to continue taking UDCA and pruritus was somewhat reduced with non-sedating antihistamine. A month after the desensitization and being on daily UDCA, patient reported a complete resolution of her pruritus and was able to tolerate UDCA without any issues.
Lessons Learned
We believe this is the first case of an immediate allergic reaction followed by successful desensitization to UDCA. In the absence of any objective findings suggestive an immediate allergic reaction, it is reasonable to continue the medication after a discussion with the patient and close follow-up.
An unusual case of Bird-Egg Syndrome

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Summary
A 45-year old man presented with a 4-year history of throat closing and syncope after ingestion of egg yolk, along with excessive vomiting, throat closing, and syncope with ingestion of chicken meat. He also had a history of chronic rhinorrhea, sneezing, and itchy eyes. He grew up with pet birds in his home. He underwent skin prick testing (SPT) and was positive to feather mix (8x30mm), dust mites (7x30mm), raw egg yolk (18x50mm), chicken (8x25mm), turkey (6x8mm), feathers (9x10mm), and negative to raw and cooked egg whites, and hard-boiled yolk. He was diagnosed with bird-egg syndrome. Normally, patients with bird-egg syndrome have more severe reactions to egg yolk than chicken. Interestingly, our patient had more severe reactions to chicken than egg yolk.

Patient Presentation
A 45-year old otherwise healthy man presented to the allergy clinic after having multiple episodes of vomiting, throat closing, and occasional syncope with ingestion of certain foods. He described developing a sensation of throat closing, excess salivation, and eventually syncope after eating less-than-fully cooked egg (yolk). He had no hives, vomiting, or respiratory symptoms. He denied any symptoms with fully-cooked yolk, raw egg whites, or cooked egg whites. He also reported a more severe reaction to cooked chicken meat; he had a sensation of throat closing, severe vomiting and syncope after eating cooked chicken meat. He was able to tolerate other meats such as pork and beef, though stated that he had never tried turkey or other bird meat. He also reported chronic rhinorrhea, sneezing, watery and itchy eyes. He had pet birds growing up, and currently had an African Grey Parrot in his home. Patient reported that his brother also had documented allergies to cooked chicken and raw egg yolk, though his reactions were usually hives and vomiting. On exam, he was noted to have boggy, pale, and enlarged inferior turbinates.

Diagnosis
The patient underwent skin prick testing to aeroallergens and various foods and was found to be positive to bird feathers, egg yolk, and chicken meat. Because of his known recurrent exposures to pet birds, he was diagnosed with bird-egg syndrome.

Testing
Patient underwent skin prick testing to aeroallergens and was positive to feather mix (8x30mm) and dust mites (7x30mm). Prick test was positive for raw egg yolk (18x50mm), chicken (8x25mm), turkey (6x8mm), feathers (9x10mm), and negative to raw and cooked egg whites, and hard boiled yolk. Because the patient was found to be positive to bird feathers, egg yolk, and chicken meat in the setting of recurrent exposures to pet birds, he was diagnosed with bird-egg syndrome.

Treatment
After the patient was diagnosed with bird-egg syndrome, he was told to avoid less-than-fully cooked egg yolk and bird meat. He was given an epinephrine autoinjector for accidental exposures. A joint decision
was made with the patient to give away his pet bird. Patients with bird-egg syndrome often have improvement in symptoms after decreased exposure to birds.

**Patient Outcomes**
Unfortunately, patient was lost to follow up subsequently. It is unclear how his symptoms are now that his exposure to bird has been minimized.

**Lessons Learned**
Bird-egg syndrome is uncommon, with few case reports in the literature describing the phenomenon. It is thought that patients are sensitized to serum albumin (Gal d 5) via the respiratory tract through repeated exposure to pet birds via feathers and droppings [1]. Serum albumin is also present in chicken muscle tissue and egg yolk, therefore patients subsequently develop food allergy to chicken meat (occasionally with other poultry too) as well as to egg yolk. This differs from typical egg allergy, in which patients can tolerate egg yolk, but not egg whites. This is due to the fact that egg yolk contains serum albumin, whereas egg whites have ovalbumin (Gal d 2), ovomucoid (Gal d 1), con albumin (Gal d 3), and lysozyme (Gal d 4) - the contributing allergens for most patients with the usual egg allergy [4]. Patients with bird-egg syndrome typically have more severe reactions to ingested egg than chicken. Serum albumin is partially heat labile and because patients typically eat cooked meats but not completely cooked-through eggs, they have a milder reaction to poultry than egg, as the protein is altered by the heat from cooking [3]. Interestingly, our patient reported more severe reactions to cooked chicken rather than to egg. It is possible that another protein may be involved. Despite the fact that there are over 25 million domestic birds in the U.S., the incidence of bird-egg syndrome is still incredibly low [5]. This case highlights some unusual findings in an already rare phenomenon.
TACI Mutation Displaying CVID Phenotype Despite Normal Immunochemistry

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Summary
A 18-year-old female with a past medical history of childhood eczema and molluscum contagiosum presented with recurrent infections including pneumonia, multiple bouts of sinusitis, and MRSA-positive skin abscesses requiring nearly 3 years of rotating antibiotics. During this time, the patient developed 5 separate episodes of shingles along with an abrasion that transitioned into a limb-threatening infection with concern for osteomyelitis requiring intravenous antibiotics. Additionally, she was diagnosed with mononucleosis, displaying significant lymphadenopathy, progressive polyarthralgia, and ongoing purpura prompting ongoing rheumatologic/hematologic evaluation. Extensive immunochemistry testing revealed normal NK cell, mitogen/antigen testing, B-cell phenotyping, and immunoglobulins. Family history was positive for a brother with CVID and a sister with IgA deficiency. Genetic testing revealed heterozygous TACI mutation with pathogenic variant in TNFRSF13B (C104R) gene. The patient’s father was found to be a healthy carrier. The patient subsequently started IVIG infusions with substantial improvement of her recurrent infections.

Patient Presentation
Despite an unremarkable childhood, the patient began developing recurrent infections at the age of 18; two years after suffering multiple sports-related concussions. The patient was referred for initial immunology evaluation after developing numerous cases of sinusitis/otitis media, shingles, bacterial pneumonia, and MRSA-positive skin abscesses of the arms and face within the prior year resulting in a considerable amount of missed time in school. Family history was significant for a brother diagnosed at age 12 with CVID on IVIG therapy after he presented with recurrent sinopulmonary infections starting as early as 6 weeks of age. The patient also has a sister who was diagnosed at 3 months of age with IgA deficiency who presented during childhood with numerous episodes of shingles and mononucleosis. Interestingly, both parents had an unremarkable infectious medical history.

Diagnosis
The patient’s extensive immunochemistry work-up and secondary immunodeficiency work-up was grossly unremarkable after revealing repeatedly normal NK cell, mitogen/antigen testing, B-cell phenotyping, and quantitative immunoglobulins. However, clinically, the patient presentation was markedly consistent with CVID in the setting of a strong, positive family history, recurrent sinopulmonary bacterial infections, exclusion of secondary causes and known heterozygous TACI mutation with pathogenic variant. Given the severity of the infections and recurrent hospitalizations, the patient was started on IVIG infusions with excellent response.

Testing
Given recurrent, predominantly bacterial infections and significant family history, the patient was initially evaluated for primary immunodeficiency disease through testing of humoral immunity (specific antibody deficiencies) and cellular immunity. Additionally, the patient was HIV
negative and the initial CBC was unremarkable. Initial quantitative immunoglobulins shown mild hypogammaglobulinemia—however, repeat levels were within normal limits with normal IgG subclasses. Additionally, the patient demonstrated normal titer response to pneumococcal/tetanus vaccinations with grossly unremarkable evaluation of B-cell phenotype using flow cytometry. NK cell and mitogen/antigen testing were negative, including normal responses to candida and normal phytohemagglutinin (PHA) skin test. Complement testing was unremarkable with normal CH50/mannan binding lectin. Given the positive family history and grossly normal immunochemistry work-up, genetic testing of the patient and family members was obtained for the evaluation of family-inherited mutations. Genetic testing revealed heterozygous TACI mutation with pathogenic variant in TNFRSF13B (C104R) gene in the patient, her two siblings and father (healthy carrier).

**Treatment**
Throughout the course of several years, the patient was on numerous, rotating antibiotics (amoxicillin, azithromycin, sulfamethoxazole/trimethoprim, doxycycline) for prophylaxis and treatment of active infections against common CVID pathogens such as Haemophilus influenzae, Streptococcus pneumoniae, and Staphylococcus aureus. She required several hospital admissions for IV antibiotics including vancomycin for MRSA skin infection. Interestingly, the patient began developing allergic reactions to multiple classes of antibiotics prompting eventual desensitization to penicillin. Additionally, the patient received pneumococcal vaccinations with an appropriate titer response. Given recurrent infections and CVID-like presentation, the patient was initiated on IVIG therapy for prevention of further CVID-related infections and complications. Due to ongoing lymphadenopathy, purpura and joint pain, the patient was also referred to hematology/rheumatology for ongoing evaluation.

**Patient Outcomes**
Following the initiation of IVIG therapy ten months ago, the patient has not required any further hospitalizations due to infections. The patient remains on prophylactic antibiotics and returns to the clinic for close follow-up/monitoring every four weeks while receiving IVIG infusions.

**Lessons Learned**
We present a unique case of a family-shared, heterozygous TACI mutation (C104R TNFRSF13B variant) with variable presentations including a patient displaying profound CVID phenotype, despite normal immunochemistry. Per the literature, 8%-15% of CVID cases have been associated with TACI gene mutations (1). Heterozygous TACI gene variants have been associated with a variety of phenotypes including CVID, autoimmunity, lymphoproliferative disease such as splenomegaly and tonsillar hypertrophy, and asymptomatic due to incomplete penetrance (2, 3). In contrast, homozygous TACI gene variants lead to a profound deficiency of humoral response but have actually shown to be protective against autoimmunity due to lack of functional TACI (4). No reports, to date, have demonstrated TACI mutation resulting in a hybrid of profound CVID phenotype with normal immunochemistry. This presentation displays the complexity and variability of CVID among family members with TACI; demonstrating an association, but further evidence, that additional environmental and genetic factors likely play a role. Similar cases can
be identified regarding the complexity of CVID presentation among family members with TACI mutation seen in (1,2). Additional research is needed to further understand the correlation/importance of familial genetic mutations and their roles in the development of CVID.
Subcutaneous Immune Globulin Induced Cutaneous Hypersensitivity Reaction

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Summary
Subcutaneous immune globulin (SCIG) is used to treat common variable immunodeficiency (CVID). Adverse reactions to SCIG may include infusion site reactions, rashes, and severe hypersensitivity reactions. We describe a case of SCIG induced cutaneous hypersensitivity reaction that persisted with a formulation change of SCIG but resolved with using intravenous immune globulin (IVIG).

Patient Presentation
A 56-year-old male with CVID presented with recurrent sinusitis, decreased IgG, decreased IgA, and poor anti-pneumococcal antibody response. He started treatment with SCIG 20% liquid and a couple weeks later developed highly pruritic nummular skin lesions. The lesions were initially at the injection site, later spread throughout the body but spared the face. With subsequent SCIG doses the lesions increased in size and became more pruritic.

Diagnosis
The patient was diagnosed with a cutaneous hypersensitivity reaction to SCIG. The patient had not started any other medications except SCIG when the skin lesions developed. The skin lesions appeared initially at the injection site and worsened with repeat dosing of SCIG including when the SCIG formulation was changed. A skin biopsy was consistent with a hypersensitivity reaction. The skin lesions resolved with discontinuing SCIG.

Testing
A biopsy of a skin lesion was performed to determine the etiology of the skin lesions. The biopsy showed spongiotic dermatitis with eosinophils, which was consistent with a hypersensitivity reaction due to a drug exposure. A complete blood count with differential was drawn to screen for a central process causing eosinophilia. He did not have peripheral eosinophilia.

Treatment
He was switched to another SCIG 20% liquid formulation, which is produced using a different manufacturing procedure, without improvement of the skin lesions. Subcutaneous IG was then discontinued and he began IVIG treatment.

Patient Outcomes
After stopping SCIG and subsequently starting IVIG, he had gradual resolution of the skin lesions.

Lessons Learned
This case shows a SCIG induced cutaneous hypersensitivity reaction which has not been previously described. This case demonstrates changing to IVIG can allow for continued IG treatment with resolution of the adverse cutaneous hypersensitivity reaction caused by SCIG.
Figure: Punch biopsy from midback skin (A); epidermis showing scattered foci of spongiosis with bland appearing lymphocytes (B); superficial perivascular and interstitial infiltrate (C); with eosinophils on closer view (D, arrows).
Diagnosis: Spongiotic Dermatitis with Eosinophils.
A Previously Undescribed Cause of Angioedema

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Summary
A 9-year-old male presented with multiple episodes of lip and tongue swelling. Multiple encounters had no clear trigger or potential allergic source. He had several ICU admissions and received multiple doses of epinephrine, including epinephrine drips, ultimately with poor response. Laboratory workup, including C4, C1esterase inhibitor, C1q, tryptase, and IgE, were normal. He was diagnosed with idiopathic angioedema and discharged on high-dose fexofenadine, ranitidine, and diphenhydramine, with Doxepin later added. On his final admission, examination showed protruding lips and uneven tongue swelling with no prevention of talking or breathing, and resolved within 1 minute. Poor response to medications and unusual rapid resolution appeared inconsistent with angioedema. Additional history revealed previous episodes of musculoskeletal conversion disorder, which resolved with psychotherapy. He reported recent bullying; parental argument immediately preceded the last episode of swelling. His swelling was thought to be secondary to conversion disorder and he was discharged with psychology follow-up.

Patient Presentation
A 9-year-old male presented with 6 episodes of lip and tongue swelling for which he presented to the hospital. I encountered this patient on his last admission. His first episode was thought to be secondary amoxicillin but this allergy was later cleared. His second episode was thought secondary to aspirin exposure. However his later encounters had no clear trigger or potential allergic source. He was admitted to the pediatric ICU on 4 of his 6 episodes. He had been treated on multiple occasions with repeated epinephrine injections, as well as epinephrine drips, in addition to continuous Albuterol. Allergy was consulted to facilitate in diagnosis. His past medical history included mild intermittent asthma, for which had not used Albuterol in over 2 years, environmental allergies (dust mite, dog, cat, and cockroach), musculoskeletal conversion disorder (leg weakness) that resolved with therapy, anxiety disorder. Family history included possible angioedema in patient’s father with lip swelling associated with alcohol and blood pressure medications.
The patient and his family were not initially forthcoming about social history, however on his last admission more history was obtained. He was in the 4th grade. He reported social isolation and bullying, which had caused him to change schools. His parents were separated and he reported not spending much time with his father. An argument with his father had preceded one of his episodes of swelling that required admission. Photos show his face at baseline, 12 minutes later during an episode, and 11 minutes later after swelling resolved.

Diagnosis
The differential diagnosis for recurrent episodes of lip and tongue swelling included hereditary angioedema, anaphylaxis, allergic reaction, or idiopathic angioedema. However due to his normal C4, C1esterase inhibitor, C1q, tryptase, and IgE, hereditary angioedema, anaphylaxis, and allergic reaction appeared less likely. In addition, he had poor response to epinephrine drips, making an allergic source or
anaphylaxis less likely. On his final admission, more psychosocial history was obtained, revealing previously unknown stressors, including bullying and parental discord. His swelling would also rapidly resolve and recur within minutes. This appeared inconsistent with pathologic angioedema. He was diagnosed with idiopathic angioedema secondary to conversion disorder. The diagnosis of idiopathic angioedema is defined as at least 3 episodes of angioedema within 6-12 months without clear etiology, which was consistent with this patient’s case. The fact that he had multiple psychosocial triggers, an argument with his father preceded his most recent episode, and his history of musculoskeletal conversion disorder, caused us to consider conversion disorder causing his lip and tongue swelling.

**Testing**
Due to his multiple episodes of lip and tongue swelling, we first elicited history to determine if there was a common source or trigger for the reactions. Although 2 of the episodes were initially thought to be secondary to medications, this was inconsistent with the rest of his episodes. We then obtained serologic workup to assess for hereditary angioedema, anaphylaxis, and allergic reaction. Laboratory workup included C4, C1esterase inhibitor quant and function, C1q, which were normal, making hereditary angioedema less likely. He had multiple tryptase levels that were normal, making anaphylaxis less likely. His IgE was also normal, making an allergic process less likely. He also had workup for known triggers of angioedema and urticaria, assessing for hepatidites, viral respiratory panel, and vasculitidies, but these were unrevealing.

**Treatment**
As he was thought to have conversion disorder causing idiopathic angioedema, he was seen by a psychologist while admitted to the hospital, and discharged with psychology follow up. However due to multiple episodes requiring a high acuity of treatment, he was discharged on high-dose fexofenadine, ranitidine, and diphenhydramine, with Doxepin later added. These medications were added for histamine blockade as some idiopathic edema is histaminergic and may respond to antihistamines.

**Patient Outcomes**
Not available

**Lessons Learned**
This patient case was unusual as he presented to the hospital 6 times for his recurrent lip and tongue swelling. His recurrent episodes were causing his family distress as he had several ICU admissions. Multiple etiologies were considered but a pathological source was not identified. This caused the team to consider a psychosomatic etiology of his swelling. To our knowledge, this is the first reported case of angioedema secondary to conversion disorder. This case demonstrates the need for psychosocial evaluation in patients with angioedema with an unusual presentation to prevent unnecessary healthcare cost and associated morbidity.
Scrotal Edema: the Clue to 40 Years of Undiagnosed Hereditary Angioedema

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Summary
A 56-year-old Caucasian male with no history of abdominal symptoms presented to a neighboring hospital with severe abdominal pain and was hospitalized for over two weeks with an extensive workup including CT scans, ultrasounds, and endoscopies that were all unremarkable. Symptoms recurred and he presented to our hospital for a similar exhaustive work up. His symptoms resolved in a few days and avoided further invasive interventions. He was discharged home with a referral to Allergy. Further questioning revealed no previous history of abdominal events or peripheral swelling, but an unusual history for decades of recurrent episodes of scrotal edema that would "resolve with furosemide" within 1-4 days. Labs revealed low C4 levels, low C1 esterase inhibitor (C1-INH) levels and function, and normal C1q level to confirm the diagnosis of Type 1 Hereditary Angioedema. Unfortunately, he was lost to follow up while waiting for insurance approval for his C1-INH replacement therapy.

Patient Presentation
A 56-year-old male initially presented to a neighboring hospital with new reoccurrences of central, sharp abdominal pain with associated nausea, vomiting, diarrhea, decreased appetite, subjective fever, chills, and myalgias. This abdominal pain was new for him only in the past few months. Over the counter medications did not relieve his abdominal pain, but diarrhea and vomiting brought some relief. He does not take medications and his medical history was only remarkable for diet-controlled hypertension, obstructive sleep apnea and internal hemorrhoids. He denied ever smoking, drinking alcohol or use of illicit drugs. His mother had diabetes and he denies knowledge of his father's health. Prior to our encounter, he was hospitalized twice for this abdominal pain. The first time he was hospitalized for over two weeks with an extensive workup including CT scans, ultrasounds, and upper and lower endoscopies that were all unremarkable. The presumed diagnosis at that time was infectious gastritis, treated with antibiotics, and discharged home. When his symptoms recurred, he was referred to our hospital and received a similar exhaustive work up that was also unremarkable. Fortunately, his symptoms resolved after a few days and did not undergo an exploratory laparotomy. He was discharged again with a presumed diagnosis of gastritis, but was told to follow up with Allergy for concern of HAE. At the initial time of encounter in the outpatient Allergy office, his vital signs and physical exam were unremarkable, with no signs of edema of his face or extremities. He lives in a house in the country with hardwood floors with area rugs and a few house pets. He denied any particular triggers before his abdominal pain attacks, and denied association with shortness of breath. He had no other esophageal symptoms besides mild reflux symptoms that occurred intermittently for several years.

Diagnosis
C4 and C1-INH levels were checked twice with the results of: C4 levels were 4 and 13 (normal 14-40), C1-INH levels were 5 and 5 (normal 19-37), and C1-INH functions were 0% and 12% (normal >67%). Given his age of onset of symptoms and negative family history, a C1q level was checked to differentiate between acquired versus hereditary angioedema and was found to be normal. In addition to the negative abdominal workup for infectious or autoimmune processes, the lab tests confirmed the diagnosis of Type 1 HAE. After deeper questioning about swelling that would potentially involve his
extremities, face, larynx, abdomen and genitals, he did admit that he had intermittent episodes of scrotal swelling that rarely caused pain and resolved after use of furosemide in 1-4 days.

**Testing**
By the time the patient arrived to the outpatient office, he had a number of tests already performed for his abdominal pain. Stool studies for his diarrhea were negative for E. coli or other infectious etiologies. CT scan of the abdomen revealed prominent circumferential mural thickening of the duodenum and proximal jejunum with surrounding edema, which was followed up with an MRCP with negative biliary pathology and similar intestinal wall findings that were not as pronounced as on the CT. Upper and lower endoscopies were performed, showing moderate duodenitis, mild gastritis, but negative biopsies for celiac disease or eosinophilia. At the office, he was tested for food allergies and aeroallergens, which were negative. We checked C4 levels, C1-INH function and levels to rule out HAE. When these lab values all returned low, we repeated them a few weeks later in addition to a C1q level to differentiate acquired versus hereditary and it reconfirmed low levels of C4 and C1-INH levels, with a normal C1q level.

**Treatment**
After the diagnosis of Type 1 HAE was made, he was offered as needed C1-INH subcutaneous injections for acute attacks since prophylactic treatment did not seem necessary due to his low severity and frequency of his attacks. Unfortunately, while waiting for insurance approval, he was lost to follow up.

**Patient Outcomes**
After the second visit at the office when we offered him treatment, he had not experienced additional abdominal symptoms. Because of loss of follow up, we had not initiated any treatments to see any outcome.

**Lessons Learned**
HAE is a rare condition that is mostly diagnosed in patients below the age of 20. Only about 4% of cases studied presented with initial symptoms above the age of 40. Around 75% of patients had positive family history of symptoms, usually in the form of angioedema of the face and extremities. Studies showed that intermittent abdominal pain occurred in about 93% of patients and one-third of which undergo unnecessary abdominal operations. This patient never presented with the typical facial or peripheral angioedema, but did have these few episodes of severe abdominal pain that eventually led to the final diagnosis of Type 1 HAE. Fortunately, he avoided unnecessary surgical interventions but still underwent extensive workup for his abdominal pain. One lesson learned is the importance of gathering a thorough history and direct questioning of swelling, especially in this patient who did not have typical locations of angioedema. Each patient may have unique characteristics of angioedema with the age of onset of symptoms, severity and frequency, despite having extremely low levels such as in this patient. Only after further questioning did he reveal that he had scrotal edema, for which he was misdiagnosed and given furosemide. Due to the self-resolving nature of HAE in 2-5 days, the furosemide probably did not play a role in the resolution of his symptoms. Clinically correlating his abdominal symptoms and scrotal edema, we learned that it is important to have a high index of suspicion for hereditary angioedema, despite his age. Screening for HAE with C4 and C1-INH levels is inexpensive in the long run to avoid further invasive workup of abdominal pain. This is also applicable in the primary care and hospital setting to promote high-value patient care and needs ongoing education in medical training.
Use of intravenous immunoglobulin for steroid-resistant DRESS syndrome

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Training Program UCLA-Olive View Internal Medicine Residency Program

Summary
A 68 year old AA female on allopurinol 100mg daily, initiated one month prior for gout flare, presented with an acute, pruritic, erythematous papular eruption, fever, and facial edema. Hospital course was complicated by worsening peripheral eosinophilia, AKI, and hepatic dysfunction while on oral and iv steroids, for which Allergy & Immunology was consulted. Patient was found have HLA B58:01 positivity and a diagnosis of DRESS syndrome was made. She continued to worsen on IV solumedrol and was started on 1g/kg IVIG with an improvement in her cutaneous manifestations, as well as eosinophilia, AKI, and hepatic dysfunction on laboratory evaluation the following morning. Given the potential severity of DRESS syndrome, a form of drug hypersensitivity reaction, it is useful to recognize that IVIG can be used to aid in the management of this condition when refractory to oral and iv steroids in order to facilitate prompt treatment.

Patient Presentation
Our patient is a 68 y.o. female with diabetes mellitus, chronic kidney disease, hypertension, and abdominal aortic aneurysm, who presented with a pruritic rash for three days after being admitted one month prior for pneumonia, hyperglycemic hyperosmolar syndrome, and gout flare, for which she was discharged on allopurinol 100mg daily. Patient was taking no new medications or antibiotics, other than a seven day course of levofloxacin for treatment of pneumonia. On admission, patient reported facial swelling and a pruritic rash on her back, neck, and arms. Hospital course was complicated by worsening peripheral eosinophilia, acute kidney injury (AKI), and hepatic dysfunction in spite of one week of treatment with oral prednisone 80mg and iv solu medrol 80mg daily, at which time Allergy & Immunology was consulted. On our evaluation, patient endorsed a persistent diffuse rash, mouth pain, and blurry vision.
On examination, patient’s vital signs were stable, she was in no apparent distress, and had bilateral conjunctival injection, cloudy eye discharge without flaking, lip swelling with ulcerations on the lower buccal mucosa (Image 1), and erythematous papules coalescing into plaques diffusely on the chest, back (Image 2), arms, and legs bilaterally (Image 3).

Diagnosis
Given the patient’s diffuse morbilliform rash, facial edema, kidney injury, hepatic dysfunction, and peripheral eosinophilia, the patient met criteria for DRESS syndrome, a clinical diagnosis. Also consistent with this diagnosis is the patient’s positive HLA B58:01, as well as her skin and lip biopsy findings of eosinophils. The likely culprit drug was allopurinol, which is a known cause of DRESS syndrome. Additionally, the timing of her reaction fits with this diagnosis, which generally occurs approximately three to four weeks after initiation of the inciting medication.
There was also a concern for possible Stevens-Johnson syndrome given that oral and ocular involvement is infrequently seen in DRESS syndrome, and this patient developed worsening ulceration of the lower lip mucosa, conjunctival injection, and blurry vision while on appropriate treatment for presumed DRESS syndrome. However, it should be noted that the patient did not experience any desquamation of the
skin or other body surface. As noted above, workup for infection, malignancy, and vasculitis, was negative.

**Testing**
Patient was noted to have worsening peripheral eosinophilia, AKI, and hepatic dysfunction while on steroids, including an eosinophilia of 13.8%, a creatinine of 2.6, an AST of 31, and an ALT of 28. Patient underwent workup for other causes of eosinophilia including malignancy, vasculitis, and infectious etiologies. Peripheral smear was completed without findings of T cell lymphoma. ANCA was negative for vasculitis. Workup for parasitic infection including a strongyloides titer and stool ova and parasites was negative. Other infectious workup, including testing for EBV, CMV, HHV6, Coccidioides, Aspergillus, Mycoplasma, Cryptococcus, and Hisptoplasmosis, was negative. There was no evidence of granulomatous disease on CT chest to suggest sarcoidosis. HLA B58:01 was positive, consistent with a diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. Given patient’s facial edema, a tryptase level was sent which was mildly elevated, and an angioedema profile was sent, with findings of elevated C1 inhibitor protein, and C1 esterase inhibitor function >100%. Additionally, a C1q binding assay was negative, and a lymphocyte enumeration was significant for elevated lymphocytes, normal percent T-cells, natural killer cells, and very decreased B cell percent. Ultimately, the patient underwent lip and skin biopsy with Dermatology, with findings of ulceration, neutrophils, and eosinophils on lip biopsy, and mild lichenoid/interface dermatitis, superficial to mid-dermal perivascular/interstitial lymphocyte predominant with scattered eosinophils, on skin biopsy, and no infection, vasculitis, or malignancy on either.

**Treatment**
While the patient’s eosinophilia and AKI initially showed some improvement on solumedrol 80mg iv, the patient continued to worsen in terms of her cutaneous, oral, and ocular involvement, and she developed severe hepatic dysfunction and another rise in her creatinine and eosinophilia. Subsequently, we recommended a three-day course of intravenous immunoglobulin (IVIG). Within 24 hours of initiating IVIG at a dose of 1g/kg per day, the patient was noted to have an improvement in her cutaneous manifestations, in addition to her eosinophilia, AKI, and hepatic dysfunction. Laboratory findings were remarkable for a drops in eosinophilia from 6.7% to 0.2%, creatinine from 1.94 to 1.86, AST from 512 to 222, and ALT from 645 to 486.

**Patient Outcomes**
Because the patient experienced severe persistent oral and ocular involvement in spite of administration of IVIG, the following day, her iv solumedrol dose was doubled from 80mg to 160mg daily. Patient received a total of 3 days of IVIG and solumedrol 160mg iv daily until she responded, at which point her solumedrol dose was decreased back to 80mg. Patient’s laboratory abnormalities and skin manifestations responded well to IVIG and iv steroids, and she was discharged with an oral solumedrol taper for persistent oral and ocular mucosal involvement after requiring admission to the Ophthalmology Service for a higher level of care.

**Lessons Learned**
DRESS syndrome is a rare, potentially life threatening drug induced hypersensitivity reaction with skin eruption, eosinophilia, lymphadenopathy, and organ involvement such as the liver, kidney, and lung.
Management of DRESS syndrome includes prompt removal of the offending agent and systemic corticosteroids if there is concern for severe organ involvement. We showed that in isolation of having increased the patient’s dose of iv solumedrol, her manifestations of DRESS syndrome, including cutaneous, renal, hepatic, and eosinophilic, responded to initiation of IVIG. Similarly, in a case report by Santhamoorthy, Alexander, and Alshubaili (October to December 2012), a 32 y.o. female status-post meningioma excision, now on phenytoin, continued to clinically deteriorate on prednisolone but responded to IVIG within three weeks. Additionally, in a retrospective review by Marcus et al. (August 2018) of children hospitalized in a tertiary care hospital who received IVIG for severe DRESS syndrome, they found that addition of IVIG to steroids may expedite recovery. In conclusion, given the potential severity of DRESS syndrome, it is useful to recognize that IVIG can be used to aid in the management of this condition when refractory to oral and iv steroids in order to facilitate prompt treatment.
Anaphylaxis After Peanut OIT Followed by High Intensity Exercise

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Summary
Oral immunotherapy is rapidly becoming a popular management option among patients. Home dosing regimens necessitate strict precautions to regulate peanut protein absorption and subsequent reaction risk, such as exercise. However, the duration and/or intensity threshold of exercise placing patients on OIT regimens at increased anaphylaxis risk is not fully understood. Here we demonstrate a case of a 13 y/o identical twin male undergoing peanut OIT, who tolerated an updose and went to exercise, but developed anaphylaxis 3 hours later. The patient’s identical twin brother was also updosed and went to exercise but took fexofenadine 180mg prior to activity with no adverse symptoms experienced. This case of identical twins undergoing peanut OIT offers a comparison of how exercise intensity and duration may affect anaphylaxis risk and highlights how previously suggested exercise restriction of 2 hours after OIT dosing may not be a one size fits all.

Patient Presentation
The patient is a 13 y/o male who initiated peanut OIT using well described protocols. The patient had tolerated an updose to 6 peanuts and went to cross-country practice 3 hours later. He performed 200m sprint-repeats x 7 at near-maximum exertion and denied symptoms while actively exercising. During cool-down, he developed wheezing, followed by swelling and itching on his face. The patient soon developed full body hives, profuse rhinorrhea, and headache. The patient has an identical twin brother who was updosed to 5 peanuts the same day. About 3 hours later, he attended soccer practice with “moderate activity” for 90 minutes, and used fexofenadine 180mg prior to exercise. The patient’s brother did not experience any adverse symptoms during his practice.

Diagnosis
Food allergy to peanut, currently undergoing Food OIT treatment regimen. Experienced dosing-related anaphylaxis, likely secondary to increased systemic allergen absorption from intense exercise.

Testing
Presenting diagnosis made on clinical grounds.  
Testing results prior to initiation of OIT: Peanut SPT 13/40, serum total IgE to peanut 53.3 kU/L

Treatment
Patient proceeded to use Fexofenadine 180mg and Albuterol immediately for his hives and wheezing, with which he experienced improvement. Upon arrival at home, the patient used Fluticasone/Azelastine nasal spray.

Patient Outcomes
He had complete recovery of all symptoms within 24 hours. OIT dose was decreased by 50% and gradually stepped back up to reaction-provoking dose over the next 2 weeks, which he tolerated well. Further dose escalation was subsequently resumed per protocol.
Lessons Learned
This case of identical twins undergoing peanut OIT offers a comparison of how exercise intensity and duration may affect anaphylaxis risk. Previous reports have suggested exercise restrictions for 2 hours after OIT dosing, however, this time interval may also be affected by the type of exercise. Further study is required to evaluate the extent of these factors on OIT patients.
Occupational Contact Urticaria from Low Molecular Weight Substances without Respiratory Involvement

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Summary
Epoxy resins and isocyanates are low-molecular-weight highly reactive compounds widely used in paints, varnishes or cements. Both substances, due to their low molecular weight, are involved in numerous cases of respiratory affection and contact dermatitis, generally by a type IV mechanism mediated by T lymphocytes. For instance, the absorption by inhalation of volatilized isocyanates can produce toxic symptoms such as extrinsic alveolitis. In the case of epoxy resins, they are considered the industrial substances with the greatest capacity for skin sensitization. Numerous cases of severe contact eczema in workers handling these chemicals have been described. In this opportunity, two interesting and uncommon cases of occupational contact urticaria by these substances without asthma component are presented.

Patient Presentation
Two 30 and 50 year-old males: The first being a worker in a windmill factory handling epoxy resins and the second one a car painter manipulating isocyanates. They refer outbreaks of acute urticaria self-limited within 1.5 hours of exposure to these chemicals in the workplace. When out of work they do not have any symptoms. Both use respiratory and skin protection measures.

Diagnosis
Occupational contact urticaria from low molecular weight substances (epoxy resins and isocyanates) without respiratory involvement.

Testing
In the first patient (worker in a windmill factory), prick-prick with products handled in the workplace were positive for epoxy resins, negative in three healthy controls. We also performed epicutaneous tests with True test® and batteries of epoxy resins, adhesives and acrylates, being negative in immediate and late readings. The second patient (car painter) presented an ImmunoCAP positive for Isocyanate HDI (0.95 kU/l). We also performed a rubbing test with HDI isocyanate, appearing numerous urticariform lesions on the arm that extended to the rest of the body after 15 minutes and required the administration of antihistamines. This test was negative in three healthy controls. In both cases, the baseline metacholine tests were negative with a PC 20>16 mg/ml. Subsequently, while on sick leave, a specific bronchial provocation test was performed in an aerodynamic chamber of 7mm3-exposure time 30 minutes-with epoxy resins and isocyanates respectively, being both negative (no immediate or delayed fall in FEV1 was observed). The metacholine test 24h after specific bronchial provocation were negative in both patients (PC 20>16 mg/ml). No variation of the FeNO after the specific bronchial provocation test was detected.
Treatment
The recommendation was to avoid the exposure of these substances in the workplace. A change of place of work was also advised. Antihistamines were prescribed in case of reaction due to accidental exposure.

Patient Outcomes
Both patients had the opportunity to commence different jobs without exposure to these chemical substances. Thanks to this recommendation, they did not develop symptoms again.

Lessons Learned
Epoxy resins and isocyanates are low molecular weight substances causing frequent cases of allergic contact dermatitis and occupational asthma, usually by a mechanism mediated by T lymphocytes. In our case, we present two workers with immediate urticaria after exposure to these substances in their work. The skin tests in prick by prick for epoxy resins, the positivity for ImmunoCAP HDI isocyanate as well as the appearance of local and generalized urticariform lesions after the Rubbing test with isocyanate demonstrate that in both cases it is a pathology IgE-mediated. We also ruled out a contact dermatitis due to epoxy resins after the epicutaneous test.
In addition, given the high implication of these substances in occupational asthma, in order to rule out asymptomatic respiratory affection, it was decided to carry out an exhaustive study with a basal metacholine test, specific bronchial provocation and a post-bronchial metacholine test, which in both cases were normal.

References:
Angioedema in a Patient with Normal C1-Inhibitor Levels and Activity, Probably Associated With Anti-Androgen Therapy

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Summary
An 80-year-old patient with a history of chronic hypertension and benign prostatic hyperplasia presented with recurrent episodes of angioedema for the last two years. Swelling was circumscribed to tongue, lips and chin, lasted more than 24 hours, and responded poorly to antihistamines and corticoids. Treatment with lisinopril had been replaced with telmisartan 10 months earlier. Telmisartan had then been substituted with lecarnidipine. Regardless, the episodes had persisted, and had become progressively longer, more frequent, and more intense.

Blood testing showed minimally low C4 levels, and normal C1-inhibitor and C1q levels. NSAID hypersensitivity was ruled out. Long-term treatment with dutasteride was suspected as a cause and was suspended. Eight months later, the patient has not experienced any new episodes.

We believe that this constitutes a case of recurrent angioedema that was either induced or worsened by dutasteride. It highlights the importance of considering anti-androgen drugs either as separate causes or as synergistic triggers of angioedema in male adults treated concomitantly with ACEIs/ARBs.

Patient Presentation
We present the case of an 80-year-old patient who consulted in our department due to recurrent episodes of angioedema for the last two years. He described at least 5 episodes during the first year – about one every 2 or 3 months. These consisted of swelling upon waking up that was mostly unilateral and affected tongue, both lips, and sometimes the lower jaw. He did not notice wheals, lacrimation, or pruritus during the episodes. They were not accompanied by abdominal pain. Symptoms persisted 24 hours or more without treatment and showed a limited and slow response to antihistamines and corticoids. He did not recall having previous episodes of angioedema. There were no foods that could be identified as obvious causes. He recalled having a dose of naproxen hours prior to some of the episodes, but not prior to all of them. He had never noticed wheals upon friction with surfaces or sharp changes in temperature, or when coming out of the shower.

The patient had a medical history of chronic hypertension that had been treated with lisinopril for about 5 years, up until 10 months prior to consulting. Lisinopril had been suspected as a cause by an allergist and had been substituted by his primary care doctor for telmisartan. After this change, however, the episodes persisted and became progressively longer in duration and more frequent. He had consulted again and treatment with telmisartan had been substituted for lecarnidipine. Nearly 6 months into this change, the episodes continued and were more intense, responding less and less to antihistamines and corticoids. They became bilateral and began to last 48 hours.

He referred a history of benign prostatic hyperplasia that had been treated with dutasteride/tamsulosine (0.5/0.4mg daily) for at about two and a half years.

He also had a history of hypercholesterolemia and symptomatic hyperuricemia, which was treated with atorvastatin and allopurinol, respectively.

He denied previous hepatitis B or C infection. He had no history of cancer.

He had no known food or drug allergies, and no history of atopic disease.
He recounted no family history of angioedema or chronic urticaria. 
Review of systems showed no other significant findings except for an increased frequency on urination that responded to treatment. 
Physical examination showed normal vital signs and no pertinent findings. No edema present during examination in consult.

**Diagnosis**
Drug-induced angioedema, probably associated with anti-androgen therapy, with normal C1-inhibitor levels and activity

**Testing**
We conducted skin prick testing with a standard battery of allergens, including respiratory and food allergens that are most prevalent in our area. Despite the fact that symptoms were suggestive of a non-histaminergic origin, this was helpful in ruling out common histaminergic causes and reassuring the patient that there was no need to restrict his diet. 
We then conducted a provocation test with escalating doses of naproxen, reaching a total dose of 500mg. The patient no symptoms referred no symptoms upon observation in consult during the 6 hours following administration, as well as from home during the 24 hours following administration. This test was useful to rule out NSAID hypersensitivity or selective allergy to naproxen as a cause. The patient recalled having tolerated other NSAIDs in the past, but not during the past 2 years. 
We added a complete blood cell count that showed no alterations. Despite the fact that no symptoms were suggestive of hematologic disease, we used this as an initial screening for myeloproliferative disorders, which may be related to refractory angioedema. 
Erythocyte sedimentation rate was normal (12 mm/hr). 
We ordered hepatitis B and C testing that the patient was not able to complete.

We also tested for complement C4 levels, as part of the algorithm to study bradykinin related angioedema. This study showed minimally low levels of complement C4 (11,20 mg/dL, 16 -38 mg/dL). The length of the episodes, as well as the absence of urticaria and decreased C4 levels prompted us to test for C1-inhibitor levels and activity. C1-inhibitor levels and function were normal.

**Treatment**
As an initial therapeutic strategy (and diagnostic strategy), and given the lack of family history of angioedema, in a patient with normal C1-inhibitor levels and activity, we decided to substitute dutasteride/tamsulosine for tamsulosine-only, with consultation from a urologist. No other medications were changed. We speculated that dutasteride may have had a role in worsening or triggering the attacks, as described by Kampitak and Thatchai in their case published in 2011 in Annals of Allergy, Asthma and Immunology (see Lessons Learned).

**Patient Outcomes**
We conducted follow-up with monthly phone calls, as well as a consult at our department 6 months after changing treatment. Nine months later, the patient has not experienced new episodes of angioedema. He has not noticed angioedema after stopping dutasteride therapy. His urinary frequency symptoms are controlled with tamsulosine.
Lessons Learned
Drug-induced angioedema is a well-known form of refractory angioedema. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), NSAIDs and estrogen-containing compounds have long been identified as causative agents. Other medications may increase the risk of angioedema in individuals taking ACEIs.
It has been speculated by Kampitak, Thatchai et al., (Annals of Allergy, Asthma & Immunology, Volume 107, Issue 4, 376-377) that anti-androgen therapy may also induce angioedema, possibly due to inference with bradykinin production and degradation. In their article, they present a case of a patient with recurrent episodes of angioedema and a history of benign prostate hyperplasia treated with dutasteride for several months prior to the episodes, which continue despite discontinuation of ACE inhibitor and NSAID treatment. They resolve after eliminating dutasteride from the patient’s medication. We believe that this constitutes a case of recurrent angioedema that was either induced or worsened by dutasteride. Angioedema continued at regular intervals with increasing intensity despite discontinuation of both ACEIs and ARBs for nearly 6 months. Our case highlights the importance of considering anti-androgen drugs either as separate inducers, or as synergistic triggers of angioedema in male adults treated concomitantly with ACEIs/ARBs.
Contrast Allergy and IVIG

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Summary
This patient with complex congenital cardiac and pulmonary disease and known previous Stevens-Johnson syndrome (SJS) reaction to IV iodinated contrast, presented with acute onset of hemoptysis and chest pain. Cardiac catheterization was deemed medically necessary. Previous attempts of using alternative contrast reagents did not provide acceptable images. Patient was pretreated with methylprednisolone and diphenhydramine and received IV iodinated contrast during catheterization. She began having erythematous skin rash and pain following the procedure and was started on 500mg/kg/day IVIG. During hospitalization she had recurrent hemoptysis and additional catheterization was required to embolize pulmonary arterial venous anomalies. She was again pretreated with methylprednisolone and diphenhydramine prior to contrast administration. She developed a rash following second catheterization but no blistering or mucocutaneous involvement. She received a total of seven daily doses of 500mg/kg IVIG inpatient and completed a three-week course of oral antihistamines and oral steroid taper as an outpatient with no further sequelae.

Patient Presentation
Fourteen-year-old with a history of asthma, Tetralogy of Fallot with pulmonary atresia. She had required multiple cardiac procedures including outflow tract augmentation, subsequent revision of repair with homograft and bilateral pulmonary arterioplasty, additional revision of repair. Following a catheterization with iodinated contrast, she had fever, diffuse rash with painful desquamation and mucosal abnormalities. Allergy and Immunology and Dermatology consultations advised reaction consistent Stevens-Johnson syndrome and avoidance of contrast agents was recommended. Further routine imaging was attempted to be obtained with gadolinium-based contrast. This did not provide acceptable images, due to her history of complex heart disease. Patient presented to hospital with acute episode of hemoptysis and dyspnea. She was taken for urgent catheterization with iodinated contrast after premedication with diphenhydramine and methylprednisolone. During catheterization, she had particle occlusion and vascular plugging of multiple aorta-pulmonary artery collaterals. Two hours following procedure, the patient was noted to have erythematous rash of neck, axillae, trunk, and feet. Allergy was then consulted, and patient was continued on methylprednisolone, diphenhydramine, ranitidine, and received IVIG daily x four doses. Patient developed additional episodes of hemoptysis requiring treatment with catheterization and iodinated contrast. She was premedicated with methylprednisolone thirteen, seven, and one hour prior to procedure. Diphenhydramine was administered one hour prior to procedure. IVIG 500mg/kg/day was given on the day of the procedure. Ephedrine was considered and not used after discussion with Cardiologist due to her cardiac pathology. Multiple collaterals were embolized. She again developed erythema of extremities, abdomen, and back several hours following procedure which continued to spread. She received total seven doses IVIG. Discharged home on steroid taper and antihistamines.

Diagnosis
Stevens-Johnson syndrome is a clinical diagnosis. It is a severe mucocutaneous reaction, including extensive necrosis and detachment of the epidermis. SJS pathogenesis is not completely understood.
Cytotoxic T cells directed against an offending drug is the likely underlying cause through apoptotic granulysin. Acute reactions to contrast agents include physiologic, allergic-like, and delayed. Delayed reactions are usually T-cell mediated. Severe delayed reactions causing desquamation are rare. These reactions may or may not occur with repeat exposure to causative agents.

**Testing**
There is no testing for Stevens-Johnson syndrome, as it is a clinical diagnosis.

**Treatment**
Stevens-Johnson syndrome is not usually responsive to pretreatment. This patient was initially treated with IVIG and methylprednisolone. There is limited data to support combination therapy for SJS treatment. Both medications have potential for adverse effects.

**Patient Outcomes**
Patient developed rash following both administrations of contrast despite pretreatment and immediate addition of IVIG when symptoms developed. She was monitored inpatient and followed as outpatient. She did not develop fever, mucosal abnormalities, or desquamation characteristic of Stevens-Johnson syndrome.

**Lessons Learned**
To our knowledge, there is no medical literature reporting pre-treatment of patients with previous Stevens-Johnson syndrome to IV contrast. In patients with severe and/or delayed reactions to IV iodinated contrast, recommendations are usually to avoid the offending agent and attempt gadolinium-based contrast, as we advised. When iodinated contrast is required, premedication with steroids and antihistamine is attempted to be given prior to medication administration and cardiopulmonary resuscitation team available. Medications used for treatment of SJS may have been beneficial in preventing severe reactions to agents that had previously caused delayed hypersensitivity reactions. In cases of medications that have caused severe delayed hypersensitivity reactions and are necessary, it may be beneficial to consider pretreatment or treatment at onset of symptoms with medications such as steroids, antihistamines, IVIG, or Cyclosporine.