Session 3557

Interesting Cases II – Sunday, March 15, 2020

Case Report #2

Author JaneMarie Freeman
Training Program University of Alabama-Birmingham

Case Title

DAVID Syndrome: When Common Variable Immune Deficiency is More Than Hypogammaglobulinemia

Summary

9yoF with alopecia universalis presented to outpatient immunology clinic due to low immunoglobulin levels and frequent acute otitis media, sinusitis, and recent severe pneumonia. Laboratory studies revealed very low immunoglobulins, low isohemagluttinins, and normal lymphocyte flow cytometry, and she was started on intravenous immunoglobulin infusions. At follow-up, Invitae primary immunodeficiency panel was sent which revealed a pathogenic mutation in NFKB2 suggesting DAVID syndrome (Deficiency of Anterior pituitary and Variable Immune Deficiency). Subsequent laboratory data revealed low ACTH, undetectable cortisol on ACTH stimulation test with normal TSH, normal total T4, mildly low free T4, normal prolactin, and low estradiol, LH, and FSH in a pre-pubescent female. Patient was subsequently referred to endocrinology and initiated on hydrocortisone replacement with normalization of her cortisol levels and free T4 levels.

Patient Presentation

9yoF presented to outpatient immunology clinic due to low immunoglobulin levels and frequent acute otitis media, sinusitis, and recent pneumonia. She was diagnosed with alopecia universalis at age 3 and followed with dermatology until evaluation by Immunology, but other than frequent infections, had no other associated symptoms. There was no family history of immunodeficiencies, endocrinologic disorders, or autoimmune conditions. With further visits and interviews, discussion was held about a possible entity that would encompass both the alopecia and hypogammaglobulinemia which ultimately lead to the Invitate Primary Immunodeficiency Panel being sent and the diagnosis of DAVID syndrome being made.

Diagnosis

Given her known hypogammaglobulinemia and alopecia, when we received the results of the Invitae panel, it was imperative to evaluate her for adrenal insufficiency given the known association. After discussion and visit with endocrinology, the patient was initiated on hydrocortisone replacement with improvement in both her labs as well as her alopecia.

Testing

Invitae Primary Immunodeficiency Panel was obtained and revealed a pathogenic variant in NFKB2. Located on exon 22, the sequence change results in a premature translational stop signal in NFKB2 gene which is expected to delete the last 48 amino acids of the NFKB2 protein. Once the Inivtae results were

available, additional endocrine work-up was conducted and revealed low ACTH, undetectable cortisol on ACTH stimulation test with normal TSH, normal total T4, mildly low free T4, normal prolactin, and low estradiol, LH, and FSH in a pre-pubescent female

Treatment

Patient was continued on monthly intravenous immunoglobulin replacement for the CVID component to her disease. After consultation with endocrinology, she was also initiated on hydrocortisone replacement therapy for her adrenal insufficiency which subsequently corrected her thyroid abnormalities and normalized her cortisol levels.

Patient Outcomes

Patient has done well with immunoglobulin replacement and has had minimal infections. Once she was placed on hydrocortisone replacement, her cortisol level and thyroid levels normalized, energy level improved and she has already noticed return of hair growth.

Lessons Learned

DAVID Syndrome is a disease in which the underlying genetic defect causing CVID is known and represents a unique opportunity for diagnostic testing in patients with CVID. It is caused by a mutation in the NFKB2 gene which affects specific aspects of B cell maturation, peripheral lymphoid development, bone metabolism, and thymic development. The cause of ACTH deficiency in DAVID syndrome is unknown, but, perhaps, further investigation into the link between the NFKB2 pathway and adrenal or pituitary function can be investigated in the future. This case highlights the importance of utilizing the primary immunodeficiency panel in patients with hypogammaglobulinemia and evidence of other autoimmune processes like alopecia.