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Introduction: DOCK8 deficiency is a combined primary immunodeficiency (PID) that causes autosomal recessive hyper-IgE syndrome and is characterized by recurrent infections, atopy, and risk of autoimmunity and malignancy.[1] We report a case of EBV-associated smooth muscle tumors secondary to DOCK8 deficiency requiring allogeneic bone marrow transplant.

Case Description: A 21-year-old female with a history of allergies, eczema, and recurrent sinus infections in childhood presented with severe daily headaches for two years. Brain MRI revealed enhancing lesions of the anterior skull base and right ethmoid sinus, subsequently diagnosed as EBV-associated smooth muscle tumor (SMT) via biopsy. There was no history of immunosuppressive medications and she was HIV negative. Immune workup revealed low absolute T cells, no T cell function, impaired B cell memory, and loss of NK cell function. Genetics revealed compound heterozygous DOCK8 deficiency with somatic reversion of T cells. Interestingly, during treatment for appendicitis two years earlier, the patient was found to have endobronchial EBV leiomyoma requiring right lower lobe resection. She underwent gamma knife stereotactic radiosurgery of the tumors followed by allogeneic bone marrow transplant and is awaiting immune reconstitution.

Discussion: While EBV-associated SMTs have primarily been reported in association with HIV and immunosuppressive medications, their association with PID is much more rare.[2] Defective T cell immunity secondary to DOCK8 deficiency was likely central to the pathogenesis of this condition in our patient.

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HETEROZYGOUS DE-NOVO MUTATION OF IKZF1 (IKAROS): WHEN GAIN OF FUNCTION RESULTS IN IMMUNE DYSREGULATION
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Introduction: IKZF1 plays a role in peripheral lymphocyte homeostasis by favoring a Th2 response and negatively regulating follicular B cell activation. IKZF1 mutations are frequently associated with loss of function resulting in a phenotype similar to common variable immunodeficiency. We describe a rare case wherein the gene mutation resulted in gain of function (GOF) immune dysregulation.

Case Description: A 26 year-old male with recurrent infections, diffuse lymphadenopathy (figure 1), cholangitis, inflammatory bowel disease complicated by perforation, and immune thrombocytopenic purpura was found to have IKZF1 gene mutation on whole exome sequencing. Lab notable for hyper-gammaglobulinemia of IgG/E/M, peripheral eosinophilia, elevated lactate and CRP, pancytopenia, T and NK cell lymphopenia, low B cell levels, elevated IL-6, TNF-alpha, IL-10, sIL-2R, and vitamin B12 levels. Lymph node, bile duct, and bowel pathology with findings not entirely consistent with multifocal Castleman’s vs IgG4-related disease. Subsequent immune workup demonstrated partial antibody response to Prevnar-13, low mitogen stimulation assay, absent CH50 and low C4, CD4 lymphopenia, and DHR assay with oxidative burst on unstimulated patient sample. Baseline sera IKAROS levels not elevated. The patient’s presentation was attributed to IKZF1 mutation resulting in immune hyperactivity. He improved on prednisone 60mg daily, now 15mg daily. Trial of lenalidomide 5mg daily for one month was discontinued given side effects and lack of clinical response.

Discussion: Given the rare nature of IKZF1 GOF mutation, it is useful for clinicians to recognize and identify therapeutics, such as steroids and possibly hematopoietic stem cell transplant, which may be useful to reduce morbidity and mortality.
Case Description: A 49-year-old female with a history of mixed connective tissue disease, lymphocytic interstitial pneumonia, granulomatous pulmonary nodules, and recurrent aspergillosis was hospitalized after developing a new livedoid rash concerning for occultive vasculopathy on skin biopsy. Serology demonstrated positive Dilute Russell Viper Venom Time and elevated IgM cardiolipin suggestive of anti-phospholipid antibody syndrome. One month prior, she had developed a granulomatous drug reaction secondary to cephalaxin prescribed for a urinary tract infection. The patient’s history of autoimmune disease, aspergillosis infections, and granulomatous inflammation on prior skin and lung biopsies prompted extensive work-up for an underlying immunodeficiency. A dihydrorhodamine (DHR) flow cytometry test revealed dual oxidative burst peaks with 60.1% of neutrophils demonstrating normal activity. These results diagnosed the patient as an X-linked CGD carrier. Confirmatory genetic sequencing is pending.

Discussion: While traditionally thought to be clinically unaffected, female X-linked CGD carriers may exhibit significant autoimmune or infectious phenotypes due to lyonization. Diagnosing these patients has important implications for family planning and patient monitoring, as X-inactivation may shift with age. Screening for X-linked CGD is under-utilized and should be performed in all female patients with multiple autoimmune manifestations or recurrent infections from catalase-positive organisms.