Histopathologic features in a case of hyperimmunoglobulinemia D syndrome

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ABSTRACT

We describe a case of Mevalonate Kinase Deficiency (MKD) also known as Hyperimmunoglobulinemia D Syndrome (HIDS) presenting as a Sweet-like syndrome in a 5-week-old with multiple erythematous plaques, fever, aseptic meningitis, and bronchiolitis. The locations of the predominant plaques were periumbilical and periocular, which originally prompted concern for omphalitis and preseptal cellulitis. Histopathology demonstrated a neutrophilic and histiocytic dermatitis with prominent squamous syringometaplasia and leukocytoclasis in the absence of a vasculitis. This case is reported here due to the unique findings of a prominent histiocytic component in addition to the typically described neutrophilic infiltrate.

Key words: Hyperimmunoglobulinemia D syndrome, infant, mevalonate kinase deficiency, sweet syndrome

INTRODUCTION

Mevalonate Kinase Deficiency (MKD), also known as Hyperimmunoglobulinemia D Syndrome (HIDS), is an autosomal recessive metabolic autoinflammatory disease, which typically presents with fever in combination with a constellation of skin findings, lymphadenopathy, hepatosplenomegaly, abdominal pain, vomiting, diarrhea, arthralgias, and myalgias.[1] Elevated serum IgD and IgA support the diagnosis, as does elevated urinary mevalonic acid; however, the diagnosis rests on identification of disease causing mutations in each of the mevalonate kinase (MVK) alleles.[1] Commonly reported histopathologic features include mild vasculitis and Sweet-like features.[2] We review a case with a mixed neutrophilic and histiocytic infiltrate with syringometaplasia.

CASE REPORT

A 5-week-old otherwise healthy female was transferred to our institution with a 6-day history of fever of 103°F and suspicion of multifocal cellulitis not responding to three days of vancomycin, cefotaxime, and acyclovir. The patient was born of an otherwise uncomplicated pregnancy, to healthy parents, her father with a history of familial hematuria, she had no facial dysmorphism and was developmentally appropriate for her age. The patient had a recent history of nasal congestion and subsequent onset of fever and skin findings. She was admitted with a several centimeter erythematous plaque surrounding the umbilicus and transferred to our institution following development of similar plaques periorbitally (right more prominent than left) and at sites of skin trauma [Figures 1 and 2]. On presentation to our institution, the patient was anemic (Hg/Hct of 11.8/35 × $10^3/\mu L$) with an elevated white count (18.2 × $10^3/\mu L$; 47% segments, 4% bands, 29% lymphocytes, 11% monocytes, and 1% eosinophils), thrombocytosis (platelets = 694 × $10^3/\mu L$) and elevated C-reactive protein (CRP) (11.2 mg/L). One wound culture from the periumbilical plaque grew out pan-sensitive *Streptococcus aeruginosa*; however, the patient had five sets of negative blood cultures, three negative cerebrospinal fluid (CSF) cultures, and negative CSF polymerase chain reaction for enterovirus, HSV-1, 2, and six (although there was evidence

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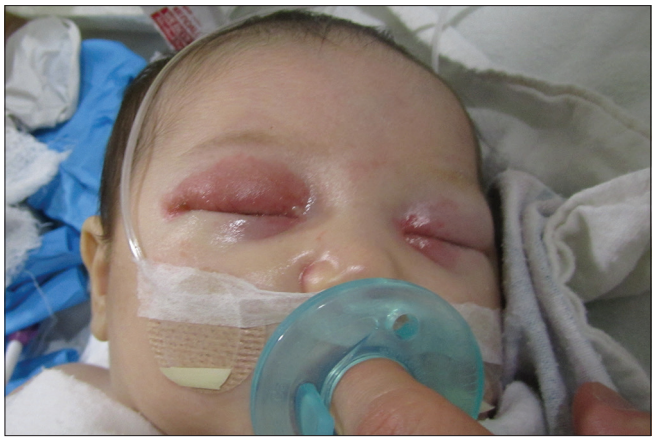

Figure 1: Periorbital plaques—warm, indurated lesions raised suspicion of preseptal cellulitis at initial presentation

of an aseptic meningitis), in addition to negative RSV and influenza. Cefotaxime was discontinued and meropenem was started. During this same timeframe, the patient developed respiratory distress requiring high flow of oxygen via nasal cannula and had evidence of pulmonary infiltrates on chest radiography. Her radiologic workup revealed mild hepatomegaly. Her anemia worsened and eventually required transfusion (Hg/Hct touched a nadir of 7.2/21.4 × $10^3/\mu L$).

Dermatology consultation was sought three days after transfer and considered the patient's presentation most consistent with Sweet Syndrome and recommended biopsy. Biopsy was deferred for 2 days, during which time the patient continued with fever over 103°F and her inflammatory markers continued to rise. The biopsy demonstrated a neutrophilic and histiocytic infiltrate that supported a Sweet-like syndrome given the clinical picture, with some hesitancy owing to the lack of significant dermal edema and the presence of histiocytes.

The dermatologist recommended that systemic steroids be initiated. However, concern for atypical Kawasaki's disease and the potentially life-threatening implications of ignoring this diagnosis prompted the primary team to pursue high-dose aspirin and IVIG with low-potency topical steroids for skin lesions. Several days later, upon completion of this therapy, the patient continued to be febrile, with continued rise in ESR and CRP. The patient was started on oral steroids, to which her fever responded quickly. The patient remained afebrile with no recurrence of skin lesions despite later atrophic scarring on the dorsal hands at the sites of the pathergic plaques. The patient was noted to be extremely irritable and systemic steroids were stopped. Trial treatment with Anakinra was started. The patient remained afebrile while on Anakinra, however she developed a positive Purified Protein Derivative (PPD) necessitating cessation of the Anakinra and treatment with isoniazid. The patient had a similar, but less severe flare of fever and skin lesions, which prompted genetic testing by rheumatology for periodic fever syndromes, inclusive of that for

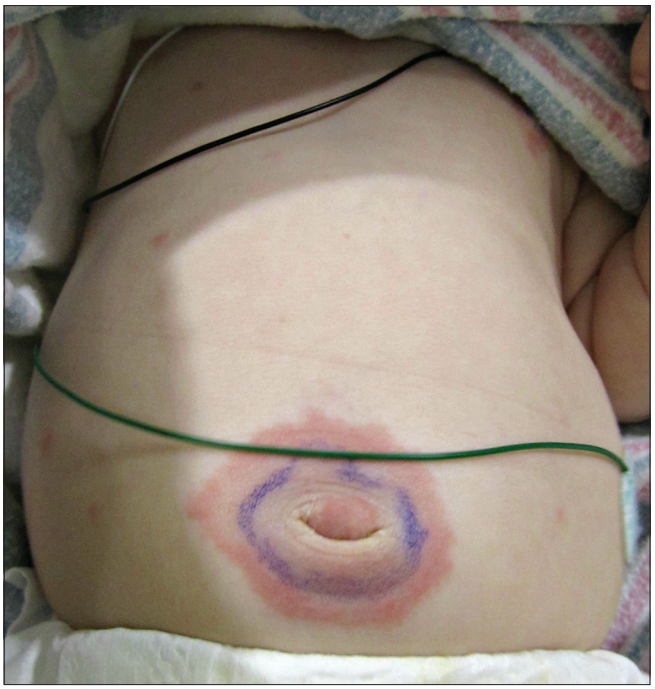

Figure 2: Periumbilical plaque—warm, indurated lesions raised suspicion of cellulitis at initial presentation

MVK deficiency. The patient was found to have heterozygous V377I and R388X mutations in the MVK gene, yielding the diagnosis of MKD, which encompasses a spectrum of disease manifestations ranging from HIDS to mevalonate aciduria.

Histopathologic findings

The punch biopsy taken from an erythematous indurated plaque of the right dorsal foot demonstrated a neutrophilic and histiocytic dermatosis. The biopsy was remarkable for the lack of epidermal involvement overlying a dermis with a perivascular, perieccrine, and interstitial infiltrate consisting of neutrophils and admixed histiocytes [Figures 3 and 4]. Leukocytoclasis was present in the absence of vasculitis. Areas within the superficial dermis demonstrated eccrine squamous syringometaplasia [Figure 5].

DISCUSSION

HIDS is an autosomal recessive fever syndrome, which presents mainly in individuals of European descent.[2] The exceedingly rare syndrome is caused by mutations in the MVK gene, which is active in the synthesis of cholesterol and nonsteroid isoprenoids [Figure 6]. Reduction in MVK activity leads to decreased intermediate and end products of the pathway, causing inflammasome activation and secretion of IL-1β. Complete absence of activity leads to mevalonic aciduria.[3,4] Clinical presentation can consist of a constellation of symptoms including fever, widespread erythematous macules and edematous papules which may become purpuric, often on the face, trunk, and extremities, aphthous

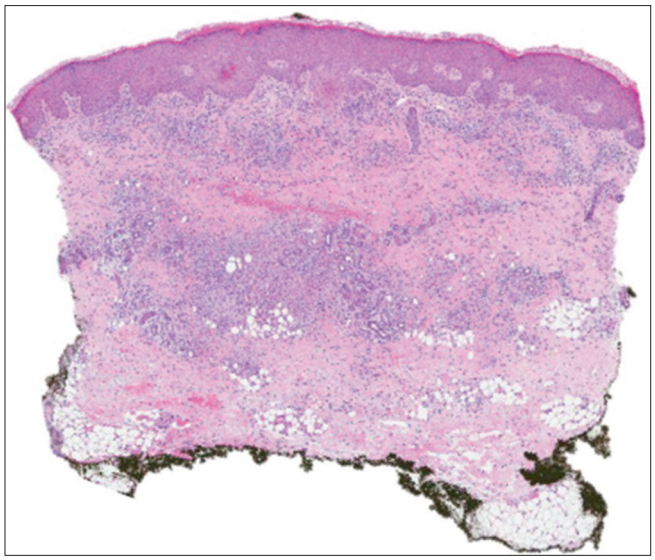

Figure 3: The punch biopsy taken from an erythematous indurated plaque of the right dorsal foot demonstrated a neutrophilic and histiocytic dermatosis. The biopsy was remarkable for the lack of epidermal involvement overlying a dermis with a perivascular, perieccrine, and interstitial infiltrate consisting of neutrophils and admixed histiocytes. Leukocytoclasis was present in the absence of vasculitis. H and E ×4

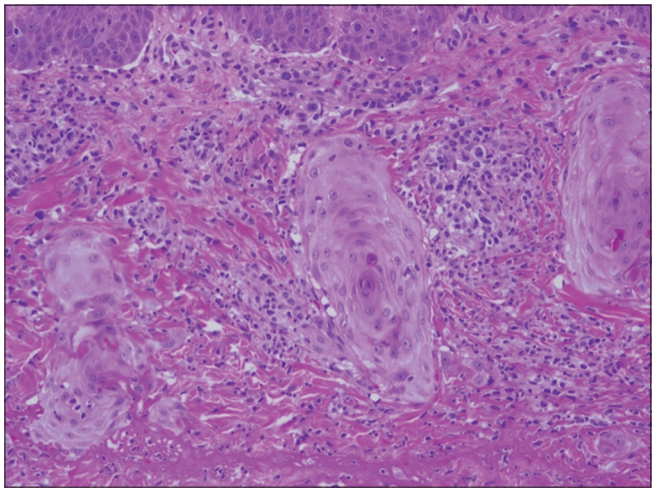

Figure 5: Areas within the superficial dermis demonstrated eccrine squamous syringometaplasia. H and E ×20

or genital ulcers, abdominal pain with diarrhea, arthralgias and myalgias, diarrhea, headache, lymphadenopathy and hepatosplenomegally.[2] For most patients, the first attack is precipitated by vaccination. Presentation is usually at a young age with 78% presenting in the first year of life, all presenting during childhood.[4,5] Those with complete absence of MVK have a more severe phenotype, which includes, in addition to the above-described features, facial dysmorphism, cerebellar ataxia, marked psychomotor retardation, and early death.[6]

Individuals with HIDS are at an increased risk of developing renal angiomyolipomas, with reports of crescentic glomerulonephritis

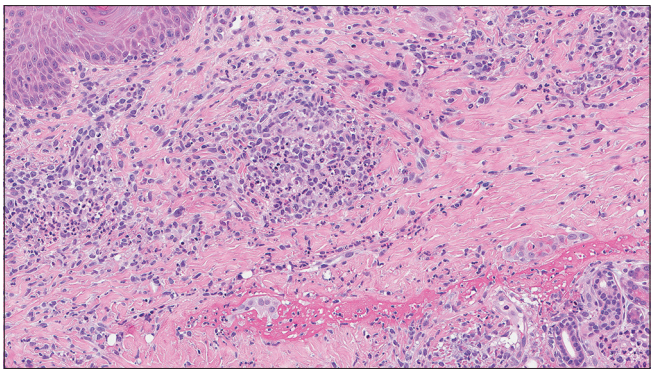

Figure 4: The punch biopsy taken from an erythematous indurated plaque of the right dorsal foot demonstrated a neutrophilic and histiocytic dermatosis. The biopsy was remarkable for the lack of epidermal involvement overlying a dermis with a perivascular, perieccrine, and interstitial infiltrate consisting of neutrophils and admixed histiocytes. Leukocytoclasis was present in the absence of vasculitis. H and E, original magnification ×20

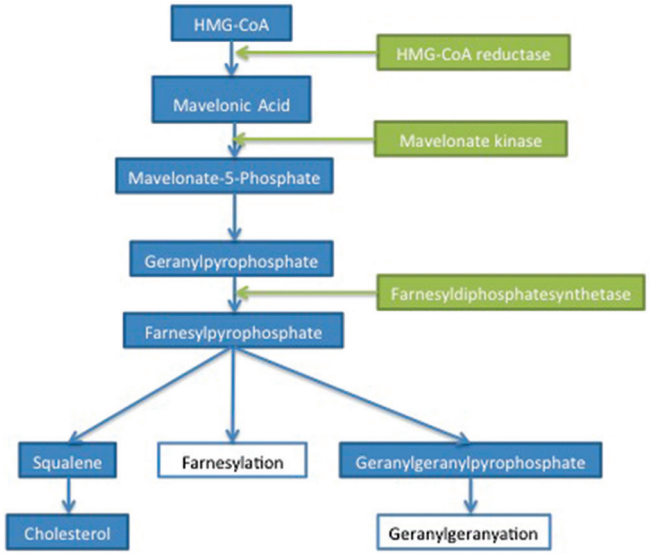

Figure 6: Mevalonate kinase is necessary for the production of cholesterol and nonsteroid isoprenoids

and membranoproliferative glomerulonephritis in effected individuals.[7] Of interest, a previously reported patient with the V377I mutation had a history of chronic hematuria.[7]

Laboratory findings include elevated serum IgD (>100 IU/mL) and IgA1, mevalonate in urine during attacks, and low lymphocyte MVK. Treatment options are evolving based on our increasing knowledge of the pathophysiology of the condition. We now know that there is increased production of interleukin-1 beta (IL-1β), tumor necrosis factor (TNF), and interleukin-6 (IL-6) in MKD.[6] Based on this understanding, treatments with TNF-alfa (TNF-α) inhibitors, anakinra, canakinumab, and tocilizumab have been trialed and found to be successful.[4] Anakinra and canakinumab are both IL-1β inhibitors and differ in that canakinumab is a long-acting form, whereas anakinra requires daily injections. Anakinra binds the IL-1 receptor, blocking IL-1α) and IL-1β

from binding and inhibiting the inflammatory effects thereof.[6] Anakinra can be used on a daily basis and decreases the frequency of attacks when used this way, but can also be used in an on-demand manner when attacks are infrequent.[6] Painful injection site reactions are common with anakinra. Canakinumab has the advantage of being longer lasting and having fewer injection site reactions, requiring treatment once every 4 weeks. Tocalizumab, a humanized monoclonal antibody against IL-6 has been found effective as well.[6] In severe nonresponsive cases, hematopoietic stem cell transplant has been effectively employed and found to be curative.[6]

Reports of the histopathology of HIDS include varied patterns. In a recent review of skin biopsies from 10 patients with HIDS, the most common findings were mild vasculitis, Sweet-like features, cellulitis-like findings, and deep vasculitis characteristics.[2] Based on the histologic findings alone, we also considered early pyoderma gangrenosum and possibly neutrophilic eccrine hidradenitis; however, neither correlated well with the clinical presentation. Upon review of the literature, no reports of a mixed neutrophilic and histiocytic infiltrate in HIDS were found. We believe this to be a distinct histopathologic variant of the cutaneous findings of MKD, based on the lack of significant dermal edema and the significant number of histiocytes, which is not a typical feature of Sweet syndrome. We present this case to increase awareness of a histopathologic variant of HIDS and to encourage consideration of this entity in the workup of recurrent febrile episodes with skin lesions.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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