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Mevalonate kinase deficiency presenting as recurrent rectal abscesses and perianal fistulae

Kara Dunn[1,*], **Brad Pasternak, MD**[1,2], **Judith R. Kelsen, MD**[3], **Kathleen E. Sullivan, MD, PhD**[3], **Noor Dawany, PhD**[3], and **Benjamin L. Wright, MD**[1,2,4]

[1]Phoenix Children's Hospital, Phoenix, AZ

[2]University of Arizona College of Medicine, Phoenix, AZ

[3]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[4]Mayo Clinic Arizona, Scottsdale, AZ

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mevalonate kinase deficiency; hyper-IgD syndrome; early-onset inflammatory bowel disease; perirectal abscess; anal fistula

We present the case of a 13-month, non-consanguineous, Hispanic male with rectal abscesses and perianal fistulae beginning at 2 months of age. At the time of initial consultation, he had undergone 11 prior surgeries for abscess drainage. His infectious history was notable for recurrent upper respiratory infections, acute otitis media, chronic diarrhea and an episode of thrush that resolved with oral nystatin at 2 months of age. He did not have a history of pneumonia, growth failure, or signs of endocrinopathy. His initial physical exam showed mild eczematous patches on lateral aspects of distal lower extremities, several well-healed surgical scars in the perianal area, and Penrose drain placement. Endoscopic examination was negative for inflammatory bowel disease (IBD). The surgical team was considering a diverting ostomy due to the frequency and severity of his perianal disease.

The patient's initial laboratory evaluation revealed a normal white blood cell count (WBC 9.8 K/μL), mild anemia (Hgb 9.5 g/dL) with a normal platelet count (381 x 10(9)/L). The white blood cell differential showed normal absolute neutrophil (4.5 x 10(9)/L) and lymphocyte (3.485 x 10(9)/L) counts and his inflammatory markers were elevated (ESR 19 mm/hr, CRP 20.3 mg/L). A hemoccult test was positive, fecal calprotectin was mildly

Corresponding Author: Benjamin Wright, MD, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259, Phone: 480-301-4284, wright.benjamin@mayo.edu.

*Kara Dunn is an undergraduate student and does not yet have an academic degree.

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elevated (205 μg/g) and blood cultures were negative. Pathology from esophagogastroduodenoscopy and colonoscopy revealed chronic nonspecific gastritis non consistent with helicobacter pylori and otherwise negative. Assessment of the patient's immune parameters demonstrated normal serum IgG (1141 mg/dL), IgM (134 mg/dL), and IgA (56 mg/dL), and an elevated IgE (599 KU/L). Titers to diphtheria and tetanus vaccines were normal and lymphocyte counts were unremarkable: CD3+ 69% (2405/mm^3 abs), CD3+CD4+ 36% (1255/mm^3 abs), CD4+CD45RA+ 62%, CD4+CD45RO+ 22%, CD3+CD8+ 29% (1011/mm^3 abs), CD19+ 17% (592/mm^3 abs), CD56+ 14% (488/mm^3 abs).

Additional immunologic/genetic evaluation revealed normal DHR stimulation with fMLP and PMA, normal functional testing for IL-10R deficiency, normal phagocytosis/bactericidal assay, normal TLR 1-8 testing, and normal IL-10R gene sequencing. Ultimately, whole exome sequencing (WES) for the proband and parents was performed at the Children's Hospital of Philadelphia. A total of 492 non-synonymous and nonsense variants with a minor allele frequency <0.1% in the Exome Aggregation Consortium (ExAC), 1000 Genomes Project and the Exoma Variant Server (EVS) were identified. Additional variant filtering was performed by selecting mutations in genes associated with very early onset IBD, autoinflammation and autoimmune disease. Analysis using inheritance models revealed a compound heterozygous mutation in the mevalonate kinase (MVK) gene (c. 803T>C, p.Ile268Thr and c.1129G>A, p.Val377Ile for RefSeq transcript NM_000431.3), which were confirmed by Sanger sequencing. IgD levels and IL-1β were normal; however, urine mevalonate levels were elevated consistent with mevalonate kinase deficiency (MKD), also known as Hyper IgD Syndrome (HIDS).

MKD is an autosomal recessive disorder with a spectrum of clinical phenotypes ranging from HIDS, characterized by recurrent fever, arthralgia, rash and abdominal pain, to mevalonic aciduria, associated with neurologic involvement, dysmorphic features, psychomotor retardation. The pathogenesis of the disorder is characterized by the accumulation of mevalonate in the urine and serum. Mevalonate is generated by HMG-CoA reductase and is an integral part of the cholesterol synthesis pathway. In the metabolic mevalonate pathway, mevalonate is phosphorylated by MVK and is transformed into its intermediate, geranylgeranyl pyrophosphate. Small GTPases, including Kras and RhoA, are geranylgeranylated by geranylgeranyl pyrophosphate, a reaction catalyzed by geranylgeranyl transferase-I (GGTase I). Geranylgeranylation is critical for cellular localization and serves to anchor these GTPases to the cellular membrane and enable their activation. Active geranylgeranylated Kras regulates the TLR-mediated PI3K/Akt1 pathway, which ultimately inhibits the production of interleukin-1 beta (IL-1β), a pro-inflammatory cytokine. When MVK is deficient, as in MKD, production of geranylgeranyl pyrophosphate is reduced, decreasing Kras geranylgeranylation and therefore impairing PI3K/Akt1 pathway activation, ultimately resulting in elevated levels of IL-1β. Concurrently, impaired activation of RhoA releases the 14-3-3 pyrin guard resulting in assembly of the pyrin inflammasome.[1] Recurrent auto-inflammatory attacks are associated with activation of caspase-1 and overproduction of IL-1β, therefore, drugs targeting the IL-1 pathway are preferred therapeutic interventions.

One of the mutations in our patient (Val377Ile) has also been described in two other patients with compound heterozygous mutations in MVK who presented with neonatal-onset, refractory colitis[2]; suggesting that this particular mutation may predispose to severe intestinal inflammation. Each was treated successfully with IL-1 antagonists. While mechanistic data in humans to explain pathogenesis is lacking, overproduction of IL-1β drives robust inflammatory responses in DSS-colitis mouse models.[3] Dysregulated innate immune responses to commensal bacteria activate inflammasome production of IL-1β through NOD-like receptor NLRP3. IL-1β-mediated expression of chemokines CXCL1, CXCL2, and CCL2 by multiple cells types results in neutrophil and monocyte infiltration.[4] Indeed, IL-β blockade and enhanced regulation of NLRP3 attenuate pathological intestinal inflammation.[5] Recent reports suggest the prevalence of monogenic IBD is inversely correlated with age of onset.[6,] Interestingly, WES of MKD patients with abdominal pain has revealed variants in additional known susceptibility loci for IBD, implying a shared genetic background between MKD and IBD.[7] In support of this observation, two large cohorts of subjects with MKD/HIDS have shown that a majority of patients have prominent gastrointestinal symptoms.[8, 9] Taken together, MKD may result in intestinal inflammation and must be considered in patients who present with early onset IBD-like symptoms, even when common phenotypic manifestations of MKD are absent.

During our patient's diagnostic evaluation he underwent drainage procedures for five additional perirectal abscesses; however, at 18 months of age his recurrent abscesses resolved spontaneously. The patient subsequently developed recurrent fevers associated with arthralgia, fatigue, and malaise. Canakinumab (2mg/kg) was initiated and dosed every four weeks. The patient has had occasional breakthrough febrile episodes with arthralgias, so his dose has been gradually titrated up to 6mg/kg every 4 weeks with marked improvement in symptoms.

MKD is a phenotypically diverse autoinflammatory disorder that may vary in severity and clinical presentation. Despite its initial classification as HIDS, characterized by periodic fevers and elevated IgD levels, MKD may not present with either of these features. This case highlights the importance of considering MKD in the differential diagnosis of infants presenting with severe, isolated perirectal disease and early-onset IBD.

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Abbreviations used

HIDS	hyper-IgD syndrome
IBD	inflammatory bowel disease
MKD	mevalonate kinase deficiency
MVK	mevalonate kinase
WES	whole exome sequencing

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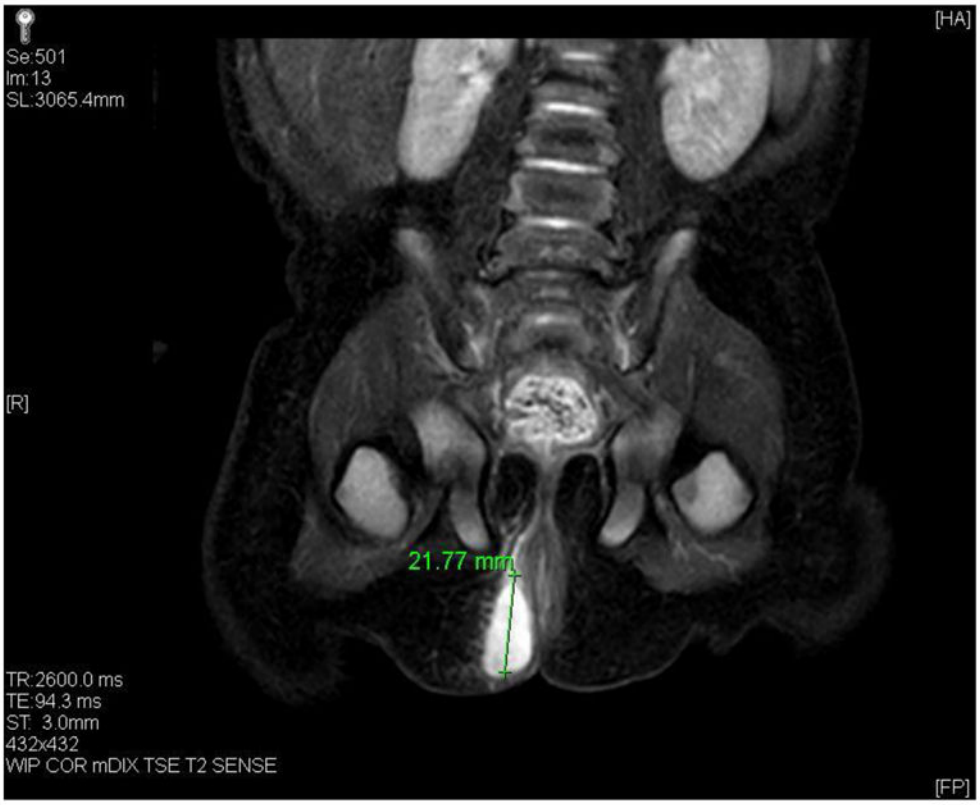

Figure 1.
MRI coronal view of rectal abscess