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MEVALONATE KINASE DEFICIENCY ASSOCIATED WITH RECURRENT LIVER DYSFUNCTION, MACROPHAGE ACTIVATION SYNDROME AND PERFORIN GENE POLYMORPHISM

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Keywords

Autoinflammatory diseases; periodic fever syndromes; hyper-IgD syndrome; reactive hemophagocytic lymphohistiocytosis

CASE PRESENTATION

History of Present Illness

This patient was a former 32 week premature female infant, born by elective caesarian section due to concern for hydrops. After delivery she was found to have ascites and ultimately conjugated hyperbilirubinemia, but was without other congenital abnormalities. She had a normal newborn screen and no family history of congenital or metabolic disorders. An extensive evaluation for biliary atresia, perinatal iron storage disorders, Wilson disease, alpha-1 antitrypsin, and metabolic diseases was unrevealing. Liver biopsy on day of life 25 showed mild chronic hepatitis with portal and periportal fibrosis and mild persistence of extramedullary hematopoiesis. She had a prolonged neonatal intensive care unit stay secondary to respiratory insufficiency, and remained on supplemental oxygen at time of discharge. Throughout her hospitalization she had persistently elevated C-reactive protein as well as aminotransferases and direct bilirubin, although these had stabilized prior to discharge.

Starting at two months of age, she developed recurrent episodes of fever, respiratory distress, abdominal distension and feeding intolerance, lasting 5–7 days and occurring every 3–5 weeks, and beginning shortly after her first round of immunizations. During episodes

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she developed transient hepatosplenomegaly and ascites, elevated aminotransferases and CRP, anemia and thrombocytopenia. Empiric antibiotics were typically started, but all cultures were negative. With her third episode she required mechanical ventilation for 5 weeks. During this prolonged hospitalization an extensive diagnostic evaluation was pursued, summarized in Table 1. Repeat liver biopsy was performed showing chronic hepatitis with moderate periportal and pericellular fibrosis. Bone marrow biopsy showed mild granulocytic hyperplasia, mild dyserythropoiesis, and increased interstitial histiocytes without hemophagocytic activity. Ultimately, due to suspected autoimmune process, methylprednisolone 2mg/kg/day was administered, after which she was weaned off all respiratory support. However, as steroids were weaned she continued to have febrile episodes lasting several days, which were managed with increasing steroids and empiric antibiotics. Due to a finding of reduced transitional B cells and concern for B cell immunodeficiency, at age 9 months she was started on monthly intravenous immunoglobulin therapy; however this did not alter the frequency of her febrile episodes.

Social and Family History

The patient lives with her parents and two healthy siblings. No travel outside the United States. No daycare exposure. Family history was unremarkable without autoimmune diseases, congenital abnormalities, or developmental delay.

Physical Exam

On examination at 11 months of age, patient appeared small for age but alert, interactive and without dysmorphic features. She had splenomegaly and hepatomegaly with estimated liver span of 6 cm. There were no signs of rash or arthritis. She had normal muscle tone and bulk. Developmental assessment demonstrated typical social, verbal and fine motor development but gross motor delay, with infant able to sit only with support and unable to roll over. The remainder of her physical exam was normal.

Case Summary

This is a now 11 month old former premature female infant with recurrent episodes of fever, elevated inflammatory markers, anemia, thrombocytopenia and cholestatic liver dysfunction.

Differential diagnosis

The differential diagnosis for this infant is broad, and includes infectious, inflammatory, metabolic and neoplastic processes, as well as both congenital and acquired conditions. Her extensive prior evaluation has been negative for infectious causes. Additionally, she has had negative testing for a large number of autoantibodies associated with known autoimmune disorders. Finally, her course does not clearly fit a primary immunodeficiency. Although the etiology of her mild decrease in transitional B cells is unclear her normal immunoglobulin levels, lack of sinopulmonary infections and negligible response to IVIG argue against a functional B cell deficiency.

Autoimmune hepatitis (AIH)—AIH is an idiopathic autoimmune disease characterized by high levels of immunoglobulins and presence of autoantibodies. It typically presents as

an acute onset severe hepatitis often progressing quickly to liver failure. Although it typically affects older children, it can occur in infancy. The two most well described subtypes are AIH-1, associated with antinuclear or anti-smooth muscle antibodies, and AIH-2, associated with anti-LKM antibodies (1), all of which were negative in this child. Autoantibody negative AIH has been reported only rarely in children and little is known regarding its etiology and pathogenesis (2).

Metabolic diseases—Metabolic abnormalities are common causes of neonatal onset liver dysfunction; however, investigation of her liver disease including repeat biopsy has not revealed any known congenital or metabolic abnormalities. One further consideration is Niemann-Pick Disease Type C, which is a lysosomal storage disease leading to progressive organomegaly and neurologic dysfunction (3). Recent work has suggested that liver and neurologic dysfunction in Niemann-Pick is an inflammatory process, although signs of severe systemic inflammation as seen in this patient are uncommon (4). Additionally, liver biopsy did not show evidence for a storage disease. Another consideration is mevalonic aciduria (MA), a severe deficiency in mevalonate kinase in the isoprenoid biosynthesis pathway, leading to dysmorphic features, progressive neonatal onset psychomotor retardation, cerebellar ataxia, visual impairment and recurrent febrile crises (5). Additionally there are rare reports of severe liver dysfunction associated with MA (6–9).

Periodic fever syndrome—The autoinflammatory periodic fever syndromes are a family of rare, heritable disorders which share the characteristic of recurrent inflammatory episodes with no or trivial triggers. They have all been linked to uncontrolled activation of the innate immune system, most notably activation of the inflammasome leading to dysregulated production of proinflammatory cytokines including IL-1β(10). They include familial Mediterranean fever, cyropyrin-associated periodic fever syndrome, TNF-receptor associated periodic fever syndrome, and mevalonate kinase deficiency (MKD), also known as hyper immunoglubulinemia D and periodic fever syndrome (HIDS). Periodic fever syndromes typically present in early childhood, but less severely affected patients may not present until late childhood or as adults. The pattern of this patient's inflammatory episodes, occurring irregularly every 1–2 months and lasting for several days, could be consistent with MKD (11). However, liver dysfunction is reported only rarely in MKD. Moreover, it is usually reported in more severely affected children who are classified as MA with the characteristic dysmorphic features, growth retardation, developmental delay, ocular, and neurological dysfunction (see above).

Familial hemophagocytic lymphohistiocytosis (HLH)—Primary or familial HLH is a rare, autosomal recessive condition characterized by episodes of overwhelming inflammation associated with multiorgan system dysfunction including cytopenias, coagulopathy, liver dysfunction, CNS abnormalities and hyperferritinemia (12). Its pathological hallmark is natural killer (NK) cell dysfuction, expansion of CD8+ T lymphocytes and hemophagocytic macrophages. It can be fatal, although can be cured with hematopoietic stem cell transplant. More than 75% of patients have identified mutations in the gene encoding perforin, or those encoding proteins involved in granule exocytosis including Munc13-4, syntaxin 11 or syntaxin-binding protein 2. This child's episodes of

hyperinflammation, cytopenias and liver dysfunction are consistent with HLH. Although no evidence of hemophagocytosis was found on initial bone marrow examination, this does not rule out HLH due to sampling error and since visible hemophagocytosis may take time to develop.

Systemic juvenile idiopathic arthritis (SJIA)—SJIA is a severe inflammatory disorder of childhood of unknown etiology (13). It is classified as a subtype of JIA, although it has several distinctive clinical and epidemiologic features, including a lack of sex bias and no peak age of onset. It is also unique in having prominent extra-articular features, such as prolonged spiking fevers, rash, lymphadenopathy and serositis. It is a clinical diagnosis, although it is notable for markedly elevated inflammatory markers including ferritin (14). Children with SJIA are also at significant risk for development of macrophage activation syndrome (MAS), an episode of overwhelming inflammation that is considered a form of secondary reactive HLH (15). While this patient's clinical symptoms resemble SJIA, the fever in SJIA is typically persistent rather than periodic. In addition, there was no report of arthritis, although this can be a late feature in some patients. Finally, while liver dysfunction can be associated with MAS, it is not typically a feature of SJIA.

Clinical Course

Ultimately this patient was transferred to our institution during an episode of fever, respiratory distress and abdominal distention. Labs were notable for white blood cells 40×10^3/μl, hemoglobin 6.4 g/dL, platelets 159×10^3/μl, CRP 13 mg/dL (normal <1mg/dl), aspartate transaminase 839 U/L and alanine transaminase 1198 U/L. An evaluation for hemophagocytic syndromes was initiated. The serum ferritin was mildly elevated at 790 ng/ml (normal 15–450), soluble IL-2 receptor was elevated at 4977 U/ml (normal <3000), and fibrinogen and triglycerides were normal. NK cell functional testing revealed a decreased proportion of cells expressing CD107A upon stimulation (8%, normal 11–35%), as well as decreased intensity of CD107A surface expression (mean fluorescence intensity 178, normal 207–678), indicative of abnormal degranulation. There was also a mildly decreased proportion of NK cells expressing perforin (83%, normal 87–95%) as well as reduced perforin intensity (MFI 92, normal 98–181). Further examination of both prior liver biopsies showed unusually abundant intersinusoidal histiocytes, highlighted by CD163 with occasional cells appearing to have engulfed nucleated white blood cells including mature neutrophils and mononucleated cells likely to be nucleated red blood cell precursors (Figure 1). Genetic testing for familial HLH revealed a R28C substitution in one allele of the perforin gene PRF1. There were no polymorphisms found in genes encoding Munc 13–4, Rab27a, Syntaxin 11, or STXBP2.

A metabolic genetics evaluation was also initiated. Urine organic acid, obtained during an inflammatory attack but not during a fever spike, confirmed a prominent peak of mevalonic acid. Genetic testing identified compound heterozygous mutations in mevalonate kinase (V310M and G336S). Given a presumed diagnosis of MKD she was started on anakinra 2mg/kg/day, and after which was without fever throughout her hospitalization. Her markers of inflammation including CRP, ESR, ferritin and sIL2R normalized, and her serum

aminotransferase levels decreased. At last follow-up three months later the patient was doing well without any further episodes of fever.

Discussion

Here, we report an infant with MKD and recurrent inflammatory episodes with liver dysfunction, successfully treated with anakinra. MKD is a metabolic autoinflammatory syndrome caused by mutations in mevalonate kinase, a key enzyme in the non-sterol isoprenoid biosynthesis pathway (11). How metabolic abnormalities in MKD lead to hyperinflammation is not fully known, although defective prenylation may potentiate activation of the inflammasome (16–18). Indeed, treatment with anti-IL-1 therapy appears to be highly efficacious in these patients (19). The diagnosis of MKD can be challenging, as IgD levels may be normal, mevalonic acid excretion may be intermittent in more mild forms of the disease, and the clinical phenotype can be difficult to recognize in infancy (20, 21). Prior to establishing the molecular basis of MKD, two distinct clinical phenotypes were mapped to mutations in mevalonate kinase: hyper immunoglubulinemia D and periodic fever syndrome (HIDS) and mevalonic aciduria (MA), though these likely represent the extremes of a phenotypic spectrum (21). Children with HIDS develop recurrent episodes of fever, abdominal pain, adenopathy, hepatosplenomegaly, rash and arthralgias. In contrast, though children with MA also have recurrent inflammatory episodes, they also exhibit dysmorphic features, growth retardation, profound developmental delay, ocular, and neurological dysfunction. While the patient presented here is on the severe end of MKD spectrum, she lacks the dysmorphic features and global developmental delay classically seen in MA (11). Similarly, significant liver dysfunction as reported here has only been reported in severely affected MA patients (6–9). Although there is some genotype-phenotype correlation in MKD, these associations are imprecise (22). This child was found to be a compound heterozygote, with one allele (V310M) previously described in severely affected patients with MA (7, 22), while the other allele (G336S) has been described in a patient with HIDS (23). Taken together, this case enhances our understanding of the clinical spectrum seen in MKD, and underscores that patients can exhibit a combination of features seen in classic HIDS and MA.

There is also emerging evidence that severe febrile attacks in MKD may resemble MAS, an episode of overwhelming inflammation leading to multisystem organ dysfunction (24–26). Indeed, multiple features support this child manifesting a hemophagocytic process such as MAS. First, her episodes were associated with elevated ferritin and sIL2r, cytopenias, decreased NK cell function, and liver dysfunction; indeed, she would satisfy diagnostic criteria for HLH (27). Second, both liver biopsies showed abundant sinusoidal histiocytes with hemophagocytosis. Although there is one previous report of a child with MKD and significant liver infiltration by CD68+ monocytes, there was no evidence of hemophagocytosis (28). Finally, she had mildly reduced perforin expression along with a heterozygous variant in the perforin gene (R28C). Perforin mutations are found in 20–50% of children with familial HLH, as well as some children with systemic juvenile idiopathic arthritis (SJIA) who develop MAS (29–31). Although there are no previous reports of MAS-like syndrome occurring in association with this sequence variant, it is a rare variant found in only 5 of approximately 2400 PRF1 alleles sequenced through our Clinical Genetics

Laboratory, and predicted to have radical effects on protein structure. It has also been identified in a child with SJIA without history of MAS (30). Interestingly, along with decreased perforin expression our patient was found to have abnormal NK cell degranulation, suggesting a second, unidentified, defect in NK cell function. Although the etiology of MAS remains unclear, a growing body of evidence supports cytolytic dysfunction as central to the pathogenesis of primary familial and secondary reactive HLH (30–34). One emerging theory is a two-hit hypothesis, in which MAS develops when a genetically susceptible individual, with defects in immunoregulatory mechanisms including NK cell function such as perforin, experiences a hyperinflammatory state due to infection or rheumatic disease (35). Indeed, studies of multiple independent cohorts of children with SJIA have found that approximately one third of those who develop MAS have polymorphisms in genes implicated in familial HLH, most commonly perforin (30, 36, 37).

Likewise, MAS is increasingly recognized as a complication of the periodic fever syndromes, including MKD (25, 38, 39). However, to our knowledge this is the first report of MAS associated with perforin variant in a child with an autoinflammatory periodic fever syndrome. Severe episodes of MAS are typically managed with intravenous corticosteroids and, if refractory, other immunosuppressive therapies (40). Here, while our patient did improve clinically with high-dose steroids, she continued to have inflammatory episodes with features of MAS until she achieved clinical remission with IL-1 blockade. This observation further supports the need to treat the underlying triggers for inflammation which trigger MAS, and highlights the emerging role of IL-1 antagonists in the management of MAS.

Hepatosplenomegaly is commonly reported in MKD; however, there are only rare reports of hepatitis (28, 41) or more severe cholestatic liver disease in some children with severe MA (6–9) (Table 2). These children are all on the severe end of the disease spectrum, with most progressing to death or end-stage liver disease. The pathophysiology of this liver disease is unknown, and it is unclear to what extent liver damage in these cases could be due to an MAS-like process, or whether specific immunosuppressive therapy would have led to improvement in liver function. Interestingly, there is one report of a child with MKD and severe liver dysfunction and a markedly elevated ferritin level; no further investigation for MAS/HLH was reported (7). This child underwent orthotopic liver transplant leading to significant functional improvement but continued febrile episodes, including biopsy-proven liver inflammation. Ultimately she underwent bone marrow transplant, leading to full clinical remission. That report as well as the present case is highly suggestive that in some MKD patients MAS-like episodes may underlie significant liver disease.

In conclusion, we report an infant with MKD and recurrent inflammatory episodes associated with liver dysfunction and histiocyte infiltration consistent with MAS. Her presentation illustrates the spectrum of disease seen in MKD, and demonstrates that patients can have severe liver disease in the absence of other features associated with MA. Taken together, we suggest that patients with MKD are at risk for MAS-like episodes, and that occurrence of liver dysfunction should lead to careful evaluation for MAS and initiation of aggressive immunosuppressive therapy for both the underlying autoinflammatory disease as well as this potentially fatal complication.

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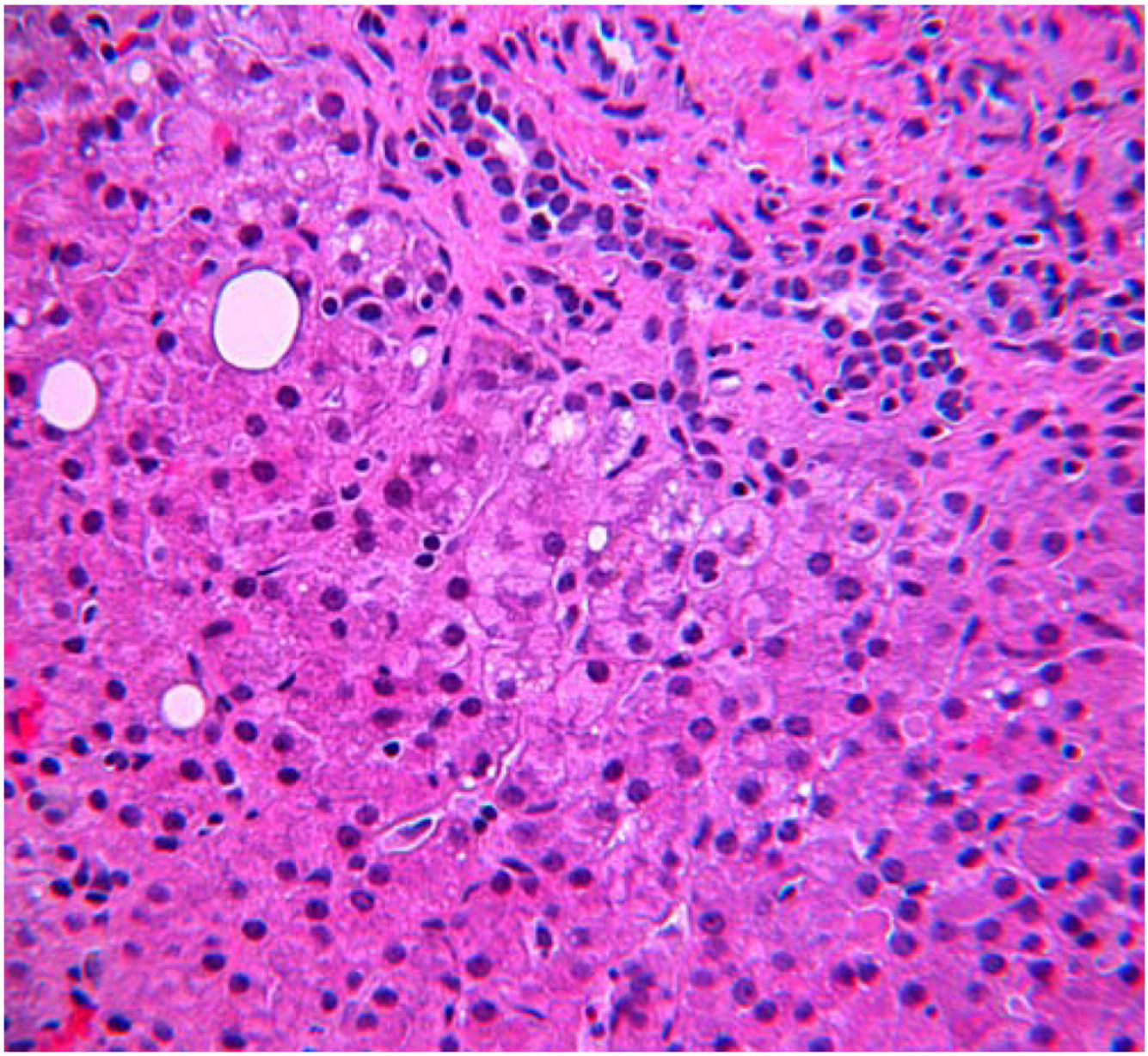
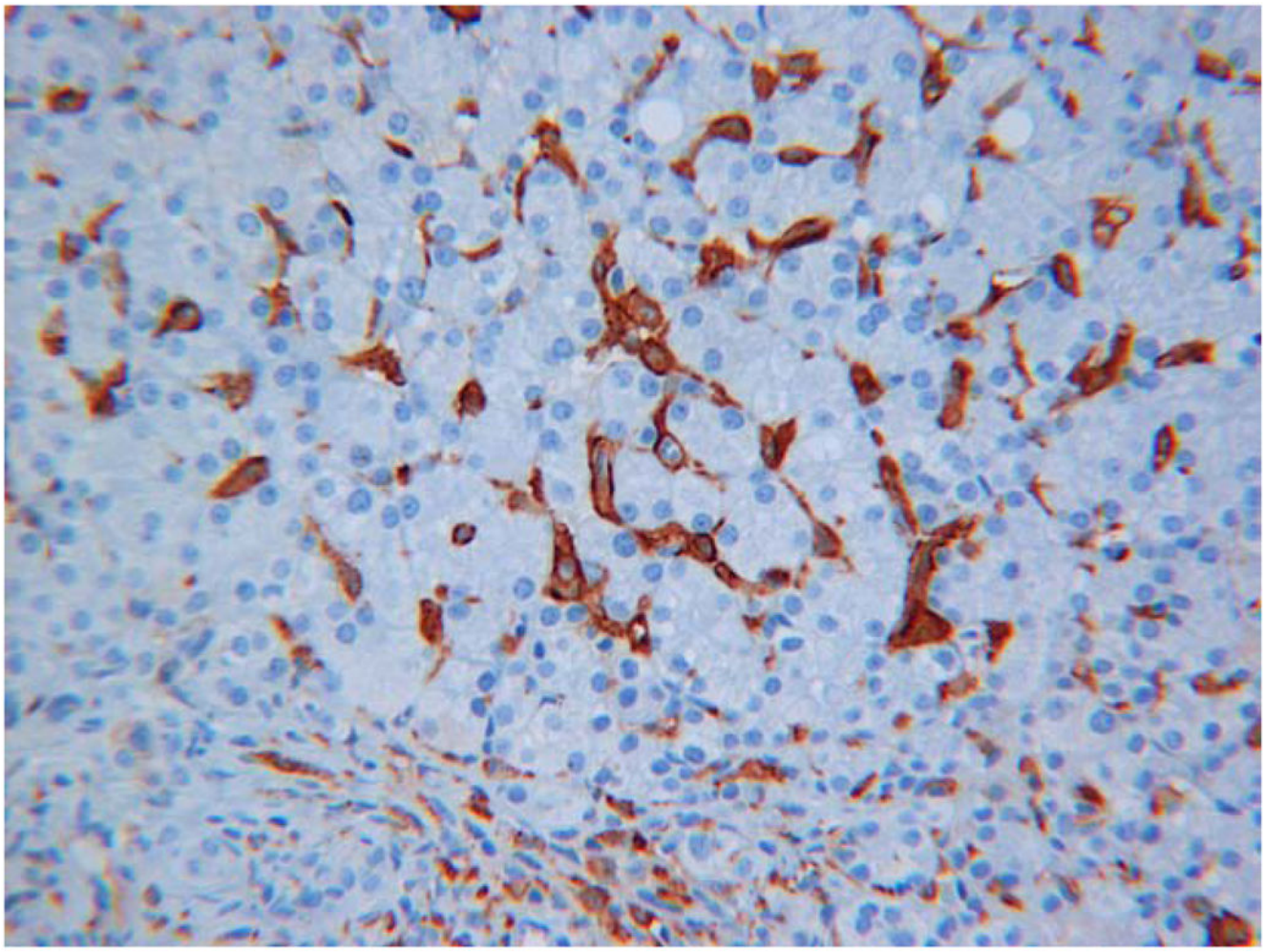
Significance and Innovation

- We present the unusual case of an 11 month old infant we evaluated for recurrent episodes of fever, elevated inflammatory markers, anemia, thrombocytopenia and cholestatic liver dysfunction, ultimately diagnosed with mevalonate deficiency. Interestingly her inflammatory episodes were characterized by extensive liver infiltration by hemophagocytic histiocytes, as well as NK cell dysfunction and perforin gene mutation, which together with other features is consistent with macrophage activation syndrome (MAS).
- This case sheds light on the diagnosis of MKD by examining a patient with severe features such as liver dysfunction occurring without other features of mevalonic aciduria.
- This case also highlights an emerging concept which is that hereditary periodic fever patients, particularly those with MKD, are at risk for MAS, and represents the first patient with genetically confirmed hereditary periodic fever with MAS in the setting of perforin gene mutation.





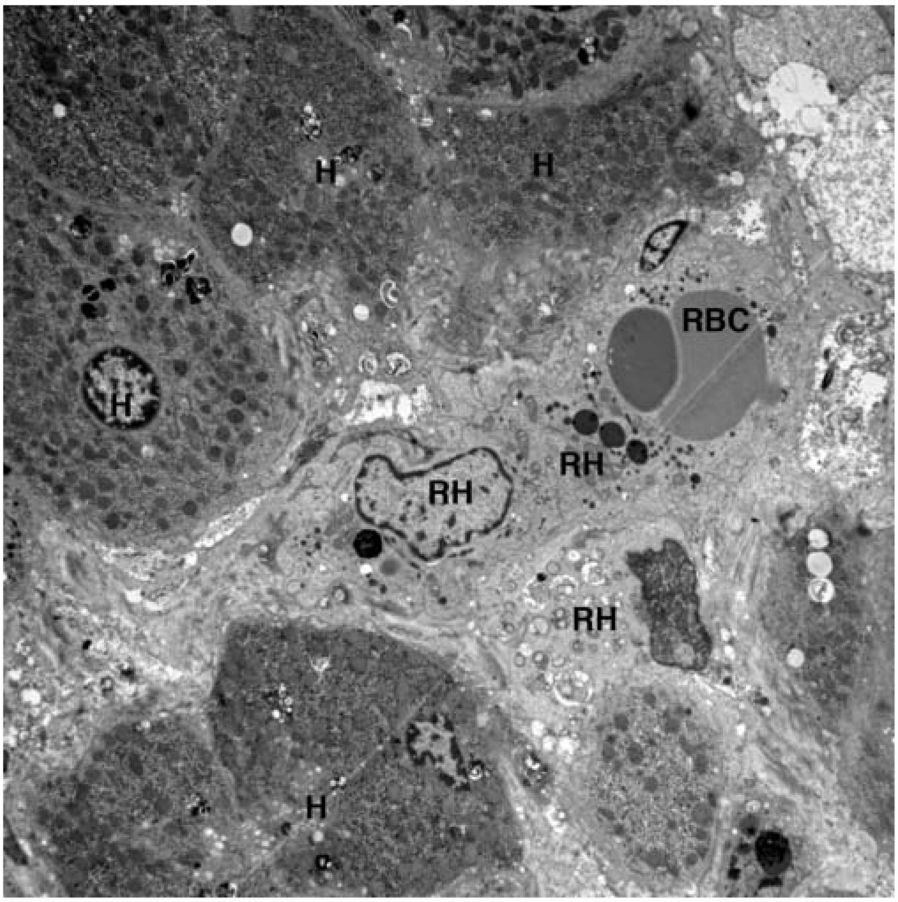


Figure 1.

(A) H&E stained section of patients liver biopsy showing mild portal area inflammation. Zone 1 hepatocytes show non-specific reactive changes and rare lipid droplets. Lobular inflammation is deceptively minor. (B) CD163 immunostaining reveals marked increase in activated macrophages within the sinusoids of the liver. (C) Transmission electron microscopy shows erythrophagocytosis of a nucleated red blood cell (RBC) in one of three visualized reactive histiocytes (RH) obstructing the sinusoids of the liver. H=hepatocyte.

Table 1

Test	Result
MPV 17-related disorder	No mutations found
Glycogen storage disease type IV GBE1 sequencing	No mutations found
CFTR mutation analysis	No mutations found
Transferrin isoelectric focusing for congenital disorders of glycosylation	Normal
Lysosomal enzyme screen	Normal
Lactate and pyruvate	Normal
Very long chain fatty acids	Normal
Anti-enterocyte antibody	Weak positive (1:20)
TTG IgA	Negative
Endomysial IgA	Negative
Gliadin IgA and IgG	Negative
Anti-nuclear antibody	Negative
Anti-neutrophil cytoplasmic antibody	Negative
Anti-Smooth muscle antibody	Negative
Anti-mitochondrial M2 antibody	Negative
Anti-liver cytosol or soluble antibodies	Negative
Anti LKM antibody	Negative
Anti-F-actin antibody	Negative
Quantitative immunoglobulins	IgG 1833 (286-1680), IgA 55 (10-131), IgM 295 (21-192)
IgG subclasses	IgG1 1520 (143-394), IgG2 100 (23-147), IgG3 154 (4-70), IgG4 1 (1-14)
Lymphocyte subpopulations	Low B-lineage lymphocyte percentages, increased CD8 T cell percentages
B cell populations	Decreased percentage of transitional B cells and CD5+ B cells
Mitogen proliferation assay	Normal
Parvovirus IgM and IgG	Negative
CMV quantitative PCR	Initial positive log 3.7, repeat negative x3
EBV quantitative PCR	Negative
Hepatitis C virus PCR	Negative
Mycoplasma IgM and IgG	Negative
Legionella urine antigen	Negative
Respiratory viral panel	Negative

Table 2

Report	Age at presentation	Age at diagnosis	Genotype	Other abnormalities	Transaminase elevation	Liver biopsy findings	Extramedullary hematopoeisis	Treatments	Outcome
Hinson et al (1998)	Perinatal	2 months	ND	None noted	Yes (moderate)	Chronic active cholestatic hepatitis	Cutaneous	unknown	Hypotonia, FTT
	Prenatal	Unknown	ND	Hypospadias, frontal bossing, low-set ears, down-slanted palpebral fissues, long eyelashes	Yes (moderate)	Marked cholestatis, portal fibrosis	Hepatic	Unknown	Died DOL 87
Raupp et al (2004)	Prenatal	Post- mortem	ND	None noted	No	ND	No	Antibiotics	Died DOL 15
	Prenatal	DOL 20	L35S homozygote	None noted	No	ND	No	Antibiotics	Died 2 months
Steiner et al (2011)	Prenatal	Post- mortem	I268T homozygote	Ventriculomegaly, short limbs, frontal bossing, cardiomegaly	unknown	Marked fibrosis with bile plugging	Cutaneous, lungs, liver, kidneys, adrenals	Antibiotics	Died DOL 20
Chaudhury et al (2012)	Prenatal	2 weeks	I268T V310M	Aortic stenosis	Unknown	Micronodular cirrhosis	No	Anakinra, HSCT	OLT age 4, normal growth and typically developing age 8

Clinical characteristics, liver findings and outcome of reported patient with MKD and cholestatic liver disease