Mevalonate kinase deficiency diagnosed in late adolescence presenting with macrophage activation syndrome

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Hyperimmunoglobulinaemia D syndrome (HIDS) currently referred to as mevalonate kinase deficiency (MKD), is a rare autosomal recessive autoinflammatory disorder. It typically presents with recurrent episodes of high-grade fever accompanied by systemic features such as abdominal pain, diarrhoea, lymphadenopathy, arthralgia, mucocutaneous ulcerations, and, occasionally, cutaneous rashes (1). Clinical manifestations usually begin in early infancy and are characterised by febrile episodes lasting approximately 3 to 7 days. While these attacks typically recur at intervals of 4 to 6 weeks, the timing of disease onset, as well as the frequency and severity of symptoms, may vary considerably among individuals (2-4). Systemic inflammation is a hallmark of MKD, but progression to life-threatening complications such as macrophage activation syndrome (MAS) remains exceedingly rare. The objective of this report is to present a rare case of late-adolescent onset MKD complicated by MAS.

We present the case of an 18-year-old male who was referred to our adult rheumatology clinic after transition from paediatric care due to recurrent febrile episodes, gastrointestinal complaints, and systemic inflammation. He initially presented to the emergency department with vomiting, diarrhoea, and high fever. Hospitalisation was initiated with presumptive diagnoses of acute gastroenteritis, electrolyte imbalance, and sepsis. Empirical intravenous cefepime was administered; however, persistent fever and hypotension necessitated escalation to meropenem and vancomycin. Despite broad-spectrum antibiotics, C-reactive protein (CRP) continued to rise (318 mg/L), blood cultures remained negative, and the patient developed pancytopenia: haemoglobin 8.9 g/dL, white blood cells (WBC) 300/mm^3, neutrophil count 140/mm^3, platelets (PLT) 44,000/mm^3. Additional findings included hyperferritinaemia (ferritin: 2263 ng/mL), hypertriglyceridaemia (372 mg/dL), and elevated lactate dehydrogenase (LDH: 603 U/L). These findings were highly suggestive of MAS, and pulse methylprednisolone (1 g/day for 3 days) followed by oral prednisolone (1 mg/kg/day) was initiated. A favourable clinical response ensued, with resolution of fever and gastrointestinal symptoms, and a marked decline in inflammatory markers (CRP: 26 mg/L, ferritin: 540 ng/mL) and recovery from pancytopenia.

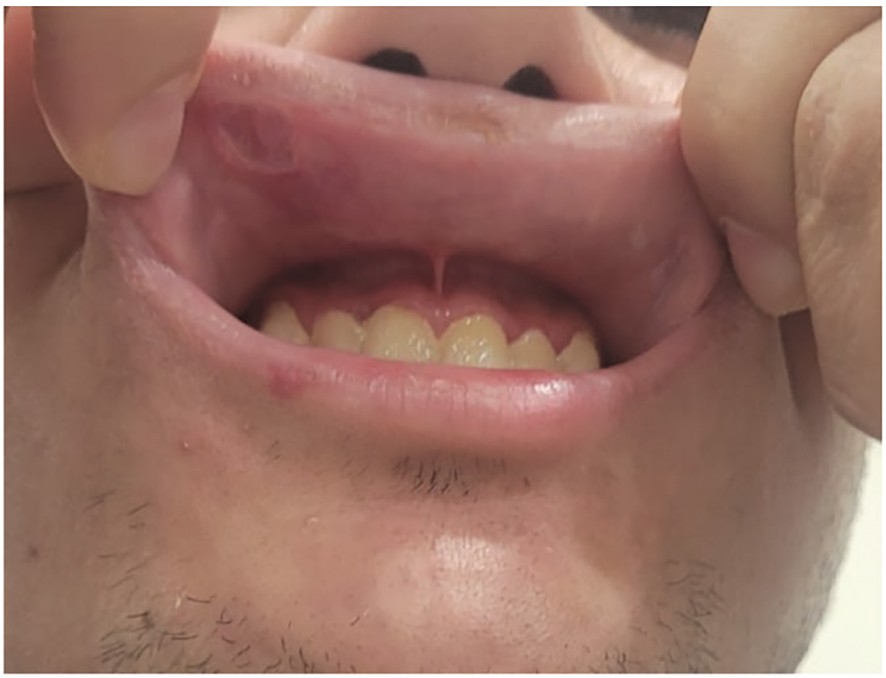

Fig. 1. A solitary, well-demarcated aphthous ulcer located on the upper labial mucosa, consistent with the patient's recurrent oral mucosal involvement during disease flares in MKD.

His medical history revealed that the patient's symptoms had begun at the age of 13, with recurrent febrile episodes, accompanied by abdominal pain, and diarrhoea occurring every 1–2 months and lasting about one week, which had escalated to near-daily symptoms during the preceding five months. Bone marrow aspiration demonstrated mild hypercellularity with granulocytic predominance but no malignant features; the presence of histiocytes containing phagocytosed monocytes supported the diagnosis of MAS. Excisional lymph node biopsy excluded lymphoproliferative disorders. On physical examination, a solitary aphthous ulcer was noted on the upper labial mucosa (Fig. 1). Colonoscopy revealed multiple colonic ulcers and deep anal fissures, while upper gastrointestinal endoscopy showed peripyloric erosions.

The differential diagnosis included Behçet's disease, haploinsufficiency of A20 (HA20), Crohn's disease, primary immunodeficiencies, and MKD. Pathergy testing and ophthalmologic examination were unremarkable. Upon tapering of corticosteroids, the patient experienced recurrence of symptoms along with neutropenia. Genetic testing using next-generation sequencing identified a homozygous V377I mutation in the MVK gene, confirming the diagnosis of MKD. The patient was initially treated with anakinra (100 mg/day); however, after three months the clinical response was insufficient, with persistent febrile attacks accompanied by abdominal pain and diarrhoea. Moreover, the patient reported significant injection-site pain, which contributed to poor adherence to daily subcutaneous administration. Consequently, therapy was switched to canakinumab (150 mg subcutaneously every 4 weeks). This regimen induced sustained remission and enabled complete withdrawal of corticosteroids. At the 12-month follow-up, colonoscopy demonstrated complete mucosal healing, and the patient remained in stable remission since without further disease flares.

MAS is a severe but rare complication of periodic fever syndromes, including MKD. While most patients develop their first inflammatory attacks during infancy, typically before the age of one year, our patient presented with MAS at the age of 18. This late and atypical presentation broadens the recognised clinical spectrum of MKD.

This case highlights the importance of considering monogenic autoinflammatory syndromes in adolescents with recurrent unexplained inflammation, particularly when gastrointestinal and mucosal findings mimic more common conditions such as Behçet's disease, inflammatory bowel disease, or primary immunodeficiencies. Delayed recognition may expose patients to life-threatening complications such as MAS. In our patient, disease onset at 13 years with progressive gastrointestinal involvement culminating in MAS at 18 years illustrates this diagnostic challenge.

In conclusion, this case illustrates a rare but life-threatening manifestation of MKD, initially presenting as MAS in late adolescence. Recurrent febrile flares with unexplained systemic inflammation in adolescents should prompt consideration of mono-

genic autoinflammatory syndromes. Early genetic confirmation and timely initiation of IL-1 blockade are essential to achieve sustained remission and prevent life-threatening complications such as MAS.

Written informed consent was obtained from the patient and/or legal guardian for the publication of this case report and accompanying image.

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