

AA amyloidosis as a rare presentation leading to the diagnosis of mevalonate kinase deficiency in a male adult: a diagnostic challenge mimicking familial Mediterranean fever

Dear Editor,

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder characterised by recurrent febrile episodes and a risk of systemic AA amyloidosis. Historically, the diagnosis was often based on clinical features and response to therapy; however, current practice emphasises the importance of genetic confirmation (1). We report a case where molecular analysis overturned a clinical diagnosis of FMF in an adult presenting with AA renal amyloidosis and nephrotic syndrome, revealing a homozygous mutation in the *MVK* gene. This gene encodes mevalonate kinase (MK); pathogenic variants in *MVK* are responsible for a spectrum of rare auto-inflammatory conditions, mainly diagnosed in childhood, collectively termed mevalonate kinase deficiency (MKD), which include milder forms, formerly known as “hyper IgD syndrome” (2-3).

A 37-year-old male of Pakistani descent, born to consanguineous parents, was referred to the Nephrology Unit in March 2024. He presented with abdominal pain

and generalised oedema (peripheral, periorbital and scrotal), alongside with peritoneal and pleural effusions.

Laboratory investigations revealed nephrotic-range proteinuria (12.4 g/day), hypoalbuminemia (1.8 g/dL), mild renal impairment (creatinine 1.5 mg/dL), and hypogammaglobulinemia (IgG 1.37 g/L). Inflammatory markers were significantly elevated: C-reactive protein (CRP) 24 mg/L and serum amyloid A (SAA) 286 mg/L (Fig. 1).

Extensive screening for secondary causes, including ANA, anti-ENA, anti-dsDNA, anti-PLA2R, anti-phospholipid antibodies, cryoglobulins, C3, C4, serum/urine immunofixation, and serum IgA, was negative or within normal limits. A renal biopsy confirmed AA amyloidosis, with amyloid deposition involving the glomeruli, arterioles, and interstitium.

The patient’s medical history was notable for a hospital admission at age 2 (without a definitive diagnosis) and recurrent monthly episodes of fever and abdominal pain, lasting 2-3 days. While the patient initially recalled these episodes starting at age 10, his mother subsequently clarified that they had commenced at 1 year of age. These symptoms remained uninvestigated and seemingly entered clinical remission in 2007, following his relocation to Italy.

Suspecting FMF, colchicine was started (1 mg/day), and Next Generation Sequencing

(NGS) for autoinflammatory gene panels was performed. Supportive therapy included furosemide, canrenone, ramipril, statins, ezetimibe, dapagliflozin and warfarin for catheter-associated deep vein thrombosis. Two months later, the patient showed clinical improvement: oedema and abdominal pain resolved, SAA levels normalised, and proteinuria decreased to 7 g/day. Based on these findings, a clinical diagnosis of FMF was made according to the Tel-Hashomer and Eurofever/PRINTO criteria (4, 5). During follow-up, due to rising creatinine and liver enzymes, colchicine was reduced to 0.5 mg/day.

Unexpectedly, NGS identified a homozygous variant (N205D) in the *MVK* gene, classified as likely pathogenic according to ACMG standards. Following the revised diagnosis of MKD, treatment was transitioned to canakinumab (150 mg every 4 weeks) in November 2024. This led to sustained clinical remission and a further reduction of proteinuria (Fig. 1). Notably, a disease flare occurred in January 2025 (disease activity, measured by the AIDAI score (6) =20) during an intercontinental trip between Pakistan and Italy, identifying travel-related stress as a potential trigger. This case demonstrates “diagnostic mimicry” where MKD presented with features resembling FMF, including response to colchicine, allowing some relevant key points highlight: first, untreated MKD, like other

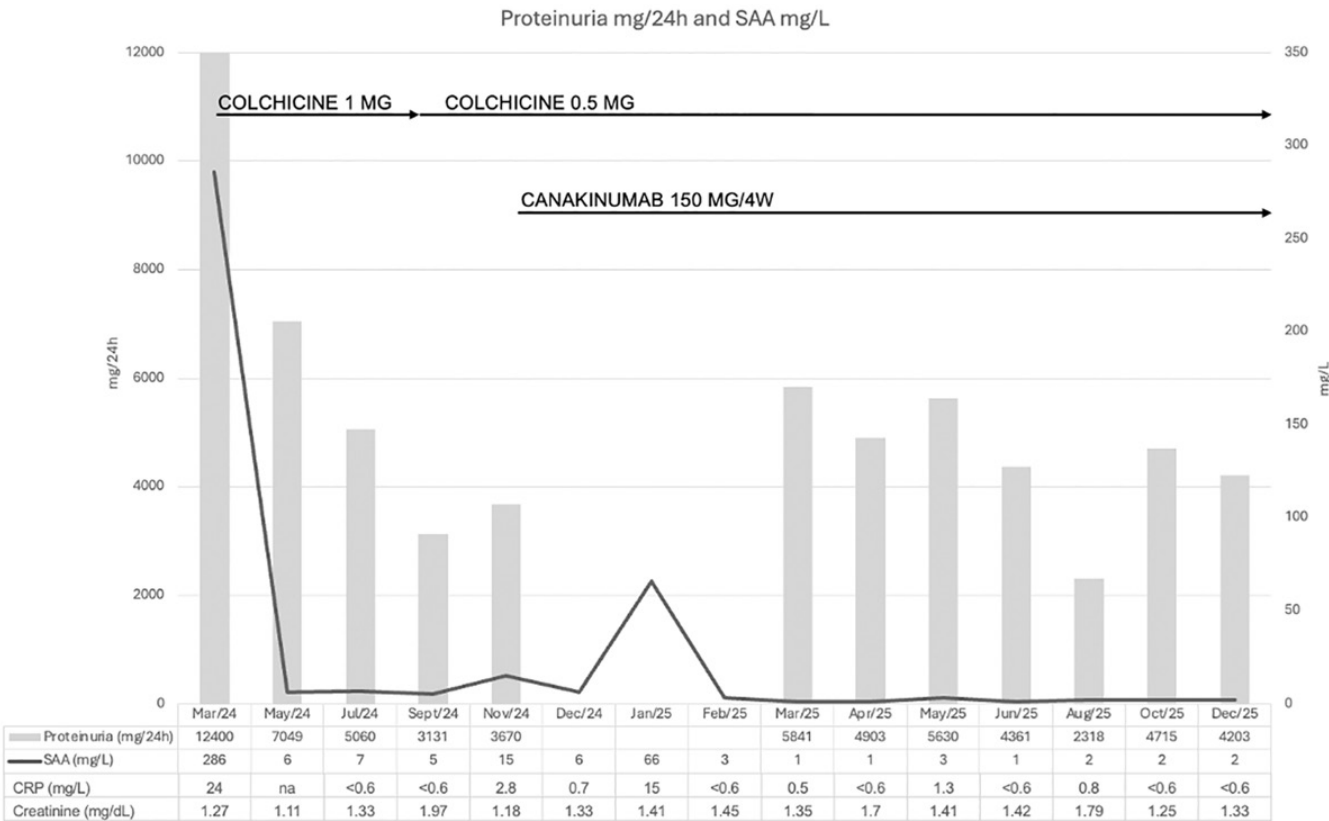


Fig. 1. Main laboratory features and treatments during follow-up.

autoinflammatory diseases, carries risks of severe complications such as macrophage activation syndrome (7) and AA amyloidosis, which affects around 6% of patients when diagnosis is established in adulthood (8). Second, genetic testing plays a crucial role in diagnosing autoinflammatory diseases, particularly given their potential to mimic each other. Finally, although MKD is more prevalent in Europe, its possible occurrence in other regions should not be overlooked (2-3).

In conclusion, along with careful medical history, precise molecular characterisation is essential for accurate diagnosis of autoinflammatory disorders presenting in adult patients, thus ensuring appropriate targeted therapies (2).

A.C. Pozzi, MD
G. Voltarel, MD
P. Airò, MD
M. Frassi, MD
I. Cavazzana, MD
F. Crisafulli, MD

Rheumatology and Clinical Immunology Unit, ERN ReCONNET, ASST Spedali Civili of Brescia; and Department of Clinical and Experimental Sciences, University of Brescia, Italy.

Please address correspondence to: Dr. Francesca Crisafulli ASST Spedali Civili and University of Brescia, Piazzale Spedali Civili, 1 25123 Brescia, Italy.

E-mail: crisafulli.francesca10@gmail.com

Competing interests: M. Frassi has received honoraria from Novartis, Sobi, Janssen, Johnson and Johnson, not in conflict with the present article. All other authors declare no competing interests.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2026.

References

1. RUSCITTI P, CASO F, VITALE A, GIACOMELLI R, CANTARINI L: The clinical management of adult patients with Familial Mediterranean fever. *Expert Rev Clin Immunol* 2025; 21(11): 1503-15. <https://doi.org/10.1080/1744666X.2025.2584302>
2. LENGVÁRI L, TAKÁCS K, LENGYEL A *et al*: Mevalonate kinase deficiency: an updated clinical overview and revision of the SHARE recommendations. *Front Immunol* 2024; 15: 1466844.

<https://doi.org/10.3389/fimmu.2024.1466844>

3. TOUITOU I: Twists and turns of the genetic story of mevalonate kinase-associated diseases: A review. *Genes Dis* 2021; 9(4): 1000-7. <https://doi.org/10.1016/j.gendis.2021.05.002>
4. SOHAR E, GAFNI J, PRAS M, HELLER H: Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967; 43: 227-53. [https://doi.org/10.1016/0002-9343\(67\)90167-2](https://doi.org/10.1016/0002-9343(67)90167-2)
5. GATTORNO M, HOFER M, FEDERICI S *et al*: Classification criteria for autoinflammatory recurrent fevers. *Ann Rheum Dis* 2019; 78(8): 1025-32. <https://doi.org/10.1136/annrheumdis-2019-215048>
6. PIRAM M, KONÉ-PAUT I, LACHMANN HJ *et al*: Validation of the Auto-Inflammatory Diseases Activity Index (AIDAI) for hereditary recurrent fever syndromes. *Ann Rheum Dis* 2014; 73: 2168-73. <https://doi.org/10.1136/annrheumdis-2013-203666>
7. BATIBAY S, BOZKURT T, DINÇSES NAS E, CILLI HAYIROĞLU S, KASAPOĞLU E: Mevalonate kinase deficiency diagnosed in late adolescence presenting with macrophage activation syndrome. *Clin Exp Rheumatol* 2025; 43 (Suppl. 136): S21-22. <https://doi.org/10.55563/clinexprheumatol/s5eeqmq>
8. RODRIGUES F, PHILIT JB, GIURGEA I *et al*: AA amyloidosis revealing mevalonate kinase deficiency: A report of 20 cases including two new French cases and a comprehensive review of literature. *Semin Arthritis Rheum* 2020; 50(6): 1370-3. <https://doi.org/10.1016/j.semarthrit.2020.03.005>