Letters to the Editors

Development of systemic amyloidosis in a patient with heterozygous P369S mutation in the *MEFV* gene

Sirs,

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder and is characterised by recurrent episodes of fever lasting 1–3 days, accompanied by serosal inflammation (1). The clinical picture of FMF results from mutations in the *MEFV* gene, which encodes the protein pyrin (2) To date, over 400 *MEFV* variants have been reported, yet the clinical relevance of the exon 3 P369S (proline-to-serine) substitution remains unclear. This rare variant is reported in 1–4% of FMF populations and is considered to have low penetrance and possibly benign impact (3). However, clinicians frequently face uncertainty when interpreting this variant in the context of FMF diagnosis, colchicine responsiveness, and amyloidosis risk (4, 5). Here, we describe a 50-year-old female of Turkish origin with a heterozygous P369S mutation who developed systemic AA amyloidosis. She presented with bilateral wrist and ankle swelling and had a long-standing history of FMF, diagnosed at age 15 at an external centre and managed with colchicine 1.5 mg/day, with good compliance to therapy. There was no known family history of FMF or amyloidosis, and the patient reported that both of her parents were asymptomatic and had never undergone genetic testing. Her symptoms recently worsened, with increasing musculoskeletal pain, frequent 2-day episodes of abdominal pain, and bilateral lower extremity oedema, in the absence of comorbidities such as hypertension, diabetes, or chronic infections. On examination, wrist and ankle swelling was noted. Rheumatoid factor, anti-cyclic citrullinated peptide (CCP), and anti-nuclear antibody (ANA) were negative. Genetic analysis revealed heterozygous P369S mutation. Polymorphism analysis of the SAA1 (serum amyloid A) gene revealed an α/α (SAA1.3 homozygous) genotype. Laboratory findings included elevated CRP: 10.8 mg/L (normal: 0–5), ESR: 46 mm/h (normal: 0–20), 24-hour urinary protein: 831 mg/day (normal: <150), low serum albumin (3.2 g/dL, normal: 3.5–5.0), and reduced eGFR (69 mL/min, normal: ≥90). Urinary findings raised suspicion for renal involvement. To enlighten the suspicion of renal involvement, diagnostic minor salivary gland biopsy revealed amyloid deposits confirmed by positive staining with crystal violet and congo red, establishing a diagnosis of AA-type amyloidosis. No secondary causes of AA amyloidosis such as chronic infections, autoimmune diseases, malignancies, or systemic inflammatory conditions were identified in clinical, laboratory, or historical evaluation. Given the patient's classic FMF features and absence of other risk factors, the P369S variant was considered the most plausible contributor to amyloidosis. Due to persistent proteinuria, anti-IL-1 therapy (anakinra) was initiated alongside colchicine at a dose of 100 mg/day subcutaneously. The patient showed improvement in inflammatory markers (CRP: 2.3 mg/L, ESR: 23 mm/h, albumin: 3.5 g/dL), and renal function remained stable. She has been attack-free for over one year under this treatment. The clinical significance of the P369S mutation remains uncertain in the literature. Ryan *et al*. reported that P369S often coexists with R408Q and presents with atypical FMF features, poor colchicine response, and no systemic amyloidosis. Notably, localised amyloid deposition in the eyelid was observed in one patient, and the mutation has been proposed as a potential modifying variant (6). Other studies noted wide phenotypic variability and suggested that exon 3 variants may be associated with atypical autoinflammatory phenotypes, not just classic FMF (7, 8). A Japanese study concluded that while P369S is not classically linked with amyloidosis, however, in cases where amyloidosis develops and no other genetic or environmental risk factors are identified, the contribution of P369S should be considered (2). Conversely, another study suggested that due to its association with frequent high fever and abdominal pain, P369S may represent a more severe mutation and could hold clinical significance in larger cohorts (9). Our case adds to the growing body of evidence suggesting that the P369S variant, may possess pathogenic potential, particularly when accompanied by classic FMF symptoms and in the absence of alternative causes of amyloidosis. The patient had exhibited typical FMF manifestations since adolescence, indicating a clinically active autoinflammatory phenotype despite the presence of only a heterozygous *MEFV* mutation. Importantly, a comprehensive clinical, laboratory, and historical evaluation ruled out other potential causes of AA amyloidosis, including environmental triggers. Moreover, previous reports have described atypical inflammatory phenotypes and even localised amyloid deposition associated with exon 3 variants like P369S, particularly in the setting of sustained inflammation. In our case, persistently elevated CRP and ESR levels despite regular colchicine use suggested ongoing subclinical inflammation, which may have contributed to progressive amyloid accumulation. The patient carried the SAA1α/α genotype, which has been reported to be associated with a higher risk of AA amyloidosis in FMF patients (10). Therefore, in this case, the presence of this polymorphism may have contributed to the development of systemic amyloidosis, possibly in combination with persistent inflammation driven by the P369S variant. Although classified as low penetrance, clinicians should consider P369S as a possible contributor in relevant scenarios. Broader prospective studies are needed to better define the clinical impact of exon 3 variants like P369S.

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