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Letters to the Editor

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A baffling case of severe systemic inflammation. Putting the pieces together: genes, environment and triggers

Rheumatology key message

- Autoinflammatory syndromes pose diagnostic challenges; the relevance of single MEFV gene mutations remains poorly understood.

SIR, Autoinflammatory syndromes with an exaggerated immune response pose important diagnostic challenges. They are diagnosed by a combination of clinical findings and genetic testing. First presentation is often in childhood, although 10% of patients develop their first symptoms after the age of 20 years [1].

Herein, we report a complex case with heterozygosity for the *MEFV* gene with atypical adult-onset Still's disease (AOSD) in a 39-year-old Colombian woman, in her third pregnancy trimester. At 33 weeks' gestation, she presented with a sore throat, polyarthralgia, myalgia and pleuritic chest pains. She had an erythematous maculopapular rash thought to be pregnancy-related pruritic eruption, and earlier in pregnancy had developed biopsy-confirmed reactive axillary lymphadenopathy. Past surgery included breast augmentation and bariatric surgery, but family history was unremarkable. She was tachycardic with wrist, MCP and PIP joint synovitis, and had bilateral pitting leg oedema that gradually spread to the abdomen, associated with worsening hypoalbuminaemia.

Inflammatory markers were raised (CRP 102 mg/l and ESR 60 mm/h), but white cell differential, ANA, ANCA, RF/anti-CCP and complement levels were normal. Chest X-ray showed unilateral consolidation. She was administered prednisolone for suspected reactive arthritis with broad spectrum antibiotic cover. After a brief clinical improvement, she deteriorated, continuing to remain afebrile. Emergency caesarean section was performed at 34 weeks due to concerns over maternofetal well-being.

On day 3 post-caesarean section she became febrile with worsening chest and joint pains. Abdominopelvic and chest CT and echocardiograph were normal. Colchicine was trialled unsuccessfully. Antibiotics were withdrawn after persistent negative microbiology tests with fever settling on day 6. She continued to deteriorate clinically with myalgia, arthralgia, and abdominal and pleuritic chest pains. At this point, the possibility of an autoinflammatory syndrome with or without atypical AOSD was considered due to raised ferritin (5154 μg/l) and CRP (300 mg/l). After multidisciplinary discussion, i.v. methylprednisolone (1 g/day) was commenced for 3 days, along with IVIGs for 5 days. This regimen provided a dramatic improvement in her inflammatory markers (Fig. 1) and clinical picture. Further investigations revealed raised serum amyloid A (703 mg/l) and genetic testing confirmed the presence of *MEFV* I591T. The patient was discharged and remains stable at 1-year follow-up on colchicine, AZA and HCQ.

FMF is the most common autoinflammatory syndrome resulting from mutations in the *MEFV* gene that encodes the protein pyrin, a regulator of inflammation and apoptosis. Gene mutations lead to inflammation with excessive IL-1 secretion [2]. Initially, five mutations (V726A, M694V, M694I, M680I and E148Q) were identified, which account for 74% of all cases [3].

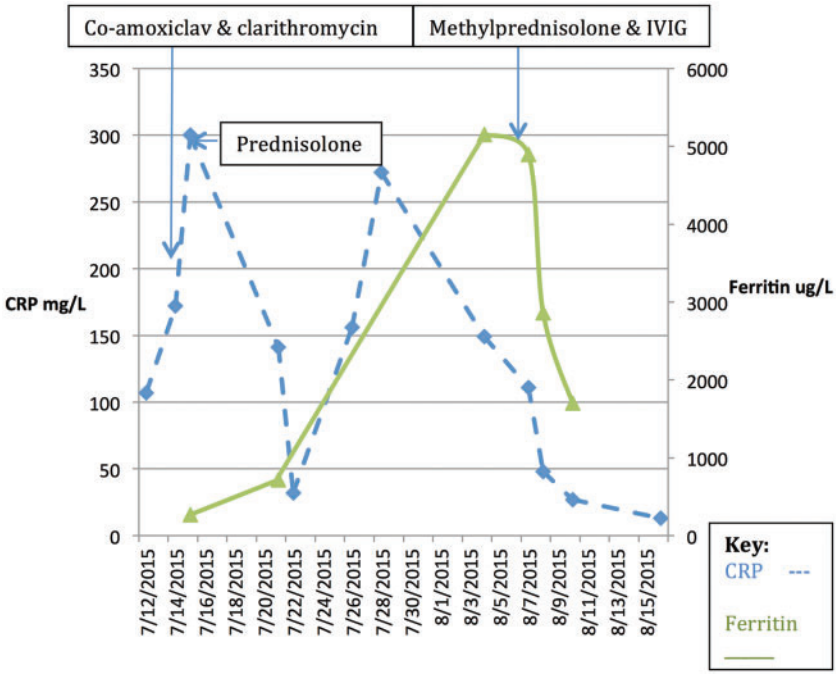
Rare mutations are preferentially found in populations not normally associated with the disease. This includes *MEFV* I591T on exon 9, described in a patient from France [3], and in a Spanish family [4], which was associated with FMF both in conjunction with a second mutation and as the sole genetic abnormality. It is proposed that other *MEFV* genes are involved in non-FMF conditions [5].

Incidence of FMF is highest in the Mediterranean region with reported cases also in Asia and South America. Classically, patients experience recurrent self-limiting episodes of fever and serositis. Pleural involvement occurs in 15% and is usually unilateral [2]. These events may be triggered by physical/emotional stress resulting in an intense acute phase reaction [2]. Use of IL-1 receptor antagonists shows promise in patients who are intolerant to colchicine. AA amyloidosis and renal failure are serious complications if untreated.

AOSD is also considered an autoinflammatory disorder. Diagnosis is made clinically and relies on the classical triad of daily spiking fevers, polyarthritis and a salmon-pink evanescent rash. Other manifestations include a prodromal sore throat, myalgia, weight loss, serositis, lymphadenopathy, hepatomegaly and macrophage activation syndrome. Laboratory findings include raised inflammatory markers, normocytic anaemia, hypoalbuminaemia and raised serum ferritin in 50% of cases. FMF-related *MEFV* variants are implicated with the disease phenotype of AOSD [6].

The present case is an example of a challenging autoinflammatory syndrome occurring in pregnancy in a patient of Hispanic ethnicity, heterozygous for an *MEFV* mutation, with no family history and who had neither FMF by the Tel-Hashomer criteria [7] nor AOSD. Nevertheless some of the clinical and biochemical manifestations, particularly the high ferritin, are more consistent with AOSD than FMF. The patient benefited from methylprednisolone and has been well as an outpatient on broad spectrum immunosuppression and colchicine, which is an effective prophylaxis agent in FMF. Colchicine has been reported to be beneficial in patients with heterozygous carriage of *MEFV* I591T [8].

Fig. 1 Relationship between inflammatory response and treatment



Furthermore, a Japanese study suggested that *MEFV* variants (excluding the very common polymorphism E148Q) are over-represented in ASOD and are associated with recurrent or severe inflammation and an increased requirement for biologics [6]. This case highlights the diagnostic dilemmas that are associated with adult-onset autoinflammatory syndromes, illustrating the importance of multi-disciplinary team input and coordinated care. Further exploration of *MEFV* I591T is required to evaluate its contribution to autoinflammatory diseases.

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