

Letter to the Editor (Case report)

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First case of pyrin-associated autoinflammation with neutrophilic dermatosis complicated by amyloidosis**Rheumatology key message**

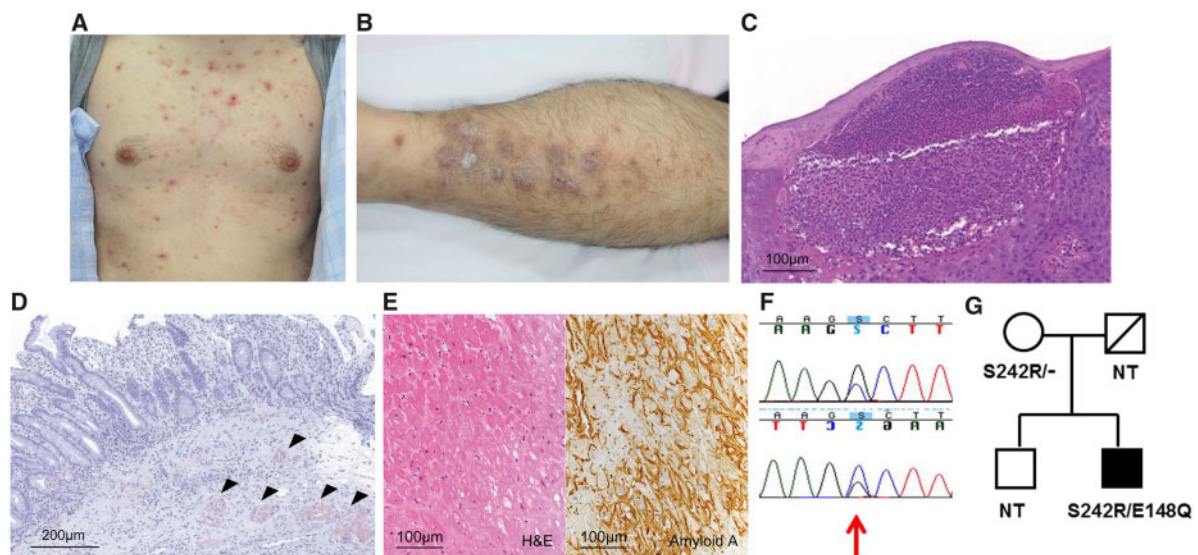
- The compound heterozygous S242R mutation and E148Q polymorphism may lead to pyrin-associated autoinflammation with neutrophilic dermatosis complicated by amyloidosis.

SIR, FMF is the most frequent autoinflammatory disease caused by mutations in *MEFV* [1], which encodes pyrin, an important protein component of the inflammasome [2]. Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) is a recently reported disease [3] caused by mutations in exon 2 of *MEFV*. These mutations activate the pyrin inflammasome by inhibition of binding to 14-3-3 proteins, which are involved in the protection of the pyrin inflammasome [3, 4]. PAAND has attracted attention as a model case of a gain-of-function mutation. Given that it is a rare disease, the reason for the occurrence of lesions on activation of the pyrin inflammasome and the persistence of inflammation

remains unclear. To the best of our knowledge, this is the first case of PAAND encountered in Japan. Furthermore, it was complicated by amyloidosis; such a case has not been reported thus far.

A 45-year-old Japanese man with intermittent fever and abdominal pain was admitted to our hospital. He had suffered from a whole-body acne-like rash since he was 5 months old (Fig. 1A). Old scars were observed on the lower thighs (Fig. 1B). Two years ago, abdominal pain, nausea and vomiting, and a mild fever of $\leq 38^{\circ}\text{C}$ occurred every 2–3 months. Blood tests showed an elevated white blood cell count (14 670/ μl , neutrophil count 12 792/ μl) and high inflammatory biomarker levels (CRP 147.8 mg/l, serum amyloid A protein 1960.9 $\mu\text{g}/\text{ml}$). Skin biopsy revealed subcorneal neutrophilic aggregates, indicating a subcorneal pustular dermatosis (Fig. 1C). Oesophagogastroduodenoscopy revealed duodenitis, which might be the cause of his abdominal pain. Histopathology of the duodenal mucosa showed neutrophilic infiltration, and Dylon staining confirmed the deposition of amyloid protein in the perivascular area (Fig. 1D, black arrowhead). Total colonoscopy did not show any lesions in the colon; however, capsule endoscopy confirmed an ulcerated lesion in the jejunum. Rectal biopsy also showed amyloid deposition. Myocardial biopsy was performed because echocardiography showed a characteristic feature of cardiac amyloidosis. The biopsy specimen showed deposition of

Fig. 1 Presentation of the reported case



(A) Skin lesions on the chest. (B) Skin lesions on the left lower thigh. (C) Haematoxylin and Eosin staining of skin biopsy specimen. (D) Dylon staining of duodenal biopsy specimen. (E) Endomyocardial biopsy showing amyloid A deposition. (F) Chromatogram showing Sanger sequencing results for *MEFV* mutations (c.726 C>G). (G) Pedigree of patient. NT: not tested.

eosinophilic, amorphous material in the myocardial interstitium (Fig. 1E, left column). Immunohistochemical staining for amyloid A was strongly positive for interstitial deposition (Fig. 1E, right column). Although renal function was not affected, proteinuria (protein-to-creatinine ratio = 1.64) was observed. A renal biopsy was not performed.

We suspected an autoinflammatory disease from his unique presentation. Hence, we searched for 25 autoinflammatory syndrome disease genes (*MEFV*, *TNFRSF1A*, *NLRP3*, *MVK*, *NOD2*, *IL1RN*, *NLRP12*, *PSTPIP1*, *PSMB8*, *PSMB9*, *PSMA3*, *PSMB4*, *POMP*, *NLRC4*, *PLCG2*, *HMOX1*, *CECR1*, *COPA*, *TNFAIP3*, *OTULIN*, *HOIP*, *HOIL1*, *CARD14*, *IL36RN* and *LPIN2*) using a next-generation sequencer, MiSeq (Illumina), and confirmed an S242R heterozygous mutation (c.726 C>G; Fig. 1F) and E148Q heterozygous polymorphism (c.442 G>C) in *MEFV*. His father was deceased but did not have similar symptoms.

In this patient, acneiform eczema had been the main symptom since childhood, but abdominal symptoms with mild fever appeared periodically at the age of 43 years. The results of endoscopy mainly revealed duodenitis or jejunal ulcerative lesions, which are abdominal symptoms, rather than serositis from FMF caused by the same *MEFV* mutation.

Given that the effects of CSs and colchicine were poor, treatment was started with tocilizumab instillation (440 mg; 8 mg/kg), administered every 4 weeks up to the second time, and every 2 weeks from the third time. Abdominal pain and fever disappeared, and tests for CRP and proteinuria were negative after 6 weeks. The rash did not change before and after treatment.

Recently, autoinflammatory syndromes other than FMF associated with *MEFV* mutations have been reported. The term pyrin-associated autoinflammatory disease has been proposed to describe *MEFV*-related autoinflammatory syndromes, including FMF [5]. The mechanism underlying the activation of the pyrin inflammasome is being elucidated; the phosphorylation site in exon 2 might be important in the pathology of PAAND. To date, PAAND has been reported in 16 patients in four families, but amyloidosis has not been described [3]. As with FMF, this complication is likely to contribute to the prognosis, and accordingly, early diagnosis is crucial [6].

Surprisingly, the proband's asymptomatic mother also harboured the S242R heterozygous mutation. In the first reported pedigree analysis of PAAND, 17 persons with the S242R heterozygous mutation had some of the symptoms of neutrophilic dermatosis, recurrent fever, arthralgia or myalgia, except for one self-reported healthy individual, similar to the proband's mother [3]. There are few reports of PAAND, suggesting that there might be more asymptomatic carriers with the S242R heterozygous mutation, similar to the proband's mother. The patient and his mother differed with respect to the E148Q polymorphism in *MEFV* (Fig. 1G). In our previous analysis of elderly patients with neutrophilic dermatosis and FMF, we identified

the compound heterozygous polymorphism L110P/E148Q/G304R [7], suggesting that the E148Q polymorphism might act as a disease modifier in this case [8]. In addition, potential roles of unknown genes that have not yet been linked to autoinflammatory disorders cannot be neglected.

In conclusion, we reported the first case of PAAND complicated by amyloidosis; rheumatologists should monitor this co-morbidity in PAAND.

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