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The expanding spectrum of clinical phenotypes associated with *PSTPIP1* mutations: from PAPA to PAMI syndrome and beyond

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DEAR EDITOR, Mutations in the PSTPIP1 gene encoding proline-serine-threonine-phosphatase interactive protein 1 were first identified in an autosomal dominant syndrome called PAPA associated with pyogenic sterile arthritis, pyoderma gangrenosum (PG) and cystic acne.[1,2]

We report a patient with an autoinflammatory syndrome called PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome.[3]

A 23-year-old man had a 3-year-history of skin ulcerations. During childhood he exhibited anemia (81 g/l), neutropenia (0,3 G/l), mild thrombocytopenia and hepatosplenomegaly. Presence of anemia and of recurrent infections prompted a bone marrow biopsy, which showed evidence for disturbed myelopoiesis beyond the promyelocytes/myelocytes level. From the age of 7 years, he developed relapsing sterile osteomyelitis affecting the left talus, tibia and fibula. In his adolescence, he suffered from relapsing sterile arthritis of one knee and elbow.

On examination, the patient had nodulocystic acne on his face and back. On the right thigh, there was an ulceration of 5 x 7 cm in diameter, while two other ulcers of 7 x 12 cm and 6 x 10 cm were found on the left and right legs, respectively (Fig. 1). The periphery showed a purple halo with undermined borders or cribriform scarring. Light microscopy studies revealed diffuse neutrophilic dermal infiltration. Special stainings, microbiological examinations and cultures remained negative. The ESR was 55 mm/h and the C-reactive protein 68 mg/L. There was a microcytic anemia (114 g/l) and neutropenia (0,69 G/l). Renal and hepatic tests as well as immunoglobulin levels were unaltered. Search for antinuclear antibodies and rheumatoid factors was negative. A pathergy phenomenon was often observed at the site of blood tests. Suspecting PAPA syndrome, we sequenced the coding sequence of *PSTPIP1*.[2] Genetic analyses identified a heterozygous pathogenic c.748G>A mutation predicted to result in the substitution of a highly conserved residue at position 250, E250K, of PSTPIP1. Since this same mutation was identified in PAMI syndrome,[1] we measured the concentrations of serum zinc, S100A8/A9 (calprotectin) and S100A12 (calgranulin C). The latter were of 140 µmol/l (11-18 µmol/l), of 2'050'000 ng/ml (< 2'900 ng/ml) and 303'000 ng/ml (< 75ng/ml), respectively. The patient was treated with prednisolone 1 mg/kg daily and topical tacrolimus with partial response after 20 weeks. To better control the ulcerations, the patient was given infliximab (5 mg/kg body weight) and prednisolone, 20 mg per day. This treatment was ineffective and stopped after 4 cycles. The patient was subsequently treated with monthly injections of canakinumab, 300 mg, with prednisone 20 mg daily. IL-1 inhibition showed no benefit and was cessated after three injections. Finally, injections of secukinumab, 300mg every two weeks with prednisone 20 mg daily resulted in a partial reduction of the ulcerations (Fig. 1c). These treatments did not improve the acne, which showed some response to oral isotretinoin only. All attempts to discontinue the corticosteroids resulted in exacerbation of PG. The patient was then also given ciclosporin 4 mg/kg daily with almost complete healing of the PG during the past 6 months (Fig. 1d) and good tolerance.

In addition to PAPA syndrome, *PSTPIP1* mutations have been associated with PG, acne and hidradenitis suppurativa with or without pyogenic arthritis.[4,5] Isolated aseptic abdominal abscesses, pyogenic arthritis and osteolytic lesions have also been linked to *PSTPIP1* variants (review table available upon request to the corresponding author).[2-7] Recently, pathogenic *de novo* mutations in *PSTPIP1* leading to the amino acid substitution E250K or pE257K have been linked to PAMI, a severe autoinflammatory syndrome characterized by pancytopenia, hepatosplenomegaly, acne and PG.[2,3] Our patient had all features of PAPA. However, he had a history of systemic inflammation, pancytopenia, hepatosplenomegaly and pyogenic arthritis in childhood. He also exhibited significant hypercalprotectinaemia and hyperzincaemia that distinguish PAMI from PAPA syndrome.[2] Our case had further episodes of osteomyelitis. The latter has been reported in PAMI but not in PAPA. In PAMI the response to either anti-IL-1 or anti-TNFα blockade is inconstant.[2,3] In contrast, PAPA usually shows a good response to anti-IL-1 blockade.[7] Our trial with a novel IL-17A antagonist,

secukinumab, showed only a partial effect. Only addition of ciclosporin possessing broad anti-inflammatory properties resulted in benefit as reported in a case with the same *PSTPIP1* mutation.[8]

The inflammatory cascade triggered by *PSTP1P1* defects seems to be affected by the type of mutations and their impact on PSTP1P1 function.[2,3] Nevertheless, defects of other genes, such as nicastrin (*NCSTN*) may result in similar clinical inflammatory manifestations.[7]

Our case illustrates the broad spectrum of phenotypes associated with *PSTPIP1* mutations which variably affect over the years only one organ up to a severe autoinflammatory disorder, management of which remains challenging.

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Figure Legend

Fig 1. Clinical photographs of the patient with PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome. (a) Nodulocystic acne affecting the face. (b) Pyoderma gangrenosum with typical features over the anterior aspect of the lower leg. (c) Partial response upon introduction of secukinumab. (d) Addition of ciclosporin resulted in clinical benefit with almost clearing of the ulcerations.