# Case report

# Haematological involvement associated with a mild autoinflammatory phenotype, in two patients carrying the E250K mutation of *PSTPIP1*

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**ABSTRACT**

**Objective.** *Hyperzincaemia/hypercalprotectinaemia (Hz/Hc) syndrome is a recently described condition caused by a specific de novo mutation (E250K) affecting PSTPIP1 gene. It has a phenotype distinct from classical pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome that includes severe systemic and cutaneous inflammation, hepatosplenomegaly, arthritis without sequelae, pancytopenia and failure to thrive.*

**Methods.** *We describe an 8-year-old boy who presented recurrent right knee swelling mimicking septic arthritis and persistent bone marrow involvement, without cutaneous involvement.*

**Results.** *Molecular analysis of the PSTPIP1* gene *revealed the presence of a heterozygous E250K mutation. No growth failure was detected nor in the patient neither in his mother, carrying the same variant. Blood zinc and calprotectin MRP8/14 concentrations of the patient were found to be markedly increased. Therapy with anakinra was started with rapid disappearance of clinical symptoms and normalisation of CRP levels in 24 hours, but persistence of bone marrow involvement.*

**Conclusion.** *The patient described has a milder phenotype, with no skin features, minor episodes of arthritis with no sequelae and normal growth. Compared to the patients with de novo mutations described in the literature, familial cases seem to have a milder phenotype. Our case further confirms the lack of efficacy of anakinra on bone marrow involvement.*

## Introduction

Proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) is a cytoskeleton-associated adaptor protein that modulates cytoskeletal organisation, T-cell activation and interleukin-1 β (IL-1β) release. Heterozygous mutations in PSTPIP1 cause the dominantly inherited pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. Recently, a specific *de novo* mutation (E250K) of PSTPIP1 has been identified as the cause of hyperzincaemia/hypercalprotectinaemia (Hz/Hc) syndrome. The term PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome has been proposed. This condition, characterised by severe systemic and cutaneous inflammation, hepatosplenomegaly, arthritis, pancytopenia and failure to thrive (1-2), has a phenotype distinct from classical PAPA syndrome.

We observed a patient carrying the E250K mutation with a mild phenotype. He is an 8-year-old boy with normal growth rate: body weight 24.5 kg (50th centile) and height 122.5 cm (25–50th centile), referred to our attention for recurrent right knee swelling. In the first episode, at 7 years of age, synovial fluid analysis showed a white cell count of 59.000/mm$^3$ with a sterile culture; he received ceftriaxone. Hepatosplenomegaly and leukopenia (ranging from 500 to 1220/ mm$^3$) with neutropenia (ranging from 330 to 770/ mm$^3$) were noted. A bone marrow aspirate showed trilinear dysplasia. His past medical history was significant for intermittent pancytopenia and elevation of inflammatory parameters, with no relevant infections. An additional episode of right knee swelling was reported after one month and resolved spontaneously in 48 hours after treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Subsequently, other two mild episodes of right knee

pain without swelling were reported. In the subsequent months neutropenia and increase in inflammatory parameters were confirmed and persisted in the absence of arthritis (Table I). No other symptoms were reported. He has never experienced skin disease, or persistent lymphadenopathies. Because of the history of recurrent arthritis with one episode suggestive of pyogenic sterile arthritis, and persistent elevation of the inflammatory parameters (Table I), PAPA syndrome was suspected. After written consent by the parents, *PSTPIP1* gene analysis revealed the presence of a heterozygous E250K mutation. His mother reported acne and psoriasis with resolution in adulthood, and a history of arthralgias and increase in inflammatory parameters during childhood. These episodes were treated with glucocorticoids and NSAIDs. She also reported persistent anaemia and leukopenia that did not resolve after splenectomy performed at 21 years of age. No clinically relevant infections were reported. His mother also carried the E250K mutation. Consistently with previous reports (1-2), blood zinc and calprotectin MRP8/14 concentrations of the patient were found to be markedly increased: 388 micromol/L (normal values <0.05) and 2600 microg/mL (normal values <0.5), respectively. Treatment with anakinra resulted in rapid normalisation of inflammatory parameters; neutropenia persisted (Table I). No episodes of knee arthritis have been observed in the subsequent 8 months.

**Table I.** Inflammatory markers and WBC before and after initiation of therapy.

| Before anakinra | ESR (mm/h) | CRP (mg/dl) | SAA(mg/L) | WBC/mmc | Neutrophils |
|---|---|---|---|---|---|
| -6 months | 33 | 5.7 | Not available | 2560 | 767 |
| -5 months | 23 | 8.4 | Not available | 2550 | 930 |
| -3 months | 57 | 4.98 | 335 | 2420 | 746 |
| -1 month | 48 | 6.1 | 330 | 2820 | 740 |
| Start of anakinra | 25 | 4.05 | 189 | 2380 | 430 |
| + 1 month | 2 | <0.05 | <1 | 1990 | 440 |
| + 4 months | 3 | 0.06 | 1.31 | 2170 | 290 |
| + 7 months | 5 | <0.05 | 2.4 | 1760 | 270 |
| + 10 months | 4 | <0.05 | <1 | 1730 | 360 |

WBC: white blood cells; ESR: eryhrocyte sedimentation rate; CRP: C- reactive protein; SAA: Serum amyloid A.

A literature search identified 15 cases with the E250K mutation (1-8). All of them show persistent hyperzincaemia (range 52-211 micromol/L) and hypercalprotectinaemia (MRP8/14 range 600-8800 microgr/mL), that are the cornerstones for the diagnosis. Our patient had levels within the reported range. Noteworthy, compared to the patients with sporadic mutations described in the literature, he has a milder phenotype, with no skin features, minor episodes of arthritis with no sequelae and normal growth. The finding of such markedly elevated levels of zinc and calprotectin was unexpected in our patient with a mild phenotype. However, another familial case with mild phenotype has been reported lacking the severity of spontaneous cases (2).

PAPA syndrome is an "inflammasomopathy" associated with elevated IL-1β production (9-10). Other therapeutic options have shown unsatisfactory response in PAPA and particularly in E250K carriers (2). Based on the data reported in the literature (11-13) we used anakinra, (2 mg/kg per day subcutaneously). Treatment was followed by the disappearance of all manifestations. No subsequent episodes of arthritis were observed. Anakinra was, however, ineffective on bone marrow involvement. Nine of the reported 15 E250K patients received an IL-1 inhibitor, with a good response of the arthritis and normalisation of the inflammatory parameters in 6 patients. In our patient neutropenia was not affected by anakinra (Table I), consistently with the lack of response of neutropenia in the majority of the patients treated with anakinra (2). This finding supports the hypothesis that bone marrow involvement is not affected by PSTPIP1-mediated inflammation and that its pathogenesis is actually unknown.

In conclusion, these familial cases, despite the persistent haematological involvement, that appear to be the prevalent feature, have a mild autoinflammatory phenotype, without growth failure and without or with minor cutaneous symptoms. These presentations appear in contrast with the patients with a de novo E250K mutation, reported (2, 7). It is possible that familial cases have a milder phenotype of PAMI syndrome (2) confirming that PSTPIP1-associated diseases show variable expressivity. The reason for this variability has not been identified. Multicentre longitudinal studies and the use of registries for autoinflammatory diseases (as EUROFEVER) may help to clarify this issue. It is tempting to speculate that unexplained episode of pyogenic arthritis, with persistence of increased inflammatory markers, may prompt suspicion of PSTPIP1- disease. Serum calprotectin measurement and/or genetic analysis are warranted, depending on local availabilities.

## References


1. SAMPSON B, FAGERHOL MK, SUNDERKOTTER C *et al*.: Hyperzincemia and hypercalprotectinemia: a new disorder of zinc metabolism. *Lancet* 2002; 360: 1742-49.
2. HOLZINGER D, FASSL SK, DE JAGER D *et al*.: Single amino acid charge switch defines clinically distinct proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1)-associated inflammatory diseases. *J Allergy Clin Immunol* 2015; 136: 1337-45.
3. FESSATOU S, FAGERHOL MK, ROTH J *et al*.: Severe anemia and neutropenia associated with hyperzincemia and hypercalprotectinemia. *J Pediatr Hematol Oncol* 2005; 27: 477-80.
4. ISIDOR B, POIGNANT S, CORRADINI N *et al*.: Hyperzincemia and hypercalprotectinemia: unsuccessfull treatment with tacrolimus. *Acta Paediatr* 2009; 98: 410-2.
5. DEMIDOWICH AP, FREEMAN AF, KUHNS DB *et al*.: Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). *Arthritis Rheum* 2012; 64: 2022-7.
6. SUGIURA T, GOTO K, ITO K *et al*.: Effects of cyclosporine A in hyperzincaemia and hypercalprotectinaemia. *Acta Paediatr* 2006; 95: 857-60.
7. LINDWALL E, SINGLA S, DAVIS WE *et al*.: Novel PSTPIP1 gene mutation in a patient with pyogenic arthritis, pyoderma gangreno-

sum and acne (PAPA) syndrome. *Semin Arthritis Rheum* 2015; 45: 91-3.
8. LEE H, PARK SH, KIM SK *et al*.: Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA syndrome) with E250K mutation in CD2BP1 gene treated with the tumor necrosis factor inhibitor adalimumab. *Clin Exp Rheumatol* 2012; 30: 45.
9. SHOHAM NG, CENTOLA M, MANSFIELD E *et al*.: Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci USA* 2003; 100: 13501-6.
10. SMITH EJ, ALLANTAZ F, BENNETT L *et al*.: Clinical, Molecular, and Genetic Characteristics of PAPA Syndrome: A Review. *Curr Genomics* 2010; 11: 519-27.
11. DIERSELHUIS MP, FRENKEL J, WULFFRAAT NM *et al*.: Anakinra for flares of pyogenic arthritis in PAPA syndrome. *Rheumatology* (Oxford) 2005; 44: 406-8.
12. DEMIDOWICH AP, FREEMAN AF, KUHNS DB *et al*.: Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). *Arthritis Rheum* 2012; 64: 2022-7.
13. CAORSI R, PICCO P, BUONCOMPAGNI A *et al*.: Osteolytic lesion in PAPA syndrome responding to anti-interleukin 1 treatment. *J Rheumatol* 2014; 41: 2333-4.