

A Case of Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome Accompanied by Nephrosclerosis, Splenomegaly and Intestinal Lesions

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Abstract

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a rare autosomal dominant autoinflammatory disorder, caused by a missense mutation in the *PSTPIP1* gene. Cutaneous and articular manifestations are characteristic but little is known about organ involvement of this disorder. Here, we describe the case of a patient with PAPA syndrome who was admitted to our hospital for evaluation of proteinuria. He had a history of recurrent abdominal attacks with lesions resembling Crohn's disease. A renal biopsy revealed nephrosclerosis, which was presumed to be due to a long history of systemic inflammation. He also showed marked splenomegaly with pancytopenia. These manifestations should be kept in mind during the follow up of this syndrome.

Keywords: PAPA syndrome; Nephrosclerosis; Splenomegaly; Pancytopenia; Perianal abscess; Crohn's disease; PSTPIP-1

Introduction

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a rare autosomal dominantly inherited autoinflammatory disorder (OMIM ID #604410) caused by a missense mutation in *PSTPIP1*, the gene for proline/serine/threonine phosphatase-interacting protein 1 (PSTPIP-1) [1,2]. Typically, pyogenic sterile arthritis recurs in childhood and is often triggered by minor trauma. These symptoms tend to improve by adolescence, while the skin manifestations, pyoderma gangrenosum and severe cystic acne exacerbate instead [3,4]. The molecular mechanism by which mutation in the *PSTPIP1* causes PAPA syndrome remains uncertain. Interestingly, PSTPIP-1 is shown to interact with pyrin, of which mutations are known to associate with familial Mediterranean fever. It has been suggested that the pyrin is a negative regulator of inflammation, and mutated PSTPIP-1 exhibits increased binding affinity for pyrin to inhibit its anti-inflammatory activity, leading to overproduction of IL-1 β [5]. To the contrary, others have suggested that pyrin is a pro-inflammatory molecule, and according to their hypothesis, binding of the mutated PSTPIP-1 to pyrin increases its activity [6].

Here we describe our clinical experience with a case of PAPA syndrome. Besides the triad of symptoms, the patient presented with organ involvement of nephrosclerosis, marked splenomegaly, and intestinal lesions resembling inflammatory bowel diseases, which misled the physicians into making an incorrect diagnosis. Since organ involvement of PAPA syndrome has scarcely been known, this report will afford a better understanding of this disorder.

Case Report

A 21-year-old Japanese man was admitted to our hospital in August 2011 for evaluation of proteinuria. He had been diagnosed with juvenile idiopathic arthritis (JIA) and Crohn's disease for a long time, but his arthritis was not typical of JIA, or Crohn's disease was not histologically proven. During careful reconsideration, his pathognomonic clinical course reminded us of PAPA syndrome, which was then genetically proven by a finding of a mutation in *PSTPIP1* (c.748G>A, leading to

E250K in exon 11). This case was considered to be sporadic because the mutation was not found in other members of his family.

In retrospect, the patient had a history of frequent febrile attacks, splenomegaly, and elevated levels of C-reactive protein (CRP) since the age of 9 months. He had experienced recurrent pyogenic arthritis mostly in the elbows or knees since the age of 6 years. Cultures of the synovial fluid had been negative and prednisolone (PSL) 5-30 mg daily was given, which was effective but unable to bring about sustained remission. His arthritis gradually ameliorated with age, while he developed painful cystic acne on the face which often required incision and drainage of the abscess (Figure 1), and occasionally developed pyoderma gangrenosum around the neck and the lower extremities since the age of 15 years. In addition, he developed frequent abdominal pain and diarrhea. Colonoscopy revealed small multiple colon ulcers, ileocecal stenosis, and perianal abscesses, which resemble the findings of Crohn's disease, but pathological examination of the biopsy specimen revealed no granuloma. There were no findings suggesting amyloidosis or tuberculosis. He also developed proteinuria since the age of 14 years.

On admission, hematological values were as follows: hemoglobin 10.2 g/dL, WBC 4,000/ μ L, and platelet count 14.3 \times 10⁴/ μ L. Blood chemistry revealed normal creatinine and transaminases, increased uric acid of 8.8 mg/dL and an increased lactate dehydrogenase of 912 IU/L. CRP was 3.64 mg/dL. Urine test showed proteinuria of 0.9 g/day, but the sediment did not contain increased cells or casts. X-ray revealed marked splenomegaly, which was confirmed by CT scan (Figure 2). A

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Received August 24, 2013; **Accepted** September 20, 2013; **Published** September 29, 2013

Citation: Yamamoto A, Morio T, Kumaki E, Yamazaki H, Iwai H, et al. (2013) A Case of Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome Accompanied by Nephrosclerosis, Splenomegaly and Intestinal Lesions. J Genet Syndr Gene Ther 4: 183. doi:10.4172/2157-7412.1000183

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renal biopsy was performed which revealed focal segmental glomerular sclerosis accompanied by arteriosclerotic lesions (Figure 3). There were no findings suggesting glomerulonephritis or amyloidosis. We did not find arteriosclerosis in the larger vessels by abdominal CT scan or carotid duplex.

Treatment for this patient has remained challenging. Prior to the visit to our hospital, he had been given methotrexate which had to be stopped because of methotrexate related diarrhea. Infliximab caused an anaphylactic reaction. After the current admission, adalimumab 40 mg biweekly was commenced which resulted in decreased serum CRP levels from 3.64 mg/dL to 1.78 mg/dL, but skin lesions did not improve. Dose increase to 80 mg biweekly was not tolerated because of symptoms of fatigue and weakness. Subsequently, he had a trial of anakinra (100 mg daily) without significant benefit, and it was discontinued because of severe injection site reactions. Colchicine was not effective. Dramatic improvement of his acne was observed only after treatment with diaphenylsulfone (75 mg daily), but it caused severe neutropenia which required a hospitalization. In all, his skin manifestations remain poorly controlled with 10-15 mg daily of PSL. Currently in 2013, the patient is exhibiting slowly progressive pancytopenia (hemoglobin 7.5 g/dL, WBC 2,200 / μ L and platelet 7.3×10^4 / μ L) supposedly due to the splenomegaly, accompanied with hyperuricemia (11.3 mg/dL).

Discussion

Prominent clinical features of PAPA syndrome include recurrent pyogenic sterile arthritis, pyoderma gangrenosum and severe cystic acne, but only limited information is available regarding the organ involvement. In addition to the above triad, the current case had nephrosclerosis, splenomegaly and intestinal lesions. In literature, occurrence of proteinuria is occasionally noted [1,3], but details remain unknown because of lack of histological data. Renal biopsy of this patient revealed nephrosclerosis, resembling hypertensive nephrosclerosis usually observed in senior patients. He has no risk factors for



Figure 1: Cystic acne accompanying erythema.

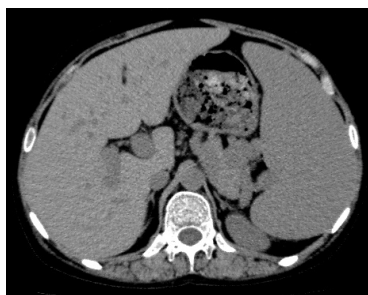


Figure 2: Splenomegaly detected by computed tomography.

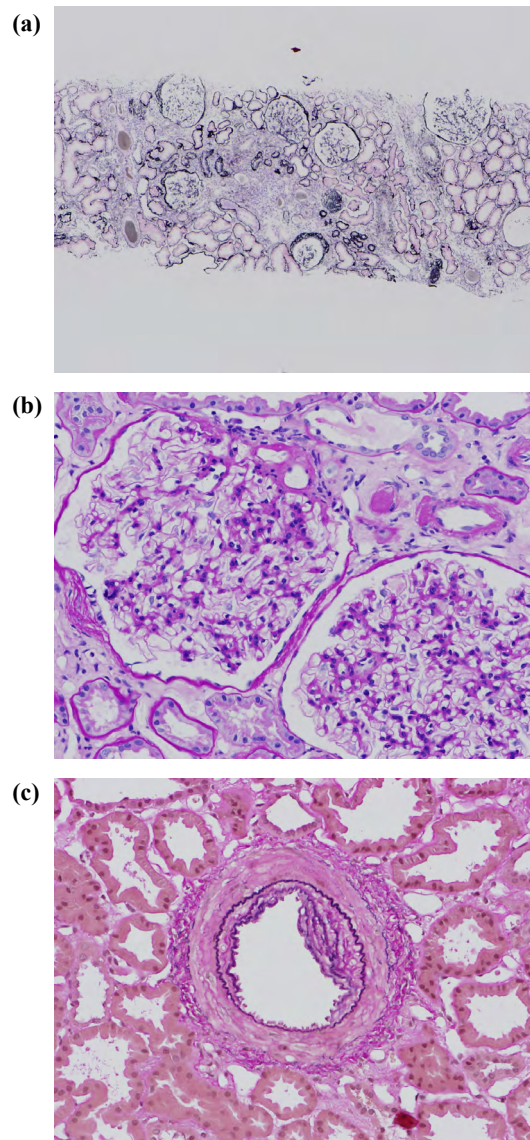


Figure 3: Pathological findings of a renal biopsy: a. Fifteen out of 30 glomeruli were collapsed and indurated (PAM $\times 40$). b. There was no evidence of glomerulonephritis such as endocapillary proliferation, mesangial cell proliferation, crescent formation, or thickening of the basement membrane. Proliferation of mesangial matrix was only partially detected (PAS $\times 200$). c. Arteriole was hyalinized (Elastica van Gieson $\times 200$).

arteriosclerosis such as hypertension, hyperlipidemia, diabetes mellitus or smoking, and we therefore presume that the nephrosclerosis in this case has resulted from persistent systemic inflammation. Analogous to this speculation, in a study of renal findings in rheumatoid arthritis (RA), in which 132 necropsied patients between 1958 and 1984 with the median age of 65 years were included, benign nephrosclerosis was found in 90 % of the patients [7]. Severity of the nephrosclerosis was positively related to the duration of RA, suggesting a possibility that RA or therapy is an additional factor in the etiology of nephrosclerosis.

To our knowledge, this is the first report showing the intestinal lesions in PAPA syndrome, which was similar to Crohn's disease. It is noteworthy, however, that pyoderma gangrenosum is often associated with systemic inflammatory diseases including ulcerative colitis and

Crohn's disease [8], suggesting that common mechanisms underlie between the cutaneous and intestinal manifestations of these disorders.

As for the splenomegaly, a recent report described a case of PAPA syndrome presenting with cervical lymphadenopathy and splenomegaly with thrombocytopenia and hemolytic anemia that developed at the age of 6 months [4]. Later, the patient's platelet count was described to normalize. She also had an E250K mutation, but it is unclear whether common pathological mechanisms are involved in the splenomegaly of this case and the present case.

A standard treatment strategy for PAPA syndrome has not been established. Corticosteroids are beneficial for arthritis but less effective for skin lesions [9]. Biological agents targeting IL-1 β or TNF- α have been used, but the responses vary [3,4,10-15]. One of the reasons for the difficulty in medical management of PAPA syndrome may be ascribed to frequently observe adverse reactions. Further research is imperative to elucidate the pathophysiology of PAPA syndrome and establish a standard therapeutic strategy

Conflicts of Interest

H.K. has served as a consultant to Chugai Pharmaceutical and has received research grants from Eisai Pharmaceutical and Takeda Pharmaceutical. N.M. has received research grant from Abbott, Astellas Pharmaceutical, Chugai Pharmaceutical, Daiichi Sankyo Pharmaceutical, Eisai Pharmaceutical, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical and Teijin Pharmaceutical. All other authors have declared no conflicts of interest.

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This article was originally published in a special issue, **Genetic Disorders** handled by Editor(s). Dr. Xiaobo Li, Yeshiva University, USA