Letters to the Editors

Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA syndrome) with E250K mutation in CD2BP1 gene treated with the tumour necrosis factor inhibitor adalimumab

Sirs,

PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, and acne) is an autosomal dominant auto-inflammatory disease of early onset, primarily affecting the skin and joints. Two missense mutations, A230T or E250Q variant in the CD2-binding protein 1 (CD2BP1) gene on chromosome 15, are well-known to cause PAPA syndrome (1). And two additional missense mutations, E250K or D260N variant was registered recently (2). We herein report our experience treated with tumour necrosis factor-α (TNF-α) inhibitor, adalimumab, in a patient with PAPA syndrome with E250K gene mutation.

A 26-year-old man was referred for multiple papulopustular lesions on the face, leg ulcers and numerous ulcer scars on his back and legs. Painful swelling on left elbow joint was developed at 1 year old. At that time, he was diagnosed with septic arthritis and underwent surgical debridement. His left knee became swollen and painful at the age of 3 and then managed with surgical intervention. And the next year, arthritis at right knee was treated with intra-articular steroid injection. At 13 years of age, he developed pyoderma gangrenosum and multiple ulcerations on the cheek, back and both legs. In the subsequent years, pyoderma gangrenosum on the leg and cystic acne on the face recurred. He received oral steroids and some immunosuppressants such as cyclosporine. During last few months, cystic acne and pyoderma gangrenosum on leg and back were aggravated. Laboratory tests in our clinic including rheumatoid factor, antinuclear antibodies, erythrocyte sedimentation rate, C-reactive protein, IgG (immunoglobulin G), IgA, and IgM were unremarkable. These findings suggested that he had PAPA syndrome. Gene screening for CD2BP1 gene mutation revealed the patient and his mother had E250K mutation, a G-to-A transversion at the 748th nucleotide at exon 11. Serum interleukin-1β (IL-1β) and TNF-α levels were unremarkable.

Treatment was started with oral prednisolone (40 mg/day) and isotretinoin. When we tapered prednisone to 20mg/day after 1 month of treatment, pyoderma gangrenosum and acne aggravated. We started the adalimumab (40 mg semi-weekly, administered subcutaneously). After 4 months of adalimumab treatment, we could taper the methylprednisolone dosage to 6 mg per day and the pyoderma gangrenosum on the left leg and cystic acne became well controlled.

Our case showed an E250K variant, a G-to-A transition in the 748th nucleotide of exon 11 in CD2BP1 gene. This missense mutation has been registered within the INFEVERS database by Ivona Aksentijevich at 2007 as functional mutation (2). The same mutation was detected in the patient's mother, but his mother did not develop manifestations of the PAPA syndrome. She complains of non-specific symptoms, such as chronic fatigue and intermittent arthralgia and myalgia, but has never experienced cystic acne or pyogenic arthritis.

In most cases, oral glucocorticoid or intra-articular steroid injection are used for pyogenic arthritis and pyoderma gangrenosum associated with PAPA syndrome. Recently elucidation of pathogenesis induces the development of more effective treatment. Enhanced expression of TNF-α and IL-1β in peripheral blood leukocytes is a characteristic in PAPA syndrome (3). Targeting therapy against these inflammatory cytokines may lead to reduce symptoms and signs presented in PAPA syndrome. Anakinra, an IL-1 receptor antagonist, was prescribed in pyoderma gangrenosum and arthritis with PAPA patients and effectively improved skin lesion and arthritis flares (4). Etanercept, a recombinant soluble TNF receptor II/Fc fusion protein, was also used in PAPA syndrome patients and had a positive effect in some cases (3). On the other hand, Stichweh *et al*. used etanercept and anakinra for pyoderma gangrenosum in PAPA patients, but neither had a favourable response. Then they switched to infliximab and pyoderma gangrenosum was immediately improved (5). Our patient has received adalimumab continuously for 12 months with no disease flare, suggesting that adalimumab can be considered as an alternative treatment option for PAPA syndrome

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Table I. Summary of CD2BP1 gene mutation, clinical features and treatment of reported PAPA syndrome cases.

Authors	Study population	Gene mutation of CD2BP1	Unusual clinical manifestation	Effective treatment
Lindor *et al*. (6)	United States	A230T		Prednisone (60 mg daily) Azathioprine(100 mg daily)
Wise *et al*. (7)	United States	E250Q		Corticosteroid
Edrees *et al*. (8)	United States	CD2BP1, unspecified	Hypogammaglobulinaemia, high TNF-α serum level	IV gammaglobulin (400 mg/kg) Oral Accutane
Cortis *et al*. (3)	Italy	A230T	IDDM	Prednisone (2 mg/kg daily) Etanercept (25 mg/dose twice weekly)
Tallon *et al*. (9)	New Zealand	E250Q	Psoriasis, idiopathic hepatitis, testicular abnormality, learning impairment, Uveitis	Corticosteroid, Sulphasalazine, Leflunomide
Brenner *et al*. (4)	Germany	A230T		Anakinra (100 mg daily subcutaneously)
Hong *et al*. (10)	Taiwan	no chromosomal mutation		Prednisolone (60 mg daily -> tapered) Dapsone (200 mg/day) Oral isotretinoin (0.3–0.5 mg/kg/day)
Stichweh *et al*. (5)	United States	E250Q		Infliximab
Present case	Korea	E250K	Depressive mood disorder	Methylprednisone (40mg -> tapered to 6 mg) Oral isotretinoin Adalimumab