Concurrence of Incontinentia Pigmenti and Behçet’s Disease

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We report here a rare case of incontinentia pigmenti (IP) in a 10-year-old girl who developed Behçet’s disease. IP was diagnosed in infancy and Behçet’s disease was diagnosed at 10 years of age. The initial presentations of Behçet’s disease were spiking fever and recurrent painful oral and genital ulcers that were refractory to antibiotics. After corticosteroid treatment, her fever subsided and ulcers subsequently healed. The patient’s mother and sister were also diagnosed with IP. Her mother had suffered from Behçet’s disease since her teenage years and it was complicated with colon perforation. Although there are several reports on the combination of IP and Behçet’s disease, this is the first reported case of a family with such concurrence. [J Chin Med Assoc 2010;73(5):275–278]

Key Words: Behçet’s disease, family, incontinentia pigmenti

Introduction

Incontinentia pigmenti (IP) is a rare X-linked dominantly inherited genodermatosis that is usually lethal during the prenatal stage for males. In affected females, it causes abnormalities in skin, nails, teeth, hair, eyes, and the central nervous system.1 The pathogenesis of IP has been identified in mutations of the NEMO/IKKγ (nuclear factor κB essential modulator/inhibitor κB kinase, γ subunit) gene.2

Behçet’s disease is a systemic vasculitis with unknown etiology, characterized by relapsing episodes of oral ulcers, genital ulcers, skin lesions, and ocular lesions. It is believed that an autoimmune process and a human leukocyte antigen (HLA)-B51 are the most strongly associated risk factors.3

There have been 2 case reports of IP concurrent with Behçet’s disease.4,5 However, these reports were of sporadic cases, and there was no familial concurrence of the 2 diseases. To the best of our knowledge, our report is the first to delineate the concurrence of these 2 diseases in a family. We describe the clinical features, immunological status, and treatment modalities. In addition, the relationship between IP and Behçet’s disease is discussed.

Case Report

A 10-year-old girl presented with recurrent painful oral ulcers. She had swirled and linear hyperpigmented lesions over her entire body (Figure 1) that first appeared in infancy, and IP had been previously diagnosed according to the criteria suggested by Landy and Donnai in 1993.6 The patient’s mother was also a case of IP—typical skin manifestations, proved by skin biopsy, and anomalous dentition. Since the age of 7 years, the patient had suffered from recurrent oral ulcers with dysphagia followed, at the age of 8 years, by recurrent urethral ulcers. The ulcers were resistant to oral antibiotics. She was admitted to our hospital at the age of 10 years after experiencing oral ulcers, difficulty swallowing and intermittent fever for several days. She had no history of eye, skeleton, or intelligence impairment. A review of her medical history revealed 4 episodes of pneumonia since the age of 4 months and 1 episode of cellulitis over her left cheek at the age of 10 years. No specific pathogens were identified in these episodes. The family history (Figure 2) revealed that her sister and mother had been diagnosed with IP during childhood. Other family members denied any history of
IP, Behçet’s disease, autoimmune disease or immunodeficiency. The patient’s mother was also diagnosed with Behçet’s disease with the initial presentations of recurrent oral and genital ulcers in her teenage years. At the age of 45 years, the patient’s mother suffered from colon ulcerations complicated with massive bleeding and underwent subtotal colectomy. In addition, the patient’s nephew, who had suffered from recurrent bacteremia from the age of 1 month, was diagnosed with immunodeficiency characterized by hypogammaglobulinemia. He is currently 1 year old and is receiving prophylactic antibiotics and monthly intravenous immunoglobulin treatment.

Physical examination of our patient showed stable vital signs and clear consciousness. Her body weight and body height were both below the 3rd percentile. Multiple small ulcers over the posterior pharyngeal wall and 1 deep ulcer of 2 cm in size over the oropharynx were observed. Scar formation over a previous bacille Calmette-Guérin vaccination site was present. Some scar formation over the genital organs without obvious active genital ulcers was observed at this time. There were brownish hyperpigmented lesions in a linear and swirled pattern on the patient’s trunk and extremities. Some acne-like papules over her face were also noted. Ophthalmologic and neurological examinations showed no abnormalities. A dental X-ray showed congenital missing teeth: 1 lower lateral and 2 upper lateral incisors. The skin pathergy reaction was negative.

The patient had leukocytosis (white blood cell count, 18,700/mm³; neutrophils/lymphocytes, 82.5%/12.7%), slightly hypochromic microcytic anemia, and thrombocytosis (610 × 10³/mm³). The results of urinalysis showed that microscopic hematuria (5–10 red blood cells/high-powered field) and blood chemistry were within normal limits. Immunological study showed high serum C-reactive protein (CRP, 15 mg/dL) and erythrocyte sedimentation rate (ESR, 114 mm/hr). Levels of serum immunoglobulin (Ig)G (2,350 mg/dL), IgA (679 mg/dL), and IgM (175 mg/dL) were elevated. The titer for antinuclear antibodies was 1:40 (fine speckled type) while the serum complement (C3, 174 mg/dL; C4, 32.1 mg/dL) and double-stranded DNA antibody level (21.6 WHO units/mL) were both within normal limits. Flow cytometry values for the lymphocyte subpopulation were as follows: CD3, 52% (normal range, 52–78%); CD4/CD8 ratio, 0.97 (normal range, 0.9–3.4); CD19, 9% (normal range, 8–24%); and CD56, 35% (normal range, 6–27%). The patient’s HLAs were HLA-A*1001, HLA-B*1301, 4601 and HLA-Cw*0102,0304.

The diagnosis of Behçet’s disease was made on the basis of recurrent genital ulcers, oral aphthosis, and acne-like skin lesions. Treatment with colchicine 0.15 mg twice daily was administrated initially, but the fever persisted and there was no ulcer healing. The fever subsided 2 days after administration of prednisolone 10 mg twice daily and scar formation over the oral ulcers developed in the following days. The patient is currently receiving prednisolone 10 mg daily and the dosage will be increased if the ulcers recur. The ESR was approximately 20–50 mm/hr, and there were no
fever episodes or genital ulcers after corticosteroid administration.

Discussion

We have described the concurrence of IP and Behçet’s disease in 2 members of a family. To the best of our knowledge, this phenomenon has never been reported in the literature. Interestingly, Behçet’s disease in both cases had pediatric onset, which accounts for only 5.4% of all Behçet’s disease cases.7

The patient’s mother was a sporadic IP patient and, unfortunately, a genetic predisposition for this disease appears to have been passed on to her daughters. Males from IP mothers in this family were miscarried or presented with immunodeficiency. IP results from mutations in the NEMO gene; however, only males who carry less deleterious mutations can survive.8

There is accumulating evidence that IP might be accompanied by functional and/or structural abnormalities of the immune system. Defects in leukocyte chemotaxis, lymphocyte defects, and defective immune tolerance have been reported in association with IP.9

The underlying cause of Behçet’s disease is unknown. There are many reports about the involvement of the immune system in Behçet’s disease, including leukocytosis, elevated CRP, ESR and high levels of IgG, IgA and IgM.3 In addition, there is an increase in T-cell subsets including CD8 and CD56 in Behçet’s disease.10,11 HLA-B*51 is a strong risk factor and is associated with excessive action of neutrophils in Behçet’s disease.12 The expression of HLA-B*51 and HLA-A*2 is high in familial Behçet’s disease.13

The immunological status of our patient was evaluated. Scar formation over the bacille Calmette-Guérin site indicated intact T-cell function. A pathergy test was negative in our case, although it is common in some populations.14 The laboratory findings including neutrophilia, hypergammaglobulinemia, elevated CRP, ESR and an increase in the proportion of CD8+, and CD56+ T-cells were consistent with previous immunological phenotypes of Behçet’s disease. Both HLA-B*51 and HLA-A*2, which are reported to be associated with familial Behçet’s disease, were negative in our patient.

The diagnosis of Behçet’s disease is based on clinical manifestations, and the criteria of the International Study Group for Behçet’s Disease are most widely used.15 Various sets of diagnostic criteria are currently in use, but none of them have been validated. According to the International Study Group criteria, the diagnosis of Behçet’s disease is made on the basis of recurrent oral ulcers plus 2 of the following clinical manifestations: recurrent genital ulcers, eye lesions, skin lesions, and a positive pathergy test. If only 1 of the criterion is present along with oral ulcerations, the term “incomplete Behçet’s disease” is applied. Diagnosis of pediatric Behçet’s disease is even more difficult because some manifestations, such as acne-like skin lesions, may be present only after adolescence. A large review of pediatric Behçet’s disease showed that only 25% were the complete type, whereas 75% were the incomplete type.16 It appears that the pathergy test is not suitable for the diagnosis of pediatric Behçet’s disease because only 17.5% of pediatric Behçet’s disease cases have a positive pathergy test.16 Uveitis is uncommon in pediatric Behçet’s disease. The mean age at the time of uveitis onset is 30.8 years with a male predominance.17 However, once uveitis has occurred in Behçet’s disease, the final visual acuity is worse than that in other forms of uveitis.18

The pathogenesis of IP results from NEMO gene mutations, but there is no evidence of the involvement of the IkB kinase pathway in Behçet’s disease. There are only 2 case reports of Behçet’s disease in IP patients. There does not appear to be any relationship between the pathogenesis of these 2 diseases based on previous data. However, Ammann et al reported an association of IP in 2 of 6 children with Behçet’s disease.19 In the present report, the patient and her mother were both diagnosed with concurrence of IP and Behçet’s disease. Genetic anticipation may play a role in pediatric or familial Behçet’s disease.20 Impaired neutrophil chemotaxis has been proposed as a common pathogenesis in the 2 diseases.4 Since there are few data regarding a common pathogenesis in these 2 diseases, we investigated possible associations between IP and Behçet’s disease. Further studies on a possible pathogenetic link between Behçet’s disease and IP are now required to clarify their association.

References