

Coexistence of Behçet's disease with ankylosing spondylitis and familial Mediterranean fever: a rare occurrence

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Abstract

Behçet's disease (BD) and familial Mediterranean fever (FMF), which are two separate diseases sharing some clinical features, may also coexist in the same patient. Further investigations are needed to understand whether this coexistence is due to either chance or geographical distribution patterns of these diseases or to common etiopathogenetic characteristics. Spondylarthritis as part of the clinical picture in these two diseases has been questioned and probably it is not a prominent characteristic of any of them. We report a 35-year-old Tunisian man who had an association of BD, FMF and Human Leukocyte Antigen (HLA) B27 positive ankylosing spondylitis. Although that spondylarthritis is an infrequent joint involvement of FMF and BD, it must be looked for in case of association of these diseases.

Introduction

Behçet's disease (BD) is an inflammatory disease of unknown cause, characterized by a waxing and waning course in which oral and genital ulcers, skin lesions, uveitis, obstructive vasculopathy and other inflammatory manifestations may flare up and then ameliorate.¹ Familial Mediterranean fever (FMF) is an autosomal recessive systemic autoinflammatory disease presenting episodic attacks of fever, accompanied by abdominal, chest, or joint pain and the gradual development of nephropathic amyloidosis of the AA type.² Spondylarthritis as part of the clinical picture in these two diseases has been questioned and probably it is not a prominent characteristic of any of them.^{3,4} The following patient had both BD and FMF, and Human Leukocyte Antigen (HLA) B27 positive ankylosing spondylitis.

Case Report

A 35-year-old Tunisian man was referred to our hospital with sudden onset of severe abdominal pain and fever. He had hip and back pain for 10 years and until the last 4 years he didn't notice any physical impairment. He had accepted his pain as the result of his heavy work. During the previous 2 years he had noticed oral ulcers recurring with a frequency of about once a month, which would disappear in 4-7 days. Genital ulcers recurred one year later, resolving with scar tissue. The patient had a thrombosis of the left popliteal vein six months ago. A pathergy skin test was positive. The patient was thus diagnosed with BD. His ocular examinations were repeatedly normal. He had protracted bouts of abdominal pain irregularly recurring three at five times in a year and spontaneously resolving for at least 15 years. The abdominal pains continue for 2-3 days and it was accompanied with feverish chills. He denied any thoracic pain and only mild arthralgia of the ankles. His oral and genital ulcers did not show any temporal relation with his painful attacks. A younger sister had similar complaints of abdominal pain with fever of about 38°C since the age of 22 years. She denied low back pain, arthralgia or orogenital ulcers.

On physical examination, the patient had generalized abdominal tenderness with rebound, two scrotal scars of old ulcers and fever of 38°. Bowel sounds were diminished but audible. The patient had a serious kyphotic posture and severe restriction of the spine in all planes. His hip joints were also bilaterally severely restricted.

Positive laboratory findings were as follows: leukocytes count $10.6 \times 10^9/L$, erythrocyte sedimentation rate 64 mm/h, C-reactive protein 23 mg/L, fibrinogen 5.1 g/L. Tissue typing showed the presence of HLA-B27 antigen, HLA-B51 typing was negative. A radiological examination showed characteristic features of ankylosing spondylitis both in cervical and lumbar region of spine and bilateral sacroiliac ankylosis with mild bilateral coxofemoral joint involvement. Abdominal ultrasonography and upper gastrointestinal endoscopic study were normal. Polymerase chain reaction demonstrated a homozygote E148Q mutation in the MEFV gene. Colchicine 1 mg/day and Salazopyrine 2 g/day were started. The patient has experienced only two attacks of abdominal pain and fever during the follow-up period of 5 years.

Discussion

Our patient was diagnosed as having a complete form of BD⁵ based on recurrent oral and

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genital aphthosis, and positive pathergy skin test, and venous thrombosis. Nevertheless, the patient has since shown periodic fever with recurrent abdominal pain due to peritonitis, which is an atypical symptom in BD, and DNA analysis demonstrated a homozygous mutation in the MEFV gene, leading to a diagnosis of FMF.⁶

In spite of the distinct clinical features between BD and FMF, they share several common characteristics. First, both diseases are chronic relapsing inflammatory disorders caused by abnormal neutrophil activation.^{7,8} The gene responsible for FMF, MEFV, is located on chromosome 16p13.3 and consists of 10 exons and 781 codons. The product of the MEFV gene, named pyrin/marenostrin, is expressed in neutrophils, monocytes, dendritic cells, and synovial fibroblasts. Pyrin is cleaved by caspase-1 and the cleaved N-terminal fragment translocates to nucleus and enhances ASC-independent nuclear factor (NF)- κ B activation through interactions with p65 NF- κ B and I κ B- α , leading to enhanced inflammatory responses.⁷ Neutrophils also play an important role in the development of BD;^{1,8} they are found in the lesions of BD patients without evidence of bacterial infection. Cytokines and chemokines secreted from antigen presenting cells and T cells are suggested to cause neutrophil hyperactivation. Activated neutrophils secrete some cytokines which prime themselves and also stimulate Th1 cells. Among other functions of the neutrophil, is the generation of reactive oxygen species.⁸ Therefore, the abnormal neutrophils can be therapeutic

targets for BD and FMF. Colchicine is used as the first line therapy for both diseases, because the agent suppresses neutrophil motility and chemotaxis through inhibiting microtubule functions.⁹

Authors have noted two elements acting upon the presence of both diseases, one is geographic and the other is ethnic.^{2,9} As matter of fact, individuals of Sephardic Jewish, Armenian, Turkish, and Arab descent are more likely to be affected by FMF² whereas people living along the ancient Silk Road, which extends from the Mediterranean to eastern Asia, reveal take much more subjects to BD than in the other areas. Such incredible predominance of the disease is also related with HLA-B51 which is almost present in 60 to 70% of BD patients from the previous mentioned areas,⁹ the frequency of HLA-B51 in Tunisian patient with BD was 30%.¹⁰ Besides, many non-HLA genes along with environmental factors contribute to the increasing risk of the disease. Some researches have revealed that MEFV gene is one of vulnerable genes which are liable to yield BD, mainly for patients with vascular involvement, in France¹¹ and Turkey¹² and Israel,¹³ where BD and FMF are prevalent. Coexistence of both diseases is not common even in the Mediterranean countries.¹⁴

Although Tunisia is one of the countries where BD and FMF and ankylosing spondylarthritis are prevalent.^{10,15,16} our case report is the first observation of coexistence of these diseases. Chance occurrence of these two rare diseases in the same patient, who also has HLA-B27 positive ankylosing spondylitis, had not been reported. To the best of our knowledge, there is only a unique case report of association of BD, FMF and HLA-B27 negative bilateral sacroiliitis.¹⁷

Widely differing frequency of sacroiliitis and ankylosing spondylitis have been found in different series of patients with BD. Some investigators³ have reported an increased prevalence of sacroiliitis and ankylosing spondylitis in patients with BD, but others⁴ have declared prevalence similar to that of the general population. The reasons for these different results are probably because of high observer variability in reading anteroposterior radiographs of the sacroiliac joints,⁴ and different origins of series of BD as well as different diagnostic criteria used.^{1,5}

Spondylarthritis is an infrequent form of joint involvement in FMF. Over the years, few

cases of FMF with seronegative spondylarthritis have been reported,¹⁸ While the most of published cases with spondylarthritis in FMF are also HLA-B27 negative and have no radiological lumbar spine involvement,¹⁸ a recent study suggests that HLA-B27 positivity may play a role in the development of sacroiliitis and the severity of seronegative spondylarthropathy.¹⁹

In conclusion, we report an unusual observation of coexistence of BD and FMF and HLA-B27 ankylosing spondylitis. Although this coexistence may be due to either chance or geographical distribution patterns of these diseases, common etiopathogenetic characteristics of BD and FMF are identified. The spondylarthritis is a possible form of joint involvement in both FMF and BD. Thus, in clinical practice, we propose to look for ankylosing spondylitis in case of association of these diseases.

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