Complete manifestations of Behçet's disease

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Behçet's disease (BD) is a chronic, relapsing, inflammatory disease characterized by recurrent oral aphthae and any of several systemic manifestations that include genital aphthae, ocular disease, skin lesions, neurologic disease, vascular disease, or arthritis. Hippocrates may had described BD in the fifth century B.C.; however, the first official description of the syndrome was attributed to the Turkish dermatologist Hulusi Behçet in 1924. In 1930, the Greek physician Adamantiades reported a patient with inflammatory arthritis, oral and genital ulcers, phlebitis, and iritis.[1] Since then, the syndrome has been referred to as BD.[1,2]

The manifestations of BD are thought to be caused by an underlying vasculitis. Although this disease is recognized worldwide, the prevalence is highest in the eastern Mediterranean, the Middle Eastern, and East Asian countries, thus the nickname Silk Road disease. The disease tends to be more severe in areas where it is more common. Prevalence rates all over the world are increasing, probably because of improved recognition and reporting. Behçet's disease occurs primarily in young adults. The mean age at onset is between 25 and 30 years. The incidence of disease in males and females is approximately equal along the Silk Road, but in Japan, Korea, and Western countries the disease occurs more frequently in women. Case confirmation can be challenging because many patients labeled as having BD have oral ulcers as the primary or sole manifestation.[3]

CASE REPORT

A 35-year-old man was referred to the Division of Rheumatology by the Department of Dermato-Venereology with chief complaint of having pain in his ankle for 3 days. The pain had worsen with activity and caused difficulty in walking or moving the ankle. There was no fever, swelling, or any history of trauma. During physical examination, we found tenderness of achilles tendon without any other sign of inflammation. There was also history of pain and stiffness in his shoulder and knee 2 weeks prior, but those symptoms had disappeared without treatment.

Five years prior to admission, the patient started to develop painful and irritating multiple oral ulcers. This symptom persisted despite treatments given by general practitioners and dentist, and continued for years without improvement (figure 1).

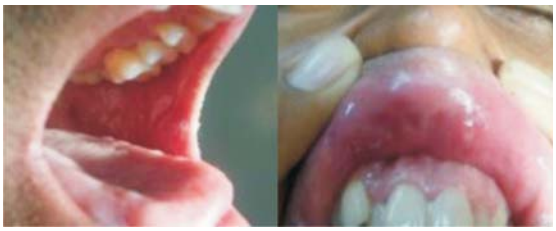

Figure 1 Multiple oral ulcers.

One year prior to admission, the patient had multiple ulcers on his genitalia. The lesions were located in the glans and ventral part of penis, scrotum, and inguinal (figure 2). There was no history of multiple sex partners or previous sexually transmitted disease. He was subsequently referred to the Department of Dermato-Venereology.

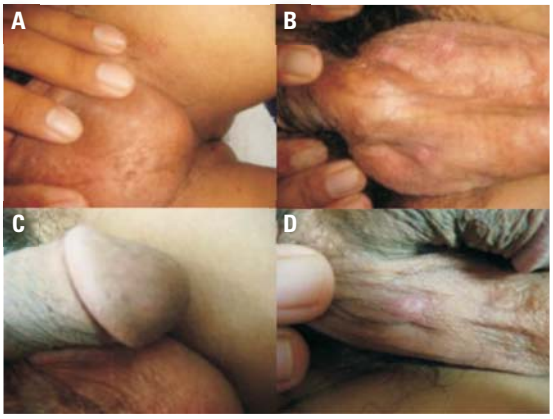

Figure 2 Genital ulcers: (A) scrotum and inguinal; (B) scrotum; (C) glans penis; (D) ventral part of penis.

At the same time, the patient also complained of having skin lesions in the form of red acne-like papules. These lesions were found on his chest (anterior and posterior), face, and neck (figure 3). The dermatologist performed some laboratory investigation and administer topical ointment and methylprednisolone 24 mg a day for a week. After a few months of therapy, the skin and genital lesions disappeared, but the oral lesions persisted.

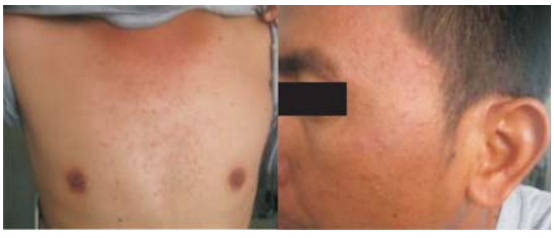

Figure 3 Acneiform lesions on chest and face.

Two weeks prior to admission, the patient complained of blurred vision of his right eye. There was history of redness, but there was neither pain nor discharge from the eye. The Department of Ophthalmology then confirmed that the patient had panuveitis of the right eye.

Routine laboratory investigation only revealed leukocytosis ($14.55 \times 10^3/mm^3$). The X-ray of the pelvis and foot were normal. The investigation of C-reactive protein was 51 mg/L, antinuclear antibodies was positive with titer of 1/100 and a speckled pattern, anti–double-stranded DNA was negative, and complement component (C)3 and C4 were within normal limit. We also performed the examination of antibody for some viruses and parasites infection like herpes simplex virus (HSV), cytomegalovirus (CMV), and *Treponema pallidum*. We found positivity of IgM of HSV II and IgG of anti-CMV. The rapid test for human immunodeficiency virus of this patient was negative.

We gave the patient high dose of steroid at the beginning of therapy: methylprednysolone at 1 mg/kg bodyweight for 2 weeks and then tapered it down. The patient also received topical corticosteroid as the treatment for his eye. After 2 weeks of treatment, the symptoms of blurred vision did not show any improvement, but the arthralgia had diminished. An additional treatment with acyclovir for 1 week were also administered, but with no effect on his symptoms. We then made the decision to give the patient azathioprine with a dose of 50 mg to 150 mg. His symptoms improved, and he reported 80% recovery of his vision. The patient was then confirmed to have attained remission from the disease.

DISCUSSION

The common clinical feature in patients with BD is the presence of recurrent and usually painful mucocutaneous ulcers.[4] Aphthous oral ulcers is usually the first and most persistent clinical feature of BD. Lesions occur in crops and some patients may have them during most of the course of the disease. Aphthae occur as ulcers that are 2 to 12 mm or larger. These are discrete, painful, round or oval red-rimmed lesions that affect mainly the nonkeratinized mucosa of the cheeks, the border of the tongue, the soft palate, and the pharynx. Genital ulcers resemble oral aphthae but occur less frequently. They occur as single or multiple lesions of the vulva and in the vagina, or on the scrotum or penile shaft. Skin lesions are also common in BD.[3]

Oral aphthae are present in almost all patients with Behçet's, and the differential diagnosis of recurrent oral ulcers includes herpes simplex, benign aphthous ulcers, inflammatory bowel disease, Stevens-Johnson syndrome, and other systemic rheumatic diseases such as systemic lupus erythematosus. Herpes can be ruled out with culture or Tzanck preparation. Dental prosthetics and oral hygiene products can cause oral irritation and ulceration. Medications such as methotrexate can cause oral ulcers. Other causes of oral ulcers or stomatitis include pemphigoid, pemphigus vulgaris, cicatricial pemphigoid, lichen planus, and linear IgA disease.[5]

Many other disorders may be associated with the presence of small vessel cutaneous vasculitis, inflammatory eye disease, neurologic disease, vascular disease, arthritis, or unexplained systemic illness. These include systemic lupus erythematosus, inflammatory bowel disease, sarcoidosis, reactive arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile arthritis, familial Mediterranean fever and other periodic febrile syndromes, other vasculitides, multiple sclerosis, systemic infections such as tuberculosis, human immunodeficiency virus, syphilis, and malignancies.[5] Based on history, physical examination, and laboratory investigations of serum antibody for some viruses, we can rule out the other differential diagnosis and conclude that this patient have the manifestations of BD. The International Study Group criteria for the diagnosis of BD are shown in table 1.

Table 1 International Study Group criteria for Behçet's disease[3]

Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month period
Plus 2 of:	
Recurrent genital ulceration	Aphthous ulceration or scarring, ulceration observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by physician in postadolescent patients not receiving corticosteroid treatment
Positive pathergy test	Read by physician at 24 to 48 hours

Cutaneous lesions occur in over 75 percent of patients with BD. The skin manifestations vary and may include acneiform lesions, papulo-vesiculo-pustular eruptions, nodules, erythema nodosum (septal panniculitis), superficial thrombophlebitis, pyoderma gangrenosum-type lesions, erythema multiforme-like lesions, and palpable purpura. Biopsy of erythema nodosum lesions reveal a septal panniculitis, with medium vessel vasculitis in up to half of lesions.[6] The skin lesion of this patient were acneiform. Unfortunately, we did not performed skin biopsy because this patient have already received steroid treatment.

Acneiform lesions may be more common in those with associated arthritis.[7,8] This is comparable with the symptoms of arthralgia of this patient which came at the same time as skin lesion. An intermittent, symmetric oligoarthritis of the knees, ankles, hands, or wrists affects one half of the patients with BD; arthralgia is also common. An erosive or destructive arthropathy is unusual. Inflammatory cells of the synovium and synovial fluid are primarily polymorphonuclear leukocytes.[3]

Ocular disease occurs in 25 to 75 percent of BD patients. Ocular inflammation typically follows mucocutaneous symptoms by a few years, but it often progresses with a chronic, relapsing course affecting both eyes. This manifestation may require systemic immunosuppressive treatment and may irreversibly impair vision, and even progress to blindness if left untreated.[3]

Overall, the clinical manifestations of this patient were characterized for BD. The symptom of recurrent oral ulcers

came first followed by genital ulcer and skin lesion with arthralgia. Panuveitis was confirmed after few years of first manifestation.

The positivity of antibody for HSV II and CMV was related to the pathogenesis of BD. Studies suggest a possible pathogenic role of certain bacterial antigens that have cross-reactivity with human peptides. The cross-reactive self-antigens may include the heat shock proteins, a family of 60 to 90 kDa proteins produced by many cells in response to stress. These proteins have significant sequence homology between human and bacteria. T cells and/or antibodies may recognize epitopes shared by both host and infectious organism heat shock proteins, thereby initiating and/or perpetuating Behçet's disease.[3,9,10]

European League Against Rheumatism (EULAR) recommendations for the management of BD stated that any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids.[11]

Eye involvement in BD follows a remitting and relapsing course and the recurrent inflammatory attacks result in irreversible damage and visual loss. Suppression of the inflammation and the prevention of recurrences of ocular attacks should be the goals. Azathioprine is widely accepted as the initial agent for ocular involvement of BD.[11]

Placebo-controlled randomized controlled trial (RCT) showed that azathioprine 2.5 mg/kg/day decreased hypopyon uveitis attacks (number needed to treat (NNT) = 4), stabilized visual acuity, and decreased the development of new eye disease (NNT = 2). Moreover, the 7-year follow-up of these patients showed that the beneficial effect of azathioprine continued in the long-term. Local and systemic corticosteroids for eye involvement, especially during attacks, are generally used with no evidence from RCTs. Corticosteroids rapidly suppress the inflammation but potential side effects, including cataracts and glaucoma, can cause concern.[11]

From the review of 880 Turkish patients with Behçet's uveitis, 68 percent were male, mean age of onset was 28.5 years for men and 30 for women. Ocular disease was bilateral in 78.1 percent, and panuveitis was the most common finding. Risk of losing useful vision at 10 years was 30 percent for men and 17 percent for women, but prognosis was better in the 1990s than in the 1980s.[12] Surprisingly, this patient showed remarkable improvement after we added azathioprine 50 mg to 150 mg a day. Hopefully, the visual loss in this patient will reverse to normal. However, it is important to remember that BD typically has a waxing and waning course characterized by exacerbations and remissions.

CONCLUSION

Behçet's disease is a chronic, relapsing, inflammatory disease characterized by recurrent oral aphthous ulcers and numerous potential systemic manifestations. These include genital ulcers, ocular disease, skin lesions, neurologic disease, vascular disease, and arthritis. The disease is believed to be caused by vasculitis. The disease is characterized by exacerbations and a relapsing/remitting course.

Azathioprine revealed good improvement in ocular involvement of BD and this immunosupressant is recommended by EULAR. However, frequent ophthalmologic examinations are essential for patients with ocular disease, and periodic monitoring of the eyes is recommended for all patients. A careful history and examination, with attention to the vascular and neurologic systems, should be part of the physician's assessment.

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