Behçet’s disease in 2 Filipinos: a case report

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INTRODUCTION

Behçet’s disease is a chronic multisystem disease that is characterized by vasculitis. Recurrent oral aphthous ulcers, genital ulcers, skin and ocular lesions, and arthritis are the most frequent clinical manifestations. There may also be involvement of other organ systems such as gastrointestinal and neurologic. The disease may present with a chronic relapsing progressive course and a potentially poor prognosis, with males presenting with systemic symptoms having a mortality of 0-6%. It is a rare disease with increased prevalence in Middle Eastern countries, Mediterranean, China, and Japan. According to the Health Information System of the Research Institute for Tropical Medicine Department of Dermatology, only 8 patients with Behçet’s Disease were seen at the outpatient clinic from 2005 up to present, with the youngest at 19 years old and the oldest at 49 years old. There was equal distribution of males and females.

Due to the rarity and distinct clinical presentation of the disease, knowledge and clinical expertise are needed in order to promptly establish the diagnosis and institute management. We report two cases of Behçet’s disease in Filipinos on the basis of history, clinical presentation, and skin biopsy findings.

Hemochromatosis, a chronic iron overload disorder, was originally described by Trousseau in 1865 but coined by von Recklinghausen in 1889, who determined that iron deposition caused pigmentary changes. This disease can be either hereditary or acquired. Hereditary hemochromatosis is an autosomal-recessive systemic iron overload disease with 85-90% of patients homozygous to C282Y mutation in the human hemochromatosis protein (HFE) gene, or heterozygous to C282Y mutation and H63D mutation. Secondary or acquired hemochromatosis is due to ineffective erythropoiesis, parenteral iron overload and liver disease.

CASE REPORTS

We encountered two patients with Behçet’s Disease. Case 1 is a 27-year-old male who presented with a 7-year history of recurrent oral ulcers, usually on tongue, occurring at least 4 episodes per year. Lesions were later associated with purpura on the legs, papules and pustules on the face, and scrotal ulcers. Pathergy test done was negative.

Several skin punch biopsies were done on the lesions. A 4-mm skin punch biopsy of a papule showed spongiosis of the epidermis with vacuolar alteration of the basal cell layer. Dermal findings were mild superficial perivascular and periadnexal inflammatory infiltrate of lymphocytes and neutrophils.

A 4-mm skin punch biopsy of a purpura showed acanthosis and spongiosis of the epidermis. Dermal findings were mild perivascular and periadnexal inflammatory infiltrate of neutrophils, lymphocytes, histiocytes, and few plasma cells. There was mild red blood cell extravasation noted.

Another 4-mm skin punch biopsy of a hyperpigmented patch showed mild spongiosis of the epidermis with prominent basal cell layer hyperpigmentation. Dermal findings were mild superficial perivascular and periadnexal inflammatory infiltrate of lymphocytes. Mild red blood cell extravasation was noted.

All histopathological findings were consistent with Behçet’s syndrome.

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Case 2 is a 37-year-old female who presented with a 1-year history of recurrent oral ulcers, with 6 episodes occurring in a year. Lesions were later associated with multiple erythematous papules, pustules, and nodules on the face, trunk, extremities, and genital area. Patient was previously seen and managed by OB-gynecologist as a case of recurrent herpes simplex virus. HSV II IgG was negative. RPR and HIV Ag/Ab were non-reactive. Persistence of lesions, associated with unilateral swelling and tenderness of the left ankle, prompted consult at our institution. On consult, pathergy test was negative.

Figure 2 shows the histopathologic findings of Case 1. Fig. 2-a. A punch biopsy of papule shows spongiosis of the epidermis with vacuolar alteration of the basal cell layer. Mild superficial perivascular and periadnexal inflammatory infiltrate of lymphocytes and neutrophils was seen in the dermis. Fig 2-b. Punch biopsy of a papule highlights the inflammatory infiltrate consisting predominantly of lymphocytes. Fig. 2-c. Punch biopsy of a purpuric macule showing inflammatory infiltrate of neutrophils with mild red blood cell extravasation. Fig, 2-d (H & E, x400).

Figure 3 shows the various lesions seen in Case 2. Fig. 3-a. Papulopustules resembling acne. Fig. 3-b Oral ulcers. Fig.3-c. Nodule on the foot.
As with Case 1, several skin punch biopsies were performed on the lesions. A 4-mm skin punch biopsy of a pustule showed spongiosis of the epidermis. Dermal findings were telangiectasia of blood vessels, mild edema, and a superficial and deep perivascular inflammatory infiltrate of lymphocytes, neutrophils, and red blood cells. Few pigment-laden macrophages were seen.

Histopathological diagnosis was perivascular dermatitis with neutrophils, consistent with a pustular lesion of Behcet’s disease.

A 4-mm skin punch biopsy done on the nodule showed acral skin with a normal epidermis. Dermal findings were mild superficial perivascular inflammatory infiltrate of lymphocytes. The subcutaneous tissue showed a lobular inflammatory infiltrate of lymphocytes and hyaline change. Histopathological diagnosis was lobular panniculitis consistent with Behcet’s syndrome.

Referrals to rheumatology confirmed the diagnosis of Behcet’s disease for both patients. Both patients were initially given low doses of oral glucocorticoids (15mg for 5 days, 10mg for 5 days, 5mg for 5 days). Case 1 was given Dapsone 100mg once a day. Case 2 was given Colchicine 500mcg once a day. Both patients were noted to have resolution of lesions while under maintenance therapy for several months.

DISCUSSION

Behcet’s Disease is a rare disease with worldwide distribution. It is also termed as “Silk Disease” due to its prevalence in countries along the ancient silk route, such as Mediterranean and Middle East countries, Japan, and China.

Young individuals, 20–40 years of age, are most commonly affected, with a male to female ratio of usually 1:1.3

Poor prognosis is usually determined by ocular and central nervous system involvement. Cardiovascular, pulmonary and gastrointestinal system involvements are the major causes of mortality. Studies show that males have a higher prevalence of ocular, nervous system, pulmonary system involvement, large vessel thrombosis, thrombophlebitis and pathergy positivity. A more severe course is expected in patients who manifest the disease at a younger age (particularly under 25 years old). 4,5

The etiology and pathogenesis of the disease remain unclear. However, genetic predisposition has been investigated. Genes, such as encoding tumor necrosis factor, transporters in antigen processing proteins and MHC (major histocompatibility complex class I chains) have been determined to play a role in the development of the disease. Particularly, HLA-B51 is known to be strongly associated with the disease. Varying amounts of the genes may determine the disease manifestations and systemic involvement. Increased HLA-B51 and decreased HLA-B35 frequency in patients were found in patients with thrombophlebitis. Increased HLA-A29 and decreased HLABw6 frequency were found in patients with ocular involvement. Decreased HLA-Cw2 frequency was associated in patients with erythema nodosum, while
decreased HLA-Cw7 frequency was associated in patients with genital ulceration. Venous thrombosis may most likely to occur in patients with increased HLA-B51 and with absence of HLA-B35.4,5

There is also an ongoing hypothesis of an environmental trigger in BD patients with genetics susceptibilities. Several infectious agents have been investigated, especially bacteria (Streptococcus, Mycoplasma, Helicobacter pylori (HP)... and viruses (Herpes simplex virus 1 and 2, Hepatitis virus, Parvovirus B19).5

Hypersensitivity of T cells (αβ T cells and γδ T cells) to multiple antigens also appear to play a critical role in the pathogenesis of the disease.5

The diagnosis of Behçet disease is based on clinical signs. There is no pathognomonic laboratory test or histologic characteristics specific to the disease. Several sets of criteria have been developed to aid clinicians in the diagnosis. The most popular of these is the criteria of the International Study Group and those of the Behçet Disease Research Committee of Japan. However, issues on the selectivity and specificity of these criteria have been encountered.1

### Table 1. Revised Diagnostic Criteria of the Behçet’s Disease Research Committee of Japan

- **Main points**
  - Main symptoms
  - Recurrent oral aphthous ulcers
  - Skin lesions
    - a. Erythema nodosum
    - b. Superficial thrombophlebitis
    - c. Papules Skin hypersensitivity
      - Ocular lesions
        - a. Iridocyclitis or sequelae
        - b. Posterior uveitis or sequelae
      - Genital ulcers
      - Additional symptoms
        - Arthritis without deformity or sclerosis
        - Epididymitis
        - Gastrointestinal lesions represented by ileocecal ulcerations
      - Vascular lesions
        - Central nervous system lesions moderate or severe
        - Criteria for diagnosis of disease types
      - Complete types: four main symptoms
      - Incomplete types: three main symptoms or two main and two additional symptoms or typical ocular lesions and another main symptom or two additional symptoms
      - Suspected disease: typical main symptoms not fulfilling the criteria for an incomplete type
      - Special lesions: certain gastrointestinal, vascular, and nervous system lesions
      - Clinical laboratory data contributing to the diagnosis (not essential)
    - Negative or positive pathergy test
    - Negative or positive prick test to vaccinate for streptococci
    - Inflammatory response
    - Positive HLA-B51
    - Other pathologic findings
    - Additional points
    - Nontypical symptoms should not be diagnosed as Behçet disease.

### Table 2. Revised International Criteria for Behçet Disease (International Team for the Revision of ICBD; coordinator: F. Davatchi)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Points</th>
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<tr>
<td>Ocular lesions (recurrent)</td>
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</tr>
<tr>
<td>Oral aphthosis (recurrent)</td>
<td>2</td>
</tr>
<tr>
<td>Genital aphthosis (recurrent)</td>
<td>2</td>
</tr>
<tr>
<td>Skin lesions (recurrent)</td>
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</tr>
<tr>
<td>Central nervous system</td>
<td>1</td>
</tr>
<tr>
<td>Vascular manifestations</td>
<td>1</td>
</tr>
<tr>
<td>Positive pathergy test</td>
<td>1</td>
</tr>
</tbody>
</table>

Based on the Revised Diagnostic Criteria of the Behçet’s Disease Research Committee of Japan, both patients may be classified as incomplete type since both were able to manifest three main symptoms (recurrent oral aphthous ulcers, skin lesions, and genital ulcers). Based on the Revised International Criteria for Behçet Disease, both patients had BCD scores of 5 (recurrent oral aphthosis 2, recurrent genital aphthosis 2, recurrent skin lesions 1). A score of ≥4 indicates the presence of Behçet’s disease.

Among the disease manifestations, recurrent oral ulcers are the most predominant and has been found to occur in 98% of patients. Oral ulcers are among the earliest manifestations of the disease and may be described as painful. In order to classify oral ulcers as recurrent, episodes must occur at least three times in 12 months.6

Genital ulcers may also be tender and recurrent. As opposed to oral ulcers where lesions heal without scarring, genital lesions may heal with scarring. Scarring of scrotal lesions is considered specific to the disease. 6

Eye manifestations may occur as iritis/iridocyclitis with hypopyon and retinal vasculitis. Loss of visual acuity and complete blindness may occur. Hence, patients must be referred to ophthalmology for assessment. Appropriate treatment must be given to patients with ocular symptoms to prevent progression of the disease. 6

Skin lesions typical of the disease consist of pustular vasculitic lesions (including pathergy lesions), erythema nodosum-like lesions, Sweet-like lesions, pyoderma gangrenosum-like lesions, and palpable purpuric lesions of necrotizing venulitis. All of these lesions are characterized in their early stages by a neutrophilic vascular reaction. Lesions resembling acne and folliculitis have a prevalence of 71%.6

Aside from the typical symptoms, a pathergy test may also be done to further confirm the diagnosis. A positive pathergy test is a hypersensitivity reaction elicited...
by a sterile needle prick or an intracutaneous injection of 0.1-mL isotonic salt solution using a 20-gauge needle without prior disinfection of the injection site. The skin prick is generally placed at an angle of 45, 3 to 5 mm intracutaneously on the volar forearm. An erythematous papule or pustule measuring >2mm within 48 hours is a positive pathergy test. This is caused by dermal inflammation, composed of lymphocytes, neutrophils, and eosinophils, mainly localized around the vessels.1,6

However, the pathergy test was negative in both patients. A negative pathergy test does not necessarily indicate absence of the disease. A positive pathergy test has a prevalence of 60%. Pathergy test is non-specific to the disease and may also be positive in pyogenic granuloma and Sweet’s Syndrome, as well as Crohn’s disease and Ulcerative colitis. It is said to differ among countries, with countries in Japan and Turkey having the most frequency of positivity. The test is also shown to be more positive in males. Blunt needles produce more positive results as compared to sharp needles.6

The management is both symptomatic and empirical, but is generally specific to the clinical features of each patient. Both of our patients received short courses of low dose oral corticosteroids. Corticosteroids are commonly used to treat clinical manifestations of Behçet’s disease as a monotherapy or in combination with immunosuppressants. Corticosteroids have been widely used almost for all lesions of the disease and are an effective choice especially in mucocutaneous lesions, acute uveitis, and neurologic disease.6,7

Apart from corticosteroids, the treatment of Behçet’s Disease includes anti-inflammatories and immunosuppressants. Both patients were maintained on anti-inflammatory medications. For the purpose of discussion, we will focus on the treatments received by the patients presented. Case 1 was maintained on Dapsone 100mg 1x/day while Case 2 was maintained on Colchicine 500mcg 1x/day.

Dapsone inhibits the enhanced chemotactic activity of neutrophils. In a double-blind, crossover study of 20 patients, Sharquie et al., patients were given dapsone 100 mg daily or placebo for 3 months and showed significant reductions in the number, duration, and frequency of oral ulcers and number of genital ulcers in dapsone-treated patients. There was also a significant decrease in the frequency of nodules and papulopustules. Hemolytic anemia and methemoglobinemia, may occur patients with glucose-6-phosphate dehydrogenase deficiency.10

Colchicine, on the other hand, is another anti-inflammatory agent that affects cell migration and cytokine release. It inhibits leukocyte production of superoxides and release of various cytokines and pyrogens. It also inhibits neutrophil adhesion, extravasation and recruitment by altering neutrophil L-selectin expression and endothelial cell E-selectin distribution. It suppresses the release of the chemotactic agent leukotriene, as well as altering neutrophil deformability.8,9

Promising results with colchicine (0.5–2 mg/d p.o.) have been reported especially in mucocutaneous and articular findings. An RCT of colchicine enrolled 35 BS patients with mainly mucocutaneous lesions to receive 1.5mg/day colchicine vs placebo for 24 weeks. Colchicine was found to be superior to placebo in treating erythema nodosum, and to some degree, joint manifestations.8

The investigators of the previous study revisited the issue and compared colchicine (1-2mg/day, adjusted to body weight, not exceeding 200mg/day) with placebo for 2 years in patients with active mucocutaneous lesions. Colchicine was found to be effective in treating genital lesions, erythema nodosum, and arthritis. More favorable effect was observed in women. Its main adverse effects are oligozoospermia, amenorrhea, or dysmenorrhea, malaise, hair loss, gastrointestinal complaints (nausea, vomiting, diarrhea).9

A combination of colchicine and dapsone may also be beneficial. In a study by Lynde et al., fifty-five patients with complex aphthosis were treated according to a therapeutic ladder, starting with colchicine and adding dapsone to treatment of patients who did not have a substantial response (>75% improvement) to colchicine in 12 weeks or who discontinued colchicine use because of adverse effects. Most patients (44 [80%]) had a substantial response to therapy and had no serious adverse effects. Patients noted the benefit within 4 to 8 weeks, with maximum benefit by 12 weeks.11

Male sex, younger age of onset, and increased number of organs involved at the diagnosis are associated with a more severe disease and, therefore, require more aggressive treatment. A sensitive compound to colchicine.6

Prognosis of the disease depends on the clinical involvement and may result in considerable morbidity and mortality. Loss of visual acuity and neurological disease are major causes of morbidity and disability. Involvement of nervous, gastrointestinal, and large vascular systems may be lethal or can leave irreversible deficits. Disease course usually gets better with the passage of time with decrease in mortality rate.6

CONCLUSION

Diagnosis of Behcet’s Disease is made clinically. Pathergy test and skin punch biopsy, though non-specific, support the diagnosis. The clinician must be aware of the constellation of symptoms that characterize the disease since treatment is specific to the clinical features of each
patient. This will also prevent systemic complications associated with the disease.

REFERENCES


