

Retrospective Study of Behcet's Disease seen at the National Skin Centre, Singapore

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Abstract

This retrospective study characterises the clinical manifestations and outcome of 34 patients diagnosed with Behcet's disease seen at the National Skin Centre from 1990 to 1997. The 2 diagnostic criteria used were the International Study Group and the O'Duffy criteria. Seventy-six per cent satisfied both criteria and the remaining 24% satisfied only the incomplete form of the O'Duffy criteria. We found that the male to female ratio was 1:1.8. The mean age of presentation was 33 years (range 21 to 63 years). The majority were Chinese (73%). In our series, patients had prominent mucocutaneous involvement. These findings may be attributed to patient selection to a tertiary dermatology clinic. Oral (100%) and genital (99%) ulceration were the 2 commonest symptoms. The other cutaneous features included papulo-pustular or acneiform eruption (26%), erythema nodosum (14.7%) and positive pathergy test. Five patients (15%) had arthritis, 1 patient had recurrent thrombophlebitis and 2 patients had eye complications. The outcome of our patients was generally good with minimal functional impairment and no mortality detected. Our patients were primarily outpatient referrals and this may explain why systemic complications were rare in our series.

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Introduction

Behcet's disease, first described by a Turkish dermatologist, Dr Hulusi Behcet, is a multisystem inflammatory disorder of unknown aetiology. The diagnosis of Behcet's disease is based on clinical criteria because there are no pathognomonic laboratory features. In our study, 2 sets of clinical criteria were employed — the International Study Group (ISG) and O'Duffy criteria. The clinical features consist of both cutaneous and extracutaneous manifestations. The main cutaneous features include recurrent oro-genital ulceration, erythema nodosum and papulo-pustular lesions.

This paper presents the epidemiology and clinical profile of 34 patients in our department seen over an 8-year period and discusses the current knowledge about the disease.

Materials and Methods

We studied 34 patients with Behcet's disease presenting to the National Skin Centre (NSC) in Singapore from 1990 to 1997. The case records of these patients were reviewed and those patients who were no longer on follow-up were interviewed via telephone to determine their clinical course and possible systemic complications that may have occurred.

Inclusion Criteria

All patients satisfied either the ISG (Table I) and/or the O'Duffy criteria (Table II). All patients had recurrent oral ulcers for at least a year. They were evaluated initially and annually by an ophthalmologist and if appropriate by a rheumatologist or other medical specialties.

Exclusion Criteria

Patients with a positive anti-nuclear antibody (ANA) test or with positive herpes simplex (HSV) culture results were excluded. All patients with genital ulceration secondary to a sexually transmitted disease were excluded. In addition, patients with inflammatory bowel disease, Reiter's disease or erosive arthritis were excluded.

Results

Thirty-four patients were included into our study. Twenty-six (76%) patients satisfied both criteria. The remaining 8 (24%) patients were classified under the incomplete form based on O'Duffy's criteria. In this second group, 7 patients had recurrent oro-genital ulceration without other cutaneous manifestations while 1 patient with recurrent oral ulcers had a positive pathergy

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TABLE I: DIAGNOSTIC CRITERIA ACCORDING TO THE INTERNATIONAL STUDY GROUP FOR BEHCET'S DISEASE

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 the followings:	
Recurrent genital ulceration	Aphthous ulceration or scarring 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 on corticosteroid treatment
Positive pathergy test	Read by physician at 24 to 48 hours

TABLE II: O'DUFFY CRITERIA FOR THE DIAGNOSIS OF BEHCET'S DISEASE

Criteria	Aphthous stomatitis Aphthous genital ulceration Uveitis Cutaneous pustular vasculitis Synovitis Meningoencephalitis
Diagnosis	At least three criteria present, one being recurrent aphthous ulceration
Incomplete form	Two criteria present, one being recurrent aphthous ulceration
Exclusions	Inflammatory bowel disease, systemic lupus erythematosus, Reiter's disease and herpetic infections

test. The male to female ratio was 1:1.8 (12 males, 22 females). There was a predominance of Chinese patients ($n = 25$; 73%). There were 6 Malay patients (18%) and 3 Indian patients (8%). The age at presentation ranged from 21 to 63 years. The mean age of onset was 37 years with the majority falling within the third to fourth decades. The disease duration varied from 1 to 13 years with a mean of 5 years.

Recurrent oral ulceration (Fig. 1) of more than one year's duration was common to all patients. Twenty-two (65%) patients presented with recurrent painful ulceration. All the 3 forms of aphthous ulcers-major, minor and herpetiform ulcers were described. Recurrent genital ulcers (Fig. 2) were observed in 33 (97%) patients, making it the next commonest symptom. Oral ulceration generally preceded genital ulceration when both were present (75%). In males, the most common site of genital ulcer was on the penis and in female, the vulva. How-

ever, genital ulcers did occur on the scrotum, cervix and vagina as well.

Twenty-four out of the 34 patients (70%) had other cutaneous manifestations. The other skin lesions were papulo-pustular eruptions (Fig. 3), erythema nodosum (Fig. 4) and positive pathergy test. Five patients (14.7%) had erythema nodosum, 9 patients (26%) had papulo-pustular or acneiform eruptions. Pathergy test was performed in 22 patients of whom 13 had a positive pathergy test. Pathergy test was not performed in the remaining 12 patients because they had satisfied the main criteria under ISG.

All patients underwent eye screening. Eye complications were rare with only 2 patients detected to have eye complications. One Chinese male patient had iritis and 1 Indian male patient had uveitis. In the latter patient, recurrent thrombophlebitis of the arms and leg veins occurred as well as arthritis. Prolonged fever of more than 10 days' duration was observed in 3 male patients (8%). Fever did not respond to empirical antibiotics therapy but resolved rapidly with colchicine alone or with the addition of prednisolone. Five patients (15%) had arthralgia or arthritis. All these 5 patients were males. Arthritis was mainly mono-articular affecting the ankles, shoulders or elbows. Only 1 Malay patient had seronegative symmetrical polyarthritis involving the fingers. None of the patients had neurological, gastrointestinal, cardiovascular or renal complications. Skin biopsies were performed in 5 patients. Histologies consistent with vasculitis were reported in 3 patients. In the other 2 patients, histological examinations were reported as inconclusive and spongiotic dermatitis.

The treatment of Behcet's disease was dependent on the particular clinical manifestation of the individual patient. Majority of our patients received topical corticosteroid either alone or in combination with systemic therapy for mucocutaneous involvement. Colchicine was the most frequently used systemic therapy. Steroid therapy (intralesional or oral) was frequently used in combination with colchicine. Most skin lesions improved with prednisolone or colchicine. One Malay patient had severe and recurrent oro-genital ulceration and papulo-pustular eruptions on the forearms, requiring the use of dapsone and thalidomide.

Discussion

Behcet's disease is a systemic vasculitis of unknown aetiology and is named after Hulusi Behcet, a Professor of Dermatology in Istanbul, who first published his observations on two patients with the triple symptom complex of hypopyon-iritis, recurrent oral and recurrent genital ulcerations in 1937.'

The diagnosis of Behcet's disease is based on clinical criteria. There are several sets of diagnostic criteria for Behcet's disease such as the O'Duffy, Japanese and



Fig. 1. Multiple oral ulcerations on the tongue.



Fig. 2. Genital ulcer on the penis.

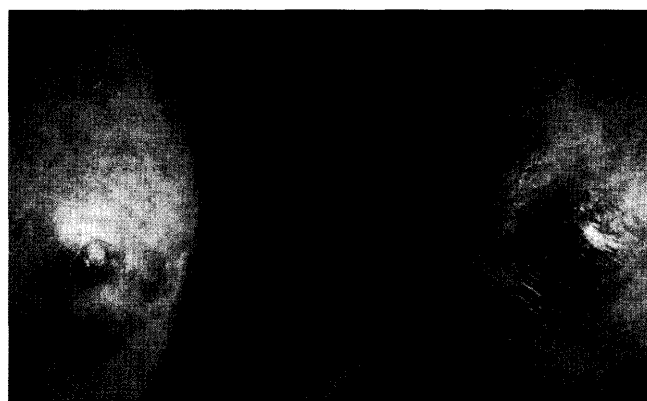


Fig. 3. Papulo-pustular lesions on the extensor surface of both elbows.

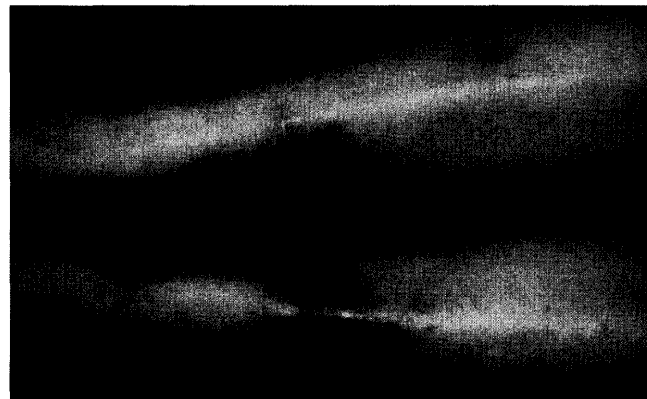


Fig. 4. Erythema nodosum on the lower legs.

International Study Group and this has led to some confusion and hindered interpretation of different trials. In our study, we used 2 sets of diagnostic criteria. The first set of diagnostic criteria was proposed by the ISG.

ISG² was an agreed set of diagnostic clinical criteria to be quoted in all future published works. We recognised that the sensitivity and specificity of the ISG criteria was higher compared to the other diagnostic criteria and there was a skew towards cutaneous features. Thus, patients who were unable to satisfy the ISG criteria were also recruited if they satisfied the O' Duffy criteria.

The onset of Behcet's disease usually occurs in the third or fourth decades with a geographical variation in the male to female sex ratio. In our study, there is a slight female preponderance with the majority falling between the third and fourth decades. Although the prevalence of Chinese patients appears to predominate as compared to the other races, it is consistent with the racial distribution locally.

It has been suggested that male sex is associated with more severe disease.^{3,4} It is notable in our study that males tended to have more extracutaneous and severe clinical presentations. Our patients with Behcet's disease had predominately mucocutaneous disease and minimal extracutaneous manifestations; this may be

due to a bias in patient referral to NSC.

There are very few epidemiological surveys on the prevalence of Behcet's syndrome worldwide. High prevalence of Behcet's disease has been reported in Turkey, Japan, Iran and mainland China and this geographical region was nicknamed "The Silk Route Disease", suggesting that the disease followed the medieval silk route between Europe and the Far East. To our knowledge, there are no similar epidemiological studies on Behcet's disease done in Asian countries. There were only 34 diagnosed cases of Behcet's disease seen at the NSC over an 8-year period from 1990 to 1997, this suggests that Behcet's disease is relatively uncommon in Singapore.

Several large series in Japan⁵ and Turkey³ showed a significant association with HLA-B5. It seems that HLA-B51 is linked to a more severe disease and may be associated with specific manifestations of the disease. Initial studies showed that HLA-B51 antigen positivity in Behcet's disease is more frequent in patients with uveitis than those without it. However, recently Azizlerli G et al⁶ conducted a study which demonstrated a positive association between genital ulceration and the presence of HLA-B51 antigen but failed to show a similar association with eye involvement, oral ulceration, pseudofolliculitis, erythema nodosum (EN) lesions

and arthritis. Despite the HLA association, familial clustering⁷ is only occasionally observed. Our study did not suggest any familial tendency and the HLA status was not evaluated in our patients.

Behcet's disease has both cutaneous and extra-cutaneous features. The skin lesions in Behcet's disease include oro-genital ulcers, erythema nodosum, papulo-pustular (pseudofolliculitis) and a positive pathergy test.⁸ Aphthous-like stomatitis is the first manifestation of Behcet's disease in 25% to 30% of patients in some series, although figures as high as 75% have been cited. As compared to other studies, majority of our patients (75%) first presented with oral ulceration followed by genital involvement. The ulcers are frequently painful, multiple and generally heal without sequelae within a week. Genital ulcers are of similar nature to oral ulcers and the common sites of occurrence are on the penis in males and vulva in females.

Eye involvement is perhaps the most disabling complication and it tends to be more frequent and severe in males. Typically, recurrent attacks of anterior and posterior uveitis, hypopyon and iridocyclitis occur and blindness is the major cause of morbidity in Behcet's disease.⁴ The other ocular complications are cataracts, glaucoma, scleritis, vitreous haemorrhage, optic neuritis, conjunctivitis and neo-vascularisation of the retina. Our patients seemed to have minimal eye disabilities. The 2 affected patients are both males and their eye involvement did not result in permanent visual impairment. Arthritis has been described as a frequent complication in Behcet's disease. The arthritis is usually, subacute, self-limiting and non-deforming.⁹ It is most commonly monoarthritis or a symmetrical oligoarthritis. The knee, wrists, elbows and ankles are most frequently affected. Rarely, the arthritis may be erosive and this has been reported in Japanese patients.⁹ In our study, only 5 (15%) patients complained of arthritis which was non-deforming. Four of the patients presented with monoarthritis but a Malay patient had symmetrical polyarthritis of the small joints of the hands. In our study, the arthritis was adequately controlled with non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine.

Neurological symptoms, although uncommon, carry a poor prognosis. Central nervous system involvement usually conforms to one of the following patterns: meningo-encephalitis, benign intracranial hypertension, cranial nerve, pyramidal, cerebellar, spinal cord or peripheral nerve involvement and confusional state. In our review, none of our patients had central nervous system involvement.

Gastrointestinal, haematologic, pulmonary and renal involvement have been described. Gastrointestinal ulceration appears to be rarely reported in most studies apart from those reported in the Japanese population.

The symptoms may mimic inflammatory bowel diseases and patients may present with abdominal pain, melaena or rarely intestinal perforation. Pulmonary symptoms such as cough, dyspnoea, chest pain and haemoptysis occur and are thought to be due to pulmonary vasculitis. Chest X-rays may show pulmonary infiltrates, pleural effusions and prominent pulmonary arteries. Ventilation-perfusion scans may show perfusion defects in the presence of a normal chest X-ray. Computerised tomography may aid in the diagnosis of pulmonary aneurysm. Arterial and venous vessels can be affected at various anatomical sites.⁴ Thrombophlebitis, aneurysms of the aorta, carotid arteries, femoral or popliteal arteries and occlusion of the hepatic vein causing the Budd-Chiari syndrome may occur. Other rare reported manifestations include pancreatitis, epididymitis, glomerulonephritis¹⁰ and type AA amyloidosis with associated nephrotic syndrome.¹¹ None of our patients demonstrated the above-mentioned complications. Our patients appear to have a more benign clinical spectrum of the disease. We recognised that our series are primarily outpatient case referrals and therefore biased for less severely affected patients.

The mainstay of treatment for Behcet's disease is immunosuppression. However, the choice of therapy is often dependent on the particular clinical manifestations exhibited by individual patients. The options include topical and systemic corticosteroid, colchicine, dapsone, azathioprine, thalidomide and cyclosporin A. In our experience, patients with primarily mucocutaneous disease were first treated with moderately potent topical corticosteroids. Severe aphthous ulcers can be managed effectively with intralesional triamcinolone. Our study concurs with other studies that colchicine is a relatively safe drug which is useful in reducing the size, frequency and duration of mucocutaneous lesions.¹²⁻¹⁴

Dapsone can be used singly or in combination with colchicine. The mechanism of action of dapsone in neutrophilic dermatoses is thought to be related to inhibition of neutrophil migration.¹⁴ Oral thalidomide^{15,16} has been proven to be an effective treatment for mucocutaneous lesions of Behcet's disease. However, adverse effects such as teratogenicity, depression and peripheral neuropathy limit its usefulness as a first-line therapy. Systemic corticosteroid and cytotoxic agents such as azathioprine¹⁷ and cyclophosphamide are best reserved for patients with significant systemic involvement. One Malay patient with refractory disease was given thalidomide and his mucocutaneous lesions resolved after 4 weeks. Unfortunately, the patient developed depression and insomnia and thalidomide had to be discontinued.

Although Behcet's disease is a relatively rare clinical entity locally, it is important to bear in mind this diagno-

sis whenever one encounters a patient with recurrent oro-genital ulceration. This group of patients requires long-term follow-up in view of possible fatal systemic complications. As the diagnosis and treatment of Behcet's disease demand the cooperation of several specialities, an increased awareness of the condition will facilitate the diagnosis and subsequent management.

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