Behçet's disease

A rare vasculitis not to be missed

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A high index of suspicion for Behçet's disease is needed because of the risk of multisystem involvement and potential catastrophic complications that may develop if the disease is left untreated.

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Behçet's disease is a rare episodic, multisystem vasculitis characterised by recurrent oral and genital ulceration. First described by Hippocrates, it owes its name to the Turkish dermatologist Hulusi Behçet, who recognised the characteristic clinical triad of recurrent aphthous ulcers, genital ulcers and uveitis. However, as an autoimmune small vessel vasculitis, Behçet's disease may involve many other organ systems, including joints, the nervous system, lungs, gastrointestinal tract and kidneys.

The peak age of onset of Behçet's disease is between 20 and 40 years, although it can occur at any age, and as early as age 3 to 4 years. A male to female ratio of 1:1.5 exists in children;[1] however, no sex predilection has been noted in adults.[2] There is a high prevalence of the disease in the countries along the ancient 'Silk Road' from Japan to the Mediterranean Sea.[3]

Behçet's disease can have multiple presentations. Although it is an uncommon disease in Australia, health professionals need to be able to recognise the common features and potentially life-threatening aspects of the disease early, to allow appropriate referral of the affected patient and/or management without delay.

PRESENTATION

The combination of painful oral and genital ulcers with either eye symptoms or an inflammatory arthritis should suggest a diagnosis of Behçet's disease (the most common presenting symptoms are shown in Box 1).

Common features

Oral and genital ulcers

Oral ulcers are the principal lesions required to make the diagnosis of Behçet's disease,[4] and are often the initial presenting complaint (Figures 1 and 2). They are classified into three distinct forms (Box 2), and can be found on the tongue, gingiva, buccal and labial mucosa, soft palate and pharynx. The ulcers are painful, usually multiple, may resolve spontaneously but usually relapse. External triggers, including poor oral hygiene, dental caries and chronic tonsillitis, can predispose to oral ulceration in people with Behçet's disease.[5] Smoking is believed to have a protective effect against oral ulceration in people with Behçet's disease, but this is not a recommended therapeutic strategy.

Genital ulceration is often recurrent and included in the formal diagnostic criteria for Behçet's disease. Genital ulcerations commonly occur on the scrotum and penis in men (Figure 3), and on the vulva, cervix

1. COMMON PRESENTING SYMPTOMS OF BEHÇET'S DISEASE

- Oral ulcers (92 to 100%)
- Genital ulcers (65%)
- Skin lesions (vasculitic; 80%)
- Ocular lesions (inflammatory or thrombotic; 50%)
- Oligoarthritis (asymmetrical, large joint; 50%)

Figure 1. Oral ulcers.

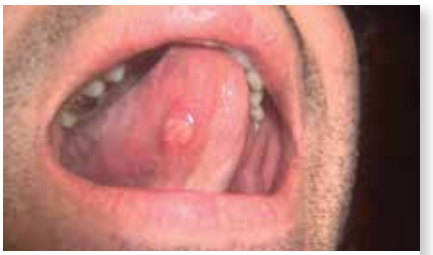

Figure 2. Oral aphthous ulcer.

Courtesy of the Behcet's syndrome community on RareConnect: www.rareconnect.org/en/community/behcet-s-syndrome.

and in the vagina in women (Figure 4). The lesions are painful and resemble the oral ulcers of Behçet's disease, but are larger and deeper and heal with scarring. Genital scarring can help with retrospective diagnosis – if an individual has only oral ulceration and uveitis, it is important to look for evidence of past genital ulceration if Behçet's disease is suspected.

Skin lesions

Cutaneous lesions are common in Behçet's disease and occur in approximately 80% of affected patients (Box 3 and Figure 5).

Erythema nodosum is a common skin manifestation, which is characterised by small tender reddened nodules under the skin caused by medium vessel vasculitis, most commonly on the anterior shin and extensor aspects of the limbs (Figure 6). Erythema nodosum, however, is not specific to Behçet's disease, and can occur in many systemic diseases. The pathergy phenomenon (development of a papule or pustule-like lesion after a saline injection into the skin) or dermographism are more pathognomonic.

Figure 3. Penile ulcer.

Eye disease

Eye involvement is frequent and suggestive of the diagnosis of Behçet's disease. It usually follows oral and genital lesions by a few years. Eye lesions vary from mild conjunctivitis to uveitis (Figure 7), vitritis and retinal vessel occlusion (Figure 8) and subsequent atrophy.[6] Recurrent inflammatory attacks to the eye may irreversibly damage vision; panuveitis must be recognised and treated as a medical emergency as it can rapidly progress to blindness.

Arthritis

The arthritis associated with Behçet's disease is characteristically an asymmetrical oligoarthritis of the lower limbs, commonly the knees and ankles, occurring in half of patients with the disease. It is a nonerosive, nondeforming inflammatory arthritis, presenting as pain, stiffness and joint swelling. The arthritis is similar to that seen in reactive arthritis; the key feature that differentiates these two immune-mediated joint diseases is the presence of oral ulceration in people with Behçet's disease.

Figure 4. Female genital ulcer.

Courtesy of Dr Andrew T. Goldstein, Director, The Centers for Vulvovaginal Disorders, WA, USA.

2. CLASSIFICATION OF ORAL ULCERS IN BEHÇET'S DISEASE

Minor ulcers
Less than 10 mm in diameter
Superficial
Heal without scarring

Major ulcers
More than 10 mm in diameter
Deep and painful
Heal with scarring

Herpetiform ulcers
Not very common
Large and painful
Interfere with eating

Interestingly, individuals with reactive arthritis have an increased incidence of the genetic marker HLA-B27, whereas in Behçet's disease its presence seems to indicate a milder form of disease.

Less common features

Thrombosis

The underlying vasculitis of Behçet's disease predisposes to thrombosis. This is thought to occur by vascular wall inflammation and damage. It is most commonly a vasculitis of the small vessels, although medium and larger vessels can be affected, and venous involvement is more common than arterial. This can lead to deep vein thrombosis, superficial thrombophlebitis, small vessel vasculitis or aneurysms. Venous thrombosis is the major vascular pathology seen and accounts for 85 to 93%

3. SKIN MANIFESTATIONS IN BEHÇET'S DISEASE

Common
Erythema nodosum
Pseudofolliculitis
Acneiform lesions
Pathergy phenomenon

Rare
Pyoderma gangrenosum
Sweet's syndrome
Dermographism

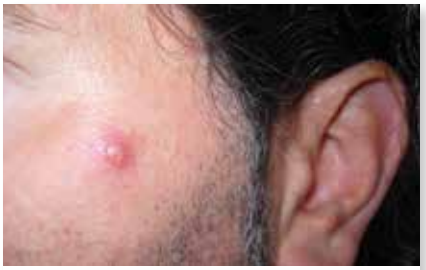

Figure 5. Skin lesion.

Courtesy of the Behçet's syndrome community on RareConnect: www.rareconnect.org/en/community/behcet-s-syndrome

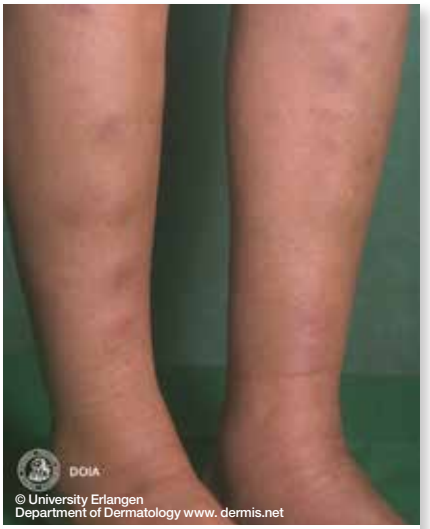

Figure 6. Erythema nodosum

4. INTERNATIONAL STUDY GROUP DIAGNOSTIC CRITERIA FOR BEHÇET'S DISEASE[9]

Recurrent oral ulcers, plus any two of the following:

- genital lesions
- typical defined eye lesions
- typical defined skin lesions
- positive pathergy test

of presentations of vasculitis in people with Behçet's disease. Venous thrombosis is responsible for various systemic manifestations, including neurological, gastrointestinal and renal Behçet's disease.

Neurological involvement

Neurological involvement in people with Behçet's disease is rare, requiring a high index of suspicion, but it is considered the most devastating of the Behçet's disease spectrum. Coined 'neuro-Behçet's', central nervous system involvement can be due to either focal lesions in the brain parenchyma or involvement of blood vessels in the brain.[7] Patients may present with hemiplegia, partial sensory loss, ophthalmoplegia or even seizures. Peripheral nervous system involvement is unusual. Neurological involvement mandates prompt referral of the patient to a specialist.

Gastrointestinal involvement

Gastrointestinal involvement in people with Behçet's disease may mimic Crohn's disease, and occurs at any site from the mouth to anus. Patients may develop anorexia, abdominal pain or diarrhoea. The most common site of ulceration is the terminal ileum and caecum, which may perforate leading to an enteric fistula.[8] Gastrointestinal Behçet's is often difficult to distinguish from inflammatory bowel disease and extra-intestinal involvement is similar in both conditions. The patient needs to be referred to a gastroenterologist for consideration of endoscopy and further assessment.

Renal involvement

Renal involvement is rare and less severe than in most other systemic vasculitides. It may manifest as haematuria and proteinuria, slowly progressing to renal insufficiency. Routine urinalysis and estimated glomerular filtration rate should be carried out to screen and/or monitor for possible progressive renal involvement.

Figure 7. Uveitis.

Courtesy of the University of Michigan Kellogg Eye Center, USA.

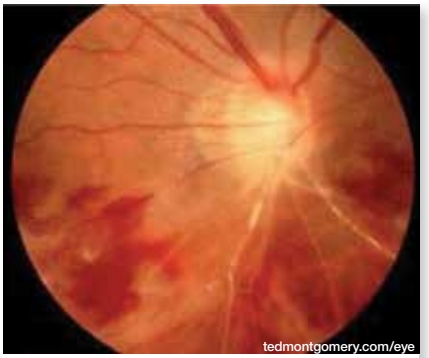

Figure 8. Retinal vein thrombosis.

AETIOLOGY

The cause of Behçet's disease is still not understood. Several studies have shown a strong association with HLA-B51 and HLA-B5. However, the disease is not limited to one ethnicity or geographic region. As with most autoimmune diseases, a genetic predisposition underpins a more complicated interplay of environmental factors, pathogens and immunological responses. Together with the immunological and inflammatory changes seen at a tissue level, endothelial dysfunction plays a role in vascular damage, and endothelial activation of affected blood vessels leads to inflammation and thrombosis of the vessels.

DIAGNOSTIC CRITERIA

The diagnosis of Behçet's disease remains a clinical one. The International Study Group for Behçet's Disease published diagnostic criteria for Behçet's disease in 1990, which remain the most widely accepted diagnostic standard (Box 4).[9] There is no specific diagnostic test for Behçet's disease, although inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein or ferritin may be elevated and a positive pathergy test in the setting of clinical features supports the diagnosis.

MANAGEMENT

It is crucial to recognise Behçet's disease at the initial stages and promptly refer the

patient to a rheumatologist or immunologist. It is important to have a high index of suspicion of the disease because of the risk of multisystem involvement and potential catastrophic complications that may develop if the disease is left untreated.

Glucocorticoids are the mainstay of treatment for people with Behçet's disease. Mucocutaneous lesions may respond to topical corticosteroids, colchicine or thalidomide. Acneiform lesions can benefit from topical antimicrobials used for acne vulgaris, including benzoyl peroxide, clindamycin and erythromycin. Colchicine has proven beneficial in people with erythema nodosum, and women seem to be more responsive than men. Topical sucralfate is safe and inexpensive. It may provide symptomatic benefit and accelerate healing of both oral and genital ulcers.[10] Oral prednisolone may also be necessary as a short course (less than two weeks) to settle recalcitrant mucocutaneous lesions not responding to topical treatment. Colchicine is helpful for the treatment and prevention of inflammatory arthritis in Behçet's disease, at a dose of 500 µg orally once or twice daily. There is a growing body of evidence to show that thalidomide is effective for skin and joint manifestations of Behçet's disease. However, its toxicity, particularly neurotoxicity, usually outweighs its potential benefit.

Eye disease in people with Behçet's disease needs to be managed by an ophthalmologist. Early referral of the patient is mandatory because of the significant threat to vision, and detailed ophthalmological assessment and specialised interventions are required (Box 5). Oral or periocular injection of corticosteroids can be helpful in people with anterior uveitis, whereas systemic, periocular or intravitreal corticosteroids may be required in those with posterior uveitis. Dilation of the pupil with mydriatics prevents posterior synechiae and improves symptoms in people with anterior uveitis.

Vision-threatening disease or involvement of the nervous system, gastrointestinal system, kidneys and large vessels represents systemic disease requiring specialist intervention. This usually involves the use of immunosuppressive therapies, which require regular monitoring by the specialist for toxicity and infection. Traditionally, pulsed methylprednisolone, intravenous cyclophosphamide, maintenance cyclosporin or azathioprine are used to control the autoimmune-mediated vasculitis. Combination therapy with one or more immunosuppressant agents may be more effective than monotherapy, helping to optimise therapeutic efficacy while minimising adverse effects.

Recent advances in the management of autoimmune disease have seen the use of monoclonal antibodies, such as the tumour necrosis factor (TNF) alpha inhibitors, for the management of patients with serious disease refractory or intolerant to other immunosuppressive agents. TNF alpha inhibitors are significantly less toxic than traditional immunosuppressive agents. However, they are very expensive and are not currently funded by the PBS for Behçet's disease. Infliximab and adalimumab, both TNF antagonists, are promising agents for refractory ocular disease, and etanercept (also a TNF antagonist) is effective in mucocutaneous disease. Rituximab, a monoclonal antibody directed against CD20 on the surface of circulating B cells, can be useful in retinal vasculitis.[11] There are also reports of clinical benefit using interferon alfa 2a and 2b for ocular and neurological disease.[12] Of these therapies, only infliximab and interferon alfa are TGA approved for management of refractory Behçet's arthritis and ocular disease. All of these therapeutic strategies need to be initiated and managed through tertiary centres.

PROGNOSIS

Behçet's disease is a lifelong illness. It typically has a waxing and waning course with frequent relapses and remissions. Mortality and morbidity increase with early age of onset, male sex, frequent relapses and presence of panuveitis. Involvement of the central nervous system, gastrointestinal system (bowel perforation, gastrointestinal bleeding) and cardiopulmonary disease (pulmonary embolism, myocardial infarction) are associated with a poor prognosis.[13]

5. MANAGEMENT OPTIONS FOR MANIFESTATIONS OF BEHÇET'S DISEASE

Oral and genital ulcers
- Topical or oral corticosteroids
- Colchicine

Skin manifestations
- Topical corticosteroids
- Colchicine
- Thalidomide

Arthritis
- NSAIDs
- Colchicine

Eye disease
- Anterior uveitis: oral or periocular corticosteroids
- Posterior uveitis: oral, periocular or intravitreal corticosteroids
- Refractory ocular disease: pulsed methylprednisolone, cyclosporin, azathioprine, cyclophosphamide, tumour necrosis factor alpha inhibitors, interferon alfa

Nevertheless, aggressive management at an early stage of the disease can ameliorate its symptoms and retard its progression.

CONCLUSION

Behçet's disease is a chronic relapsing and remitting disease with protean manifestations. Clinicians need to keep in mind Behçet's disease in their list of differential diagnoses for multisystem diseases. The diagnosis is essentially clinical and requires a high index of suspicion. The key to management lies in early diagnosis and prompt referral of the patient to an appropriate specialist for timely treatment to prevent serious complications. MT

REFERENCES

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

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REFERENCES

1. Kari JA, Shah V, Dillon MJ. Behçet's disease in UK children: clinical features and treatment including thalidomide. Rheumatology 2001; 40: 933-938.
2. Zouboulis CC. Epidemiology of Adamantiades-Behçet's disease. Ann Med Interne 1999 (Paris); 150: 488-498.
3. James DG. 'Silk route disease' (Behçet's disease). West J Med 1988; 148: 433-437.
4. Saadoun D, Wechsler B. Behçet's disease. Orphanet J Rare Dis 2012; 7: 20.
5. Kaneko F, Togashi A, Saito S, et al. Behçet's disease (Adamantiades-Behçet's disease). Clin Dev Immunol 2011; 681956.
6. Eguia A, Villarroel M, Martínez-Conde R, Echebarría MA, Aguirre JM. Adamantiades-Behcet disease: an enigmatic process with oral manifestations. Med Oral Patol Oral Cir Bucal 2006; 11(1): E6-E11.
7. Hirohata S, Kikuchi H, Sawada T, et al. Clinical characteristics of neuro-Behçet's disease in Japan: a multicenter retrospective analysis. Mod Rheumatol 2012; 22: 405-413.
8. Seyahi E, Fresko I, Melikoglu M, Yazici H. The management of Behçet's syndrome. Acta Reumatol Port 2006; 31: 125-131.
9. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990; 335: 1078-1080.
10. Alpsoy E, Er H, Durusoy C, Yilmaz E. The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease: a randomized, placebo-controlled, double-blind study. Arch Dermatol 1999; 135: 529-532.
11. Davatchi F, Shams H, Rezaipoor M, et al. Rituximab in intractable ocular lesions of Behçet's disease; randomized single-blind control study (pilot study). Int J Rheum Dis 2010; 13: 246-252.
12. Kuemmerle-Deschner JB, Tzaribachev N, Deuter C, Zierhut M, Batra M, Koetter I. Interferon – a new therapeutic option in refractory juvenile Behçet's disease with CNS involvement. Rheumatology 2008; 47: 1051-1053.
13. Park KD, Bang D, Lee ES, Lee SH, Lee S. Clinical study on death in Behçet's disease. J Korean Med Sci 1993; 8: 241-245.