REVIEW

Behçet's disease

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Summary: Behçet's disease (BD) is a chronic, relapsing multisystem vasculitis with predominant involvement of the oral and genital mucosa. It has a worldwide distribution, but the prevalence is highest in Central Asia and the Far East (along the ancient 'Silk Route'). Genetic, environmental, immunological and haemostatic factors play a role in the aetiopathogenesis. The International Study Group for BD proposed criteria for the diagnosis of this condition, the essential feature being recurrent oral ulceration. Genital ulcers and skin manifestations are common, while ocular changes are the most important cause of morbidity. Almost any organ in the body can be involved, and systemic involvement may portend a poorer prognosis. There is no pathognomonic test for BD and the diagnosis is made on clinical findings. Treatment of BD would require multidisciplinary cooperation, and early referral to an ophthalmologist is advisable to prevent ocular morbidity. Topical and systemic agents (colchicine, dapsone and thalidomide) are useful in controlling exacerbation of the oral and genital ulcers. Severe disease may require immunosuppressive agents and, more recently, biological agents have been used successfully. It tends to follow an unpredictable course, and the eventual prognosis depends on the systemic involvement.

Behçet's disease (BD) is a systemic vasculitis characterized by recurrent oral and genital ulcers, cutaneous lesions, ocular, gastrointestinal and neurological manifestations.[1] It was described by Hippocrates in the fifth century BC and recognized as a syndrome by Dr Hulushi Behçet, a Turkish physician, in 1937.[2] BD is a clinical diagnosis and, in 1990, the International Study Group for Behçet's disease proposed the criteria for the diagnosis of the condition.[3]

EPIDEMIOLOGY

BD exists worldwide, although there are significant regional differences. It is common along the 'Silk Route' countries that lie in a central strip of Asia, extending from Northwest China to the Mediterranean basin. This corresponds to the medieval trade route between the Far East and Europe. Turkey has the highest incidence of BD in the world (80–300 per 100,000).[4] The prevalence in the UK is quite low, ranging from 0.3 to 0.64 per 100,000 population.[5] BD shows a male preponderance in the Middle Eastern countries, but women are more commonly affected in Japan and Korea.[6] The onset is typically in the third or fourth decade of life, and it is rarely seen in children or patients above the age of 50. Late onset BD seems to have a more complicated and aggressive course.[7] Familial occurrences have been reported.[8]

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AETIOLOGY

Genetic, environmental, immunological and haemostatic factors contribute to the development of BD.

Genetic

The histocompatibility locus antigen (HLA) B51 allele is frequently expressed in patients with BD who live along the Silk Road (up to 80%), but not among Caucasians in Western countries (about 13%).[9] It affects the severity of disease since it is more common among patients with posterior uveitis or progressive central nervous system disease.[10] HLA B51 positivity has been linked with neutrophilic hyperfunction in transgenic mice; the presence of HLA B51 molecule, however, was not enough to induce clinical BD on its own.[11] It is not known if HLA B51 participates directly in the pathogenesis, or is associated with BD due to linkage disequilibrium to a nearby gene. Mutations within the major histocompatability complex, including allelic variants in the tumour necrosis factor (TNF) and intercellular adhesion molecular genes, and factor V Leiden mutations, have also been implicated.

Infections

Streptococcal antigens may be a provoking factor in disease activity. Lymphocytes from patients with BD released lymphokines that stimulated neutrophilic function when incubated with streptococcal antigens.[12] *Streptococcus sanguis* is found in higher concentrations in the oral flora of patients with BD and could contribute to recurrent

aphthosis. DNA from herpes simplex virus type 1 has been isolated from lymphocytic nuclei in patients with BD, suggesting possible involvement of this virus.[13]

Immunology

Immunological mechanisms play a major part in the aetiopathogenesis of BD.[14]

(a) Heat shock proteins (HSP): These molecules are produced by eukaryotic cells in response to stress. A 65-KD HSP has been isolated in patients with BD that stimulates proliferation of $\gamma\delta$ T-cell lymphocytes. More active disease was associated with higher number of $\gamma\delta$ T cells.[15]
(b) Neutrophil function: Neutrophil activity is increased in BD as evidenced by increased superoxide production,[16] chemotaxis and phagocytosis.[17] The excessive production of lysosomal enzymes eventually leads to tissue injury.[18]
(c) Cytokine mediators: Proinflammatory T-helper type 1 lymphocytes-mediated cytokines like interleukin (IL)-1, IL-6, IL-8,[18] IL-18[19] and tumour necrosis factor α (TNF α)[19,20] are elevated in sera of BD patients. Elevated IL-6 levels in the cerebrospinal fluid correlates with neurological involvement seen in BD.[21]
(d) Autoimmune mechanisms: Circulating immune complexes have been found in patients with BD, although the nature of the antigen has not been elucidated.[22] Immune-mediated occlusive vasculitis is demonstrated histologically in BD.[23] Anti-endothelial antibodies are a frequent but non-specific finding in BD.[24] Other putative autoantigens include immunoglobulin-like receptors, tropomyosin, oxidized low-density lipoprotein and retinal S antigen.[25]
(e) Other immunological changes: Activated monocytes in BD produce TNF α, IL-6 and IL-8 and are related to disease activity.[26] Natural killer (NK) cell numbers can increase in peripheral blood[27] and total peripheral blood T cells (CD3) are decreased.[28] However, NK cell activity is diminished, correlating with increased levels of prostaglandin E2, which suppresses NK cell activity.[29]

Endothelial and clotting factors

(a) Endothelial cells: Endothelial cell antibodies have been identified in BD. Increased E-selectin expression in endothelium and a pronounced inflammatory cell binding to endothelial cells could play a part in the aetiology of BD.[30]
(b) Clotting factors: Thrombomodulin, a cell surface glycoprotein of endothelium, shows increased levels in BD.[31] Plasma endothelium 1 concentrations are raised, indicating vasoconstriction (as it is synthesized by injured vascular endothelial cells).[14] Plasma fibrinolytic activity and levels of circulating factor XII are reduced in BD.[32]

CLINICAL FEATURES

Oral ulcers

This is usually the initial symptom and is seen at some time during the clinical course in all patients. It can precede other manifestations by many years.[33] It manifests as minor or major aphthous ulcers (Figures 1 and 2), or herpetiform ulcers (Figure 3). Typically, it is circular with an erythematous border and the floor of the ulcer has surface slough or a pseudomembrane. Minor aphthae usually heal in about 10 days without scarring. Major aphthous ulcers, however, can be deeper, more painful and leave scars on healing. The common sites of oral ulcers are the buccal mucosa, gingivae, lips, soft palate and pharynx.[13]

Genital ulcers

Genital ulcers occurs in 80–90% of BD and are located in the vulva, vagina and cervix uteri in women, and in the prepuce and scrotum in men. They tend to be similar in appearance to oral ulcers although they are deeper and more painful (Figures 4). Ulcers have also been described on the penile shaft, clitoris, urethra, anus, perineum, groin and inner thighs.[5] Since vaginal and cervical ulcers can be asymptomatic, a speculum examination is essential for all patients with BD (unless severe pain precludes it). Genital ulcers can sometimes be the initial manifestation of BD.[34] Epidydimitis is common but urethritis is unusual,

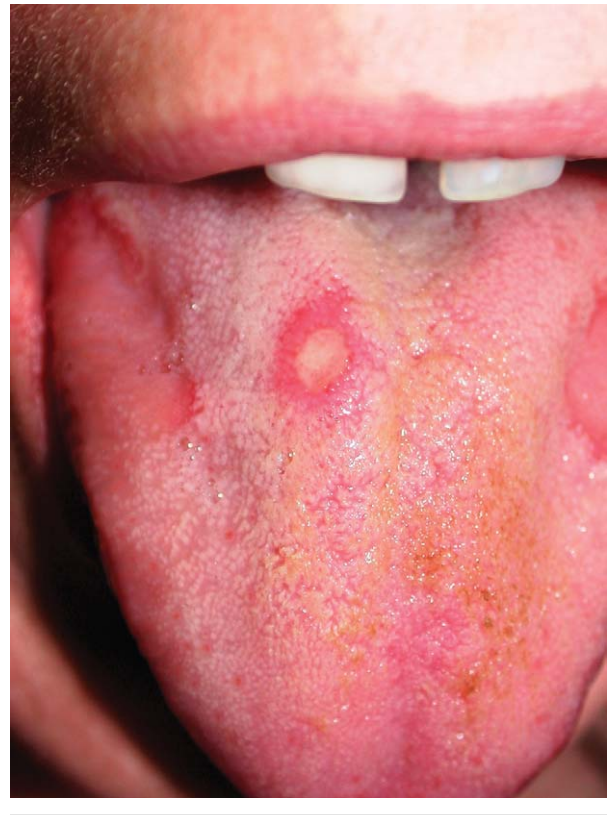

Figure 1 **Aphthous ulcer in dorsum of tongue; note the healed area in lateral margin of tongue**

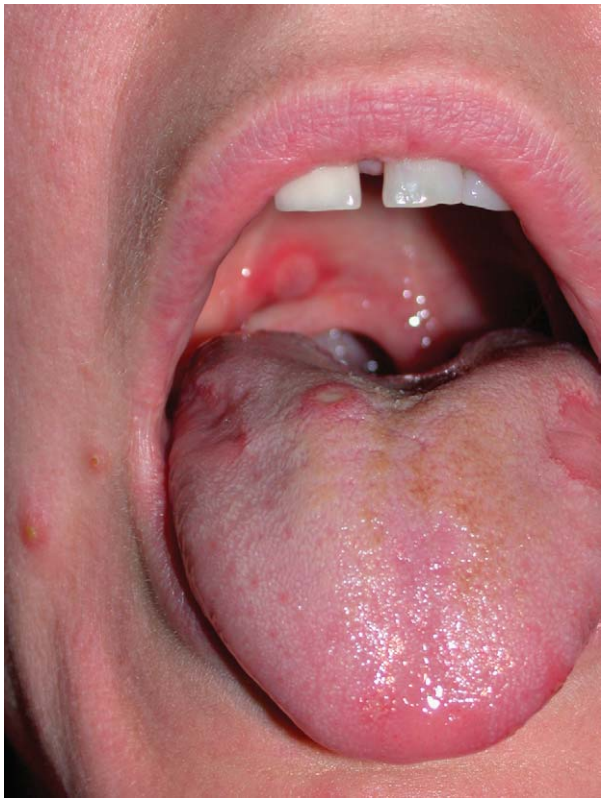

Figure 2 **Ulcers in tongue and palate associated with pustules on cheek**

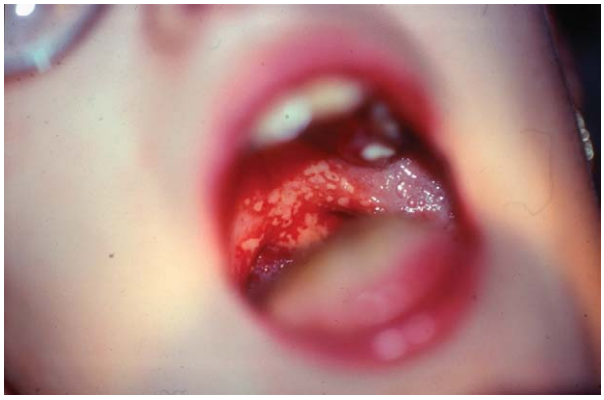

Figure 3 **Herpetiform aphthous ulcers in palate**

distinguishing it from Reiter's syndrome.[25] Genital ulcers heal in a few weeks, usually with scarring.[35] Vulval ulceration can cause difficulty with micturition (Figures 5 and 6) and dyspareunia and may hinder walking.[2] Vaginal ulcers rarely lead to bladder or urethral fistulae.

Cutaneous lesions

Skin manifestations are observed in about 80% of BD patients. Papulopustular lesions are sterile pustules that

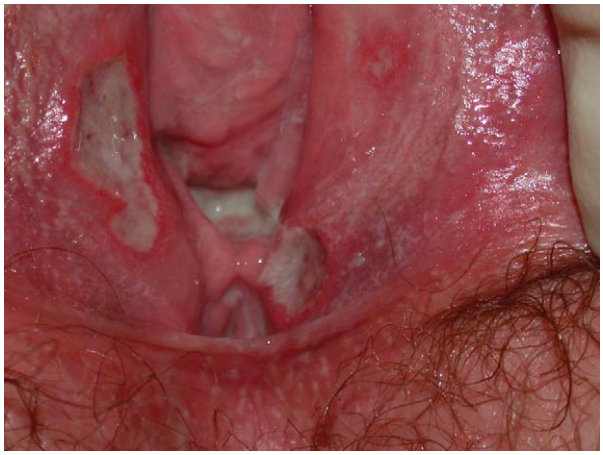

Figure 4 **Deep, sloughy ulcer in right lateral margin of vagina**

commonly occur in the back, face (Figure 2) and chest. Pseudofolliculitis and acneiform lesions occur in men and are distributed in the seborrhoeic areas, especially along the hairline. Erythema nodosum-like lesions, characterized by painful purplish nodules, are seen in the lower limbs but can occur in the arms, neck and face.[36] Superficial thrombophlebitis can be confused with early lesions of erythema nodosum. Rarely, non-specific eruptions and erythema multiforme-like lesions have also been described (Figure 7).[37]

Eye disease

Ocular involvement is reported in up to 70% of patients.[38] It is usually bilateral, occurs within 2-3 years of disease onset, and is more common and severe in men than in women. Ocular symptoms can vary from a gritty sensation and blurring of vision to severe pain and blindness.[39] Panuveitis (including anterior and posterior uveitis), retinal vasculitis, optic neuritis, scleritis, keratitis and retinal neovascularization have been associated with BD.[40] Conjunctivitis is rare.

Musculoskeletal

Arthralgia or arthritis occurs in about half of BD patients, with predominant involvement of the knees, wrists, ankles and elbows. Non-erosive arthritis is most commonly observed, with each episode lasting a few weeks. Deformities and destructive changes are rare.[41]

Cardiovascular

BD is a systemic vasculitis that affects arteries and veins. Superficial thrombophlebitis, deep vein thrombosis, arterial obstruction and aneurysms have been reported. Occlusion of major veins and arteries can cause bleeding, infarctions and organ failure.[4] Vascular lesions in the lung predisposes to recurrent haemoptysis.[42]

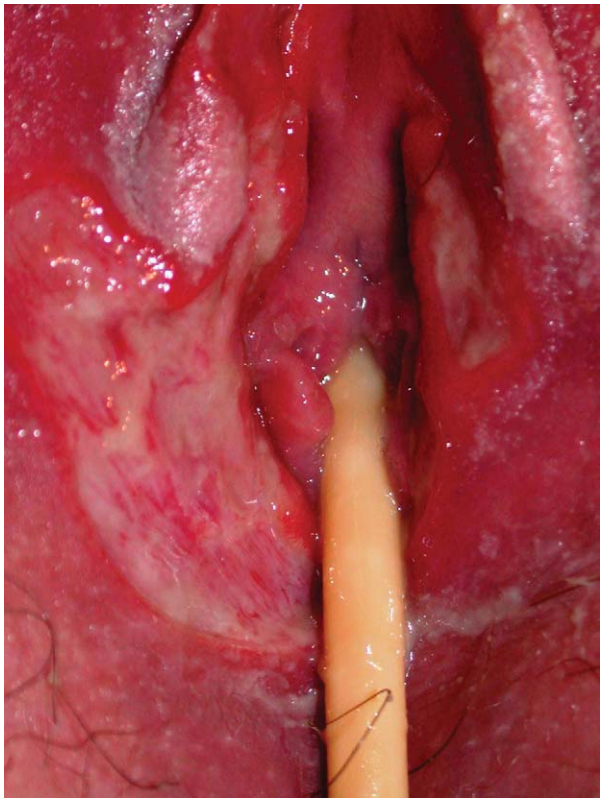

Figure 5 **Severe ulceration causing urinary retention necessitating catheterization**

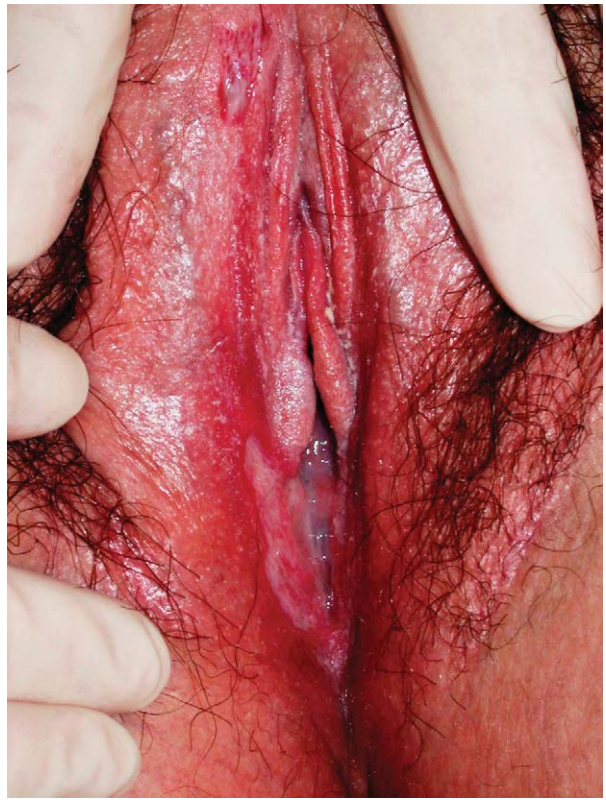

Figure 6 **Same ulcer as Figure 5, healing with oral corticosteroids**

Gastrointestinal

Mucosal ulcers are common in BD and occur along the entire gastrointestinal tract. Abdominal pain, diarrhoea, malena and, sometimes, perforation are potential complications.[43]

Central nervous system (CNS)

Progressive involvement of the CNS is more common in men and occurs in 10–20% of patients.[44] Meningoencephalitis, peripheral nerve involvement, neurological deficits and psychiatric symptoms have been associated with BD. Neurological changes can be progressive and lead to paralysis and death. Dementia intervenes in terminal disease.

Other

Renal damage is unusual and is often due to amyloidosis.[45] Many patients experience non-specific symptoms, particularly severe fatigue and generalized malaise. Pancreatitis is very rare.[46] External ear involvement with facial paralysis and Horner's syndrome has also been observed.[47]

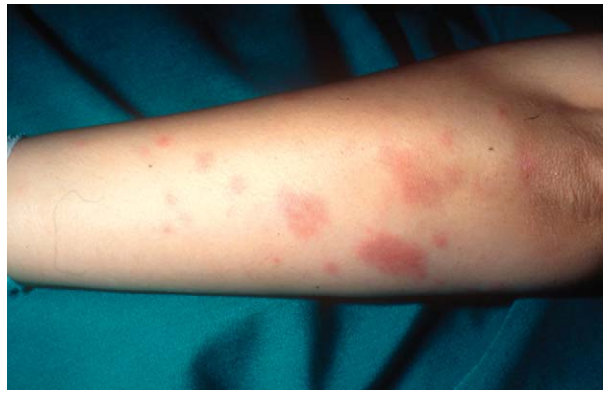

Figure 7 **Erythema multiforme-like rash. Targetoid lesions were seen in the trunk**

DIAGNOSIS

The diagnosis of BD rests upon clinical criteria, in the absence of any specific laboratory test.[48] The International Study Group for BD formed the criteria for the diagnosis of BD in 1990.[3]

The major criterion is the appearance of minor, herpetiform or major aphthous ulceration at least three times in a 12-month period. At least two minor criteria should be associated with this, including:

(1) recurrent genital ulceration or scarring observed by the physician;
(2) eye lesions such as anterior uveitis, posterior uveitis, cells in the vitreous on slit lamp examination or retinal vascularization;
(3) skin lesions such as erythema nodosum or papulo pustular lesions;
(4) positive pathergy test interpreted at 24–48 hours, performed with oblique insertion of a 20-gauge or smaller needle (Figure 8).

Recurrent aphthous stomatitis and herpes simplex infections are the commonest causes of oral and genital ulcers that can simulate BD. Conditions like Sweet's syndrome, pyoderma gangrenosum and inflammatory bowel syndrome give rise to oral aphthous lesions and can mimic BD.[48] Reiter's syndrome is often confused with BD by non-dermatologists due to the mucocutaneous and arthritic changes.[49] MAGIC (mouth and genital ulceration with inflamed cartilage) syndrome, which is a combination of oral and genital ulceration, ocular disease and chondritis, can be considered in the differential diagnosis.[50] Oral and/or genital ulceration also occurs in syphilis, chancroid and immunobullous skin disorders like pemphigus and erythema multiforme.

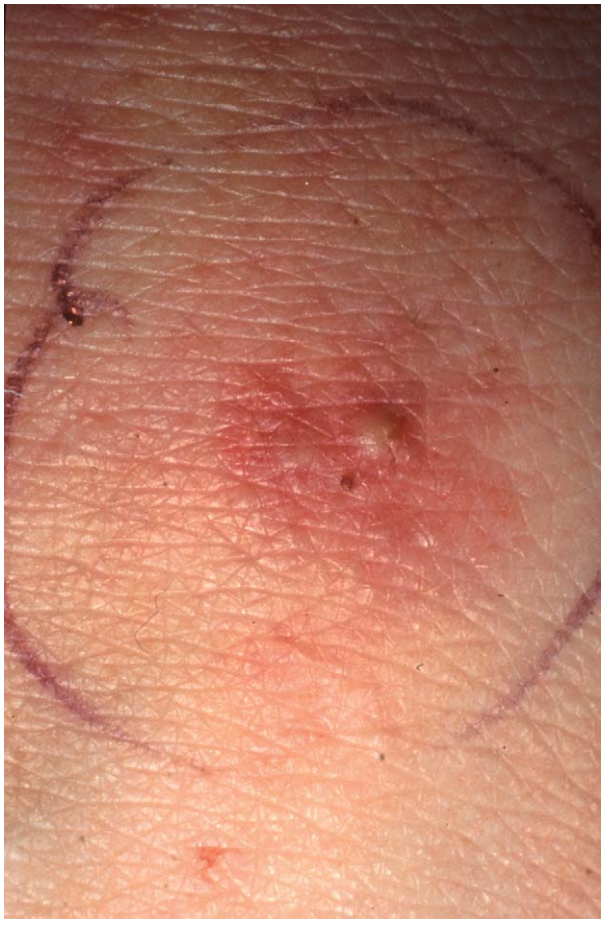

Figure 8 **Pustule developing 48 h after insertion of sterile needle**

TREATMENT

The management of BD should involve close liaison with other specialists, as it is a multisystem disorder. Treatment of the oral and genital ulcers involves topical measures initially, with more potent medications required if these prove ineffective. Ocular manifestations should be treated early, as progression to blindness is a potential morbidity in this disorder. Systemic involvement would require immunosuppression to facilitate remission.

Oral and genital ulceration

Topical corticosteroids in the form of creams, mouth washes, gels, pastes or sprays could be used, although long-term use may cause surface atrophy.[25] Topical lignocaine before meals can be considered for pain control.[51] Recent reports suggest the usefulness of topical tacrolimus in the control of oral and genital lesions. A randomized, double-blind study has shown the effectiveness of sucralfate in this condition.[52] Intralesional corticosteroids, amlexanox 5% paste and tetracycline suspensions are anecdotally reported to be effective.[13]

Colchicine and dapsone are considered the first-line oral medications for mucocutaneous and genital lesions.[25] Dapsone at 100 mg a day can clear oral and genital aphthae, and control erythema nodosum-like lesions seen in BD.[53] Colchicine, 0.6 mg, orally two or three times a day, can decrease the frequency and severity of the ulceration.[54] Thalidomide has been used successfully in oro-genital ulceration, but the associated teratogenicity and the peripheral neuropathy limits its use.[55] A recent multicentre, double-blind, placebo-controlled study has shown the effectiveness of rebamipide, a gastro-protective drug, in the treatment of oral aphthosis (dose 300 mg/day).[56] Other more aggressive therapies are required if no response is gained from these agents, and are listed below under the treatment for systemic involvement.

Ocular management

Anterior uveitis is treated with mydriatics/cycloplegics (to prevent posterior adhesions of the iris) and steroid eye drops. Oral prednisolone,[57] colchicine and methotrexate can be used for resistant disease. Posterior uveitis and renal vasculitis require more urgent attention. Predisolone or dexamethasone eye drops with intra-vitreal triamcinolone acetonide is considered in progressive ocular involvement. Intravenous corticosteroids have been used in acute exacerbation of disease, including acute uveitis and neurological disease.[58] Tacrolimus, a calcineurin inhibitor, has been successful in the treatment of refractory posterior uveitis.[59] Azathioprine reduces the incidence, severity and frequency of eye disease, and also has a favourable effect on arthritis, oral and genital ulceration.[60]

Systemic disease

Potent immunosuppressives can bring about remission in patients with severe systemic manifestations. Corticosteroids (pulse methylprednisolone 1 g/day for three days in acute stages; oral prednisolone 1–2 mg/kg/day) are effective first-line agents.[51] Other agents that have been used include azathioprine,[60] chlorambucil,[61] ciclopsorin,[62] tacrolimus,[63] cyclophosphamide[64] (including a pulse regimen) and methotrexate.[65] The use of TNF-α inhibitors (biological agents), such as infliximab (chimeric monoclonal antibody to TNF-α)[66] and etanercept (a dimeric soluble TNF receptor antagonist),[67] has shown favourable results in BD with severe oro-genital ulceration, but the cost and the limited availability of efficacy data are the main problems associated with the wider use of these agents.[25] Interferon-α has been successfully used in the treatment of systemic manifestations.[68]

Other measures

The correction of haematinic deficiency and treatment of thrombotic disease with warfarin are some of the general measures that are proven to be helpful in BD. Weekly methotrexate in the management of neurological symptoms, sulphasalazine in gastrointestinal disease and anti-CD52 monoclonal antibodies have been tried in active BD.[25] Other alternative therapeutic strategies include immunoablation (autologous haemopoietic stem cell transplantation)[69] and the use of oral tolerizing agents (peptide 336–351 linked to recombinant cholera toxin B subunit).[70] A report suggests the use of plasma exchange for severe BD.[71]

PROGNOSIS

BD is a relapsing and remitting condition, with mucocutaneous and arthritic manifestations more likely to occur first. Young men have a higher mortality and morbidity than women. Ophthalmic involvement is the leading cause of morbidity. Death can result from systemic manifestations like neurological involvement, vascular disease, bowel perforation or as a complication of immunosuppressive therapy.[72] Newer treatments seem to be more promising in the reduction of overall mortality and morbidity.

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