



# Behçet's Syndrome Society

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## The Skin in Behçet's Disease

Behçet's Disease (BD) is a systemic inflammatory disease which has an unpredictable course. Mucocutaneous, ocular, vascular, articular, gastrointestinal, urogenital, pulmonary and neurological involvement are documented.

Since its original description, many different criteria have been used to make the diagnosis. All have included the presence of "typical skin lesions" and a positive pathergy test. In the currently favoured International Study Group (ISG) classification criteria, typical skin lesions include erythema nodosum (EN)-like lesions, pseudofolliculitis, papulopustular lesions and acneiform nodules (in post adolescent patients not being treated with oral corticosteroids).

Other recognised skin manifestations, which are not included in the ISG criteria, are pyoderma gangrenosum-like lesions, Sweet's syndrome-like lesions, cutaneous vasculitis lesions which may present as palpable purpura, bullous or necrotizing lesions, facial and acral vesicopustules, extragenital ulcers and superficial thrombophlebitis.

Skin involvement is a major feature of BD occurring in 44-88% of patients. In a recent study of 661 Turkish patients 55.4% had papulopustular lesions, 44.2 % had erythema nodosum-like lesions and positive pathergy tests were documented in 37.8%. Thrombophlebitis occurred in 10.7%.

In terms of disease severity skin involvement is usually classified as mild disease, it can however cause significant morbidity and adversely affect quality of life. Skin lesions tend to occur early in the course of the disease. This is in contrast to neurological, large vessel and gastrointestinal manifestations, which seem to occur later, sometimes up to 5-10 years after diagnosis.

Several studies have shown a delay of between 5 and 10 years between the onset of symptoms and diagnosis. This is particularly so in patients who present with mucocutaneous lesions (oral, genital ulcers and skin lesions) compared with those presenting with eye, gut or large vessel disease.

One of the difficulties in establishing the diagnosis in this situation is that apart from the pathergy reaction, the clinical appearances of the skin lesions in Behçet's disease are often indistinguishable from similar lesions occurring in other conditions. For instance the erythema nodosum-like lesions of BD are clinically indistinguishable from those which occur in association with streptococcal infection, sarcoidosis, inflammatory bowel disease, rheumatoid arthritis or no underlying disease. The diagnosis therefore relies on the constellation of symptoms and signs and also on histological appearances of a skin biopsy. Various different patterns of inflammation are recognised but neutrophils (a type of white blood cell) are commonly involved. Typical findings include inflammation in and around blood vessels (leukocytoclastic vasculitis +/- red cell extravasation / mural thrombus / necrosis) in the skin and subcutaneous fat (mixed lobular and septal panniculitis). Acneiform lesions tend to show inflammation around hair follicles (suppurative and occasionally granulomatous folliculitis).

### **Papulopustular lesions, Acneiform and Folliculitis-like lesions**

These are the commonest skin lesions present in over 50% of cases (in some studies > 95% of cases). They resemble acne lesions in that they are small red spots (papules), which develop over the course of 24-48 hours into pustules. They are non-infective (sterile). They may be centred around hair follicles (folliculitis) or resemble larger acne-like nodules. Unlike typical acne lesions, they are seen more often on the trunk and legs rather than the face. In my opinion, the literature is confusing in that it describes acneiform and folliculitis lesions separately from papulopustular lesions. Clinically and histologically it would be difficult to distinguish between these lesions. The histological features can be non specific and include a diffuse dermal neutrophilic infiltrate, with or without abscess formation. The current ISG classification also mentions pseudofolliculitis- to most dermatologists this represents a process in which inflammation is caused by ingrowing hairs. This type of clinical picture is NOT seen in Behçet's patients and so the terminology is confusing again. My feeling is that it is perhaps best to refer only to papulopustular lesions and state their site and whether they are centred around hair follicles or not.

### **Pathergy**

The definition of a positive pathergy test is the presence of a papule or pustule 24-48 hours after oblique insertion of a 20-gauge or smaller needle into the skin under sterile conditions. This is often seen at blood test sites. Microscopic features have included leukocytoclastic vasculitis in some studies and neutrophilic infiltrates with intraepidermal pustules in others.

### **Erythema Nodosum-like lesions**

These are present in roughly 40% of patients. They are hot, red, tender swellings measuring several centimetres in diameter. Lesions are found most often on the lower legs, but can occur at any site. They are commoner in women. Lesions usually resolve over 2-3 weeks and may leave a bruise-like area or increased pigmentation. Microscopic examination is slightly different to lesions of classical erythema nodosum: there is typically a lobular or mixed lobular and septal panniculitis. The infiltrate can be lymphocytic, neutrophilic or histiocytic and there may be an associated vasculitis.

### **Superficial thrombophlebitis**

Present in 10-30% of patients, this is often confused with erythema nodosum. Red tender subcutaneous nodules are arranged in a line. An inflamed vein is palpable as a thickened cord beneath the overlying red skin.

### **Pyoderma gangrenosum**

This tends to present either as an acne-like pustule, haemorrhagic blister, or as a tender red nodule (lump), often on the legs. Lesions become blue centrally and then ulcerate rapidly, and have a bluish raised thickened edge, which is sometimes undermined. The central necrosis (area of dead skin) develops into a red oedematous ulcer crater. Healing leaves an atrophic or cribriform scar. 20% show a Koebner response; new lesions provoked by trauma, including pin-prick. Pyoderma gangrenosum is not an infective process but it is important to exclude other causes of similar rapidly progressive ulcers, especially infection with microaerophilic Streptococci and Clostridium species. Microscopic examination shows a sterile abscess in which venous and capillary thrombosis, haemorrhage, necrosis and massive cell infiltration are seen. Sometimes there is an overlap with lymphocytic or leukocytoclastic vasculitis

### **Sweets syndrome-like lesions**

These tend to begin as tender, non-itchy red plaques or papules, which sometimes have a yellowish centre. Because of the associated inflammation and swelling (oedema) in the skin they appear raised and sometimes blisters and pustules develop within the plaques. Lesions can occur anywhere on the body, but favour the face and extremities. Histology

characteristically shows a diffuse nodular and perivascular neutrophilic infiltrate with leukocytoclasia and endothelial swelling but without fibrinoid necrosis. Occasionally the inflammation is deeper causing erythema nodosum-like lesions

### **Vasculitis**

True vasculitic lesions may present as non-blanching, red to purple, flat spots known as purpura, blisters (bullae) or if the skin is damaged beyond repair, it turns black or sloughs off at the site of the lesion (necrosis). On microscopy there is infiltration of neutrophils with leukocytoclasia, endothelial swelling and fibrinoid necrosis.

### **Extragenital ulcers**

These resemble the oral and genital ulcers and can be painful. They are small roundish ulcers, which are well circumscribed, have a red halo and yellow or grey base. They may last several weeks.

### **Management**

There is some evidence to suggest that effective early treatment may control and perhaps change the course of BD in some patients.

For ulcers, topical or intralesional steroids, topical sucralfate and topical lidocaine gel are helpful.

Controlled studies have shown that colchicine, thalidomide, dapsone, azathioprine, interferon alpha and etanercept are effective to some degree in treating mucocutaneous lesions of BD. (reviewed in *Sfikakis PP et al. Rheumatology 2007; 46:736*, *Alpsoy E et al. Yonsei Med J 2007;48:573* and *Hatemi G et al. 2008 Ann Rheum Dis.*)

Colchicine 1-2mg/day has been shown in double blind and open trials to be effective in treatment of erythema nodosum-like lesions and oral ulcers (*Yardacul S et al. Arthritis Rheum 2001;44:2686*).

There is evidence in double blind trials that Dapsone 100mg daily can be of benefit to oral ulcers and cutaneous lesions (*Sharquie Keet al. J Dermatol 2002;29:267*)

Trials have shown improvement of follicular lesions with Thalidomide 100mg-300mg daily (eg *Hamaryudan V et al. Ann Int Med 1998;128:443*).

An open label study of indomethacin 25mg 4 times daily in 30 patients was effective in treating erythema nodosum-like lesions, pustular lesions and ulcers. (*Simsek H. Int J Dermatol 1991;30:54*)

Methotrexate has been used for neutrophilic vascular reactions and Cyclosporine 5mg/kg, for oral aphthae, erythema nodosum-like lesions, pyoderma gangrenosum, folliculitis/acneiform lesions and thrombophlebitis.

Oral corticosteroids 30-60mg daily may also be used as monotherapy or in combination with the above therapies.

For more severe disease high dose oral steroids (1-3mg/kg/day) may be used in combination with methotrexate, cyclosporine (up to 10mg/kg), azathioprine (up to 3mg/kg), chlorambucil or cyclophosphamide.

Resistant cases may require pulsed methylprednisolone (1g/ day for 5 days in 150ml of 5% dextrose over 1 hour), Interferon alpha, high dose intravenous immunoglobulin, or newer, biologic agents such as anti-TNF (so-called biological) agents. A double blind placebo controlled trial of Etanercept 25mg x2/wk in 40 males showed an effect on oral ulcers and nodular lesions- in the 1<sup>st</sup> week (85% clearance of nodular lesions at 4wks vs 25% with placebo (*Melikoglu M et al. J Rheumatol 2005; 32:98*). Relapse was seen after 3 months in some patients and it didn't affect the pathergy response.

Infliximab has also been used with excellent results in patients with severe mucocutaneous disease (*Estrach C et al. Rheumatology 2002;41:1213 and reviewed in Sfrikakis PP et al. Rheumatology 2007; 46:736*)

Management decisions should be individualised. Current recommendations are that etanercept or infliximab may be used for skin disease in patients with poor quality of life, or who are intolerant of adequate doses of azathioprine (2.5 mg/kg/day), colchicine (1.5mg/day) or thalidomide (up to 300mg/day) and who require prednisolone at a dose of >7.5mg/day.

***Dr Cate Orteu, June 2008***