

7. Behçet's Disease and the Skin

Note: This Factsheet contains a lot of medical terminology and we suggest you may want to ask your GP or Dermatologist to interpret it for you.

How is the skin affected by Behçet's disease?

Since the original description of Behçet's disease, 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-like lesions, pseudofolliculitis, papulopustular lesions and acneiform nodules (in postadolescent 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 necrotising lesions, facial and acral vesicopustules, extragenital ulcers and superficial thrombophlebitis.

Skin involvement is a major feature of Behçet's disease, occurring in 44–88% of patients. In a 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.

Complications

Papulopustular, acneiform and folliculitis-like lesions

These are the most common skin lesions, being present in more than 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 than on the face.

The literature is confusing, in that it describes acneiform and folliculitis-like lesions separately from papulopustular lesions. Clinically and histologically, it would be difficult to distinguish between these lesions. The histological features can be nonspecific and include a diffuse dermal neutrophilic infiltrate, with or without abscess formation. The current ISG classification also mentions pseudo folliculitis – 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 disease patients, so the terminology is confusing again. 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 (inflammation in and around blood vessels) 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 they can occur at any site. They are more common in women. Lesions usually resolve over 2–3 weeks and may leave a bruise-like area or increased pigmentation. Microscopic examination shows slight differences from 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 or haemorrhagic blister, or as a tender red nodule (lump), often on the legs. Lesions become blue centrally and then ulcerate rapidly; they 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. About 20% show a Köebner response, with new lesions provoked by trauma, including pinprick. 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.

Sweet's 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, and 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 and have a red halo and a yellow or grey base. They may last several weeks.

Diagnosis

Several studies have shown a delay of 5 to 10 years between the onset of symptoms and diagnosis of Behçet's disease. This is particularly so in patients who present with mucocutaneous lesions (oral or 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 Behçet's disease are clinically indistinguishable from those that 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 with or without 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).

Treatment

There is some evidence to suggest that effective early treatment may control and perhaps change the course of Behçet's disease 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 Behçet's disease.¹⁻³

Colchicine 1–2 mg/day has been shown in double-blind and open-label trials to be effective in treatment of erythema nodosum-like lesions and oral ulcers.⁴

There is evidence from double-blind trials that dapsone 100 mg daily can be of benefit for oral ulcers and cutaneous lesions.⁵ Trials have shown improvement of follicular lesions with thalidomide 100–300 mg daily.⁶

An open-label study in 30 patients found that indomethacin 25 mg four times daily was effective in treating erythema nodosum-like lesions, pustular lesions and ulcers.⁷ Methotrexate has been used for neutrophilic vascular reactions and cyclosporine 5 mg/kg for oral aphthae, erythema nodosum-like lesions, pyoderma gangrenosum, folliculitis/acneiform lesions and thrombophlebitis. Oral corticosteroids 30–60 mg daily may also be used as monotherapy or in combination with the above therapies.

For more severe disease, high-dose oral steroids (1–3 mg/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 150 ml of 5% dextrose over 1 hour), interferon-alpha, high-dose intravenous immunoglobulin or newer so-called biologic drugs such as anti-TNF agents. A double-blind placebo-controlled trial of etanercept 25 mg twice weekly in 40 males showed an effect on oral ulcers and nodular lesions in the first week (85% clearance of nodular lesions at 4 weeks versus 25% with placebo).⁸ Relapse was seen after 3 months in some patients, and it did not affect the pathergy response. Infliximab has also been used with excellent results in patients with severe mucocutaneous disease.^{1,9}

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 (1.5 mg/day) or thalidomide (up to 300 mg/day) and who require prednisolone at a dose of more than 7.5 mg/day.

References

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