How is the skin affected by Behçet’s?

Since the original description of Behçet’s, many different criteria have been used to make the diagnosis. All have included the presence of “typical skin lesions”, as this is said to occur in over 75% of patients. In the most recently developed International Criteria for Behçet’s Disease (ICBD) classification criteria, typical skin lesions include erythema nodosum-like lesions, inflammatory papulo-pustular lesions (also referred to as pseudo-folliculitis in some cases), and characteristic skin ulcers (aphthosis). A positive pathergy test is supportive although no longer considered essential for the diagnosis.

Other recognised skin manifestations, which are not included in the ICBD criteria, are acneiform lesions (often seen in Behçet’s but not characteristic), pyoderma gangrenosum-like lesions and Sweet’s syndrome-like lesions. Vascular manifestations may also present in the skin as palpable purpura, bullous or necrotising lesions, facial and acral (hands and feet) vesicopustules, extragenital ulcers and superficial thrombophlebitis.

In terms of disease severity, skin involvement is usually classified as mild disease. It can, however, have a significant impact on patients 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.

Erythema nodosum-like lesions

These are present in roughly 40% of patients. They are hot, red, tender swellings measuring several centimetres in diameter. They are found most often on the lower legs, but they can occur at any site. They are more common in women. They usually resolve over 2–3 weeks and may leave a bruise-like area or increased pigmentation. Microscopic examination shows slight differences from changes seen in classical erythema nodosum: there is typically a lobular or mixed lobular and septal panniculitis (these are histological patterns of inflammation of the layer of fat under the skin). The infiltrate may be largely composed of different inflammatory immune-system mediated cells, such as lymphocytes, neutrophils or histiocytes, and there may be an associated vasculitis (inflammation of the blood vessels).

Papulo-pustular 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 papules (small red spots), which develop over the course of 24–48 hours into pustules (small white bumps containing pus) – so called papulo-pustular lesions. They are non-infective (sterile).

They may appear to be centred around hair follicles, and so are sometimes called pseudo-folliculitis (folliculitis-like lesions), or acneiform (resembling 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.

**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 occur in the skin at sites other than the genitals and may last several weeks.

**Pyoderma gangrenosum**

This tends to present either as an acne-like pustule, or haemorrhagic blister (blood-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 (swollen) ulcer crater. Healing leaves scarring which may be atrophic (thinned or depressed) or cribiform (perforated with small pits). About 20% show a Köebner response, with new lesions provoked by trauma, including at the site of needle insertion for blood tests. Pyoderma gangrenosum is not an infective process, but it is important to exclude other causes of similar rapidly progressive ulcers including infection. Microscopic examination shows a sterile abscess in which the blood vessels are affected, with venous and capillary thrombosis (blood-clot formation inside vessels), haemorrhage (bleeding), necrosis (tissue injury) and massive cell infiltration are seen. Sometimes there is an overlap with lymphocytic or leukocytoclastic vasculitis (inflammation in and around blood vessels).

**Sweet’s syndrome-like lesions**

These tend to begin as tender, non-itchy red plaques (larger elevated area of skin) or papules (small spots), which sometimes have a yellowish centre. Because of the associated inflammation and swelling 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 infiltrate composed of neutrophils (white blood cells), with leukocytoclasia (disintegration of neutrophils) and endothelial swelling (affecting the internal lining of blood vessels) but without fibrinoid necrosis (a type of tissue injury). Occasionally, the inflammation is deeper causing erythema nodosum-like lesions.

**Vasculitis**

This is defined as inflammation of the blood vessels. True vasculitic lesions may present as purpura (non-blanching, red-to-purple, flat spots), and bullae (larger fluid filled blisters); 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.

**Superficial thrombophlebitis**

Present in 10–30% of patients, this is often confused with erythema nodosum. It presents as red, tender, subcutaneous nodules (lumps under the skin) which are arranged in a line. An inflamed vein is palpable as a thickened cord beneath the overlying red skin.
**Pathergy**

A positive pathergy test is the presence of a small papule or pustule that develops 24-48 hours after a skin-prick with a small needle, or after intracutaneous injection of 0.1ml saline into the skin. This is often seen at blood test sites. Microscopic features have included leukocytoclastic vasculitis in some studies and neutrophilic infiltrates with pustules in others.

**Diagnosis**

Several studies have shown a delay of 5 to 10 years between the onset of symptoms and diagnosis of Behçet’s. 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 are often indistinguishable from similar lesions occurring in other conditions. For instance, the erythema nodosum-like lesions of Behçet’s 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 are commonly involved. Typical findings include inflammation in and around blood vessels in the skin and subcutaneous fat. Acneiform lesions tend to show inflammation around hair follicles.

**Treatment**

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

**Topical treatments**

For ulcers, topical or intralesional steroids, topical sucralfate and topical lidocaine gel are helpful. For acne-like lesions, topical treatments as used in the common-type acne vulgaris are recommended.

**Systemic treatments**

In general, as topical treatments work only at the site of application, they are often combined with systemic therapy. Systemic therapy is also considered in treatment-resistant and more severe cases.

Colchicine, dapsone and indomethacin have been shown to be effective in the treatment of erythema nodosum-like lesions, and oral ulcers. Thalidomide has also shown efficacy in the treatment of follicular lesions. Benzathine penicillin has been shown to reduce the frequency of nodular lesions.

For more severe presentations, immunosuppressant medications are often prescribed. Methotrexate can be beneficial, particularly in neutrophilic vascular reactions. Ciclosporin and chlorambucil have been used to treat oral ulcers, erythema nodosum-like lesions, pyoderma gangrenosum, pseudofolliculitis/acneiform lesions and thrombophlebitis. Azathioprine can also be beneficial in the treatment of ulcers. Oral or intravenous corticosteroids may also be used alone or in combination with the above therapies. Other treatments include interferon-alpha, zinc sulphate, rebamipide and pentoxifylline.
Biologic therapies

More recently, a host of biologic agents have been used in severe and treatment-resistant cases, and in particular, the anti-TNF-alpha agents have shown promise. In one randomised controlled trial, etanercept was reported to show efficacy in the treatment of mucocutaneous lesions, particularly oral ulcers and nodular lesions, in the short-term. There are reports of benefit with other anti-TNF-alpha treatments such as infliximab and adalimumab, however no large trials have been conducted with these treatments to date. Other biologic treatments with reported success include the anti-interleukin-1 agents such as anakinra and canakinumab, which have shown efficacy and safety in a small cohort of patients. Biologics in Behçet’s are still reserved for severe cases, and the benefits and risks need to be carefully considered prior to commencing therapy.

References


