Behçet's Factsheet 7
Skin

This factsheet is also written for health professionals, so you may find a lot of medical terminology. You may find it helpful to ask your GP or Dermatologist to help interpret it for you.

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 2013 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 (apthosis). 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. In contrast to neurological, large vessel and gastrointestinal manifestations, which tend to occur later, sometimes up to 5–10 years after diagnosis, skin lesions tend to occur early in the disease course. Early identification of skin lesions is, therefore, important for early diagnosis and prevention of disease complications.

It is increasingly recognised that Behçet's often presents with multiple phenotypes encompassing varying symptom predominance. It is estimated that around one third of patients have skin manifestations without other organ involvement. Studies have suggested a positive association between arthritis and the presence of papulopustular lesions [1-5].

Papulopustular lesions (PPL)

These are the most common skin lesions, being present in more than 65% of cases (in some studies >95% of cases) [2,3].

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 papulopustular lesions. They are non-infective (sterile).

They may appear to be centred around hair follicles, and so are sometimes called *follicular papulopustular* lesions (or pseudo-folliculitis). They may also be *acneiform* (resembling larger acne-like nodules). Non-follicular papulopustular lesions refers to lesions that do not occur around a hair follicle.

It can be challenging to differentiate these lesions from typical acne lesions. It has been suggested that non-follicular PPL localised to non-seborrheic (areas with fewer sebaceous glands) may be more specific for Behçet's [2,3]. 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.

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 neutrophils in the early stage with the addition of lymphocytes at a late stage [2]. There may be an associated vasculitis (inflammation of the blood vessels).

Extragenital ulcers

These are rare (<3%), resemble oral and genital ulcers, and can be painful [3]. 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.

Superficial thrombophlebitis

Present in 10–20% of patients and more commonly seen in men [2,3], 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. An ultrasound scan may be useful in differentiating superficial thrombophlebitis from erythema nodosum. EN-like lesions show a hyperechoic pattern whereas superficial thrombophlebitis show a hypoechoic pattern [2].

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 cribriform (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 leukocytoclasis, endothelial swelling and fibrinoid necrosis.

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. This is often seen at blood test sites. Microscopic features have included leukocytoclastic vasculitis in some studies and neutrophilic infiltrates with pustules in others. Positivity rates have been shown to be affected by a variety of factors, including skin cleaning, needle size and disease activity, with variability across the disease course [3,6].

Treatment

There are a variety of treatment options available in Behçet's disease with promising ongoing research. Due to the wide-ranging manifestations of Behçet's, treatments should be selected on an individual basis. A multidisciplinary team approach is considered essential for successful management. 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

Topical or intralesional steroids, as well as topical sucralfate and topical lidocaine gel, can be used in an acute exacerbation of mucocutaneous ulcers [3,7]. For papulopustular lesions resembling acne, topical treatments as used in the common-type acne vulgaris are recommended [3,7].

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 is recommended as a first-line treatment in the prevention of recurrent mucocutaneous lesions, particularly genital ulcers and erythema nodosum-like lesions, and may also be effective for papulopustular lesions. Colchicine is effective for treating articular manifestations, so may be particularly useful in patients presenting with the papulopustular/ arthralgia phenotype. In cases refractory to colchicine treatment alone, the addition of benzathine penicillin injections may be beneficial [3,7,8]. Benzathine penicillin has been shown to reduce the frequency of nodular lesions.

Short courses of systemic corticosteroids may be used as an adjunctive therapy in acute attacks of mucocutaneous lesions, although monotherapy is not recommended [3].

Dapsone and indamethacin 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; however, its side effect profile may limit its use.

For chronic and more severe recurrent papulopustular or acne-like lesions resembling acne-congoblata or cystic acne, systemic retinoids combined with surgical interventions are sometimes helpful.

Apremilast (a phosphodiesterase inhibitor) is a key new treatment option that has proven efficacy in the treatment of active oral ulcers. Studies have suggested it may also be useful in the treatment of genital ulcers and papulopustular lesions, although further research is required [1,3,7-9].

Azathioprine and cyclosporine-A are effective in the treatment of oral and genital ulcers and are often used for patients with mucocutaneous Behcet's who have ocular involvement. Adverse side-effects limit the use of cyclosporine-A and should be avoided in patients with neurological involvement [3,7].

Other treatments which can be beneficial for mucocutaneous involvement include azithromycin, interferon-alpha, zinc sulphate, rebamipide and pentoxifylline.

Biologic therapies

Recent advances in biologic therapies have expanded the treatment options for Behçet's. In particular, the TNF-alpha inhibitors, including infliximab and adalimumab, have shown promise and are sometimes used in patients with skin disease associated with multi-organ involvement. Interferon-alpha has also been shown to reduce the frequency of ulcers and papulopustular lesions. Other agents, such as alemtuzumab, IL1-antagonists (anakinra and canakinumab), ustekinumab and secukinumab have been trialled in a small number of patients with refractory Behçet's with positive outcomes [3,7,8]. Biologics in Behçet's are still reserved for severe cases, and the benefits and risks need to be carefully considered prior to commencing therapy.

Version	Last Review Date	Authors
3.0	April 2022	Dr Christina George/Dr Cate Orteu/Dr E K Jackson

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