

Classic diseases revisited

Cutaneous sarcoidosis

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Summary

Sarcoidosis is a multi-organ granulomatous disorder of unknown cause. Skin sarcoidosis occurs in about 25% of patients with systemic disease and may also arise in isolation. A wide range of clinical presentations of cutaneous sarcoidosis is recognised. The diagnosis rests on the presence of non-caseating granulomas on skin biopsy and the exclusion of other granulomatous skin disease. The treatment and overall prognosis of cutaneous sarcoidosis is primarily dependent on the degree of systemic involvement. In patients with aggressive disease limited to the skin immunosuppressive therapy may be indicated.

Keywords: sarcoidosis; skin disease

Sarcoidosis is a multisystem disease of unknown aetiology characterised histologically by the formation of non-caseating epithelioid cell granulomas. The disease may affect any organ, especially the lungs, eyes, lymph nodes and skin. The clinical manifestations are therefore protean. Skin involvement occurs in between 20% and 35% of patients with systemic disease but may also occur in isolation.¹

Epidemiology

Sarcoidosis affects all races, ages, and both sexes but is more common, and more severe, in blacks.² It is also common in Scandinavia and in the Irish.

Aetiology

The cause of sarcoidosis remains unclear with possible genetic, immunological, environmental and infectious factors. It would seem that exposure to antigens in predisposed individuals may lead to an exaggerated immune response, with the development of granulomatous inflammation and subsequent fibrosis.

Sarcoidosis shares clinical and pathological features with tuberculosis and mycobacteria have often been implicated in the aetiology of sarcoidosis. However, polymerase chain reaction (PCR) analysis for mycobacterial DNA in sarcoid tissue has shown divergent results.³ Recently PCR has demonstrated human herpes virus 8 DNA sequences in many sarcoidal tissues, including skin, but a causal relationship between this agent and sarcoidosis has not been demonstrated.⁴

Classification

Cutaneous manifestations may be described as non-specific or specific.⁵ Erythema nodosum is the non-specific eruption while specific lesions arise due to granulomatous infiltration of the skin (box 1). A variety of different skin lesions may occur in the same patient.



Figure 1 Erythema nodosum



Figure 2 Maculopapular sarcoidosis

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Accepted 12 May 1998

Specific types of cutaneous lesions

- maculopapular
- nodular
- annular
- scar sarcoidosis
- lupus pernio
- plaque
- rare forms

Box 1

ERYTHEMA NODOSUM

Sarcoidosis is only one of many causes of erythema nodosum, which is thought to be a reactive phenomenon. Typically ill-defined tender, red nodules arise on the limbs and resolve over 2 to 3 weeks with characteristic bruising (figure 1).

Erythema nodosum is classically seen in young women as a marker of acute sarcoidosis.⁶ It is often seen in association with arthralgia, general malaise and bilateral hilar lymphadenopathy on chest X-ray.

MACULOPAPULAR SARCOIDOSIS

Lesions arise as asymptomatic macules and papules ranging in colour from red-brown to purple and in size up to 5 mm (figure 2). The commonest areas of involvement are the face and extensor aspects of the limbs. Spontaneous resolution may occur with or without atrophic scarring.

NODULAR SARCOIDOSIS

This form predominantly affects the proximal limbs and face. It is characterised by the development of well-circumscribed nodules measuring more than 5 mm across (figure 3). Again, the colour may vary from red-brown to violaceous and there may be surface telangiectasia. Lesions tend to be indolent.

ANNULAR SARCOIDOSIS

Annular forms of cutaneous sarcoidosis are well recognised.⁷ Lesions of maculopapular sarcoidosis often show annular formations. A more severe variant, often occurring on the face and resembling necrobiosis lipoidica, is also seen. Disfiguring circinate lesions arise with a leading granulomatous edge and a central atrophic area with telangiectasia (figure 4). This form tends to be persistent.

SCAR SARCOIDOSIS

Granulomatous infiltration of scars by sarcoidal tissue may occur in a number of situations, eg, surgical scars, at vaccination sites, and in tattoos.⁸ Scars become infiltrated and inflamed with a violaceous colouration (figure 5). Scar sarcoidosis activity may parallel systemic disease behaviour,⁵ but may also occur in isolation.

LUPUS PERNIO

This is more common in older patients and women.⁹ The face and nose are usually involved with the development of infiltrated blue-red plaques and nodules (figure 6). Lupus pernio is usually associated with chronic sarcoidosis, especially involvement of the upper respiratory tract, lacrimal glands and bone. The cosmetic effects of lupus pernio may be severe and lead to considerable psychological distress.

PLAQUE SARCOIDOSIS

This indolent form of the disease usually involves the limbs with diffuse plaques (figure 7). Again, these lesions may show similar features to the atrophic plaques of necrobiosis lipoidica.

RARE FORMS

Other manifestations of cutaneous sarcoidosis which have been described include nail involvement (figure 8) and angioid, ulcerative, subcutaneous, ichthyosiform, psoriasiform, and lichenoid forms.



Figure 3 Nodular sarcoidosis



Figure 4 Annular sarcoidosis



Figure 5 Scar sarcoidosis



Figure 6 Lupus pernio



Figure 7 Plaque sarcoidosis

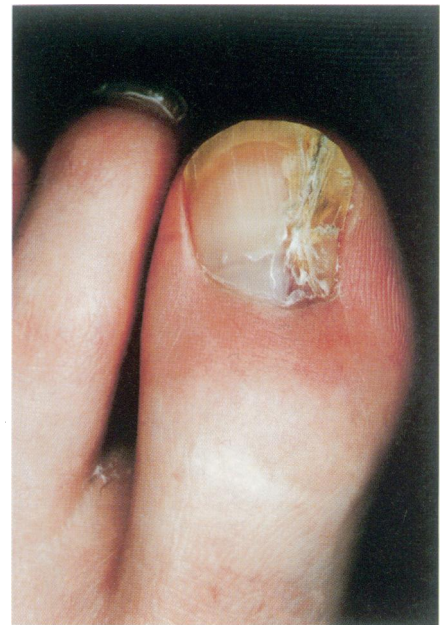


Figure 8 Nail dystrophy

Investigation

SKIN BIOPSY

Sarcoidosis is a heterogeneous disease and there is no one diagnostic test. Diagnosis rests upon demonstrating granulomatous inflammation and ruling out other causes of such inflammation. Clinically, diascopy may be helpful in demonstrating granulomatous inflammation. In this technique, a glass slide is pressed against the skin and 'apple-jelly' nodules may be seen.

Skin lesions are uniquely amenable to biopsy and this is the investigation of choice. In patients with features suggestive of systemic disease, who have skin lesions, skin biopsy is preferable to more invasive tests such as bronchoscopy and the Kveim test. Biopsy specimens typically show a dermal infiltrate of non-caseating granulomas, composed of epithelioid cells, multinucleate giant cells and a thin peripheral rim of lymphocytes (figures 9 and 10). Mycobacterial and deep fungal infection should be excluded by appropriate culture and special stains.

In the Kveim test, skin biopsy is performed 6 weeks after intradermal injection of purified sarcoidal antigen. A positive result occurs when granulomas are seen histologically. The popularity of this investigation has waned recently, due to concerns about the potential risk of transmission of infectious agents. It is still, however, of use in difficult cases.

OTHER INVESTIGATIONS

If the diagnosis of sarcoidosis is strongly suspected on clinical and pathological grounds then further investigation should be tailored to identify systemic disease and establish a baseline of disease activity. Mandatory baseline investigations should include chest X-ray, pulmonary function tests (including measurement of transfer factor), electrocardiogram, full blood count, biochemistry, serum immunoglobulins and a 24-hour urinary calcium assay.¹⁰ Measurement of serum angiotensin-converting enzyme (ACE), which is produced by sarcoidal granulomas, may be helpful in monitoring disease activity.¹¹ It is not a particularly useful diagnostic test as levels may be raised in other conditions such as diabetes and alcoholic liver disease.⁵ In our own department we refer all patients with a diagnosis of cutaneous sarcoidosis to a respiratory physician for advice and management on systemic disease.

Treatment

The acute symptoms of erythema nodosum usually respond to a combination of rest and non-steroidal anti-inflammatory agents, but occasionally a short course of systemic steroids may be required. Limited cutaneous disease may require no treatment. Alternatively, cosmetic cover, potent topical corticosteroids, or

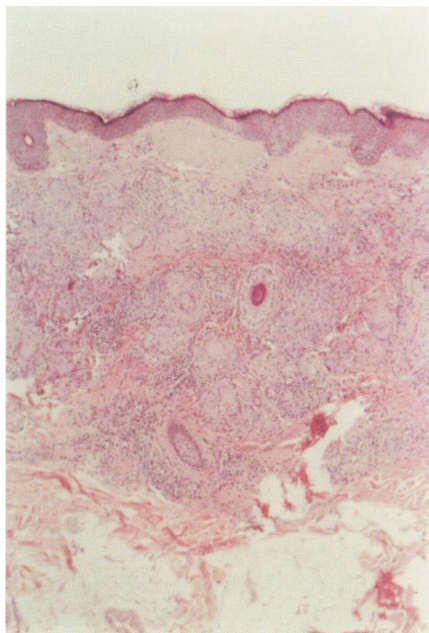


Figure 9 Sarcoid granulomas (low power)

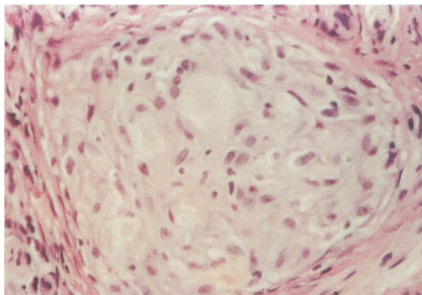


Figure 10 Sarcoid granuloma (high power)

Indications for systemic treatment

- severe respiratory disease
- hypercalcaemia
- uveitis
- neurological disease
- cardiac disease

Box 2

intralesional corticosteroids may be useful.⁶ In resistant localised disease, both surgery and radiotherapy have been reported as helpful.^{10 11}

The use of immunosuppressants in cutaneous disease is indicated in those with severe systemic illness (box 2) and those with extensive or disfiguring skin disease.

Oral corticosteroids remain the drug of first choice with daily doses of 30 to 40 mg of prednisolone for 6 to 12 weeks.^{2 12} Doses are then reduced according to clinical response and treatment is continued for 6 to 12 months. Relapse of disease may require further corticosteroid therapy.

Methotrexate has also been used to treat both systemic and cutaneous disease with good effect.¹⁵⁻¹⁹ It has been given in doses ranging from 7.5 to 25 mg weekly and is generally well tolerated. Regular monitoring of liver function tests and haematology is required during therapy. Cutaneous disease may only respond after prolonged therapy with methotrexate and 6 to 12 months of treatment may be necessary to initiate a response.

A wide range of alternative systemic drugs has been employed in treating cutaneous sarcoidosis but reports of their use are often anecdotal. Such agents include anti-malarials, thalidomide and allopurinol.²⁰⁻²²

Prognosis

With the exception of erythema nodosum and maculopapular sarcoidosis, most forms of cutaneous sarcoidosis are chronic in nature. Many forms, especially lupus pernio, are associated with systemic disease and tend to be persistent without treatment. In such cases the overall prognosis of the condition relates to the extent and severity of internal involvement.

We would like to thank Dr S Evans for providing clinical photographs for this article.

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