

## GRANULOMATOUS CUTANEOUS SARCOIDOSIS: DIAGNOSIS, RELATIONSHIP TO SYSTEMIC DISEASE, PROGNOSIS AND TREATMENT

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**ABSTRACT.** Sarcoidosis is an antigen-mediated disease of unknown aetiology, characterized by the presence of non-caseating epithelioid cell granulomas in multiple organs. Cutaneous involvement in sarcoidosis is classified as specific, when biopsy reveals non-caseating granulomas, and non-specific, typically erythema nodosum. Granulomatous skin lesions occur in 9% to 37% of patients. The skin is the second most commonly involved organ after the lung. A skin biopsy is easy to perform and enables an early diagnosis with a minor invasive procedure. Some types of specific lesions have prognostic significance and may help to predict the outcome of the systemic disease. Maculopapules, subcutaneous nodules and scar sarcoidosis are usually transient or tend to follow the course of the systemic disease. Skin plaques and lupus pernio are associated with chronic sarcoidosis. Although most cutaneous lesions of sarcoidosis do not cause significant morbidity and do not require treatment, some have cosmetic importance because they may be disfiguring and can have a strong psychosocial impact. Treatment of these lesions is a challenge since they do not respond well to conventional treatments. This manuscript reviews the clinical characteristics of the more frequent types of specific cutaneous lesions of sarcoidosis, the relationship between cutaneous involvement and systemic disease, the prognostic significance of lesions and the present state of treatment of difficult cases of cutaneous sarcoidosis. (*Sarcoidosis Vasc Diffuse Lung Dis* 2013; 30: 268-281)

**KEY WORDS:** Cutaneous sarcoidosis, lupus pernio, systemic sarcoidosis, prognosis of sarcoidosis, treatment of sarcoidosis

### INTRODUCTION

Sarcoidosis was first described at the end of the nineteenth century as a non-caseating granulomatous cutaneous disease with absence of microorganisms. Over the years it became apparent that sarcoidosis may affect other organs without involving

the skin (1). In the 1950s, Sven Löfgren reported that erythema nodosum (EN), a non-granulomatous skin lesion, combined with bilateral hilar adenopathy (BHL) on a chest radiograph, constituted a particular manifestation of acute sarcoidosis (2). Löfgren's syndrome (LS) is associated with good prognosis (3). Therefore, cutaneous manifestations of sarcoidosis are classified as specific when biopsy shows non-caseating granulomas and non-specific, typically EN, which is characterized histopathologically by septal panniculitis (4). Both types of lesion may coexist in the same patient (5).

Cutaneous involvement in sarcoidosis is important for several reasons. A sarcoid skin lesion may be

Received: 22 April 2013

Accepted after revision: 8 August 2013

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a sign of systemic disease. A skin punch biopsy under local anaesthesia is easy to perform and enables early diagnosis with a minor invasive procedure. Some types of lesions have prognostic significance and may help to predict the outcome of the systemic disease. Although the majority of cutaneous lesions of sarcoidosis rarely cause significant morbidity or mortality and do not require treatment, some of them may have cosmetic implications as they may be disfiguring and have a strong psychosocial impact. Treatment of these types of lesions is difficult and is one of the present challenges of sarcoidosis. Recently, the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) recommended several endpoints for clinical trials in cutaneous sarcoidosis, in addition to other manifestations of the disease (6).

The subject of cutaneous sarcoidosis has been reviewed on several occasions (5,7-17). This manuscript briefly summarizes the clinical characteristics of the more frequent types of specific skin sarcoidosis. Based on our recently published series on cutaneous sarcoidosis (18), the manuscript mainly focuses on the relationships between cutaneous involvement and systemic disease and on the prognostic significance of lesions. The present state of treatment of difficult cases of cutaneous sarcoidosis is also reviewed.

## EPIDEMIOLOGY

The frequency of specific (granulomatous) skin lesions in sarcoidosis ranges from 9% to 37%, according to different series (5,8,19-22). In *A Case Control Etiologic Study of Sarcoidosis* (ACCESS), the frequency of granulomatous cutaneous lesions was 16% and the skin was the second most commonly involved organ after the lung (23). Patients with sarcoidosis are often seen initially by a dermatologist (24). In contrast to EN, which is more frequent in women, the distribution of granulomatous cutaneous lesions is similar among the sexes. In ACCESS and other series, chronic skin lesions were more frequent in African Americans than in Caucasians (23).

Although cutaneous involvement in sarcoidosis may occur at any stage of the disease, specific cutaneous lesions may be a patient's first complaint or they may be a finding on physical examination in the

initial assessment of systemic disease. In patients with sarcoidosis that is initially limited to the skin, the risk of subsequent systemic involvement is unknown. In a recent Spanish report, granulomatous cutaneous lesions were present in 86 of a series of 506 (17%) patients with sarcoidosis. There was cutaneous involvement prior or simultaneous to the diagnosis of systemic sarcoidosis in 80% of patients, while it appeared during follow-up in 20% (18). The presence of granulomatous cutaneous involvement prompts the need to assess the existence of systemic sarcoidosis, and helps to confirm the histological diagnosis of sarcoidosis.

## TYPES OF SPECIFIC (GRANULOMATOUS) CUTANEOUS LESIONS AND THEIR RELATIONSHIP TO SYSTEMIC DISEASE

The most frequent forms of specific cutaneous sarcoidosis are maculopapular lesions, plaques, subcutaneous nodules, scar sarcoidosis and lupus pernio. A variety of rarer lesions have also been reported. Diverse lesions may coexist in the same patient. Typically, granulomatous lesions are erythematous and brownish or violaceous in colour with apple-jelly appearance at diascopy. They are generally multiple and do not cause symptoms, although each type of lesion has different clinical characteristics. Pruritus may occasionally be present (16,17). Table 1 shows the classification of cutaneous manifestations of sarcoidosis (17).

### *Maculopapules*

Maculopapular lesions are the most common type of granulomatous cutaneous involvement in sarcoidosis (Figure 1) (10,12,22,25). Macules are slightly infiltrated and papules may be infiltrated but of less than 1 cm in diameter. Usually, they are located on the face, particularly on the upper eyelids and around the orbits and the nasolabial folds. In addition, the occipital area of the neck, trunk and extremities and even the mucous membranes may be involved (5,7,10). Maculopapules are often transient and appear to herald the onset of the disease (7). Papules may enlarge or coalesce to form either annular lesions or plaques (10,17). Maculopapules are only slightly infiltrated, with little epidermal change.

**Table 1.** Classification of skin manifestations of sarcoidosis (17)

	Specific lesions		Non-specific lesions
Frequent types	Less frequent types	Special sites	
Maculopapular lesions	Angiolupoid	Oral cavity	Erythema nodosum
Subcutaneous nodules	Hypopigmented	Scalp alopecia	Digital clubbing
Scar sarcoidosis	Lichenoid	Nail	Sweet's syndrome
Plaques	Ulcerative	Genital	Pyoderma gangrenosum
Lupus pernio	Psoriasiform		Calcinosis
	Verrucous		Erythema multiforme
	Necrobiosis lipoidica-like		Prurigo
	Ichthyosiform		
	Erythrodermic		
	Morpheaform		

**Fig. 1.** Maculopapules

Papular lesions often resolve either spontaneously or with treatment in less than 2 years without significant scarring or with faintly atrophic macules. They are commonly associated with acute forms of sarcoidosis, such as hilar lymphadenopathy on a chest radiograph, EN, acute uveitis, peripheral lymph nodes or parotid enlargement (5,8,18,26). In consequence, they are a sign of good prognosis.

A particular form of papular lesion on the surface of the knees has been reported recently (27). The papules may have a linear arrangement over the knees and are frequently associated with EN (Figure 2), although they can also be present without EN, and may easily be overlooked. Polarizable foreign bodies are present in a high proportion of biopsies of these granulomatous lesions (27). The knees are frequently exposed to minor trauma that may introduce

**Fig. 2.** Papular sarcoidosis of the knees

exogenous particles into the dermis. These lesions can be considered a transitional form between papular and scar sarcoidosis. Therefore, the knees should always be examined when sarcoidosis is suspected (27).

### Plaques

Skin plaques occur with a similar frequency to papules. They may be simple or more commonly multiple. They are round or oval infiltrated patches, most commonly located on the limbs, face, scalp, back and buttocks (Figure 3) (5,10). They are larger than 1 cm in diameter and tend to be thicker and more indurated than papules. Plaques may have an



Fig. 3. Plaques

annular appearance with a clearer centre, especially on the forehead, and in some cases they may heal with scarring, leading to permanent alopecia on the scalp (5,7,10). In black patients they usually have a reddish-brown coloration, whereas in white patients they have a pink-yellow colouration. They have deeper granulomatous infiltration and a more chronic course than maculopapules. Skin plaques are usually persistent and are commonly associated with chronic forms of sarcoidosis, such as persistent BHL, pulmonary fibrosis, peripheral lymphadenopathy, splenomegaly and chronic uveitis (5, 8, 24-26, 28, 29). However, concomitant EN is not frequent (18). In contrast to lupus pernio, plaques are not associated with bone cysts and sarcoidosis of the upper respiratory tract (7). Plaques tend to recur after treatment. When they resolve they frequently leave permanent scarring (16).

### *Subcutaneous nodules*

Subcutaneous sarcoidosis is also known as Darier-Roussy sarcoidosis. Although the frequency of subcutaneous nodules has been estimated to be between 1.4% and 6%, in a recent series they accounted for 16% of specific skin lesions, which suggests that this variant is under-diagnosed or under-reported (19,25, 18,30). They appear as non-tender, firm, mobile, subcutaneous nodules of 0.5-2 cm in size (Figure 4) (31). They are more common on the forearms, where they tend to coalesce to form linear bands, although they have also been reported on the fingers and trunk. Subcutaneous nodules arise deep in the dermis and subcutaneous tissue (10,32,33). In contrast to EN lesions, subcutaneous nodules are typically painless or only mildly tender with pressure and the skin colour is usually normal (30,34). Multiple subcutaneous nodules in the forearms have also been reported at the site of desensitization injections administered for extrinsic asthma years earlier, and foreign bodies can be present in some cases. They may be considered a variant of scar sarcoidosis (35).

Subcutaneous nodules frequently appear at the onset of disease in association with stage I on a chest radiograph and other non-severe systemic findings of sarcoidosis, including EN (8,31,36,37). Occasionally, they may be the only initial manifestation of the disease (38), and sometimes they may also appear late in the course of sarcoidosis (19,32). Usually, they are associated with less than two years of activity of systemic sarcoidosis (18,36,39), although some authors have found that they do not have prognostic significance (32).



Fig. 4. Subcutaneous nodules

### *Scar sarcoidosis*

Infiltration of old scars is a characteristic finding in sarcoidosis. Old scars such as those resulting from surgery, trauma, acne, herpes zoster, venipuncture and other forms of skin trauma may become red or purple and indurated (Figure 5) (8,10,28). As previously mentioned, the knees are a frequent location because of non-apparent previous microscopic scars (27). Histologically, they show granulomas, often with polarizable foreign bodies whose inoculation due to a previous trauma had gone unnoticed (27,40). Infiltration of old scars has also been reported in the face years after silicone injections given for aesthetic purposes when a patient acquired sarcoidosis (41,42). The lesions tend to persist, according to the activity of sarcoidosis. In the acute phase of the disease, scar sarcoidosis may follow EN, but it may also be associated with chronic manifestations of the disease (8,10,28). Veien et al. (26) reported that 22 out of 26 patients with scar sarcoidosis showed chronic active disease 2 years after diagnosis. Granulomatous infiltration of old tattoos and the development of skin granulomatous lesions in sites previously involved with foreign-body material have been described as variants of scar sarcoidosis (43–45). Therefore, sarcoidosis should be ruled out in any scar that changes or enlarges. In addition, old scars should always be examined when sarcoidosis is suspected.

### *Lupus pernio*

Lupus pernio is the most characteristic cutaneous lesion of sarcoidosis. It is more commonly seen in black women and West Indians with long-standing



Fig. 5. Scar sarcoidosis

sarcoidosis, and is one of the hallmarks of chronic disease (13,14,22,46,47). The frequency in Caucasians varies according to the series (18,26,48). It is an indolent red-purple or violaceous indurated skin lesion that usually affects the nose, cheeks, ears, lips, forehead and digits, sometimes with a prominent telangiectatic component in the cheeks (Figure 6) (10,48). Lupus pernio results in considerable cosmetic disfigurement and can be emotionally devastating. Its treatment is one of the present challenges of sarcoidosis. Other cutaneous involvement, particularly plaques, is frequently present (48). When the nose is involved, there is commonly granulomatous infiltration of the nasal mucosa and bone, with ulceration and septal perforation. Lupus pernio often coexists with sarcoidosis of the upper respiratory tract (SURT), particularly pharyngeal and laryngeal mucosa (46,49,50). Typically, it is also associated with pulmonary fibrosis, chronic uveitis and bone cysts in the hands and feet (7). When the terminal phalanx is affected, the nail may be dystrophic (51). Spiteri et al (46), reported a series of 35 cases of lupus pernio. Intrathoracic involvement was present in 74%, SURT in 54%, bone cysts in 43%, chronic ocular lesions and peripheral lymphadenopathy in 37% each, splenomegaly in 17%, other specific skin lesions, particularly chronic plaques, in 26%, EN in 9%, and nervous system and renal involvement in 6% each. Lupus pernio usually follows a chronic course (2 to 25 years) (7,8,26,52).

### *Less frequent specific cutaneous lesions*

A wide variety of clinically atypical granulomatous cutaneous lesions have been described in sar-



Fig. 6. Lupus pernio

coidosis. Although their frequency is very low, they should be taken into account in the differential diagnosis of skin lesions with granulomatous histology (1,17). Examples are as follows: ulcerative lesions, psoriasiform plaques, hypopigmentation and cicatricial alopecia, which have been more frequently reported in African-American patients, verrucous and papillomatous lesions, ichthyosiform lesions, pustular folliculitis, lichenoid eruptions, erythrodermic eruption, angioliupoid lesions, mutilating lesions, erythema and plaques involving palms and soles, necrobiosis lipoidica-like and morpheaform lesions (13,17). Sarcoidosis may also involve the tongue and oral, nasal and anogenital mucosa (53,54). All these granulomatous skin lesions can be accompanied by features of systemic sarcoidosis, but their prognostic significance is difficult to assess (1,14).

## DIAGNOSIS

The diagnosis of sarcoidosis is based on the presence of a compatible clinical and radiological picture, histological demonstration of non-caseating granulomas with negative stains, and cultures for mycobacteria and fungi or, when available, a positive Kveim-Siltzbach test, and exclusion of other granulomatous diseases (55,56). When sarcoidosis is suspected, the search for cutaneous lesions is important, since a skin biopsy showing granulomas may avoid more aggressive diagnostic procedures. In ACCESS the skin was the second most commonly biopsied organ after the lung for the diagnosis of sarcoidosis (57). Although two biopsies with granulomas are theoretically necessary to establish the diagnosis of sarcoidosis, a skin biopsy showing non-caseating granulomas often obviates the need for additional and usually more aggressive organ biopsies, provided that the accompanying clinical and radiological picture is typical of sarcoidosis (58). In addition, in ACCESS the presence of skin sarcoidosis often results in a more rapid diagnosis than in patients with signs of pulmonary or other organ involvement (58). The characteristic histological finding in specific skin lesions is the presence of sarcoidal non-caseating granulomas. These consist of aggregates of epithelioid histiocytes, giant cells and mature macrophages, surrounded by sparse lymphocytic infiltrates composed primarily of CD4+ T-cell lymphocytes and a few CD8+ lymphocytes. The differen-

tial diagnosis of granulomatous skin lesions mainly includes tuberculosis, atypical mycobacteriosis, fungal infections, reaction to foreign bodies (particularly beryllium, zirconium, tattooing and paraffin), rheumatoid nodules, leishmaniasis and Melkersson-Rosenthal syndrome (59).

Not infrequently, the presence of polarizable foreign matter has been reported in cutaneous epithelioid granulomas in patients with systemic sarcoidosis (40,60-63). In one series, 14 out of 65 (22%) patients with systemic sarcoidosis and skin involvement showed foreign particles in the cutaneous biopsies. Foreign particles were particularly frequent in biopsies taken from skin lesions such as papules located on the knees and elbows and in infiltration of old scars (63). These sites are easily exposed to minor trauma and the introduction of foreign material could have gone unnoticed. Foreign bodies may be important in the pathogenesis of cutaneous sarcoidosis, acting as a nidus for granuloma formation when a genetically predisposed subject develops sarcoidosis. Foreign bodies in granulomatous cutaneous lesions and sarcoidosis are not mutually exclusive. Therefore, a workup to exclude systemic sarcoidosis should be undertaken (64-66).

## ASSESSMENT FOR SYSTEMIC SARCOIDOSIS

A workup for systemic sarcoidosis should be undertaken in all patients who present sarcoid granulomas on the skin (Table 2) (17,24,29,55,56). The major organs routinely assessed are the lungs, eyes, liver and heart. Assessment should include a general history (including symptoms and occupational exposure), a physical examination, a chest radiograph, pulmonary function tests (including spirometry, volumes and diffusion of carbon monoxide), an electrocardiogram, a tuberculin skin test or interferon-gamma release assay for latent tuberculosis infection, ophthalmologic examination including both slit-lamp and fundus, and routine laboratory tests, particularly blood and urine calcium levels and serum levels of angiotensin-converting enzyme (SACE) (5,67). However, SACE levels are increased in only 60% of patients with sarcoidosis and they are not specific to the disease. Conversely, some patients with cutaneous granulomas and increased SACE levels may not have systemic disease (68).

**Table 2.** Recommended basic assessment of sarcoidosis in patients presenting with specific (granulomatous) cutaneous lesions (17)

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History (including occupational and environmental exposure)
Physical examination including ophthalmologic examination (slit lamp and fundus)
Chest radiograph
Standard haematological and biochemistry profiles (including urine and serum calcium level, liver and renal function tests), and serum angiotensin-converting enzyme (SACE) level
Electrocardiogram
Pulmonary function tests (including spirometry and diffusion of carbon monoxide)
Tuberculin skin test

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In some cases, several investigations may be helpful to establish the diagnosis and the extent of sarcoidosis. However, they should not be performed routinely, but according to specific indications. High-resolution computed tomography (HRCT) of the chest can be useful to confirm the presence of suspected parenchymal or mediastinal involvement on the chest radiograph, or to study the upper airway when signs or symptoms of involvement are present. A  $^{67}\text{Gallium}$  scan may show the typical lambda sign and/or the panda sign (55,67). However, if available, whole-body  $^{18}\text{F-FDG}$  PET is more sensitive than a  $^{67}\text{gallium}$  scan for assessing the activity of sarcoidosis and for detecting occult diagnostic biopsy sites (69). Bronchoalveolar lavage usually demonstrates T-lymphocytic alveolitis with a CD4+/CD8+ ratio of 3-10/1, and a transbronchial biopsy can be performed simultaneously (55,67). Transbronchial needle aspiration (TBNA) biopsy is currently the best procedure for the pathological confirmation of the presence of granulomas in mediastinal lymphadenopathy (70). Other exams and appropriate biopsies should be performed according to the suspected organ involvement, for example, abdominal CT for liver and spleen sarcoidosis, and cranial and cardiac magnetic resonance imaging and cardiac PET if central nervous system or cardiac involvement is suspected (69). The Kveim-Siltzbach test is considered the best model of granuloma formation in humans. However, it is currently available in only a few institutions (55).

If systemic sarcoidosis cannot be demonstrated, a long-term follow-up should be undertaken, as some cases will develop systemic involvement later in the course of the disease (5,18,24,26). Nevertheless, other cases will continue to show no clinical or radiological evidence of the disease elsewhere. Some

authors classify these lesions as local sarcoid reactions and suggest they be distinguished from generalized sarcoidosis (10). However, since skin lesions in sarcoid reactions and in sarcoidosis do not differ in either their clinical or histological cutaneous manifestations, other authors believe that these cases should be accepted as sarcoidosis that is limited to the skin (26).

## PROGNOSIS

The prognosis of patients with sarcoidosis mainly depends on the extent and severity of the systemic involvement (24-26,28). In a multivariate clinical study of the prognosis in our series of patients with sarcoidosis, erythema nodosum was the best prognostic factor of systemic disease, whereas specific cutaneous lesions taken as a whole did not have prognostic significance (71,72). However, another study suggested that the good prognosis of sarcoidosis patients with EN compared with those with other skin lesions was limited to white patients (25). Granulomatous cutaneous lesions of sarcoidosis almost never cause significant morbidity or mortality. However, taken individually, some types of skin lesions have prognostic significance and may help to predict the outcome of the systemic disease. In addition, some types of lesions may be disfiguring or have cosmetic consequences that produces a strong psychosocial impact (14,46,47,73). Often, but not always, these kinds of lesions are associated with a poorer prognosis of the systemic disease.

We recently studied the prognostic significance of granulomatous cutaneous lesions of sarcoidosis (18). In our series, 86 out of 506 (17%) patients with sarcoidosis had a total of 97 histologically proven

granulomatous cutaneous lesions. However, to facilitate the statistical analysis, when a patient developed several types of cutaneous lesion, only one of them was considered the main type (usually the lesion that caused the patient's main complaint) (18). In our study, maculopapules were present in 30 patients, but were considered the main type of lesion in 28 (32.6%) out of 86 patients. Seventeen (60.7%) of these 28 patients showed stage I on chest radiograph and 19 (67.9%) were also associated with EN. The mean duration of maculopapules was 5.4 months. Only 10 (35.7%) of the patients with maculopapular eruptions required corticosteroid therapy for their systemic disease, and 8 (28.6%) showed persistence of activity more than 2 years after the diagnosis (18).

Subcutaneous nodules were present in 14 (16.3%) out of 86 patients and in all of them they were considered the main type of lesion. Eleven (78.6%) patients showed stage I on chest radiograph and 4 (28.6%) were associated with EN. The mean duration of these lesions was 19.07 months. Six (42.9%) patients with subcutaneous nodules required corticosteroid therapy for their systemic disease, and 6 (42.9%) showed persistence of activity more than 2 years after the diagnosis (18).

Scar sarcoidosis was present in 14 patients, although it was considered the main type of lesion in 7 out of 86 patients (8.1%). Five (71.4%) of these 7 patients showed stage I on chest radiograph and 3 (42.9%) were associated with EN. The mean duration of scar infiltrations was 21 months. Only one (14.3%) patient required corticosteroid therapy for his systemic disease, and 3 (42.9%) showed persistence of activity more than 2 years after the diagnosis (18).

Plaques were present in 33 patients but were considered the main type of lesion in 31 (36%) out of 86 patients. Sixteen (51.6%) of these 31 patients showed pulmonary involvement and only 4 (12.9%) were associated with EN. The mean duration of skin lesions was 58.67 months. Twenty-one (67.7%) of the patients with plaques required corticosteroid therapy for their systemic disease, and 24 (77.4%) showed persistence of activity more than 2 years after the diagnosis (18).

Lupus pernio is not frequent in Spain. It was present in only 6 (7%) patients and was considered the main type of lesion in all these cases. Three patients showed stage I on chest radiograph and stages II, III and IV were present in one patient each. None

of the 6 patients had EN. The mean duration of lupus pernio was 101.33 months. Four (66.7%) patients required corticosteroid therapy for the systemic disease, and all showed persistence of activity more than 2 years after the diagnosis (18).

For the statistical analysis, patients were classified into two groups in our study. The first group included patients with maculopapular and subcutaneous lesions, and the second included patients with plaques and lupus pernio. Group comparison showed that maculopapules and subcutaneous nodules were significantly associated with EN ( $P < 0.001$ ,  $\chi^2$  test) and radiological stage I ( $P < 0.01$ ,  $\chi^2$  test). By contrast, plaques and lupus pernio were significantly associated with the requirement for systemic corticosteroid therapy ( $P = 0.01$ ,  $\chi^2$  test) and persistence of systemic sarcoidosis activity for more than two years ( $P < 0.001$ ,  $\chi^2$  test). Significant differences were also found between these two groups in mean duration of the cutaneous lesions (10.10 months in the group with maculopapules and subcutaneous nodules vs. 67.20 months in the group with plaques and lupus pernio;  $P < 0.001$ ,  $t$ -test) and in the duration of activity of systemic sarcoidosis (36.48 months vs. 85.39 months, respectively;  $P < 0.01$   $t$ -test). Scar sarcoidosis was not associated with either acute or chronic forms of systemic sarcoidosis. The study concluded that the initial evaluation of the clinical type of skin involvement may provide prognostic information about the outcome of the systemic disease (18).

Several studies have also confirmed lupus pernio and plaques as the most severe forms of cutaneous sarcoidosis (14,22,46,47,73) because of the lesions themselves and the association with more severe systemic disease (26). In summary, maculopapules, subcutaneous nodules and scar sarcoidosis are usually transient and resolve spontaneously or tend to follow the course of the systemic disease. Skin plaques are usually persistent, and lupus pernio always follows a chronic course. Both skin plaques and lupus pernio are associated with more severe pulmonary and extrathoracic involvement, and with a more protracted course of the systemic disease (18,25,26).

## TREATMENT

Most patients with sarcoidosis will not require treatment, since the disease often remits spontaneous-



ly or remains stable, is only mildly symptomatic and, in the case of the skin, is not associated with cosmetic disfigurement. However, treatment is indicated when there is progressive systemic pulmonary or extrapulmonary involvement (56). Systemic corticosteroids are the most effective treatment. Although sarcoidosis of the skin is not life-threatening, treatment is indicated when cutaneous lesions are cosmetically disfiguring, symptomatic, ulcerative, progressive or with a propensity to scarring and when they may have a strong psychological and social impact on the patient and alter his quality of life. However, when the only indication for treatment is cutaneous involvement, with the primary aim being to improve the patient's quality of life, the benefits and side-effects must be considered carefully. Treatment of these types of lesions is particularly difficult and is one of the present challenges of sarcoidosis. Only a few randomized trials have assessed treatment of cutaneous sarcoidosis, and most of the data are derived from small uncontrolled prospective studies, retrospective analyses, case series and case reports.

Another important aspect in the treatment of skin sarcoidosis is the assessment of therapeutic response. Recently, the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) recommended several endpoints for clinical trials in cutaneous sarcoidosis. These included: overall assessment by physician or patient; a count of the number of lesions; photographs; the extent and characteristics of the lesions, including the area of involvement, erythema, induration, and desquamation using a scoring system such as the Lupus Pernio Activity and Severity Index (LuPASI) (73); and skin biopsies that can correlate biomarkers of disease activity with clinical change (6,74). However, none of these endpoints assesses the quality of life changes during skin treatment. In consequence, rather than a simple measure, the group recommended a combination of parameters that should include objective measurements of quality of life and psychosocial status (6). Most of the agents used for systemic sarcoidosis are also used for cutaneous sarcoidosis. Selection of the most appropriate individual agent should be based on a consideration of factors such as the patient's acceptance of the treatment regimen, drug monitoring requirements, and drug adverse effects.

### *Corticosteroids*

Data on the efficacy of these agents for cutaneous involvement are limited. Most skin lesions do not need treatment. In general, only chronic cutaneous lesions, particularly lupus pernio that involves the face and extensive plaques that may cause scarring, may require per se oral steroid treatment (75). In a recent retrospective study of 116 treatment courses in 54 patients with lupus pernio, monotherapy with systemic corticosteroids was associated with complete or near resolution of skin lesions in 20% of the courses and at least some improvement in 72% (47). Prednisone 20 to 40 mg/day followed by a taper to the lowest feasible dose has been recommended. Although corticosteroids are rapidly effective in skin involvement they do not usually produce sustained remission. Furthermore, their prolonged use often results in adverse effects, which may counteract the benefits of a treatment that is principally given for a cosmetic objective (76). The dose of corticosteroids may be decreased or the treatment stopped by the introduction of a steroid-sparing immunosuppressive agent. Topical and intralesional therapies with ultra-potent corticosteroids may be useful in localized disease. However, these therapies often fail to achieve complete resolution and may induce skin atrophy and hypopigmentation (76,77).

### *Antimalarials*

Although chloroquine and hydroxychloroquine have been widely used in sarcoidosis for over fifty years (75,78,79), data on their efficacy for cutaneous sarcoidosis are limited to a few small uncontrolled studies. These drugs inhibit antigen processing and presentation. They have often been used as the first-line therapy for cutaneous sarcoidosis, with the usual doses being 250–500 mg daily for chloroquine and 200–400 mg daily for hydroxychloroquine. The response to treatment often takes at least four weeks, with maximum treatment responses observed at 12 weeks. Relapse after discontinuation of treatment is common (87,79). Adverse effects include gastrointestinal symptoms and ocular (corneal deposits and central retinopathy), neurological or haematological toxicities. Eye examination at least once a year is recommended (80). The risk of ocular toxicity seems lower with hydroxychloroquine.

### *Methotrexate*

Methotrexate inhibits purine synthesis and at low-doses has an anti-inflammatory effect. It has been widely used as a steroid-sparing agent in several forms of systemic sarcoidosis, including those with cutaneous involvement (81,82). The recommended initial dose is 10 to 15 mg once a week. This may be increased up to 25 mg and tapered to a maintenance dose of 5 to 15 mg weekly. The overall response rate appears to be over 80% for skin lesions (81). However, the therapeutic response may take as long as six months (82). Most adverse effects are dose-dependent and include haematological, gastrointestinal, hepatic and pulmonary toxicities. Mucositis, nausea and vomiting can be eliminated by dividing the dose into two (on two consecutive days per week). Oral folate 1 mg/day is also recommended. The dose must be adjusted in patients with renal failure and must be avoided if serum creatinine is greater than 3 mg. The presence of liver sarcoidosis is not a contraindication for methotrexate. Routine white cell count, renal function and liver function tests are recommended, although liver tests are not predictive of hepatic injury on biopsy. Some authors have recommended performing liver biopsy after each 1 to 1.5 grams of cumulative therapy (approximately every two years) (82). Similar to antimalarials, relapse of sarcoidosis is common after the discontinuation of therapy. Both antimalarials and methotrexate can be used alone or in combination with low-dose corticosteroids (76).

### *TNF- $\alpha$ antagonists*

Infliximab is a chimeric monoclonal antibody directed against tumour necrosis factor alpha (TNF- $\alpha$ ) (83). Since 2001, several case reports and small series have reported stabilization or improvement after infliximab treatment of recalcitrant multi-organ sarcoidosis in which not only corticosteroids but also other conventional steroid-sparing agents had failed (84-88). An elevated baseline C-reactive protein level appears to identify a subset of chronic sarcoidosis patients who will respond better to infliximab therapy (89). However, larger studies in pulmonary or extrapulmonary sarcoidosis and the expense of the therapy have limited the initial enthusiasm for infliximab (90,91).

As regards skin sarcoidosis, Stagaki et al. retrospectively studied 116 courses of treatment in 54 pa-

tients with lupus pernio. More than 75% of all treatment regimes containing infliximab resulted in resolution or near resolution of lupus pernio lesions, compared with regimens with systemic corticosteroids, with or without additional steroid-sparing agents. By contrast, although more than 70% of patients treated with corticosteroids had some improvement in lupus pernio lesions, fewer than 25% of them showed resolution or near resolution (47). However, Panselinas et al. reported that after the initial success of infliximab therapy the disease frequently relapses within three months of treatment suppression, and patients often need an increase in the dose of prednisone as maintenance therapy (92).

Infliximab is administered intravenously in doses of 3 to 5 mg/kg/dose at 0, 2, 6, 12, 18 and 24 weeks (90,91). Adverse effects include infusion reactions and an increased risk for infections, especially tuberculosis, and malignancy, particularly lymphoma (93). During treatment with infliximab, human antichimeric antibodies may develop. Concomitant use of low-dose methotrexate may prevent this risk (83).

Other biological agents have been used in the treatment of cutaneous sarcoidosis. Etanercept, a soluble tumour necrosis factor inhibitor, was reported to be effective in a patient with lupus pernio (94). Adalimumab, a monoclonal antibody that targets TNF- $\alpha$ , has also been used successfully in patients with resistant cutaneous sarcoidosis (95-97). Anecdotal reports suggest that rituximab, the anti-CD20 monoclonal antibody, may also be beneficial in patients with sarcoidosis (83). Although biologic agents are a useful alternative or additional therapy, they should only be used in recalcitrant cases.

### *Tetracycline*

Tetracycline derivatives inhibit granuloma formation. A potential antibacterial effect, including activity against *Propionibacterium acnes*, a putative agent for sarcoidosis, has also been suggested (98). In a non-randomized open study, 12 patients with chronic cutaneous sarcoidosis were treated with minocycline 100 mg twice a day for a median duration of 12 months with a two-year follow-up. Eight patients showed complete response and two a partial response. Although remission persisted for an average of 15 months after discontinuation of therapy, three patients relapsed and were treated with doxy-

cycline 100 mg twice daily (99). Side-effects of tetracyclines include nausea, photosensitivity and pigment changes in teeth and skin.

### *Thalidomide*

Thalidomide may be effective in sarcoidosis due to its capacity to block TNF- $\alpha$  (75). Thalidomide, 50 to 400 mg daily, has been used for chronic disfiguring cutaneous sarcoidosis after failure of more conventional treatments. Several small series and case reports have demonstrated that most patients showed a complete or partial response after one to five months of treatment (100). Improvement was also evident on histopathological examination of biopsy specimens after treatment (101). Teratogenicity and peripheral neuropathy have limited the use of thalidomide.

### *Other agents*

Pentoxifylline inhibits spontaneous TNF- $\alpha$  production from the sarcoid granuloma. It has been used at a dose of 400 mg three times daily as a steroid-sparing agent in the treatment of pulmonary sarcoidosis, but its efficacy for cutaneous sarcoidosis is not known. Adverse effects include gastrointestinal symptoms and mild bleeding diathesis (75). Recently, apremilast, a new phosphodiesterase type inhibitor that blocks the synthesis of proinflammatory cytokines and chemokines, has been reported to be useful in a group of patients with lupus pernio (102).

Mycophenolate mofetil attenuates lymphocyte proliferation. It has been used at a dose of 30 to 45 mg/kg/day in a short series of five patients with mucocutaneous manifestations of sarcoidosis who had failed to respond to corticosteroids and other therapies (103,104). Oral isotretinoin (0.4 to 1.3 mg/kg/day), a retinoid with an immunomodulatory effect, has been used successfully in some case reports for the treatment of cutaneous sarcoidosis. Side effects include teratogenicity and cheilitis (105,106). Improvement of refractory cutaneous and systemic sarcoidosis has been reported with leflunomide, a suppressor of TNF- $\alpha$ , with a loading dose of 100 mg/day for 3 days followed by 20 mg daily, either concurrently with methotrexate or alone. The most common adverse effects include gastrointestinal symptoms, hepatotoxicity and hypersensitivity reactions, and the extra cost limits its use (107).

Anecdotal cases of cutaneous sarcoidosis improving with azathioprine, allopurinol, melatonin, chlorambucil, mepacrine, fumaric esters, radiation, topical tacrolimus, ultraviolet light, laser and plastic surgery have all been reported (48,75,76). Rotational therapy with several of the aforementioned agents for short periods of time to minimize side effects may be an alternative for recalcitrant cases.

## CONCLUSION

The skin manifestations of sarcoidosis are classified as either specific when biopsy reveals non-caseating granulomas or non-specific, typically EN. The most frequent specific (granulomatous) skin lesions are maculopapules, subcutaneous nodules, scar sarcoidosis, plaques and lupus pernio. Skin biopsy allows early diagnosis of sarcoidosis through a non-aggressive procedure. Cutaneous lesions have prognostic significance. EN is usually associated with good prognosis and spontaneous resolution. Maculopapular lesions and subcutaneous nodules are more often associated with remission of the systemic disease at two years, while plaques and, mainly, lupus pernio are hallmarks of chronic disease. Most cutaneous lesions of sarcoidosis are only mildly symptomatic and do not require treatment. For moderate to severe skin lesions, antimalarials, corticosteroids and methotrexate, alone or in combination, may be useful as first-line therapies. However, chronic skin lesions, particularly lupus pernio, are disfiguring and can have a strong psychological and social impact. Treatment of these lesions is a challenge since they do not respond well to conventional therapies. Biological agents may have a role in these recalcitrant forms of cutaneous sarcoidosis.

## TAKE-HOME POINTS

1. The skin is the second most commonly involved organ in sarcoidosis, after the lung.
2. Cutaneous involvement in sarcoidosis is classified as either specific when biopsy reveals noncaseating granulomas or non-specific, particularly erythema nodosum.
3. The most frequent forms of specific cutaneous sarcoidosis are maculopapules, plaques, subcutaneous

nodules, scar sarcoidosis and lupus pernio.

4. Foreign bodies in biopsies with granulomatous cutaneous lesions may be present in patients with systemic sarcoidosis.
5. Maculopapules, subcutaneous nodules and scar sarcoidosis usually resolve spontaneously or tend to follow the course of the systemic disease, whereas plaques and lupus pernio tend to persist and are associated with chronic systemic sarcoidosis.
6. Treatment of cutaneous sarcoidosis is indicated when skin lesions are symptomatic and so cosmetically disfiguring that they alter the patient's quality of life. The benefits and side-effects of treatment must be considered carefully.
7. Oral corticosteroids, antimalarials, methotrexate and TNF- $\alpha$  antagonists are the most useful drugs to treat difficult cases of cutaneous sarcoidosis.

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