Skin manifestations of sarcoidosis

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Summary

The skin manifestations of sarcoidosis are classified as specific, where biopsy reveals non-caseating granulomas, and non-specific, typically erythema nodosum. 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. In sarcoidosis, erythema nodosum is usually associated with bilateral hilar lymphadenopathy on the chest radiograph, this being known as Löfgren's syndrome. Cutaneous lesions have prognostic significance. Löfgren’s syndrome 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. 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 treatments. The introduction of biological agents has been an important although not definitive advance in the treatment of cutaneous sarcoidosis.

The first descriptions of cutaneous sarcoidosis were reported at the end of the nineteenth century by Sir Jonathan Hutchinson and Ernest Besnier. A few years later Caesar Boeck was the first to describe the histopathology of these cutaneous lesions, which were characterized by the presence of non-caseating granulomas and the absence of microorganisms [1]. For a long time the disease was regarded as the special concern of dermatologists. However, at the beginning of the twentieth century Schaumann drew attention to its systemic nature, and over the years it gradually became apparent that sarcoidosis could affect other organs without involving the skin, and that the granulomatous skin lesions appeared only in some patients [2]. In the 1950s, Sven Löfgren reported a further manifestation of acute sarcoidosis [3–6], namely erythema nodosum (EN), a non-granulomatous skin lesion, combined with bilateral hilar
adenopathy (BHL), and this is now known as Löffgren’s syndrome (LS). These findings were subsequently confirmed by James a few years later [7].

As a consequence, the cutaneous manifestations of sarcoidosis are classified as specific and non-specific. Specific skin lesions contain non-caseating granulomas, which is the characteristic histopathological finding in tissue affected by sarcoidosis. The most typical non-specific lesion is EN, characterized histopathologically by panniculitis. Both types of lesions may coexist in the same patient [8].

There are three main reasons why it is important to recognize skin sarcoidosis, both specific and non-specific. Firstly, a skin biopsy is easy to perform and enables an early diagnosis. Secondly, some types of lesions have prognostic significance and may help to predict the outcome of the systemic disease. Thirdly, although the cutaneous lesions of sarcoidosis almost never cause significant morbidity or mortality, their cosmetic importance (they may be disfiguring) can have a strong psychosocial impact. One of the present challenges of sarcoidosis is that these types of lesions are particularly difficult to treat.

Specific (granulomatous) cutaneous lesions

Epidemiology

The frequency of specific (granulomatous) skin lesions in sarcoidosis ranges from 9% to 37%, depending on the series [8–13]. 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 [14]. Patients with sarcoidosis are often seen initially by a dermatologist [15]. 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 whites [14]. Some studies have focused on the relationship between skin sarcoidosis and the systemic manifestations of the disease [10,15–19]. Specific cutaneous lesions are usually an early disease manifestation, and in some series more than 30% of patients apparently showed isolated cutaneous sarcoidosis [15,16,20,21]. The risk for the development of systemic involvement in patients who present with disease that is initially limited to the skin is not known. In a recent Spanish study, granulomatous cutaneous lesions were present in 86 of a series of 507 (17%) patients with sarcoidosis [22]. There was cutaneous involvement prior or simultaneous to the diagnosis of systemic sarcoidosis in 80% of patients, while it appeared during follow-up in only 20% [22]. The presence of granulomatous cutaneous involvement prompts the need to assess the potential presence of systemic sarcoidosis, and at the same time it helps to confirm the histological diagnosis of sarcoidosis.

Diagnosis

The correct recognition of specific skin lesions is particularly important since a diagnostic skin biopsy is a safe and straightforward procedure. The diagnosis of sarcoidosis can be made more rapidly in patients with specific cutaneous involvement than other forms of the disease [23]. In ACCESS, the skin was, after the lung, the second most common biopsied organ for the diagnosis of sarcoidosis [23]. Although two biopsies with granulomas are theoretically necessary to establish the diagnosis of sarcoidosis, a skin biopsy showing non-caseating granulomas of unknown cause often obviates the need for additional and usually more aggressive organ biopsies, provided that the systemic, accompanying clinical and radiological picture is typical of sarcoidosis.

The characteristic histological finding in specific skin lesions is the presence of non-caseoidal 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 (figure 1). The differential diagnosis of granulomatous skin lesions is very wide and mainly includes tuberculosis, atypical mycobacteriosis, fungal infections, reaction to foreign bodies (particularly beryllium, zirconium, tattooing and paraffin), rheumatoid nodules, leishmaniasis and Melkersson-Rosenthal syndrome [24]. Classically, the finding of polarizable foreign matter in cutaneous epithelioid granulomas enabled sarcoidosis to be ruled out, and the lesion was considered a local sarcoidal tissue reaction [25]. However, such material has been reported to be present in some cutaneous biopsies from patients with systemic sarcoidosis. 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 those biopsies taken from skin lesions such as papules located on the knees and elbows and infiltration of old scars (figure 2) [25]. These sites are easily exposed to minor trauma and the inoculation of foreign material could have gone unnoticed. Although foreign bodies cannot be
considered the cause of sarcoidosis they 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 and, therefore, a workup to exclude systemic sarcoidosis should be undertaken [20,25–32]. Cutaneous biopsy specimens showing granulomas should be examined under polarized light to look for evidence of foreign bodies. They should also be stained for mycobacteria and fungi [28,33,34].

Frequent types of specific cutaneous lesions

The skin manifestations of sarcoidosis have a wide variety of morphologies. Indeed, cutaneous sarcoidosis is known as the great imitator, and its diagnosis requires a high index of clinical suspicion [35]. The most frequent and characteristic forms of specific cutaneous sarcoidosis are maculopapular lesions, subcutaneous nodules, scar sarcoidosis, plaques and lupus pernio. Lesions are generally multiple, erythematous and brownish or violaceous in colour, and frequently do not cause symptoms, although each type of lesion has different clinical characteristics [36]. Diascopy, in which a microscopic slide is compressed against a cutaneous lesion, reveals a yellowish-brown or apple-jelly colour in sarcoidal skin lesions. This finding is better appreciated on plaques and papules in patients with a lighter skin colour. Although this is a useful test to identify signs of granulomatous cutaneous disease during the skin examination it is not pathognomonic of sarcoidosis [37].

Maculopapular lesions

In some series maculopapular lesions are the most common type of granulomatous cutaneous involvement in sarcoidosis (figure 3) [13,18,38,39]. Maculopapules are only slightly infiltrated, with little epidermal change, and are usually red-brown to purple in colour and less than 1 cm in diameter. Less often they may be skin-coloured, yellow-brown or hypopigmented. They are commonly disseminated and located on the face, particularly on the eyelids, around the orbits and the nasolabial folds, on the scalp, occipital area of the neck, trunk, buttocks, and extremities, and mucous membranes may even be involved [2,8,16,38]. Diascopy shows the typical apple-jelly colour characteristic of granulomatous skin lesions. These lesions are sometimes transient and appear to herald the onset of the disease [16]. In other cases, papules may enlarge or
Acute sarcoidosis may present in a macular (Figure 3) or papular (Figure 4) form. Macular lesions often resolve without significant scarring, while papular lesions may coalesce to form either annular lesions or plaques. Papular lesions often resolve without significant scarring, either spontaneously or with treatment. After resolution, faintly discoloured or atrophic macules may remain at the previously involved sites. 

Maculopapular lesions are commonly associated with the acute forms of sarcoidosis such as BHL on the chest radiograph, EN, acute uveitis, peripheral lymph nodes or parotid enlargement. Maculopapular lesions usually disappear spontaneously and may be regarded as a sign of good prognosis, since in most cases the systemic disease is inactive within less than two years. Recently, a particular form of papular lesion involving the surface of the knees has been reported, it being referred to as papular sarcoidosis of the knees. The papules may have a linear arrangement over the knees and are frequently associated with EN (Figure 4). Interestingly, a high proportion of biopsies of these granulomatous lesions show the presence of polarizable foreign bodies. The knees are frequently exposed to minor linear trauma that may inoculate exogenous particles in the dermis. These lesions can be considered a transitional form between papular and scar sarcoidosis. At times they can also be present without the associated EN, and may easily be overlooked. Therefore, when faced with a case of possible sarcoidosis the clinician should always examine the knees to check for these characteristic cutaneous lesions, which are readily accessible for skin biopsy.

The differential diagnosis of maculopapular lesions includes xanthelasma, acne, rosacea, lupus erythematosus, syringoma, lichen planus, granuloma annulare and adenoma sebaceum.

Subcutaneous nodules

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, therefore suggesting that this variant is under diagnosed or under-reported. Subcutaneous sarcoidosis is also known as Darier-Roussy sarcoidosis. It is more common in middle-aged women and appears as non-tender, firm, mobile, subcutaneous nodules 0.5–2 cm in diameter (Figure 5). These nodules may range from one to 100 in number, sometimes appearing in clusters, and arise deep in the dermis and subcutaneous tissue of the extremities and trunk. 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. In contrast to EN lesions, subcutaneous nodules are
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Subcutaneous sarcoidosis also scar sarcoidosis ural ular acne, scars trauma (figure forearm)

The differential diagnosis of subcutaneous nodules includes tuberculosis, deep mycoses, cutaneous metastases from visceral neoplasms (including melanoma), epidermoid cysts, lipomas, rheumatoid nodules and erythema induratum.

**Scar sarcoidosis**

Infiltration of old scars is a characteristic finding in sarcoidosis (figure 6). In one series of 170 patients with cutaneous sarcoidosis, 15 (9%) presented scar infiltration. When a patient acquires sarcoidosis, old scars resulting from surgery, trauma, acne, herpes zoster, venipuncture and other forms of skin trauma may become red or purple and indurated. Histologically, they show granulomas, often with polarizable foreign bodies whose inoculation from the previous trauma had gone unnoticed. Scar infiltration may be the only skin manifestation of sarcoidosis and can be asymptomatic. The diagnosis of scar sarcoidosis may be missed because the lesions can be misdiagnosed as hypertrophic scars or keloids. Scar sarcoidosis may precede systemic disease, tends to persist according to the activity of systemic sarcoidosis, and usually resolves slowly and spontaneously. A new scar infiltration in patients with sarcoidosis in remission suggests a reactivation of the disease. In the acute phase of the disease, scar sarcoidosis may follow EN, whereas in chronic sarcoidosis it is seen associated with long-standing pulmonary and mediastinal involvement, uveitis, peripheral lymphadenopathy, bone cysts or parotid enlargement. In the report by Veien et al., 22 out of 26 (85%) patients with scar sarcoidosis showed chronic active disease two years after diagnosis. However, in a recent study about the prognosis of systemic sarcoidosis, scar infiltration was not associated with either acute or chronic forms of systemic sarcoidosis, thereby suggesting that it does not have prognostic significance. Granulomatous infiltration of old tattoos and the development of skin granulomatous lesions in sites that previously contained foreign body material have been described as variants of scar sarcoidosis (figure 7). Scars sarcoidosis has also been reported after silicone injections. 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.

**Plaques**

Skin plaques have a similar frequency to papules. They consist of one or multiple round or oval infiltrated patches, brownish red in colour, and may be due to a confluence of papules. They are larger than 5 mm in diameter and tend to be thicker and more indurated than papules. Histologically, granulomas are present throughout the entire dermis. In black patients they usually have a reddish-brown coloration, whereas in white patients they have a pink-yellow coloration. Diascopy reveals tiny grey-yellow dots, which have a deeper granulomatous infiltration and more chronic course than do maculopapules.
They are most commonly located on the extensor surface of the extremities, face, scalp, back and buttocks (figures 8 and 9) [2,8,38]. Plaques may have a central clear area with an annular appearance, especially on the forehead, resembling other annular skin diseases (figure 10) [41]. In black patients, plaques may develop a hypopigmented surface. They sometimes heal with scarring, leading to permanent alopecia on the scalp. In a few cases, plaques have been reported in sun-exposed areas [2,8,15,16,38].

Due to their prognostic value, plaques should be distinguished from papules. Skin plaques are usually persistent and are commonly associated with chronic forms of sarcoidosis, such as persistent BHL, pulmonary infiltrates, pulmonary fibrosis, peripheral lymphadenopathy, splenomegaly and chronic uveitis [8,10,15,17–20]. However, concomitant EN is not frequent [22]. In contrast to lupus pernio, plaques are not associated with bone cysts and sarcoidosis of the upper respiratory tract [16]. Patients with plaques usually have chronic sarcoidosis with persistence of disease activity for more than two years [8,20]. In a recent prognostic study, plaques were associated with chronic disease and the need for corticosteroid therapy [22]. After treatment, plaques tend to recur, and when they do resolve they frequently leave permanent scarring [36].
A number of other cutaneous disorders have to be considered in the differential diagnosis. Plaques may simulate psoriasis, lichen planus, discoid lupus, granuloma annulare, necrobiosis lipoidica, cutaneous T-cell lymphoma, Kaposis’s sarcoma, secondary syphilis, morphea, leprosy and leishmaniasis [41,58].

**Lupus pernio**

Lupus pernio was first described by Besnier at the end of the nineteenth century and is the most characteristic cutaneous lesion of sarcoidosis [2]. It is more commonly seen in black women and West Indian with long-standing sarcoidosis and is one of the hallmarks of chronic fibrotic disease [34,42,59–61]. The frequency in Caucasians varies according to the series [20,22,62].

Lupus pernio is an indolent, red-purple or violaceous, indurated plaque-like and nodular fibrotic skin lesion which usually affects the nose, cheeks, ear lobes, lips and forehead, sometimes with a prominent telangiectatic component (figure 11). The alar rim of the nose is often affected [2,38]. It less commonly involves the dorsal hands, finger and toes, and, on radiograph, lytic and cystic bone lesions in the hands and feet can be present in bone underlying lesions of lupus pernio [38,41]. When the terminal phalanx is affected the nail may be dystrophic [63]. Lupus pernio frequently results in considerable cosmetic disfigurement. It commonly coexits with other cutaneous involvement, particularly with plaques [62]. When the nose is involved there is often adjacent granulomatous infiltration of the nasal mucosa and bone. In some cases, ulceration and septal perforation may be present [64]. Lupus pernio often coexists with sarcoidosis of the upper respiratory tract (SURT) (involvement of nasal, pharyngeal and/or laryngeal mucosa) [59,65,66]. When severe, SURT can result in airway obstruction [67]. Lupus pernio is typically associated with pulmonary fibrosis, chronic uveitis and bone cysts [16,61,68]. In 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 at onset in 9%, and nervous system and renal involvement in 6% each [59].

Lupus pernio usually follows a chronic course, and in some cases a 25-year follow-up has been reported [10,16,69]. All the 22 cases of lupus pernio reported by Veien et al. from their series of 188 patients with skin sarcoidosis showed chronic active disease at two-year follow-up [20]. In the prognostic study by Marcoval et al., lupus pernio, together with cutaneous plaques, was associated with chronic disease and the need for systemic corticosteroid therapy [22]. The differential diagnosis of lupus pernio includes lupus erythematosus, lupus vulgaris, benign or malignant lymphocytic infiltrate, rhinophyma, Wegener granulomatosis and tertiary syphilis [35].

**Less frequent specific cutaneous lesions**

A great variety of clinically atypical granulomatous cutaneous lesions have been described in sarcoidosis. Although their frequency is very low they should nonetheless be taken into account in the differential diagnosis of skin lesions with granulomatous histology, not least as some of them have prognostic significance as regards the outcome of the systemic disease.

**Angiolupoid sarcoidosis**

In one series, 8% of patients with cutaneous sarcoidosis were affected by angiolupoid sarcoidosis [70], a variant of plaque sarcoidosis characterized by the presence of prominent large telangiectasias. It predominantly affects women, usually as a single raised plaque on the bridge of the nose, central face, ears or scalp. The lesions are orange-red or reddish-brown in colour and, due to the marked telangiectatic component; they have a more vivid hue than other forms. There is little tendency to spontaneous resolution [70]. Angiolupoid sarcoidosis may be mistaken for rosacea or a large basal cell carcinoma [71].

**Hypopigmented sarcoidosis**

Macular hypopigmentation is occasionally observed in dark-skinned persons of African descent with sarcoidosis. In one series, it was observed in 8 out of 145 patients with sarcoidosis, mostly Afro-Caribbeans [9]. Lesions manifest as hypopigmented, well demarcated, round to oval patches located mainly on the limbs [38,72]. Erythematous papules can be found in the centre of some lesions, leading to an appearance that resembles a fried egg. The differential diagnosis includes leprosy, post-inflammatory hypopigmentation, idiopathic guttate hypomelanosis and pityriasis lichenoides chronic. The presence of interphase dermatitis that can be associated with granulomatous cutaneous lesions of sarcoidosis may explain the development of hypopigmentation [73]. However,
Although hypopigmented sarcoidosis is usually considered a specific cutaneous lesion of sarcoidosis, the lesions may not show dermal granulomas at biopsy [74].

**Lichenoid sarcoidosis**

Lichenoid sarcoidosis is estimated to be present in 1–2% of cases of skin sarcoidosis [75] and has been described more often in children [76–80]. Clinically it presents with multiple, 1–3 mm, flat-topped or dome-shaped erythematous or skin-coloured maculopapules that may involve extensive areas of the trunk, limbs and face. Wickham striae are absent. The differential diagnosis includes lichen planus, lichen nitidus, lichenoid drug eruptions, lupus erythematosus and papular mucinosis [78,79].

**Ulcerative sarcoidosis**

Patients with sarcoidosis may also develop ulcerative lesions. Veien et al. reported that 1% of white patients with sarcoidosis develop ulcerative lesions [20]. In another series of 147 patients with cutaneous sarcoidosis, 7 (4.8%; all African-American, 5 women) developed ulcerative sarcoidosis [81]. More than 50% of patients with ulcerative sarcoidosis reported in the literature are black [82], and the incidence of ulcerative sarcoidosis among Japanese people seems to be the same as that among the black population [83]. Not infrequently the ulcers are the initial sign of sarcoidosis, and they generally develop in papulonodular lesions, although some appear de novo [82]. Ulcers can also develop in atrophic lesions [81]. Ulcerated granulomatous cutaneous lesions of sarcoidosis are located primarily on the lower legs and tend to heal with scarring [82]. Trauma superimposed on atrophic plaques has been proposed as the principal pathogenic mechanism [81]. Ulcerative sarcoidosis may mimic other ulcerative conditions such as venous stasis ulcerations. Therefore, the diagnosis of sarcoidosis should be considered in any ulcer with granulomatous inflammation [82].

**Psoriasiform sarcoidosis**

Psoriasiform lesions are found in 0.9% of patients with sarcoidosis [61]. This condition is a form of plaque sarcoidosis that presents with well-demarcated, erythematous, scaly plaques that may be clinically indistinguishable from psoriasis [84]. There is evidence that some of the cases represent sarcoidosis occurring in lesions of psoriasis, analogous to sarcoidal granulomas infiltrating scar tissue. Other cases reported are simply well demarcated, scaling, sarcoidal plaque-like lesions occurring in typical locations of psoriasis [85]. However, psoriasis lesions are usually redder in colour, have larger scales than do sarcoidal plaques, and may heal without scarring [36].

**Verrucous sarcoidosis**

Lesions of verrucous sarcoidosis consist of well demarcated, exophytic, hyperkeratotic plaques or discrete papillomatous, skin-coloured papules [86]. Most cases involve the lower extremities. Lesions may resemble warts, prurigo nodularis or hypertrophic lichen planus [86]. Verrucous sarcoidosis seems to predominate in African-American men [87].

**Necrobiosis lipoidica-like lesions**

Necrobiosis lipoidica-like lesions consist of pink to violaceous plaques with depressed centres located on the shins [88]. A series of three patients with sarcoidosis who developed necrobiosis lipoidica-like lesions has recently been reported [89]. The granulomatous nature of necrobiosis lipoidica and sarcoidosis may explain this resemblance and makes differential diagnosis difficult.

**Ichthyosiform sarcoidosis**

On rare occasions, cutaneous sarcoidosis can produce large, adjacent scales mimicking acquired ichthyosis. Ichthyosiform sarcoidosis has been described in 23 independent reported cases, mostly in black people [36]. The lesions present adherent, irregular, polyclonal, dry, grey or brown scales varying in size from 0.1 cm to 1 cm, most commonly located on the lower extremities [90,91]. Biopsy reveals both typical sarcoidal granulomatous inflammation and, in most cases, the changes seen in ichthyosis vulgaris (compact orthokeratosis with a diminished granular layer) [91,92].

**Erythrodermic sarcoidosis**

This term is used to describe the rare presence of large areas of skin with significant erythema, induration and scaling evocative of the changes seen in erythroderma (diffuse erythema with scaling covering more than 90% of a patient’s skin) [93]. Erythrodermic sarcoidosis typically begins with slightly infiltrated, erythematous to yellow-brown plaques that subsequently coalesce over large areas. In contrast to classic exfoliative erythroderma some areas of skin are usually spared [94]. Some patients with erythrodermic sarcoidosis with scaling have also been described as acquired ichthyosiform erythroderma. The absence of large, thick, polygonal scales differentiates erythrodermic sarcoidosis from ichthyosiform erythroderma. As in other atypical forms of sarcoidosis, histopathological evaluation is necessary to exclude more common causes of erythroderma [95].

**Morpheiform lesions**

The development of clinically indurated and atrophic plaques indistinguishable from morphea has also been described in sarcoidosis. The lesions were predominantly located on the thighs of black woman [96]. In some cases these lesions may occur in a linear distribution resembling linear morphea [97]. In addition to epithelioid granulomas, dermal sclerosis is observed histopathologically [96–98].

**Other specific lesions of sarcoidosis, rarely reported**

Other less common specific lesions of sarcoidosis are lupus discoid-like lesions [99,100], lesions resembling lichen sclerosus [101], follicular lesions [102], pseudotumoural sarcoidosis [103–104], lichen planus-like lesions [105–107], and nodular lupus erythematosus [108–110].
and lesions resembling breast carcinoma [103], palmar erythema [104], itchy granulomatous eruption [105], photo-induced lesions of sarcoidosis [106], lipodermatosclerosis-like lesions [107], and cellulitis-like lesions [108]. Finally, the development of oedema in the lower extremities, generally one-sided, can also be a rare specific manifestation of sarcoidosis [109].

**Special locations of specific sarcoidosis**

**Sarcoidosis of the oral cavity**

Oral lesions are infrequent in sarcoidosis [110,111]. A recent review of the English-language literature detected only 47 patients with lesions in the soft tissue of the oral cavity [110]. In the majority of published cases, sarcoidosis lesions of the oral mucosa are unique. The most frequent localization is the buccal mucosa, followed by the gums, lips, floor of the mouth, tongue and palate [110]. Clinically, the lesions usually consist of diffuse enlargement at the submucous level or a firm, nodular lesion, with normal overlying mucosa [111]. Papules, superficial ulcerations [111,112] and strawberry gums [113] have also been described. Oral lesions of sarcoidosis are usually symptomless and are discovered as slow growth enlargements of the mucous membrane [111]. The similarity between skin and oral mucous membrane suggests that it may be possible in the oral cavity to observe the equivalent of the various forms of specific cutaneous lesions of skin sarcoidosis, from self-limited acute forms that appear at the onset of systemic disease to persistent chronic lesions [114]. Oral lesions may constitute the first sign of systemic sarcoidosis, and systemic sarcoidosis must be borne in mind in the differential diagnosis of oral granulomatous lesions [114].

**Scalp alopecia**

Scalp alopecia is rarely reported in sarcoidosis [100,115–118]. Sarcoidal alopecia predominantly affects African-American women. Indeed, in a review of reported cases published in 2000, 20 out of 22 patients were African-American [117]. When specific cutaneous lesions of sarcoidosis involve the scalp, scarring alopecia may occur where the granulomas lead to the destruction of hair follicles [36]. Scale is usually absent, although follicular plugging, as seen in discoid lupus erythematosus, may also be present [100]. In more advanced lesions, the alopecia may be indistinguishable from pseudopelade of Brocq. However, other cutaneous signs of sarcoidosis, particularly involving the face, are often present [117].

**Nail sarcoidosis**

Nail involvement in sarcoidosis was reported in one of 400 sarcoidosis patients in one series [119] and in three of 188 patients in another [20]. Nail lesions reported in sarcoidosis include opacity, splinter haemorrhages, thinning, pitting, thickening, transverse layering, longitudinal ridging, onycholysis, subungual hyperkeratosis, clubbing, paronychia, pterygium, red or brown discolouration of the nail bed, and trachyonychia [120–122]. Disease progression can eventually result in total loss of the nail (anonychia) due to nail matrix atrophy caused by granulomatous infiltration [121]. Surrounding skin changes may be minimal, but in the majority of reported cases patients with sarcoidal nail dystrophy have bony cysts in the underlying terminal phalanx [121,123]. The presence of nail dystrophy in a patient with systemic sarcoidosis signifies a chronic course of disease [121].

**Genital sarcoidosis**

Four patients with vulval sarcoidosis had been reported prior to 2005 [124,125]. Clinically, the lesions consist of semitranslucent, reddish-brown papules and nodules [125]. The differential diagnosis of granulomatous disease of the vulva includes tuberculosis, Crohn’s disease, syphilis, foreign body reactions and lymphogranuloma venereum [125]. The first case of documented vaginal sarcoidosis has recently been described [126]. In the male genitalia, sarcoidosis usually presents with testicular or epididymal masses without cutaneous lesions [127,128]. However, several cases of cutaneous scrotal or penile lesions have occasionally been reported as indurated papules, painful nodules or swelling of the scrotum or penis [127,129].

**Assessment for systemic sarcoidosis**

Box 1 shows the recommended basic assessment for systemic sarcoidosis in patients presenting with specific cutaneous lesions [8,33,130,131]. It should be noted that SACE levels are increased in only 60% of patients with sarcoidosis and they are not specific to the disease [132]. Other ancillary tests such as thoracic high-resolution computed tomography (HRCT), whole-body $^{68}$gallium scan, brain and cardiac magnetic resonance imaging, and whole-body $^{18}$F-FDG PET may also be helpful to

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**Box 1**

**Recommended basic assessment for sarcoidosis in patients presenting with specific (granulomatous) cutaneous lesions**

- History (including occupational and environmental exposures)
- Physical examination
- Ophthalmological examination (slit lamp and ophthalmoscopic examination)
- 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
establish the diagnosis and the extent of sarcoidosis. However, they should not be performed routinely but according to selected indications [133]. If systemic sarcoidosis cannot be demonstrated in a patient with skin granulomas, a long-term follow-up should be undertaken, as some of these cases will develop systemic involvement later in the course of the disease [8,15,20–22]. Nevertheless, some 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 [16,38]. 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 having sarcoidosis limited to the skin [20].

Prognosis
The prognosis of patients with sarcoidosis mainly depends on the extent and severity of the systemic involvement [15,17,18,20]. However, some types of skin lesions have prognostic significance and may help to predict the outcome of the systemic disease. Although by themselves the cutaneous lesions of sarcoidosis almost never cause significant morbidity or mortality, some of them may be disfiguring or have a cosmetic importance that produces a strong psychosocial impact. Often, but not always, these kinds of lesions are associated with a poorer prognosis of the systemic disease. The outcome of the different types of cutaneous lesions has been discussed in the respective sections above. In summary, maculopapular lesions, 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 are associated with more severe pulmonary and extrathoracic involvement, as well as with a more protracted course of the systemic disease [18,20]. In a multivariate study of the prognosis of sarcoidosis the presence of specific cutaneous lesions taken as a whole did not have prognostic significance [134,135]. However, a recent study of 86 cases with specific cutaneous lesions focused on the relationship between the types of lesions and the severity and chronicity of the disease [22]. Patients were classified into two groups according to the type of specific cutaneous lesion. The first group included patients with maculopapular and subcutaneous lesions, and the second those patients with plaques and lupus pernio. Group comparison showed that maculopapules and subcutaneous nodules were significantly associated with EN, radiological stage I, and remission of the systemic disease at two years after the diagnosis. By contrast, plaques and lupus pernio were significantly associated with chronic persistent disease and the need for corticosteroid therapy due to the severity of systemic involvement and the persistence of systemic sarcoidosis activity for more than two years. Significant differences were also found between the duration of 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; \( P < 0.001 \)) and in the duration of systemic sarcoidosis activity (36.48 months vs. 85.39 months, respectively; \( P < 0.01 \)). 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 as regards the outcome of the systemic disease [22].

Treatment
Most patients with sarcoidosis will not require treatment since the disease often remits spontaneously or remains stable, 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 involvement, either pulmonary or extrapulmonary. Systemic corticosteroids are the most effective treatment. The recommended treatment for pulmonary sarcoidosis is prednisone, 30–40 mg daily with gradual reduction to maintenance levels of 10–20 mg every other day. Severe uveitis, neurosarcoidosis or symptomatic cardiac involvement requires a dose of 1 mg/kg per day [33]. Although sarcoidosis of the skin is not life-threatening it can, in a minority of patients, be devastating and may have a strong psychological and social impact. Treatment of these types of lesions is particularly difficult and is one of the present challenges of sarcoidosis. Treatment is also indicated when cutaneous lesions are cosmetically disfiguring, symptomatic, ulcerative, progressive or with a propensity to scarring. Indeed, skin lesions of sarcoidosis require treatment primarily if they are of cosmetic importance to the patient. However, when the only indication for treatment is the cutaneous involvement, with the primary aim being to improve the patient’s quality of life, the risks and benefits of treatment must be considered carefully. 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 [41]. Another important aspect in the treatment of skin sarcoidosis is the assessment of therapeutic response. Perhaps the simplest method in this regard is an overall assessment by physician and patient, counting the number and the size of lesions. Baughman et al. evaluated a lupus pernio activity and severity index based on parameters such as erythema, induration, desquamation and area of involvement, using a scoring system such as LuPASI [136]. At all events, even if a treatment significantly reduces the size of a lesion it may still be significant for the patient from a cosmetic point of view. Therefore, it is necessary to include health-related quality of life and psychosocial status when assessing the response to therapy for cutaneous sarcoidosis.
Most of the agents used for systemic sarcoidosis are also used for cutaneous sarcoidosis. Selection of the most appropriate individual agent should be based upon consideration of factors such as the patient’s acceptance of the treatment regimen, drug monitoring requirements, and drug adverse effects.

**Corticosteroids**

Although systemic corticosteroids are the most effective treatment for sarcoidosis there are limited data on the efficacy of these agents for cutaneous involvement. Most skin lesions do not need treatment. Some lesions, such as plaques and certain cases of infiltrating papules or subcutaneous nodules, are associated with chronicity but they have minor cosmetic importance. Topical and intralesional therapies with ultrapotent corticosteroids may be useful in localized disease. However, these therapies often fail to achieve complete resolution without simultaneously inducing skin atrophy and hypopigmentation.

Only chronic cutaneous lesions, particularly lupus pernio, which involves the face, and extensive plaques, which may cause scarring, may require per se oral steroid treatment [33,140]. 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 treatment courses and at least some improvement in 72% [60]. However, the optimal dose of corticosteroids for skin sarcoidosis is not known. 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 remissions. Furthermore, their prolonged use often results in adverse effects such as Cushingoid features (buffalo hump, redistribution of body fat, purple striae and moon face), weight gain, hyperglycaemia, osteoporosis, hypertension, peptic ulcer, acne, insomnia, weakening of proximal upper and lower extremities, increasing irritability and even psychosis. These deleterious effects may counteract the benefits of a treatment that is principally given for a cosmetic objective [139]. The dose of corticosteroids may be decreased or the treatment stopped by the introduction of a steroid-sparing immunosuppressive agent.

**Antimalarials**

The antimalarial agents chloroquine and hydroxychloroquine have immunomodulatory properties and have been used to treat rheumatologic disease such as rheumatoid arthritis and lupus erythematosus. Although they have been widely used in sarcoidosis for over fifty years [141], data on the efficacy of antimalarial drugs for cutaneous sarcoidosis are limited to a few small uncontrolled studies. They have, however, been reported to be more useful for cutaneous than for pulmonary sarcoidosis [141–143]. Indeed, antimalarials 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 being observed at 12 weeks [142]. Relapse after discontinuation of treatment is common [141]. Adverse effects include gastrointestinal symptoms, particularly nausea, which is dose related, and ocular (corneal deposits and central retinopathy), neurological or haematological toxicities. Eye examination at least once a year is recommended [144]. The risk of ocular toxicity seems lower with hydroxychloroquine. However, chloroquine seems more effective, although this has not been systematically tested [140].

**Methotrexate**

Methotrexate used at low-doses is able to suppress granuloma formation [139], and it has been widely used as a steroid-sparing agent in several forms of systemic sarcoidosis including pulmonary, ocular and neurological sarcoidosis [145,146]. Several studies have reported methotrexate to be very useful for skin sarcoidosis. 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 [145]. However, the therapeutic response may take as long as six months [146]. Most adverse effects are dose-dependent and include haematological, gastrointestinal, hepatic and pulmonary toxicities [146]. Methotrexate pulmonary hypersensitivity may be difficult to differentiate from exacerbation of pulmonary sarcoidosis. Mucositis, nausea and vomiting can be eliminated by dividing the dose in half (on two consecutive days per week). Oral folic acid 1 mg/day is also recommended. The dose must be adjusted in patients with renal failure. Methotrexate must be avoided if serum creatinine is greater than 265 μmol/L. 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) [146]. 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 [139].

**Tetracycline**

It is hypothesized that tetracycline derivatives may act in sarcoidosis by inhibiting granuloma formation [58]. A potential antibacterial effect, including activity against Propionibacterium acnes, a putative agent for sarcoidosis, has also been suggested [140,147]. 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. Maximal
response was achieved with between one and six months of treatment. Patients remained in remission for an average of 15 months after discontinuation of therapy. Three patients relapsed and were treated with doxycycline 100 mg twice daily [148]. Improvement in subcutaneous and tattoo sarcoidosis has also been reported following doxycycline treatment [55]. Adverse effects of tetracycline antibiotics include nausea, photosensitivity and pigment changes in teeth and skin. Less commonly they may cause autoimmune haemolytic anaemia and autoimmune hepatitis [140].

**Thalidomide**

Thalidomide may be effective in sarcoidosis due to its capacity to block tumour necrosis factor-alpha (TNF-α), a crucial cytokine for the formation and maintenance of sarcoid granulomas [140]. 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 [149–151]. Improvement was also evident on histopathological examination of biopsy specimens after treatment [152]. Teratogenicity and peripheral neuropathy have, however, limited the use of thalidomide. Other dose-dependent adverse effects include somnolence, thrombosis, constipation, dizziness and rash. A dose of 200 mg a day is usually well tolerated by most patients [140].

**Infliximab**

Infliximab is a chimeric monoclonal antibody directed against TNF-α [153]. It is an expensive therapy, and was first used to treat sarcoidosis in 2001 [154]. Since then several case reports and small series have reported stabilization or improvement after infliximab treatment in cases of cutaneous and pulmonary sarcoidosis, neurosarcoidosis and multi-organ disease [155–159]. In general, infliximab has been used to treat cases of recalcitrant sarcoidosis in which not only corticosteroids but also other conventional steroid-sparing agents, such as methotrexate, hydroxychloroquine, cyclophosphamide and others had failed [160]. An elevated baseline C-reactive protein level appears to identify a subset of chronic sarcoidosis patients who will respond better to infliximab therapy [161]. Larger studies have, however, limited the initial enthusiasm for infliximab. Baughman et al., in a study of 138 patients with chronic pulmonary sarcoidosis treated with infliximab, demonstrated that the therapy resulted in a statistically significant improvement in forced vital capacity of only 2.5% compared with placebo group at the 24th week of treatment (P < 0.038) [162]. Judson et al. also reported a moderate benefit of infliximab in the treatment of extrapulmonary manifestations of sarcoidosis [163]. As regards skin sarcoidosis, Stagaki et al. retrospectively studied 116 courses of treatment in 54 patients with lupus pernio. Regimes containing infliximab were clearly superior to regimes with systemic corticosteroids, with or without additional steroid-sparing agents, in the treatment of lupus pernio. More than 75% of all treatment regimes containing infliximab resulted in resolution or near resolution of lupus pernio lesions. 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 [60]. 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 a maintenance therapy [164]. Infliximab is administered intravenously in doses of 3 to 5 mg/kg/dose at 0, 2, 6, 12, 18 and 24 weeks [162,163]. Adverse effects include infusion reactions and an increased risk for infections, especially tuberculosis, and malignancy, particularly lymphoma [165]. An interferon-gamma release assay for latent tuberculosis infection is recommended to be performed before treatment. During treatment with infliximab human anti-chimeric antibodies may develop. Concomitant use of methotrexate may decrease this risk [153]. Other biological agents may also have a role in the treatment of sarcoidosis. Etanercept, a soluble tumour necrosis factor inhibitor, was reported to be effective in a patient with lupus pernio [166]. However, it was frequently associated with treatment failure when administered for progressive pulmonary sarcoidosis [167]. Adalimumab, a monoclonal antibody that targets TNF-α, has also been used successfully in patients with resistant cutaneous sarcoidosis [168–170]. Anecdotal reports suggest that rituximab, the anti-CD20 monoclonal antibody, may also be beneficial in patients with sarcoidosis [153].

**Other agents**

Although pentoxiphylline has been used as a steroid-sparing agent in pulmonary sarcoidosis [171], its efficacy for cutaneous involvement is not known. Mycophenolate mofetil has been used to treat a few patients with mucocutaneous manifestations of sarcoidosis who had failed to respond to corticosteroids and other therapies [172,173]. Prolonged treatment with oral isotretinoin has been used successfully in some case reports for cutaneous sarcoidosis [174,175]. However, it is a potent teratogen [139]. Anecdotal cases of cutaneous sarcoidosis improving with allopurinol [176,177], leflunomide, either concurrently with methotrexate or alone [178], melatonin, chlorambucil, fumaric esters, radiation, topical tacrolimus, ultraviolet light, laser surgery and plastic surgery have all been reported [62,139,140].

**Non-specific (non-granulomatous) cutaneous lesions**

**Erythema nodosum**

EN is the most common form of non-specific (non-granulomatous) skin manifestation of sarcoidosis. It is a
Skin manifestations of sarcoidosis

panniculitis and, clinically, is characterized by the presence of rounded or oval, slightly raised, non-ulcerative painful red nodules on the skin and subcutaneous fatty tissue, 1–6 cm in diameter, sometimes coalescing. These tend to be symmetrical in distribution and are usually located bilaterally on the lower extremities, particularly on the anterior tibial surface, although they may also involve the ankles, the lower parts of the thighs, and the forearms (figure 12). Nodules are self-limiting, resolving in one to six weeks. They evolve from bright red to a brownish-yellow discoloration resembling bruises. Old lesions often coexist with the appearance of new nodules, such that nodules at various stages of evolution may be observed. Accompanying systemic symptoms such as fever, malaise and arthralgias may also be present [179]. Although it has been suggested that EN is a circulating immune complex-mediated process, the potential pathogenic role of circulating immune complexes is not clear [180]. The histopathology of EN shows a neutrophilic perivascular reaction with septal panniculitis in the deep dermis and subcutaneous tissue, the epidermis appearing normal. Granulomas are characteristically absent. No histological changes are observed among the various causes of EN and histology of EN is not useful for diagnosis [179]. EN has been associated with a wide spectrum of infections, drugs and systemic diseases, and it may also be idiopathic. The frequency of the different causes of EN mainly depends on the geographical origin of the series. In early series, the percentage of EN cases associated with sarcoidosis varied between 8% and 74% [181]. However, as the frequency of primary tuberculosis and acute streptococcus infection decreased, sarcoidosis became a more frequent cause [182]. In recent studies, 10–22% of patients with EN were classified as having sarcoidosis [183].

Löfgren’s syndrome

In sarcoidosis, EN nearly always occurs in the acute phase associated with the presence of BHL on the chest radiograph. Occasionally, however, it may occur in other contexts or even as a manifestation of chronic disease. The association of EN with BHL was first recognized as an acute, benign form of sarcoidosis by Löfgren and Lundbäck [3–6], and subsequently by James et al. [7]. This form of sarcoidosis is known as LS. Its acute presentation probably represents an excellent example of an interplay between specific HLA polymorphisms, exposure to antigenic environmental triggers, and genetically determined T-cell responses that distinguish it from other clinical forms of sarcoidosis.

Epidemiology

LS occurs more commonly in young Caucasian females, particularly those from northern European countries, Ireland and Spain, whereas it is uncommon in the United States, especially among Afro-Americans, and in Japan [6,11,12,69,184]. Although LS may occur at any time of the year there is a clustering for late winter and early spring, which strongly suggests that environmental factors may be important in the aetiology of the disease [184,185].

Genetics

Differences in the incidence of EN in the sarcoidosis population may predominantly be due to genetically determined variations in reactivity, in tandem with environmental factors. For years, studies of the human leukocyte antigen (HLA) complex in patients with sarcoidosis, including LS, have shown an association between HLA type and the clinical presentation and outcome of sarcoidosis. At least two genetic markers, HLA class II haplotype DRB1*0301-DQB1*0201 and CCR2-haplotype 2, have been clearly associated with both LS and good prognosis [186]. However, Grunewald and Eklund recently reported that almost half their subgroup of DRB1*03-negative patients with LS developed non-resolving disease within two years, whereas almost every DRB1*03-positive patient showed a resolving disease [187]. Taken together, these genetic findings strongly support the notion that LS represents an entity that is distinct from non-Löfgren sarcoidosis.

Immunopathogenesis

During its initial stage, LS is characterized by a high-intensity lymphocytic alveolitis on the bronchoalveolar lavage. Despite this, LS usually shows a good prognosis [188]. Consequently, it has been hypothesized that the good outcome associated with this clinical form of sarcoidosis could be due to differences in the inflammatory process compared with other clinical forms of sarcoidosis, in addition to the host’s own genetic susceptibility. Accordingly, Ho et al. reported that a newly identified subset of T-cells with immunoregulatory functions, namely CD1d-restricted natural-killer T-cells, was absent or greatly reduced.
in the peripheral blood of patients with all forms of sarcoidosis except those with LS. They suggested that this defect might contribute to the amplified and prolonged immune response that distinguishes sarcoidosis, except in the majority of cases with LS, which is characterized by a well-defined start and end of immune activity [189].

Clinical description
Clinically, EN associated with sarcoidosis has no special characteristics distinct from those associated with other causes. Polyarthralgias, predominantly in the ankles and knees, are frequent, although other peripheral large (wrists, elbows) and small joints may be involved [185]. Interestingly, periarticular ankle inflammation (PAI) is often very prominent (figure 13) and the disease frequently presents in this form, which may or may not be followed by the development of EN. In a series of 186 patients with LS, 35 (19%) presented with PAI alone that was not followed by EN, 46 (25%) presented both concomitantly, and 92 (49%) presented with EN but without periarticular ankle involvement [185]. PAI without EN has been recognized as a clinical variant of classic LS [190,191]. It is found predominantly in men, whereas EN is seen preferentially in women [192]. Swelling of the ankle is caused by a combination of periarticular oedema and tenosynovitis, sometimes with red colouration of the skin, and is accompanied by mild to disabling pain on joint motion or walking, but without true arthritis [190].

BHL (stage I) on the chest radiograph is usually already present when EN appears [181]. Consequently, when faced with a patient presenting with EN and/or PAI a chest radiograph should always be performed to confirm or exclude sarcoidosis. However, in a few cases the chest radiograph may be normal at the time of the appearance of EN, with radiographic manifestations becoming evident a few weeks thereafter. BHL is sometimes accompanied or followed by parenchymal pulmonary infiltration (stage II), usually with predominance in the middle and upper lobes, in the typical sarcoidosis pattern. In the case of doubtful hilar lymphadenopathy on the chest radiograph a thoracic CT or 67 gallium scan usually help to confirm its presence [185].

In LS extrathoracic manifestations other than EN may occur concurrently with or appear soon after EN, and they include constitutional symptoms such as malaise, fatigue and fever (usually low-grade), anterior uveitis and peripheral facial palsy, sometimes bilateral [185]. Specific (granulomatous) skin lesions including infiltration of old scars, papules (particularly in the knees) and subcutaneous nodules may appear concomitantly with EN and go unnoticed [8,40,48]. The SACE level may be normal in the initial phase of the disease in approximately 50% of patients with LS. Thus, it is not a reliable parameter to assist diagnosis in this stage of the disease. However, it usually increases within the first three months following onset [188]. This supports the notion that EN signals the beginning of the disease.

Diagnosis
The diagnosis of LS is basically clinical and routine histological confirmation is not usually necessary. The association of EN with radiologically unequivocal BHL on the chest radiograph virtually confirms a diagnosis of sarcoidosis [185]. In some cases, however, histological confirmation of sarcoidosis is important. The most useful biopsy procedures are a skin punch biopsy of specific skin lesions, in the event that they are present [40,48]. Recently, endobronchial ultrasonography-guided transbronchial fine-needle aspiration has demonstrated a high diagnostic yield for mediastinal sarcoidosis [193]. Patients without histological confirmation should be followed up at least until the hilar adenopathy is resolved [185].

Treatment and prognosis
Although EN become self-limiting within a few weeks, rest, non-steroidal anti-inflammatory drugs, potassium iodide (300 mg orally three times daily) or a short course of low-dose corticosteroids may be useful in treating symptoms [185]. The indications for conventional corticosteroid treatment in LS are the same as those for sarcoidosis, i.e. symptomatic and progressive pulmonary involvement with functional derangement or extrathoracic involvement of the vital organs, both of which are very infrequent in LS.

Sarcoidosis presenting at onset as LS is indicative of a favourable prognosis and usually resolves spontaneously within a period of a few months to less than two years [6,181]. In a study using multivariate statistical analysis the presence of EN proved to be the strongest predictive factor for a favourable prognosis [134,135]. However, the good prognosis of sarcoidosis presenting with EN seems to be limited to Caucasians [18], whereas black and West Indian patients showed a worse

Figure 13
Periarticular ankle inflammation without erythema nodosum

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**TABLE 1**

**Classification of skin manifestations of sarcoidosis**

<table>
<thead>
<tr>
<th>Specific lesions</th>
<th>Less frequent types</th>
<th>Special sites</th>
<th>Non-specific lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular lesions</td>
<td>Angiolupoid</td>
<td>Oral cavity</td>
<td>Erythema nodosum</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>Hypopigmented</td>
<td>Scalp alopecia</td>
<td>Digital clubbing</td>
</tr>
<tr>
<td>Scar sarcoidosis</td>
<td>Lichenoid</td>
<td>Nail</td>
<td>Sweet’s syndrome</td>
</tr>
<tr>
<td>Plaques</td>
<td>Ulcerative</td>
<td>Genital</td>
<td>Pyoderma gangrenosum</td>
</tr>
<tr>
<td>Lupus pernio</td>
<td>Psoriasiform</td>
<td></td>
<td>Calcinosi</td>
</tr>
<tr>
<td>Verrucous</td>
<td>Erythema multiforme</td>
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<tr>
<td>Necrobiosis lipoidica-like</td>
<td>Ichthyosiform</td>
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<tr>
<td></td>
<td>Erythrodermic</td>
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<td>Morpheaform</td>
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prognosis [181]. Recurrence many years after complete spontaneous resolution has occasionally been reported in sarcoidosis, and more frequently occurs in patients with LS [194].

**Other non-specific lesions**

**Digital clubbing**

Digital clubbing has been reported as a non-specific manifestation of sarcoidosis [195–197], and was recently observed in three out of 93 patients with sarcoidosis [198]. Some authors have suggested that it is a sign of bad prognosis [199]. Pseudo-clubbing originated by granulomatous phalangeal bone involvement has also been reported in sarcoidosis [200], and must be differentiated from true digital clubbing.

**Sweet’s syndrome**

At least 13 patients with Sweet’s syndrome associated with sarcoidosis have been reported [201–206]. Patients with this association tend to be younger than those with idiopathic Sweet’s syndrome, and 12 of the 13 cases were women [206]. The diagnoses of Sweet’s syndrome and sarcoidosis were usually made at the same time, at the beginning of the disease [205]. In most cases sarcoidosis was acute, usually LS, and so the presence of lesions of Sweet’s syndrome is probably a good prognostic sign in sarcoidosis [206].

**Pyoderma gangrenosum**

Sarcoidosis has exceptionally been described in association with pyoderma gangrenosum, the first two cases being reported in 1984 by Powell et al. [207]. A further four cases have since been described [208–211]. Although the association may be fortuitous, one case showed a clear-cut relationship between the biopsy of an EN nodule and the beginning of pyoderma gangrenosum [211].

**Calcinosi**

Although hypercalcemia occurs in around 5–10% of cases of systemic sarcoidosis, cutaneous calcinosi has only exceptionally been described as a rare non-specific lesion of sarcoidosis [212,213].

**Erythema multiforme**

Although erythema multiforme has been reported as a non-specific lesion of sarcoidosis in several reviews, there are no recently published cases with this association. It is indistinguishable clinically and histopathologically from erythema multiforme of other causes [214].

**Prurigo**

Prurigo has been described in association with sarcoidosis in some old papers [215]. However, in recent years there have been no reported cases with this association. Table 1 shows classification of skin manifestations of sarcoidosis.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.
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