Sarcoidosis

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Key Points

- Sarcoidosis is a multisystem, granulomatous inflammatory disorder which commonly involves the skin.
- African Americans are disproportionately affected in the United States
- Etiology and proposed triggering antigens are unknown.
- Sarcoidosis is one of the "great imitators" and can present with nearly any clinical morphologic lesion type.
- The nose, particularly the nasal alar rim, as well as the periorbital and perioral areas, scars, and tattoos are frequent sites of cutaneous involvement.
- Non-caseating epithelioid granulomas are the hallmark pathologic sign of sarcoidosis.
- Patients with cutaneous sarcoidosis require thorough evaluation for the extent of systemic disease.
- Treatment of cutaneous sarcoidosis requires a stepwise approach which includes topical, intralesional and systemic therapies.

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Interdisciplinary Introduction

Sarcoidosis is a multisystem, inflammatory disorder of unknown etiology that can affect every organ system in the body [1, 2]. The disease is characterized by the development of non-caseating granulomas, which can cause disease through either active inflammation or scarring and fibrosis. Sarcoidosis occurs worldwide and can affect patients of any race, ethnic group, or age [3]. Patients likely inherit a genetic predisposition for developing the disease, which, coupled with an environmental, infectious, or antigenic exposure, triggers an immune cascade, leading to granulomatous inflammation, which may spontaneously remit, persist, or lead to subsequent fibrosis.

Patients with sarcoidosis nearly always have lung involvement, which can range from incidental hilar adenopathy identified on routine chest radiography to devastating lung disease requiring transplantation. The skin is the second most commonly affected organ, with 30% of sarcoidosis patients displaying signs of cutaneous inflammation due to the disease [4, 5]. The eyes, joints, and lymph nodes are also frequently affected, and many patients develop disease-related fatigue. Patients can also develop granulomas in the heart, nervous system, liver, kidneys, or bone marrow, while the metabolic effects of the disease can lead to significant complications, morbidity or mortality.

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Sarcoidosis is classically defined by evidence of granulomatous inflammation in more than one organ system, highlighting the multidisciplinary nature of this disease [6, 7]. Cooperation between patients' primary doctors (frequently pulmonologists or rheumatologists) and dermatology is essential in both the diagnosis and management of sarcoidosis.

While there are characteristic clinical, laboratory, and radiographic features that can be suggestive of the disease, pathologic confirmation is generally recommended to make the diagnosis. Superficial and easily accessible, the skin is the organ of choice for biopsy if skin lesions are present. Cutaneous sarcoidosis is a protean disease, one of the "great imitators," and can present with almost any primary lesion morphology; diagnosis requires evaluation by an experienced dermatologist and a low threshold to biopsy [8].

Once a diagnosis is established, patients with sarcoidosis require thorough evaluation for the extent of disease, with treatment depending on the most severely affected organ system. While certain therapeutic options will broadly treat all sarcoidal inflammation, in some cases each affected organ system may respond differently. Whether in diagnosis, management of cutaneous involvement, or alleviation of treatment-related cutaneous side effects, the dermatologist has an essential role to play in the treatment of patients with sarcoidosis [9].

Epidemiology & Risk Factors

Sarcoidosis occurs in patients of all races, and ethnic backgrounds, and has been described in all age groups. The overall rates vary, with the incidence highest in Sweden (64 per 100,000) and the UK (20 per 100,000) and the lowest in Spain and Japan (both 1.4 per 100,000) [10, 11]. In the United States, the highest-risk group is African Americans, with an incidence of 35–64 per 100,000 [12]; African American women have a 2–3% lifetime risk of developing sarcoidosis and tend to develop more severe disease [13]. Fewer than 5% of patients will die from sarcoidosis, usually due to advanced lung disease and fibrosis or from severe cardiac involvement [2, 14].

Overall the disease exhibits a bimodal age distribution, with incidence peaks in the mid-twenties to thirties and, in women, another small peak from 45–65 in some countries [15]. The disease is less common in children, teenagers and patients older than 70, but it has been rarely reported in infants. There exist conflicting reports regarding potential seasonal variation in disease presentation and diagnosis [16–18].

Beyond racial and age variations in incidence [19], there is evidence for clustering of disease among family members, including twins [20]. Monozygotic twins are at an 80-fold increased risk of developing sarcoidosis, while dizygotic twins are at a 7-fold increased risk [21]. The largest epidemiologic study to date, A Case Control Etiologic Study of Sarcoidosis (ACCESS), documented a relative risk for developing sarcoidosis of 4.7 in patients with an affected first or second degree relative, with an excess risk among siblings [22].

Occupational exposures and environmental factors may play a role in disease development as well. Sarcoidosis closely resembles chronic berylliosis clinically, radiographically, and histopathologically. Sarcoid-like granulomatous reactions can also occur at sites of foreign bodies, such as sutures, asphalt or remote debris injury, and in response to certain tattoo pigments that contain metallic components. Clusters of sarcoidosis cases have been reported in patients with certain occupational exposures, such as US Navy shipyard personnel [23] and firefighters [24], who may be exposed to inhalation of dusts or metals; the rates in New York City firefighters increased after the terrorist attacks on the World Trade Center on September 11, 2001 [25]. The ACCESS study identified "high microbial" environments as potential risk factors, including exposure to insecticides, molds, and mildew [26].

It is often difficult to separate the effects of environment from those of genetics; one study found 40% of patients with sarcoidosis had exposure to a patient with the disease (versus 1–2% of controls). Cases occurred within

households but also in friendships and neighborhoods. This study also identified an increased rate of disease among nurses [27, 28]. Further complicating the picture, certain environmental exposures may be more likely to induce disease in patients of specific backgrounds or with certain human leukocyte antigen (HLA) haplotypes. Caucasian patients show an increased risk with exposure to industrial organic dusts, but not with metal exposure. African Americans have an increased risk with metal exposure or employment in the transportation industry [29]. Patients with HLA DRB1*1101 have an increased risk of disease with occupational insecticide exposure [29].

Sarcoidosis is not due to a single gene mutation but rather represents a complex, polygenic disease with several potential variants. Certain HLA alleles may confer risk for developing the disease in some patients, though the prevalence and impact of those alleles varies by racial/ethnic group. HLA DRB1*03, DRB1*11, DRB1*12, DRB1*14, and DRB1*15 appear to confer risk for disease overall, although HLA-DQB1 genes may be more important in African Americans [30].

HLA-B8/DR3 has been associated with increased risk for developing an acute form of sarcoidosis, Lofgren syndrome, that is characterized by hilar adenopathy, fever, arthritis, and erythema nodosum (EN) and carries an overall good prognosis with low risk for chronic disease. Similarly, patients with DRB1*03 alleles appear to have a good prognosis with protection against chronic disease [30].

Specific mutations including polymorphisms in genes encoding inflammatory cytokines (such as the *TNF* gene and the *IL23 receptor* gene) and genes involved in apoptosis and immune cell activation (such as *ANXA11* and *BTNL2)* [31, 32] have been identified as increasing sarcoidosis risk in some populations [33]. It is likely that genetic polymorphisms and HLA alleles confer risk for development of an abnormal immune response to an inciting antigenic exposure—one that is either too vigorous or cannot cease appropriately.

Pathogenesis

Sarcoidosis is a multisystem disorder characterized by granuloma formation in affected organs. In some patients it will spontaneously remit, while others will experience either chronic, active inflammation, or fibrosis and scarring. The disease phenotype may vary somewhat by race/ethnicity, country, and genetic background. As reviewed, patients inherit susceptibility risk for development of the disease, and, when exposed to an antigen, develop granulomatous inflammation. There exists substantial debate over the triggering antigen, with some experts postulating that in the future this entity will be known as "the sarcoidoses" rather than "sarcoidosis," based on different patterns of granulomatous response to different triggering antigens [34].

The development of an epithelioid granuloma, which is nearly always non-caseating, is the hallmark pathologic sign of sarcoidosis. Overall, sarcoidosis is considered a Th1-predominant disease, although the innate and Th17 arms of the immune system likely also play a role [35]. Initial granuloma formation likely involves innate phagocytic cells that engulf the disease-specific antigen. Innate immune signals such as Toll-like receptor-2 and nucleotide-binding oligomerization domain 1 appear, and tumor necrosis factor (TNF) and other inflammatory cytokines are produced [36]. Monocytes with MHC II molecules upregulate CD4+ Th1 T-helper cells after antigen regulation, leading to a Th1 cytokine predominance, with increased expression of interferon-gamma (IFNɣ) as a key inflammatory mediator, along with upregulation of interleukin-2 (IL2) and IL18 [37, 38]. Macrophages and some CD8+ T-cells elaborate TNFα, leading to persistent Th1 activity, IFNɣ elevation, macrophage signaling and accumulation, and subsequent B-cell stimulation and hypergammaglobulinemia. Recent research suggested the Th17 response may also play a role in sarcoidal granuloma formation [39]. TNFα and GMCSF lead to macrophage fusion and the formation of characteristic multinucleated giant cells within the granulomatous inflammation. Chemokines are also upregulated,

including monocyte chemotactic factor, which draws monocytes into the affected tissue. Patients may develop lymphopenia, and patients with sarcoidosis tend to display anergic responses, with reduced delayed-type hypersensitivity. Th1 cytokine production is present for the duration of active disease, with some authors suggesting that markers of those cytokines (such as the serum IL-12 receptor level) may be used to follow disease activity, though this approach is not widely used [40].

The determinants of the course that an individual patient's sarcoidosis will ultimately take – either spontaneous improvement (seen in 60% within 2–3 years [41]), chronic active granulomatous inflammation, or a fibrotic phenotype – is as yet unknown.

Some have suggested that persistent sarcoidal inflammation is due to abnormal T-regulatory cells or overall abnormal T-cell function [35, 42, 43].

Beyond the genetic risks and inflammatory pathways involved, much of the active research in sarcoidosis focuses on determining the triggering agent for the disease. In the Kveim-Siltzbach skin test, ground spleen from patients with sarcoidosis is injected intradermally, eliciting a granulomatous reaction 4–6 weeks later in patients with sarcoidosis; this finding provides some evidence for a transmissible antigen [44]. Patients have developed sarcoidosis following organ transplantation [35, 45]. Growing evidence suggests that the etiologic antigen is either a microbial infective agent, inert environmental element or compound, or autologous self-antigen, such as a misfolded protein.

Due to the clinical, radiographic, and histologic overlap between sarcoidosis and mycobacterial infections (particularly tuberculosis), a mycobacterial agent has long been hypothesized as a trigger for sarcoidosis. Mycobacteria are fastidious and can be challenging to culture, but acid-fast staining generally also fails to reveal organisms on routine testing in sarcoidosis. Additionally, despite treatment with broadly immunosuppressive agents, patients with sarcoidosis do not typically experience disseminated or reactivated mycobacterial infections.

As diagnostic techniques have advanced, however, mycobacteria have been detected with greater frequency in sarcoidal specimens. With the advent of PCR, approximately one quarter of evaluated specimens in a large meta-analysis were found to have evidence of mycobacterial genetic material, 10–20 times more frequent than in controls [46]. Proteomic testing identified the presence of mycobacterial protein catalase-peroxidase (mKatG) in sarcoidosis tissues in approximately one half of cases [47]. Additional advanced diagnostic techniques such as mass spectrometry, protein immunoblot, and deep sequencing have identified other mycobacterial compounds (heath shock proteins, ESAT6, and others) in sarcoidal specimens [35, 48, 49]. These mycobacterial antigens may trigger a Th1 cytokine response in genetically predisposed patients, leading to the observed clinical phenotypes.

It is possible that patients with sarcoidosis exhibit an abnormal immune response to a transiently present or rapidly killed mycobacterial agent, leading to robust granulomatous inflammation, and then due to genetic and immunologic factors, the granulomatous cascade continues unabated, even once the inciting agent is cleared. No studies have confirmed a mycobacterial agent as the definitive trigger of sarcoidosis, however.

Besides mycobacteria, other infectious agents have been evaluated for a possible role in inducing sarcoidosis. Numerous studies, primarily out of Japan, have shown high rates of Propionibacterium acnes in sarcoidosis tissue samples [50]. This agent has been detected by both culture and DNA identification; investigators have also demonstrated abnormal responses to *P. acnes* proteins in patients with sarcoidosis [51, 52]. TLR-2, which is involved in the host response to *P. acnes* and in acne pathogenesis, is also hypothesized to play a role in innate immune signaling in early granuloma formation. However, *P. acnes* is a common bacterium that has also been detected in tissue specimens from control patients, and its role as a potential inciting pathogen remains unclear. It is plausible that *P. acnes* may play a role in triggering sarcoidosis in specific geographic locations, countries, or in specific racial/ethnic groups, but not in all patients.

Other infectious agents identified as potential triggers of sarcoidosis include fungi (particularly cryptococcus) and viruses, including a variety of human herpes viruses (EBV, CMV, HHV6, HHV7) as well as HIV and HTLV1 [35]. Other suggested triggers include spirochetes, Borrelial species, *T. whipplei,* rickettsia, and chlamydia; however none of these organisms have been substantiated as triggers in controlled trials or epidemiologic studies [53].

Some authors have suggested that the intensely polarized Th1 cytokine skew in sarcoidosis may lead to immunologic control of an infection but failure to clear the triggering antigen, thereby causing additional granuloma formation to trap microbial antigens and triggering a relentless cycle of Th1 inflammation [35]. Based on the properties of the Kveim reagent, one group suggested that the requirements of a sarcoid-triggering antigen should be: poor solubility, resistance to heat, and resistance to chemical degradation; they identified the amyloid precursor protein serum amyloid A (SAA) as a potential pathogenic agent [54]. The same group demonstrated abundant SAA within sarcoidosis tissues and localized to the epithelioid granulomas, with lower rates seen in other granulomatous diseases [55]. Lastly, the same group demonstrated that SAA could trigger Th1 granulomatous inflammation and identified elevated SAA in sarcoidosis bronchoalveolar lavage specimens, with levels correlating to severity of pulmonary disease [35, 54, 55].

Beyond host proteins or infectious agents, other exogenous materials have been suspected as potential antigenic triggers of sarcoidosis. Among the culprits hypothesized are: pine pollen; wood burning or dust; dust of zirconium, nickel, silica, or talc, and others [56–59]. Notably, some of these elements may induce non-sarcoidal hypersensitivity pneumonitis with granulomatous inflammation, similar to chronic beryllium disease, but without the multiorgan phenotype of true sarcoidosis [53, 60–62].

There may be one antigen that triggers all of sarcoidosis, with patients displaying certain disease phenotypes based on their genetic background. Alternatively, numerous antigenic triggers may exist, and the interplay between inciting agent and the host immune response may be what determines the individual disease course.

Clinical Features

Sarcoidosis can present with a wide variety of phenotypes. The disease is classically defined by clinicoradiologic evidence of inflammation in more than one organ system, with histology demonstrating noncaseating epithelioid cell granulomas [1]. While there may exist isolated, single-organ forms of sarcoidosis or sarcoid-like disease [7], all patients with suspected sarcoidosis require a thorough evaluation of numerous organs to assess extent of disease. Sarcoidosis remains a diagnosis of exclusion, with no gold-standard confirmatory diagnostic test, and other causes of granulomatous inflammation must be excluded before a diagnosis of sarcoidosis is rendered.

The vast majority of patients with sarcoidosis have lung involvement (90%), with skin involvement (25–30%), eye involvement (25%), and involvement of other organs occurring somewhat less frequently (Table 9.1). Organ involvement may be asymptomatic at onset and can remain so throughout the course of the disease. Approximately a third of sarcoidosis patients will

Table 9.1 Organ involvement in 393 consecutive patients seen in one sarcoidosis clinic as measured by the WASOG criteria [112]

Organ system involvement or metabolic derangement	Percent (%) of patients
Pulmonary	88
Ocular	32.4
Cutaneous	27.7
Neurologic	14.4
Non-thoracic lymph node	14.2
Calcium Abnormalities	14.1
Hepatic	10.9
Splenic	6.7
Cardiac	6
Renal	1.1
Other (Marrow, Bone/Joint, ENT, Salivary/Parotid)	11.2

Adapted from Zhou, 2021 [176]

experience nonspecific symptoms, such as low-grade fevers, fatigue, malaise, or weight loss; the frequency of these symptoms may vary by ethnic group. Certain specific disease phenotypes, such as Lofgren syndrome (see below), are more likely to have significant fever [63].

The disease course in sarcoidosis may be quite variable. Disease activity can wax and wane, sometimes spontaneously, and 60% of patients may experience spontaneous remission, including complete, durable resolution of all disease signs and symptoms [1]. Patients with chronic and/or progressive disease often require persistent treatment. Some 10–20% of patients with sarcoidosis will experience longstanding, permanent sequelae from the disease, and 1–5% of patients can die of sarcoidosis, usually from severe, progressive pulmonary involvement or neuro- or cardiac sarcoidosis [1, 64–68]. The pattern of organ involvement and chronicity may vary by racial/ethnic background and geography: for example, African American patients are more likely to have skin involvement and a chronic disease course, while Northern Europeans more likely to present with Lofgren syndrome, and Japanese patients are markedly more likely to have cardiac involvement [69].

Pulmonary Sarcoidosis

The most common pulmonary symptoms in sarcoidosis patients are cough, dyspnea, and chest pan. The cough is often persistent, dry, and nonproductive. Dyspnea may occur with or without wheezing but does not routinely respond to bronchodilators. Atypical chest pain is often present but usually does not correspond to abnormalities seen on chest imaging, such as adenopathy or parenchymal lung disease. Up to half of patients are diagnosed with pulmonary sarcoidosis as an incidental finding on chest radiography when they have no or minimal symptoms [4, 70]. Physical exam is usually unrevealing; a subset of patients will have audible crackles or wheezes, however, particularly if bronchiectasis is present. In end-stage pulmonary disease, patients may exhibit distal fingertip clubbing [63].

Chest imaging is recommended for all patients with sarcoidosis. Chest x-ray findings were classified by Scadding into four stages: stage 1, adenopathy alone; stage 2, adenopathy plus infiltrates; stage 3, infiltrates alone; and stage 4, fibrosis. Over 90% of pulmonary sarcoidosis can be classified using this schema. Additionally, the chest x-ray stage can predict the outcome of the pulmonary involvement: 90% of stage 1 patients have a normal chest x-ray after 2–5 years, while only 30% of patients with stage 3 disease will experience resolution of their chest x-ray. However, resolution of the chest x-ray does not predict resolution of involvement in other organs. A patient can have a clearing of their adenopathy but persistent skin lesions or other extrapulmonary involvement.

CT scanning is more sensitive than chest x-ray for both adenopathy and parenchymal disease in pulmonary sarcoidosis. Routine CT scanning is not recommended in the assessment of sarcoidosis patients, but it may be helpful in categorizing chest radiographic findings or evaluating patients with atypical, persistent, resistant, or challenging-to-treat disease. Characteristic features seen on CT include significant adenopathy, bronchovascular thickening, micronodular disease and upper lobe infiltrates. Nodules are the most common feature of pulmonary sarcoidosis, seen in 80–100% of patients; these represent areas of granulomatous inflammation [71, 72]. Lung parenchymal involvement tends to be bilateral and symmetrical, with central and upper lung regions involved most frequently [71, 73]. In severe or progressive pulmonary disease, fibrosis may become more prominent. For a patient who presents with granulomatous skin lesions, a CT scan of chest showing symmetrical adenopathy and/or parenchymal disease is highly supportive of the diagnosis of sarcoidosis.

Cutaneous Sarcoidosis

Cutaneous sarcoidosis is one of the "great imitators" and can present with nearly any clinical morphologic lesion type. Cutaneous involvement is divided into "specific lesions" (those that dem-

onstrate granulomas histologically) and "nonspecific lesions" (reactive cutaneous phenomena that do not display granulomas upon biopsy, with EN as the classic example). Cutaneous sarcoidosis tends to be clinically asymptomatic. Lesions in certain anatomic locations and ulcerative lesions may be painful, and patients with cutaneous sarcoidosis will sometimes complain of itch. However, the clinical appearance of the lesions is generally what prompts patients to seek diagnosis and treatment.

While the specific lesions of sarcoidosis are quite varied, certain cutaneous manifestations are more common than others. Sarcoidosis tends to affect the nose (Fig. 9.1), particularly the nasal alar rim (Fig. 9.2), as well as the periorbital and perioral areas, scars, and tattoos. Common morphologies include violaceous macules, papules or plaques (Fig. 9.3), some of which may be annular in shape (Fig. 9.4); another common presentation is indurated nodules and plaques of the nose and

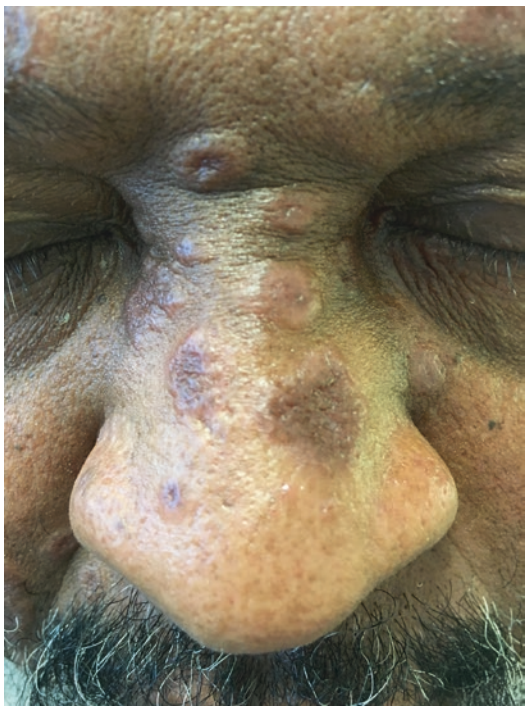

Fig. 9.1 Cutaneous sarcoidosis: plaques across the nasal bridge. This patient has no subcutaneous component to his disease, and these flat papules or small plaques, while occurring on the nose, are generally not described as lupus pernio – instead, as flat papules or plaques on the nose. Lupus pernio lesions should be more extensive and have a subcutaneous component

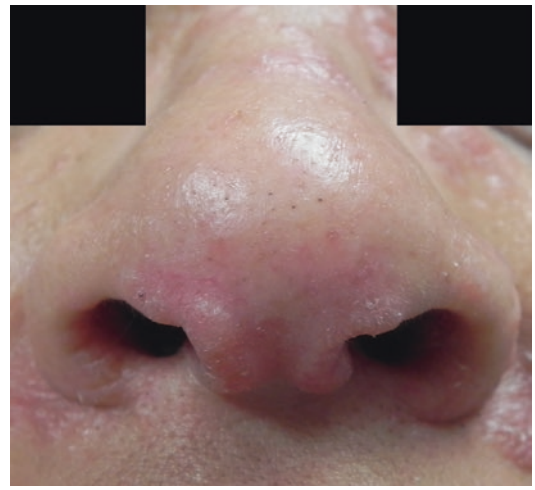

Fig. 9.2 Lupus pernio-like papules. By the strictest definition, papules on the nasal alar rim are not truly lupus pernio. However, patients with extensive papules and scaling, with some distortion of the columella, such as this patient, likely have deeper involvement, as is also the case with lupus pernio. These patients often exhibit a chronic, recalcitrant course, and the technical distinction between lupus pernio requiring plaques or nodules versus smaller lesions such as these may be irrelevant in clinical practice

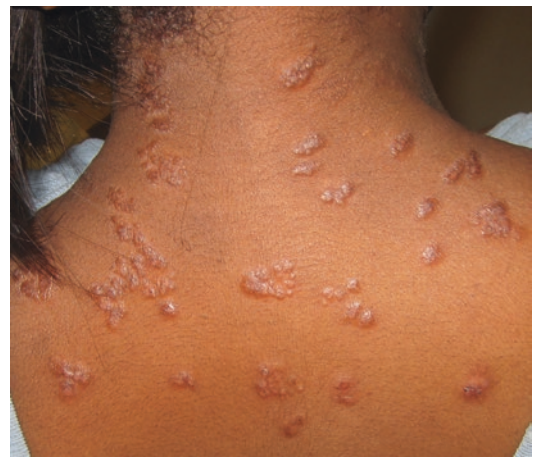

Fig. 9.3 Sarcoidosis papules. These small, raised, palpable areas of granulomatous inflammation can be red, pink, purple, or flesh-colored and may have variable scale. Neck involvement is common, but lesions can occur anywhere

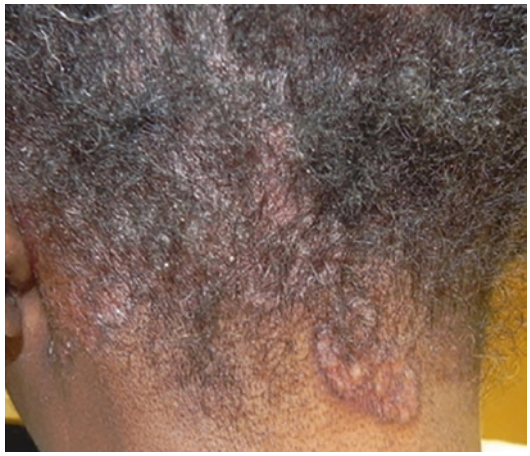

Fig. 9.4 Annular sarcoidosis. This patient has scalp involvement extending down onto the neck. The lesions are circular or annular (in rings), which is a common pattern seen in cutaneous sarcoidosis. The color can vary from the middle to the outer edge of the lesions, and they may develop scale

central face, known as lupus pernio. Flesh-colored subcutaneous nodules or plaques and papules within scars or tattoos are also common presentations. Less common morphologies include psoriasiform lesions, lichenoid papules, verrucous hyperkeratotic lesions, acquired ichthyosis, atrophic or ulcerative lesions, hypopigmented macules or patches, erythroderma, and alopecia (scarring or non-scarring). (Table 9.2) [74].

Macular sarcoidosis can be red-brown/orange, flesh-colored, or hypopigmented (Fig. 9.5); it generally presents with numerous lesions concentrated on the face or in areas of trauma. Papular sarcoidosis can present similarly, although it tends to favor sites of repetitive friction, rubbing, or trauma (such as the elbows and knees). These lesions often resolve without scarring, but postinflammatory changes may persist [75–79]. Plaques are commonly found on the face, back, and extensor surfaces; they are more likely than macular or popular lesions to be seen in patients with a chronic disease course. When treated, plaques are also more likely to leave dyspigmentation and scarring [4, 78, 80].

The term "lupus pernio" is a source of some confusion, as non-dermatologists may sometimes use it to refer to any chronic cutaneous

Table 9.2 Cutaneous sarcoidosis lesion types

Frequency	Morphology
Common	Macules/Papules
	Plaque
	Lupus pernio
	Subcutaneous
	Lesions involving scar/tattoo
Uncommon	Psoriasiform
	Lichenoid
	Verrucous
	Ichthyosiform
	Atrophic
	Ulcerative
	Hypopigmented
Rare	Erythroderma
	Photodistributed
	Alopecia (scarring or non-scarring)
	Nails
	Mucosal
	Genital
Non-specific lesions	Erythema nodosum (EN)
	Calcinosis cutis
	Digital clubbing

Adapted from Wanat and Rosenbach [74]

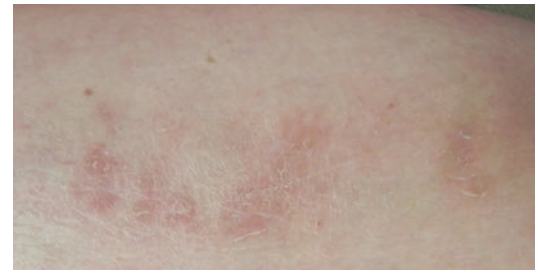

Fig. 9.5 Sarcoidosis macules: these flat, slightly red-brown lesions indicate cutaneous granulomatous inflammation due to sarcoidosis. This case exhibits fine scale, which, when extensive, can lead to acquired ichthyosis and itchyosiform sarcoidosis

lesion of sarcoidosis. By the strictest definition, however, lupus pernio refers to red-to-violaceous subcutaneous plaques or nodules, often with superficial scale, on the nose (Fig. 9.6a, b), cheeks, or central face. This morphologic variant portends a chronic, recalcitrant course and will often leave significant discoloration and sometimes scarring behind even with adequate treatment. Lupus pernio is more common in African Americans, particularly female patients. Lupus pernio is sugges-

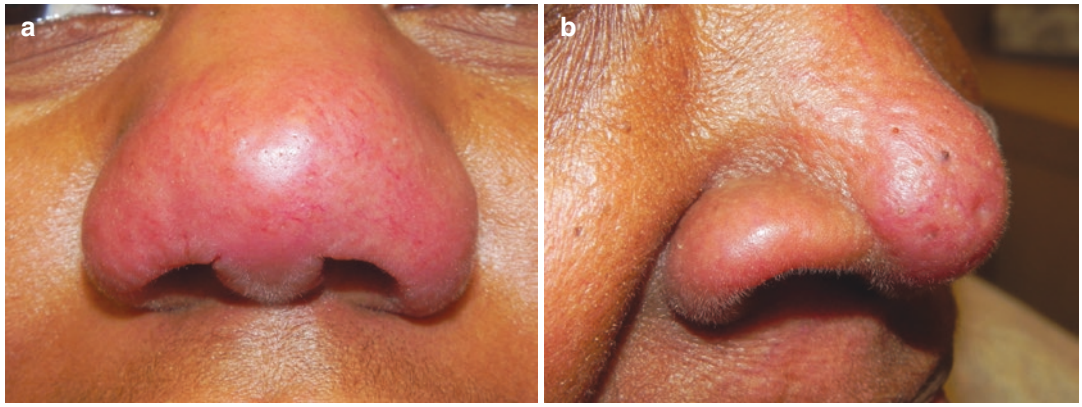

Fig. 9.6 (**a**, **b**) Lupus pernio. (**a**) violaceous, subcutaneous plaque throughout the entire nasal tip. (**b**) violaceous, slightly crusted nodule on the distal nasal tip

tive of sinus, oropharyngeal, and upper airway sarcoidosis involvement and may also be associated with arthritis, bone cysts, pulmonary fibrosis, and uveitis [81–86].

There is debate over whether all chronic facial sarcoidosis lesions represent lupus pernio. Purists argue that papular lesions on the face are a distinct entity and do not carry the same prognostic significance. In truth, the data supporting this distinction are not robust, and many patients with facial sarcoid lesions, including papular disease, can exhibit a course similar to that seen in patients with the deeper plaques and nodules of true lupus pernio.

Subcutaneous sarcoidosis, also known as "Darier-Roussy" disease, affects the deep dermis and subcutaneous tissue, including the fat (Fig. 9.7). Clinically, this entity presents as ill-defined, flesh-colored, subcutaneous plaques and nodules, which can be quite extensive. It is important to distinguish subcutaneous sarcoidosis, characterized by typical non-caseating epithelioid granulomas throughout the deep dermis and subcutis, from EN. The latter presents with red-brown, tender, inflamed nodules, typically on the anterior shins, and is characterized by a predominantly septal panniculitis on histology. Subcutaneous sarcoidosis is more common on the arms, and the lesions are neither clinically inflammatory nor painful [87–92].

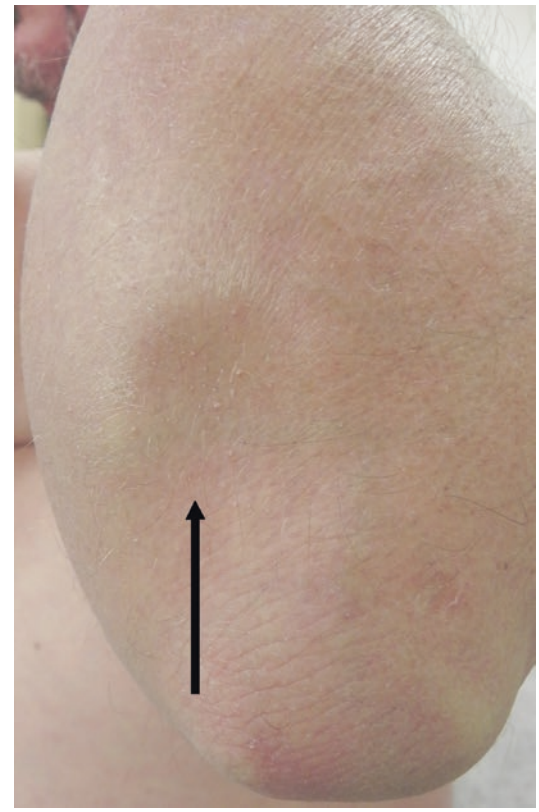

Fig. 9.7 Subcutaneous sarcoidosis: This form of sarcoidosis may be clinically subtle and only appreciable on careful palpation in some patients. The lesions will feel firmer than underlying/surrounding fat and may have a slight give to them

Sarcoidosis frequently affects scars, sites of remote trauma, and areas of foreign body deposition, including tattoos (Fig. 9.8a, b), remote traumatic injuries with debris implantation, and sites

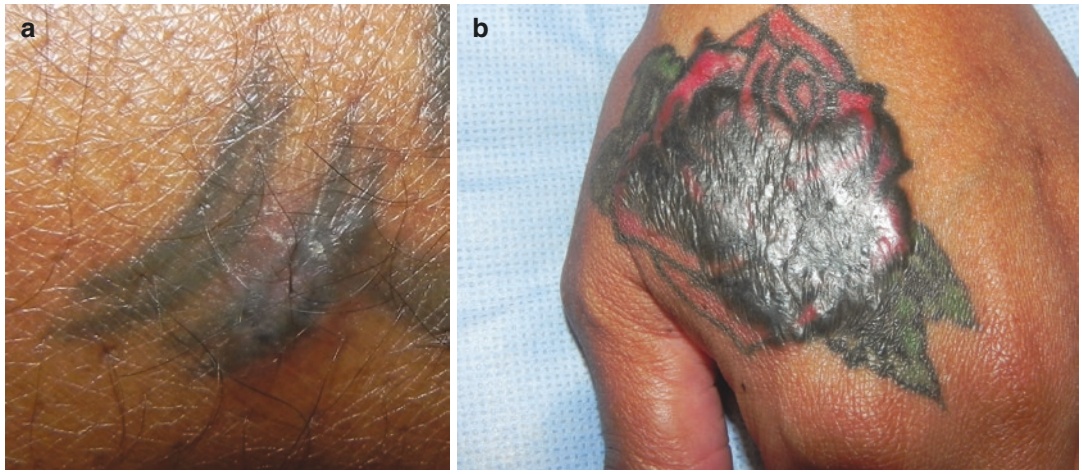

Fig. 9.8 (**a**, **b**) Tattoo sarcoidosis. (**a**) focal involvement of one portion of a larger tattoo. It is essential to completely examine all patients' tattoos, as tattoo sarcoidosis can be subtle but is a reasonable target for biopsy to demonstrate characteristic granulomatous inflammation. Skin biopsy can sometimes spare patients more invasive testing. (**b**) more extensive tattoo involvement, with a large plaque cutting across multiple colors of the tattoo. Tattoo pigment can elicit a granulomatous response; in patients with sarcoidosis, however, when the disease affects tattoos it will often cause lesions in more than one color of the tattoo

of injection (either medicinal or cosmetic). Scar sarcoidosis tends to present with red-to-violaceous papules, nodules, plaques, or subcutaneous swelling, within and immediately around scars [93]. Granulomas within tattoos warrant special consideration. The differential diagnosis can include mycobacterial infection, particularly in freshly placed tattoos, if the granulomas are confined to "shaded" areas, wherein the pigment was diluted with tap water, or if there are pustules present. The differential diagnosis also includes isolated granulomatous hypersensitivity reaction to tattoo pigment; a systemic workup to exclude extracutaneous involvement is always indicated [74].

Sarcoidosis of the digit may affect any compartment, from the bone, to the joint/tendon structure, to the skin and subcutis (Fig. 9.9). It may be clinically challenging to distinguish skin involvement from bone involvement. Hand radiographs will reveal honeycombing and bone cysts if the bone is involved.

The less common clinical presentations of cutaneous sarcoidosis are quite varied, and less is known about associations with internal organ involvement, prognostic implications, or disease course. Patients may present with psoriasiform

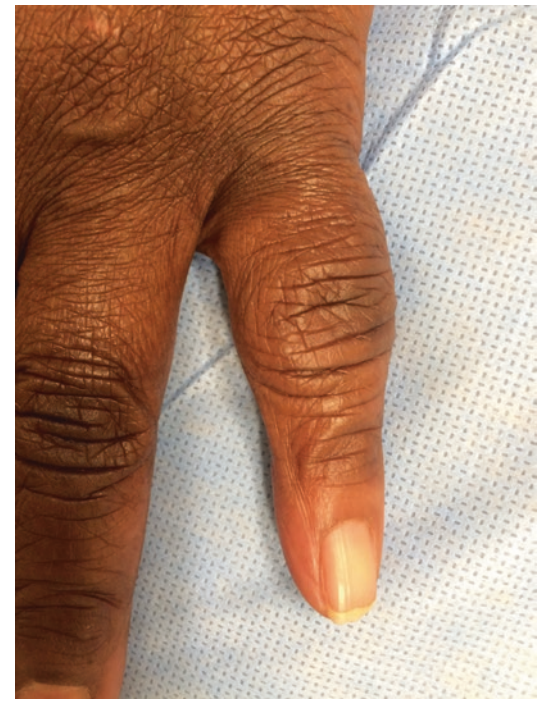

Fig. 9.9 Sarcoidosis of the digit. Sarcoid can affect any compartment of the digit, from the bone, to the joint/tendon structure, to the skin and subcutis; it may be clinically challenging to distinguish skin involvement from bone involvement. Hand radiographs will reveal honeycombing and bone cysts if the bone is involved

sarcoidosis [94] characterized by erythematous plaques with overlying silvery scale (Fig. 9.10); this entity may need to be distinguished from coexistent sarcoidosis and psoriasis [95], which have also been reported and demonstrated in one epidemiological study [96]. Lichenoid sarcoidosis is characterized by small, flat-topped, skin-colored to violaceous papules; lesions lack the characteristic "Wickham striae" seen in true lichen planus [97]. Verrucous or hyperkeratotic sarcoidosis has been described on the legs of African-American patients and may be mistaken for warts or other hyperkeratotic skin lesions [98]. Notably some patients with this form of sarcoidosis may be misdiagnosed as having early squamous cell carcinomas on superficial shave biopsies of the skin [99]. Ichthyosiform sarcoidosis looks like classic lower extremity acquired ichthyosis, with polygonal patches of dry, flaky skin resembling dried out mudflats (or fish scales); biopsy shows classic histologic findings of sarcoidosis with characteristic granulomas [100]. Ulcerative sarcoidosis is uncommon and can closely resemble necrobiosis lipoidica both clinically and histopathologically (Fig. 9.11). Typical lesions are single or grouped atrophic plaques that ulcerate and may display yellow-orange discoloration [101, 102]. Hypopigmented sarcoidosis can occur de novo as well-defined, circular or oval macules or patches; lesions often contain a palpable granulomatous component that may subtly demonstrate the characteristic violaceous hue of the disease [103]. Sarcoidosis can rarely cause erythroderma, defined as >80% body surface area erythema, often with fine scale [104].

Scalp sarcoidosis (Fig. 9.12) can present with variable clinical signs, ranging from pauci-inflammatory disease to thick scale and violaceous inflammation. It can also cause both scarring and a non-scarring alopecia [105].

Nail involvement in sarcoidosis is uncommon, but manifestations may include pitting, onycholysis, trachyonychia, or complete loss of the nail plate. Nail sarcoidosis is strongly associated with bone involvement and a chronic disease course [106].

Mucosal sarcoidosis is uncommon but can affect the buccal mucosa, gingiva, lips, and/or tongue; lesions may include papules, bland erythema, or ulcerations [107]. Genital sarcoidosis is also rare and can present with plaques, nodules, or ill-defined masses or swelling. Granulomatous lesions affecting the vulva, vagina, scrotum, penis or testicles are more likely a manifestation of underlying inflammatory bowel disease rather than sarcoidosis [74].

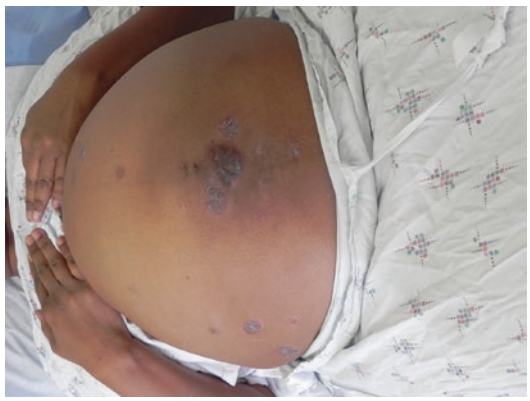

Fig. 9.10 Sarcoidosis plaques. These purple, flat, larger lesions have scale and may resemble psoriasis

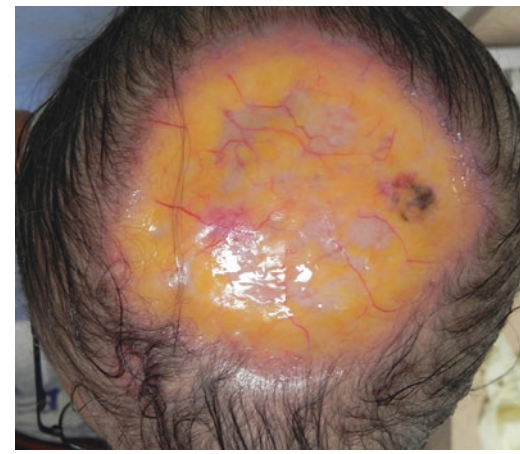

Fig. 9.11 Ulcerative sarcoidosis. This form of sarcoid can be challenging to diagnosis, as the presence of granulomatous inflammation within an ulcer may be a sign of infection, such as mycobacterial infection, and sarcoidosis is a diagnosis of exclusion. Multisystem involvement can be helpful, as in this case, where the patient had uveitis and hilar adenopathy. Ulcerative sarcoidosis will closely resemble necrobiosis lipoidica clinically and sometimes histologically

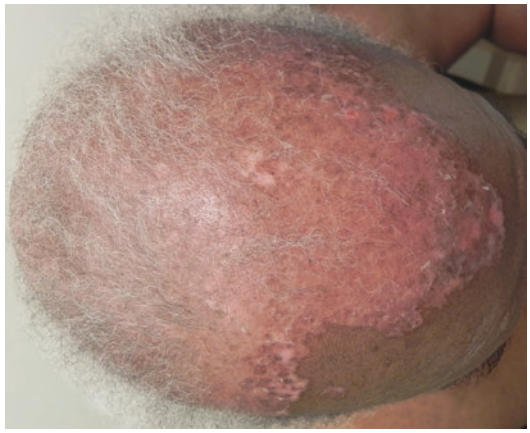

Fig. 9.12 Scalp sarcoidosis. Involvement of the scalp is relatively common in cutaneous sarcoidosis, but lesion morphology can be quite varied. Some lesions may resemble the orange, atrophic patches of necrobiosis lipoidica; others may be psoriasiform, as in this case. Patients with scalp sarcoidosis can develop either a scarring or a non-scarring alopecia

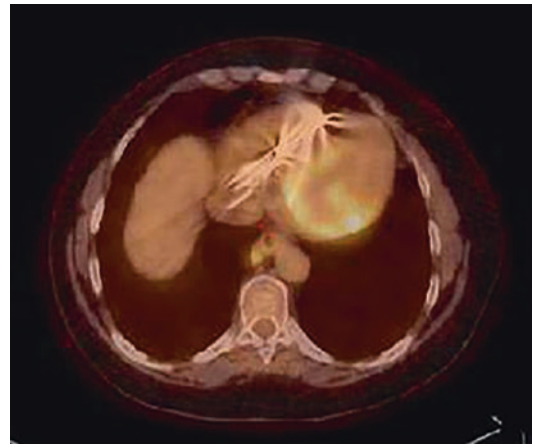

Fig. 9.13 PET CT demonstrating cardiac sarcoidosis that was not apparent on echocardiogram or cardiac MRI

Other Organ Involvement

Although the pulmonary and cutaneous presentations are the primary focus of this chapter, sarcoidosis can manifest in any organ system. Cardiac sarcoidosis warrants particular attention. Most literature cites a rate of approximately 5% among sarcoidosis patients [108]; however, autopsy studies suggest the rate is much higher, and analysis of patients who die of unexplained cardiac causes not uncommonly reveals occult cardiac sarcoidosis (Fig. 9.13). Cardiac sarcoidosis may be clinically silent in more than one quarter of patients. When it does cause signs or symptoms, the main manifestations are conduction abnormalities, ventricular arrhythmias, and heart failure [109].

Neurosarcoidosis occurs in 5–10% of cases and usually presents close to disease onset [110]. Clinically, patients can develop disease in any part of the nervous system, including cranial neuropathies (particularly facial neuropathy, optic neuropathy, or hearing loss), leptomeningeal disease (which can present with headache or more severe symptoms, such as seizures), parenchymal disease, cord involvement, or peripheral nerve involvement [110].

Ocular sarcoidosis is common, although the precise incidence is unclear and may vary by ethnicity and geography, with ranges of 13–80% reported. Most studies suggest the overall rate is approximately 25–30% [111]. The most common clinical features include uveitis, dry eyes, and conjunctival nodules.

Many patients with sarcoidosis will have granulomatous involvement of the lymph nodes, liver, or spleen; however, these findings are not clinically relevant in the majority of patients and rarely drive therapy. Lymph node involvement in sarcoidosis most commonly presents with bilateral hilar adenopathy; all sarcoid lymphadenopathy tends to be bilateral and symmetrical. Patients with active sarcoidosis may also develop metabolic abnormalities, particularly hypercalcemia, which, if persistent, can lead to symptoms, as well as potentially hypercalciuria and the development of renal stones. In a subset of patients, this will lead to renal dysfunction.

Specific Sarcoidosis Phenotypes

Lofgren noted in the 1940s that some of his patients with EN had symmetrical hilar adenopathy on chest x-ray. Approximately one third had iritis. These patients were treated with bed rest and high dose aspirin. Most experienced resolution of symptoms within weeks. Peri-articular

arthritis has also been noted in this group of patients, whose presentation is now termed Lofgren syndrome.

In one study from Sweden, over 70% of patients with Lofgren syndrome were positive for HLA type DQB1*0201/DRB1*0301. Of these, disease resolution within two years was seen in over 95% of cases. By contrast, approximately half of the patients who were DQB1*0201/DRB1*0301 negative developed chronic disease. In the United States, the role of DQB1*0201/DRB1*0301 in predicting prognosis is less clear. It is also important to note that, in contrast to the typical definition of Lofgren syndrome, the patients in the Swedish cohort presented with peri-articular arthritis and hilar adenopathy, but not EN, which is a classic feature of the syndrome.

Heerfordt syndrome, also known uveoparotid fever, is another specific sarcoidosis phenotype, characterized by parotid gland enlargement, facial nerve palsy, uveitis, and fever. In both Lofgren syndrome and Heerfordt syndrome, the clinical presentation is generally sufficient for diagnosis in the absence of biopsy findings. However, histopathologic demonstration of typical granulomatous inflammation can help confirm the clinical suspicion.

Diagnostic Considerations

Sarcoidosis is a diagnosis of exclusion, with no gold-standard confirmatory test. Patients may be presumed to have the disease when they exhibit clinical, laboratory, and/or radiographic signs of multiorgan inflammation, with at least one biopsy demonstrating characteristic "naked" epithelioid granulomas. Certain clinical features may be helpful in raising the pre-test probability of sarcoidosis (Table 9.3). In areas where there are high rates of tuberculosis or leprosy, rendering a diagnosis of sarcoidosis can be challenging, and clinicians should maintain a high index of suspicion for alternative etiologies of granulomatous inflammation.

All patients should undergo a thorough history and review of systems to identify potentially symptomatic organ systems and allow for targeted diagnostic evaluation. Certain clinicoradiographic features may be very suggestive of sarcoidosis. Researchers have suggested classifying organ involvement as either "definitive," "highly probable," "probable," or "possible," based on organ-specific features [112, 113]. Organ involvement is typically definitive if there is histopathologic confirmation of granulomatous inflammation and other potential etiologies are excluded.

Severe presentations may not require tissue confirmation. In cases of Lofgren syndrome, Heerfodt syndrome, asymptomatic bilateral hilar adenopathy, or bilateral hilar adenopathy coexisting with uveitis, sarcoidosis is highly likely [63, 114].

In nearly all other clinical scenarios, tissue confirmation of non-caseating epithelioid granulomas is advised. Factors unique to each patient may alter the risk-benefit analysis for biopsy, including severity of disease, likelihood of alternative diagnoses, organ or anatomic site affected, and need for treatment [1, 63]. Biopsy should be performed from the safest location with the highest yield; in many cases, the skin is preferable, with alternatives including superficial lymph nodes or easily-accessible ocular lesions. Due to

Table 9.3 Clinical features affecting the probability of sarcoidosis

More likely sarcoidosis	Less likely sarcoidosis
African-American or Northern European	Age < 15 or < 60
Female	History of smoking
Asymptomatic	Exposure to metal dusts, aerosols, organic antigens
Family history of sarcoidosis	History of tuberculosis
Multiorgan disease	History of recurrent infections
Suggestive laboratory findings: Lymphopenia Hypergammaglobulinemia Elevated serum calcium Elevated biomarkers (ACE, sIL2R, Vitamin D 1,25)	Systemic diseases capable of causing granulomatous inflammation Malignancy Inflammatory bowel disease Immunodeficiency Vasculitidites

Adapted from Culver [174]

the protean nature of the disease, clinicians should have a high index of suspicion and low threshold to sample cutaneous lesions, as skin biopsy is one of the diagnostic options with highest yield and lowest risk.

Histopathologically, the hallmark of sarcoidosis is the presence of extensive superficial and deep dermal epithelioid cell granulomas devoid or with a sparse rim of lymphocytes and/or plasma cells. Necrosis or caseation is usually absent, and extensive necrosis should prompt consideration for alternative etiologies, including infection or malignancy. Giant cells are variably present, and tend to be of the Langhans type, with nuclei arrayed in a peripheral arc. Asteroid bodies (eosinophilic stellate inclusions) and Schaumann bodies (calcific basophilic inclusions) are variably present and not specific for sarcoidosis. One quarter of cutaneous sarcoidosis biopsies will display polarizable foreign material, which does not exclude sarcoidosis [115–117]. Special stains for microorganisms (AFB, Fite) should invariably be negative, and tissue cultures should be performed if there is any suspicion for infection. Sarcoidosis remains a diagnosis of exclusion even with supportive pathology (Table 9.4).

Existing biomarkers (including angiotensin converting enzyme levels, vitamin D levels or ratios, and serum interleukin receptor levels) are nonspecific and do not offer sufficient sensitivity or specificity to warrant routine use. Emerging data in limited studies suggest there may be a role for novel markers such as chitotriosidase, but these findings have not been replicated in the clinical arena.

A thorough multisystem evaluation is essential in all patients with sarcoidosis (Table 9.5). Pulmonary involvement is seen in most patients with sarcoidosis. Imaging is important to evaluate the extent of pulmonic involvement and is abnormal in more than 90% of patients [71]. Chest radiography can demonstrate mediastinal nodal or lung parenchymal involvement and is used to determine the Scadding classification, as reviewed: stage 0 (normal; 8–16% of patients at presentation), stage 1 (bilateral hilar lymphadenopathy; 25–65%), stage 2 (hilar adenopathy and pulmonary infiltrates; 14–49%), stage 3 (pulmonary infiltrates without adenopathy; 10%), stage 4 (pulmonary fibrosis; 5% at presentation) [118, 119].

High resolution chest CT is the diagnostic test of choice for evaluating interstitial lung disease but is not routinely required in patients with sarcoidosis. CT is indicated if there are atypical clinical or chest radiography findings, a normal chest x-ray but persistent suspicion for sarcoid-

Table 9.4 Differential diagnosis of sarcoidosis biopsies

Lung	Skin	Other
Tuberculosis	Granuloma annulare	Brucellosis
Atypical mycobacteria	Necrobiosis lipoidica	Toxoplasmosis
Cryptococcosis	Necrobiotic xanthogranuloma	Kikuchi's disease
Aspergillosis	Cutaneous Crohn disease	Cat-scratch disease
Histoplasmosis	Rheumatoid nodule	Schistosomiasis
Coccidioidomycosis	Foreign body reaction: Tattoo, Paraffin/silicone/cosmetics	Sarcoid-like granulomatous reaction in lymph nodes associated with malignancy
Blastomycosis	Tuberculosis	Lymphoma (Hodgkin's, Non-Hodgkin's)
Pneumocystis jirovecii	Atypical mycobacteria	Inflammatory bowel disease
Mycoplasma	Deep fungal infection	Giant cell myocarditis
Hypersensensitivity pneumonitis	Malignancy: Granulomatous lymphoma	Viral infection
Pneumoconiosis: Beryllium, other	Granulomatosis with polyangiitis	Drug reaction
Drug reactions	Pyoderma gangrenosum	
Aspiration of foreign material		
Granulomatosis with polyangiitis		
Chronic interstitial pneumonia		

Adapted from Statement on Sarcoidosis [1]

Table 9.5 Suggested Systemic Work-Up in Patient with Sarcoidosis

Detailed history (family history, environmental/occupational exposures [beryllium, pine tree, microbe-rich, heavy metals,] …)
Symptomatology (dyspnea, cough, palpitations, fatigue/malaise/low grade fevers, …)
Physical examination
Chest X-ray (posterior–anterior and lateral)
Pulmonary function tests (including DLCO)
Routine ophthalmologic examination
Complete blood count
Comprehensive serum chemistries (including calcium, liver function tests, creatinine)
[a]If history of nephrolithiasis, then urinalysis with urine calcium)
Electrocardiogram
[a]If palpitations or abnormalities on EKG, consider Holter monitor and additional cardiac imaging
Tuberculin skin test or interferon-gamma release assay
Thyroid function testing
Biomarkers: serum ACE, Vitamin D25/Vitamin D1,25, …

Adapted from Wanat and Rosenbach [74]
[a]*DLCO* diffusion capacity for carbon monoxide, *ACE* angiotensin-converting enzyme

osis, or complications from pulmonary involvement [1, 71, 120]. However, CT is incomplete and unreliable in distinguishing areas of active granulomatous inflammation from areas of damage, fibrosis, and scarring.

Standard pulmonary function testing (PFT), including spirometry and diffusion of carbon monoxide, is suggested in patients with sarcoidosis. Diffusion of carbon monoxide is a useful test for detection of early interstitial lung disease [120]. PFTs can be used to evaluate for restrictive or obstructive lung disease. Most sarcoidosis is restrictive, but one third of patients will have obstructive patterns. PFTs provide information about the forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), both of which will be abnormal in the presence of obstructive disease. FVC will be reduced in restrictive lung disease. PFTs correlate only modestly with chest imaging but may be useful in tracking disease activity and monitoring for functional improvement or deterioration as the disease progresses [120].

PET scanning is increasingly utilized to assess active disease in sarcoidosis patients. While not routinely performed, it is often used when malignancy is suspected. It can detect ongoing inflammation in both lymph nodes and parenchymal infiltrates. In sarcoidosis patients, PET scanning may detect activity in multiple organs, including the bones, spleen, and liver, even in an asymptomatic patient.

MRI, especially with gadolinium enhancement, can detect sarcoidal lesions in the brain, heart, and bone. Again, the disease visualized on imaging can be more extensive than suspected clinically. MRI and PET scanning should be employed in patients with symptoms suggesting cardiac sarcoidosis, such as palpitations or evidence of congestive heart failure. Some endobronchial lesions may be amenable to endoscopic biopsies, while peripheral lesions may be accessible to CT-guided biopsy. Mediastinoscopy and surgical lung biopsies are rarely required [63].

Beyond the cutaneous and pulmonary assessment, patients should be asked about palpitations or syncope to screen for cardiac involvement, and all patients should undergo screening with an ECG. Symptomatic patients may require further testing, including echocardiogram; patients with echocardiographic abnormalities may benefit from cardiac MRI or FDG-PET imaging [109]. Depending on findings, Holter monitor screening for arrhythmias may be indicated as well.

Neurosarcoidosis is often clinically apparent; evaluation depends on the clinical symptomatology, and referral to an experienced neurologist may be beneficial. MRI with gadolinium is the primary diagnostic modality, though some patients will require CSF analysis, or EMG for suspected peripheral nerve involvement [110].

Given the high rates of ocular involvement in patients with sarcoidosis, all sarcoid patients should be evaluated by an ophthalmologist at the time of diagnosis and should be screened annually or evaluated if new symptoms develop.

It is rarely necessary to evaluate patients for hepatic or splenic sarcoidal involvement, and sarcoidosis in the marrow is relatively rare. Significant abnormalities in these organ systems

should be apparent on routine lab work and physical exam.

All sarcoidosis patients should undergo measurement of serum calcium (corrected for albumin), as hypercalcemia can be a significant problem in sarcoidosis. Patients with a history of nephrolithiasis warrant evaluation for hypercalciuria. Persistent hypercalcemia and hypercalciuria can result in renal dysfunction.

Disease and Comorbidity Assessment

Sarcoidosis is by definition a multiorgan disease, and patients with the disease tend to be followed closely by multiple physicians, each monitoring their target organ and working together to manage the patient. Even so, patients with sarcoidosis require evaluation for potential comorbid conditions.

First, patients with sarcoidosis require close monitoring for treatment-related adverse events (see below, "principles of management" section). Systemic corticosteroids are the mainstay of treatment for most patients with sarcoidosis, and these can have a range of acute and chronic side effects that require monitoring and mitigation.

Additionally, more than half of patients with sarcoidosis suffer from a comorbid disease, most commonly hypertension, diabetes, thyroid disease, and obesity [121]. Several small studies have suggested an increased risk of malignancy in patients with sarcoidosis, and sarcoidal granulomas can be found in biopsies in patients with malignancies [122]. One meta-analysis of 16 cohort and case-control studies demonstrated a moderate association of sarcoidosis with malignancy [123]. The risk appears to be greatest for lymphoma and lymphoproliferative diseases. New symptoms or radiologic findings in patients with sarcoidosis should not automatically be attributed to the underlying disease and warrant appropriate evaluation in all cases, including tissue sampling, if necessary [124, 125].

Importantly for dermatologists, patients with sarcoidosis may be at two-fold higher risk of developing both melanoma and nonmelanoma skin cancers [123, 126]. This is true for African-American patients in addition to those of other races, although it should be noted that incomplete sampling of verrucous or hyperkeratotic sarcoidosis may lead to a false pathologic impression of a superficial squamous cell carcinoma. The association between sarcoidosis and malignancy may be due to inherent sarcoidosis-related immune dysregulation, sarcoid-like reactions due to malignancies, sarcoid-like reactions due to chemotherapeutic agents, or sarcoid treatment-related/immunosuppression-related malignancy development [124].

Sarcoidosis may also occur in association with diseases other than malignancy, potentially due to shared genetic risk factors or the immune/inflammatory milieu of the disease state. Sarcoidosis and psoriasis, both Th1- and Th17-mediated diseases, appear to co-occur more frequently than would be expected by chance alone [95, 96]. Patients with sarcoidosis appear to be at increased risk for thyroid disease, an association demonstrated in case-control studies and replicated in a database study [127–131]. As both entities may present with non-specific constitutional symptoms, it is important that physicians keep this potential association in mind. Case reports have suggested other Th1-associatd diseases, such as alopecia areata and vitiligo, may occur more than expected in patients with sarcoidosis [132].

Principles of Management

The most important principle of managing sarcoidosis is that treatment should be tailored to the specific patient and clinical phenotype, depending largely on the organs involved. Many patients present with asymptomatic or minimally symptomatic disease and can safely be monitored for disease progression. Approximately half of patients will experience spontaneous improvement and resolution within the first 2 years of diagnosis. Outside this group, the goals of treatment should be to improve symptomatology and prevent morbidity, balancing the risks of the treatment with the potential therapeutic benefits.

While many treatments for sarcoidosis will affect, and improve, all aspects of disease-related inflammation, several therapeutic options (particularly localized treatments, such as eye drops, topical skin-directed therapy, or inhalers) will treat only the targeted organ. Treatments may take 2–3 months to take effect, and both patients and treating physicians should exercise patience before deeming a therapeutic trial a failure.

There is a relative lack of high-quality evidence or comparative-effectiveness data for sarcoidosis treatment, and no treatments are currently FDA approved for this indication. Historically, it has been a challenge to conduct clinical trials for sarcoidosis due to difficulty in distinguishing active inflammation from disease-related damage, as well as the subjectivity or effort-dependence of a number of endpoints. Recently validated instruments to measure cutaneous disease hold promise for future trials [133, 134]. The most widely used clinical assessment tool is the Sarcoidosis Activity and Severity Index (SASI), which can accurately and reliably capture the extent of cutaneous disease activity; several studies have demonstrated its ability to document change in skin lesions over time in response to therapy [134].

Another cutaneous sarcoidosis assessment tool, the Cutaneous Sarcoidosis Activity and Morphology Instrument, was developed to capture sarcoidosis morphology-specific information; it was subsequently validated and demonstrated excellent reliability and correlation with patient-reported outcomes measures [133, 135].

A third instrument, the Sarcoidosis Assessment Tool, was developed and validated as a sarcoidosis-specific patient-reported outcome instrument that can reliably document the impact of sarcoidosis on patient quality of life and has demonstrated sensitivity to change and clinically significant differences that correlate to disease severity [136, 137]. Taken together, these scoring systems provide the tools necessary to conduct clinical trials with a focus on responsiveness of skin disease to therapeutic intervention.

Importantly, treatment agents used in sarcoidosis may affect different organ systems at different rates. For hydroxychloroquine and methotrexate, for example, studies have found a higher rate of response for skin lesions than pulmonary disease. Neurologic and cardiac disease can be even more refractory. It can also be challenging to assess response in extracutaneous disease: one advantage of monitoring skin lesions is the ability to differentiate between active inflammation and scarring, but this can be more difficult for other organs.

Treatment of cutaneous and pulmonary sarcoidosis is reviewed in detail below. Individual treatment stratagems may vary from those described here, particularly for patients with severe cardiac or neurologic involvement, who often require combination treatment with multiple agents. Patients with suspected cardiac sarcoidosis should undergo a full evaluation with an experienced cardiologist as described above, ideally prior to initiating aggressive treatment, which can sometimes precipitate arrhythmias.

Treatment for Cutaneous Sarcoidosis

Treatment of cutaneous sarcoidosis requires a stepwise approach [141] (Fig. 9.14 and Table 9.6). Skin-directed therapeutics may be used in patients with mild disease or to treat limited recalcitrant lesions in those with moderate to severe disease. Topical treatment options include corticosteroids (applied to the skin or injected intralesionally). High-potency topical steroids can lead to resolution of isolated or sparse skin lesions, whereas intralesional injections can ameliorate thicker plaques or subcutaneous nodules [142–144]. Steroid-sparing skin-directed options include topical tacrolimus, phototherapy, photodynamic therapy, and laser therapy [74, 141]. Photodynamic therapy tends to be helpful only while treatment is maintained. Lasers can help select features of sarcoidosis, but they can also induce new lesions or exacerbations and are best used by experienced clinicians.

Systemic therapy for cutaneous sarcoidosis can be divided broadly into immunomodulatory therapies and immunosuppressive therapies. As with topical therapy, most immunomodulatory

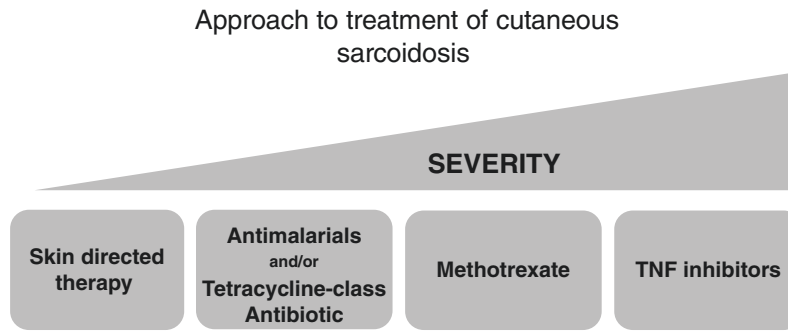

Fig. 9.14 Treatment of cutaneous sarcoidosis algorithm. (Adapted from Wanat and Rosenbach [141])

Table 9.6 Therapeutic options for cutaneous sarcoidosis

	Medication
Topical therapy	Topical corticosteroids (strength depending on anatomic site)
	Tacrolimus
Intralesional	Triamcinolone (10–40 mg/kg)
Physical	Phototherapy (UVA)
	Photodynamic therapy
	Laser[a] (Pulsed-dye, CO2, ruby, KTP)
	Surgical excision
Immunomodulatory	Hydroxychloroquine/Chloroquine
	Chloroquine
	Minocycline/doxycycline
	Pentoxifylline
	Apremilast
	Systemic Retinoids
	Thalidomide
Immunosuppressants	Prednisone
	Methotrexate
TNF inhibitors	Adalimumab
	Infliximab
JAK-inhibitors	Tofacitinib [177]

Adapted from Wanat and Rosenbach [74]
[a]Lasers should be used with caution as they can induce or worsen disease

therapies used for cutaneous sarcoidosis have little impact on extracutaneous disease. If significant extracutaneous disease is present, it is generally advisable to tailor treatment to control the extracutaneous disease, and then supplement with added skin-directed therapy as needed.

Antimalarial agents are among the medications whose use in cutaneous sarcoidosis is supported by the most evidence and experience. Two-thirds to three-quarters of patients improve on these agents [74, 145–148]. Potential adverse effects include hair loss, mild, generally self-limited gastrointestinal disturbances, and, rarely, a lichenoid skin eruption. Ocular toxicity from antimalarials is generally less common than assumed, developing only in approximately 5% of patients after more than 5 years of cumulative use. The risk of ocular toxicity increases with dose, duration, renal or hepatic impairment, and age.

Tetracycline class antibiotics, particularly minocycline, can be beneficial in treating most forms of cutaneous sarcoidosis [149, 150]. These agents are particularly helpful in cases where infectious causes of granulomatous inflammation cannot be completely excluded.

Recently, a novel regimen of concomitant levofloxacin, ethambutol, azithromycin, and rifampin has been described for the treatment of

chronic cutaneous sarcoidosis with improvements in SASI scoring [151]. Possible mechanisms of action include immunomodulation and, in cases where there is an infectious causative antigen, direct antimicrobial action [151].

Additional non-immunosuppressive systemic therapeutic options for treating cutaneous sarcoidosis include pentoxifylline, apremilast (documented SASI improvement [140]), and systemic retinoids [74, 152–154].

Systemic immunosuppressive therapies used for cutaneous sarcoidosis tend to be effective for extracutaneous disease as well. These are good options in patients who fail the above treatments, or those who have moderate-to-severe skin sarcoidosis along with mild extracutaneous disease [141].

Traditional systemic agents used in sarcoidosis include corticosteroids, methotrexate, and thalidomide. Prednisone can be helpful in obtaining quick disease control, which may be necessary in patients with rapidly progressive, disfiguring, or ulcerative cutaneous sarcoidosis. Doses should start at 20–40 mg/day with slow tapering [141, 155–157].

Methotrexate is generally the first-line systemic immunosuppressive agent used for widespread cutaneous sarcoidosis that fails to respond to antimalarials. Methotrexate is also commonly used as the first-line non-corticosteroid agent for systemic sarcoidosis; benefit is generally seen in 60–75% of patients. Usual doses range from 15 to 25 mg weekly, tapered slowly to the lowest dose able to maintain disease control. Methotrexate can take three months to start working and six months to fully take effect; patients should therefore be counseled to expect a slow response to therapy [158–161].

Azathioprine and mycophenolate mofetil are sometimes used for pulmonary, neuro-, or cardiac sarcoidosis. However, these agents are minimally effective in treating cutaneous disease in most cases.

Thalidomide has traditionally been used for recalcitrant cutaneous sarcoidosis. However, it carries a high frequency of neuropathy and risk of venous thrombosis; additionally, the federally regulated registry that exists to minimize the risk associated with its teratogenicity makes prescribing a challenge. Additionally, a recent blinded study showed a lack of efficacy of thalidomide compared to placebo in sarcoidosis [162]. While this agent may still be beneficial in a subset of patients, newer agents hold more promise and are generally the next-line drugs in patients who fail to respond to methotrexate.

Tumor necrosis factor alpha inhibitors, particularly infliximab and, to a lesser degree, adalimumab, are highly effective agents that can clear even chronic, recalcitrant skin sarcoidosis, including lupus pernio. Infliximab (3–7 mg/kg at 0, 2, and 6 weeks and then every 4–6 weeks) can lead to rapid improvement of refractory skin lesions [74, 163–168] and SASI [138] score. Adalimumab (80 mg loading dose, 40 mg weekly) has also been shown to improve refractory skin disease [169–171]; notably both agents need to be used at higher doses than dermatologists normally utilize for skin disease (such as psoriasis). Etanercept, perhaps because of its wide use, has been more associated than other agents with TNF-induced sarcoid-like granulomatous disease, and a trial evaluating etanercept in sarcoidosis was discontinued due to lack of efficacy and increased adverse events [172]. Golimumab showed a non-significant trend towards improvement in skin disease by SASI score in one randomized trial [139], whereas ustekinumab was ineffective (Table 9.7).

Treatment of Pulmonary Sarcoidosis

Pulmonary sarcoidosis is generally responsive to systemic corticosteroids, and most treatment guidelines suggest initial dosing between 20–40 mg daily, with a rapid taper to the lowest possible dose; most clinicians attempt to taper to 10 mg daily or lower [173] (Fig. 9.15). Inhaled corticosteroids may be helpful in managing cough or a reactive airway component of the disease.

Cytotoxic medications are often utilized as steroid sparing agents or in patients for whom corticosteroids are contraindicated; these agents may take months to demonstrate efficacy in many cases. Methotrexate is the most widely used and

Table 9.7 Therapeutic trials in sarcoidosis

	Study design	Photo comparisons	SASI	PGA
Infliximab [138]	DBPC	NR	Significantly different from placebo	Significantly different from placebo
Infliximab [83]	Case series	Superior to other treatments	NR	NR
Golimumab [139]	DBPC	NR	Trend towards improvement, not significantly different from placebo	NR
Ustekinumab [139]	DBPC	NR	No improvement	NR
Aprelimast [140]	OLPS	Significant improvement	Significant improvement	NR
CLEAR [140]	SMPC	NR	Significant improvement	NR

DBPC double blind, placebo controlled, *OLPS* open label prospective series, *SMPC* single masked placebo controlled, *CLEAR* concomitant levofloxacin, ethambutol, azithromycin, and rifampin, *SASI* Sarcoidosis Activity and Severity Index, *PGA* Physicians Global Assessment

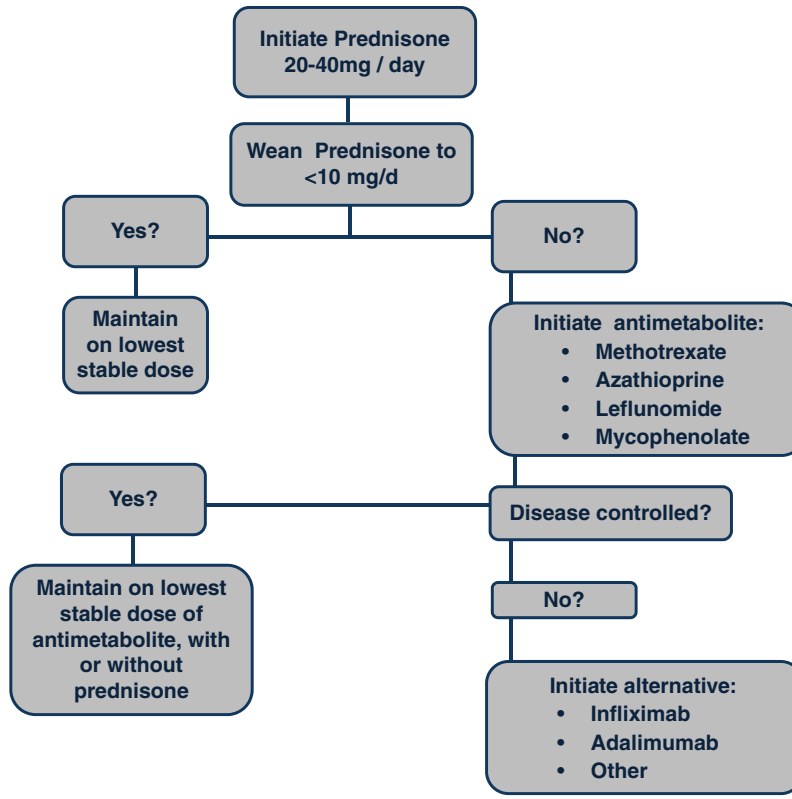

Fig. 9.15 Treatment of symptomatic pulmonary sarcoidosis. (Adapted from Baughman and Lower [175])

has the highest quality supportive evidence. It is typically dosed at 10–20 mg weekly, with supplemental folic acid. Azathioprine and mycophenolate mofetil may also be used in as steroid sparing agents. Leflunomide is typically given at 20 mg daily, and patients have approximately 50% response rate. TNF-inhibitors are often used as third line agents for pulmonary sarcoidosis but may be efficacious in many cases [173].

Summary

Sarcoidosis is by its very nature a multiorgan, multidisciplinary disease. Genetically susceptible patients are exposed to an environmental (or autologous) antigens, setting off a cascade of Th1-predominant immune inflammation, which can present with a variety of signs and

symptoms and may follow numerous disease courses. Some patients present with predominantly single-organ disease, whereas multiple sites are affected in other patients. A significant subset of patients may experience clinically asymptomatic disease. Approximately half of patients will spontaneously resolve their disease, while a significant minority of patients will experience chronic inflammation, sometimes with fibrosis, scarring, and permanent morbidity – as well as, in some cases, mortality.

All patients with sarcoidosis require initial extensive evaluation to determine the extent of disease and most affected organs. Patients must be followed closely for asymptomatic sarcoidosis-related inflammation of other organs and require close monitoring even if untreated, as the disease can wax and wane. Formal evaluation with organ-specific testing at regular intervals is indicated, as patients may be minimally symptomatic from chronic, progressive disease, which, if unrecognized, can lead to significant long-term organ dysfunction.

Treatment requires balancing the disease activity and morbidity with treatment-related risks and side effects and should be individualized. Often one treatment for sarcoidosis will improve all sites of inflammation, but organ-specific targeted therapies exist, and selection of the appropriate treatment should involve multidisciplinary discussion and close collaboration between treating physicians.

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