Cutaneous Sarcoidosis

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KEYWORDS

• Sarcoidosis • Cutaneous sarcoidosis • Lupus pernio • Sarcoidosis disparities
• Sarcoidosis in skin of color

KEY POINTS

- Sarcoidosis is a chronic, multiorgan, inflammatory disorder that commonly presents on the skin, thus there are significant implications on diagnosis and management in patients with darkly pigmented skin.
- There are significant racial disparities in prevalence, severity, and outcomes; however, there is a dearth of studies investigating the impact of structural racism.
- Clinicians should adopt a comprehensive systemic approach to working up potential patients with sarcoidosis with treatment targeting the most impacted organ systems with topical therapies, immunomodulators, and systemic immunosuppressants.

INTRODUCTION

Sarcoidosis is a chronic inflammatory disorder, which is characterized by noncaseating granulomas impairing organ function. It is a multisystem condition that can affect any organ in the body, causing significant morbidity and mortality through organ damage, chronic dysfunction, and scarring. Understanding and recognizing cutaneous sarcoidosis is paramount. Skin is the second most common organ affected in sarcoidosis, affected in approximately 25% to 40% of cases reported and, in some studies, was the initial presenting symptom in up to 88% of cases.[1–10] This article will review updates on epidemiology and pathogenesis, clinical presentation with focus on presentation in darker pigmented skin in patients of color, diagnosis, and management of cutaneous sarcoidosis to better aid dermatologists in caring for patients of color with sarcoidosis.[11–13]

EPIDEMIOLOGY

Systemic sarcoidosis occurs worldwide, affecting people of all age, sex, ethnicity, and race. Large generalizable epidemiologic assessments of sarcoidosis have been hindered by inconsistency in case definition, poor diagnostic sensitivity with varied methods, multiple subphenotypes, and varying levels of access to care.[14] This influences the accuracy of estimates of the burden of sarcoidosis as well as highlights disparities in disease manifestations, phenotype, and mortality related to age, sex, geographic location, genetic background, race and ethnicity, or environmental triggers.[15]

The best available evidence suggests that the prevalence of sarcoidosis ranges from 1 to 5 per 100,000 in countries including South Korea, Taiwan, Japan, Spain to 140 to 160 per 100,000 in Sweden and Canada.[15] In the United States,

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the estimated prevalence is on average 60 per 100,000, varying greatly based on race from 19 in Asian Americans to 140 in Black American.[16] A bimodal distribution in incidence has been demonstrated with peaks in the third and fourth decades followed by the sixth decade.[17] Women have a higher incidence of sarcoidosis compared with men and generally were older than men when diagnosed, 30 to 50 years in men versus 50 to 60 years in women.[18] In late-onset sarcoidosis, recent studies in France showed asthenia, uveitis, and specific skin lesions were more common with less pulmonary and lymphatic involvement.[19,20] Studies have detected seasonal variability in incidence, with the highest incidence rates reported during the winter and the lowest reported in autumn.[21]

Race has been noted as an important source of variation in sarcoidosis epidemiology. However, race, a social construct, has often been used in research studies as a proxy for unmeasured genetic factors, leading to generalizations regarding biologic risk. This obfuscates the role of systemic racism have as legitimate and clinically relevant cause of poor health and outcomes.[22,23] For example, racist housing practices could potentially manifest in racial minorities having increased exposure to environmental triggers leading to increased prevalence of sarcoidosis. Similarly, neighborhood disadvantage and segregated communities has been shown to increase the risk of asthma and atopic dermatitis in marginalized racial groups.[24–28] Future research should include large, matched epidemiologic studies conducted in racially diverse populations through large population data sets and registries. In addition, studies directly measuring the impact of discrimination, structural racism, and access to quality care on patients diagnosed with sarcoidosis will help clarify any impact of these factors on sarcoidosis pathogenesis and quality of life.[29,30]

Studies have consistently demonstrated a high incidence of sarcoidosis among Black women and identified this population as being at an elevated risk for systemic complications of sarcoidosis as well as severe and fatal outcomes.[31–34] In a multicenter, multiethnic European cohort, 5 clinical phenotypes were isolated with non-White patients having phenotypes with more severe internal disease and lupus pernio.[35] In the United States, the annual incidence of sarcoidosis is consistently higher among non-Hispanic Black Americans estimated at 35.5 per 100,000 compared with 10.9 per 100,000 in white Americans and 3 to 4 per 100,000 in Asian Americans.[16,17,36–38] However, in French Guadeloupe and West Africa, in which inhabitants share genetic ancestry with Black Americans, the incidence of sarcoidosis seems to be much lower.[39] This conveys that ancestry and genetics is not the full explanation for this racial disparity. In a prospective, multicenter study of sarcoidosis, Black patients were more likely to have a family income of less than US$20,000 and public insurance suggesting, that Black patients were more likely to have financial barriers, delaying timely access to care.[40]

Black patients, overall, are more likely to have cutaneous sarcoidosis. Additionally, Black patients tend to present with cutaneous sarcoidosis at a younger age, a trend, which was also observed in patients who were evaluated for ocular disease.[31,41] Additionally, the clinical subphenotype of Lofgren syndrome characterized by fever, arthritis, erythema nodosum, and bilateral hilar lymphadenopathy is associated with favorable prognosis in White patients of northern European ancestry with specific human leukocyte antigen (HLA) subtypes but is uncommon in Black and Asian populations that lack those HLA subtypes.[42,43] If extracutaneous disease was noted, Black patients had more organ systems affected, including cardiac disease and pulmonary disease, specifically pulmonary hypertension.[31] These disparities are notable as cardiac sarcoidosis and pulmonary hypertension can be fatal and serve as possible explanations of the higher mortality rate seen in this group.[44–46] In longitudinal studies, Black patients had a higher likelihood of more severe disease, new organ involvement and more frequently required systemic medication compared with White patients.[34,47–49] Furthermore, Black patients have higher rates of hospitalization up to 9 times higher compared with White patients.[41] In another retrospective study, there was a near doubling of hospitalization in Black, female and older patients in a retrospective study.[42] Moreover, the age-adjusted sarcoidosis-specific mortality rate is higher for Black Americans compared with White Americans in 2008 to 2016, up to 9 times as high in Black women compared with White women with Black patients dying at an earlier age.[50–52] This study also investigated the role of geographic location and urbanization in sarcoidosis incidence among Black Americans. They found the lowest rates of sarcoidosis in southern states and the highest rates in small rather than large metropolitan areas.[50] The extent to which institutional and structural racism contribute to these disparities warrants a dedicated study to better understand the epidemiologic complexities and to ultimately provide the most optimal care for patients with sarcoidosis.

PATHOGENESIS

The development of sarcoidosis is thought to be secondary to a genetic predisposition combined with an environmental insult causing the histologic hallmark of granulomatous inflammation.

Genetic Factors

A genetic predisposition is supported by cases showing familial clustering, a high concordance rate in monozygotic twins, and by genetic variation studies.[53–56] In Black patients with at least one first-degree relative with sarcoidosis, the risk of sarcoidosis is 2.5 to 2.9 times higher compared with White individuals, with the risk increasing with multiple affected relatives.[53,54,56] Genetic variants may increase susceptibility to environmental triggers. For example, a case-control study of first responders in the 2001 World Trade Center attacks identified specific genetic variations in firefighters who developed sarcoidosis that were not present in those who did not develop the disease.[57] Additionally, there were similarities between variants seen in cases of sarcoidosis without known environmental exposure and World Trade Center-related sarcoidosis.[57]

Sarcoidosis is considered a polygenic disease with several gene variants associated with a large array of phenotypes, prognoses, and therapeutic responses. However, most of the genetic background of sarcoidosis remains unknown.[58] The *HLA-DRB1* gene locus has been extensively identified for its importance in predicting disease progression and risks versus protection from sarcoidosis.[43,58,59] In Black Americans, *HLA*-DQB1 alleles resulted in both increased susceptibility to sarcoidosis and progression of disease in a family-based genetic association analysis.[60] Further stratification of Black families by genetically determined ancestry revealed linkage differences by subpopulation, with previously reported linkage signals on chromosome 5 at 1p22, 3p21-14, 11p15, and 17q21 specific to ancestral heritage.[61] For example, in a study involving 301 patients with Löfgren syndrome, complete resolution within 2 years occurred in *DRB1*03*-positive patients. On the contrary, *HLA-DRB1*15* (DR15) and *DRB1*14* (DR14) have been associated with chronic nonresolving disease, diffuse endobronchial involvement, and severe multiorgan involvement.[62] Other implicated genes have included ANXA11, BTNL2, XAF1, NOTCH4, IL-23R, ACE, TLR9, NOD2, tumor necrosis factor (TNF)-α, and TGF-ß1 but have yet to be associated with specific clinical phenotypes.[63–69]

In a recent whole-genome study of family with high rates of sarcoidosis, Janus kinase 2, among others, was isolated as a potential gene of interest.[70] The JAK phosphorylates signal transducer and activates STAT, a transcription factor with broad effects on cell differentiation and the immune system.[71] The JAK/STAT signal transduction pathway connected to a number of cytokines including interleukin (IL)-12 and IL-23, which mediate T helper 1 (Th1) and Th17 cell response, respectively, as well as interferon (IFN-)γ, type I interferons, IL-2, IL-4, IL-6, IL-10, IL-13, and granulocyte-macrophage colony-stimulating factor. Many of these factors and cytokines have been implicated in granuloma formation in sarcoidosis.[43,72–75] There is an increasing evidence base supporting the association of the JAK/STAT pathway in sarcoidosis pathogenesis including a study, which revealed activation of JAK-STAT signaling at the microRNA level in peripheral blood.[76] Additionally, many case series and translational investigations describe resolution of sarcoidosis and decreased JAK-STAT activity in patients treated with JAK inhibitors.[72,77–79]

Environmental Triggers

Various infectious and noninfectious antigens such as a misfolded self-antigen, or organic or inorganic environmental molecules, have been implicated as potential triggers in the immune-inflammatory events that lead to granuloma formation.[58] A dysregulated immune response against one or more disease-promoting antigens results in an inflammatory process to eliminate the offending antigen leading to granuloma formation.[43] Both environmental and occupational triggers have been hypothesized given the wide variation in incidence based on geographic location even within countries.

Infectious antigens range from stronger associations with mycobacteria and *Propionibacterium acnes* to possible links with rubella virus to more inconclusive links to *Borrelia*, *Rickettsia*, and human herpesvirus-8 that may trigger inflammation as opposed to viable infections.[43,80–87] Noninfectious exposures such as inorganic aerosolized metals or combustible materials such as wood and toner ink have been described to trigger sarcoidosis or sarcoidosis-like granulomatous diseases.[12,88–93] Additionally, sarcoidosis has been diagnosed at higher rates in firefighters, first responders, health-care workers, and agricultural employees.[92,94,95] The role of vitamin D mechanisms has yet to be conclusively explained but is being studied. Autoimmunity also has been implicated with vimentin, a cytoskeletal protein, as potential target given humoral responses to the protein have been shown to be associated to patients with *HLA-DRB1**03-positive sarcoidosis.[96,97]

As aforementioned, objective measurements of racism and the sequelae of structural racism as environmental triggers have been understudied as a risk factor for sarcoidosis. Racial discrimination can manifest in various avenues of society including employment, housing, education, health care, and can directly influence socioeconomic standings.[98–101] This can create chronic stress that results in maladaptive coping mechanisms including tobacco smoking, which has been linked to ocular sarcoidosis and possibly cutaneous granulomas in retrospective studies.[102,103] A retrospective study from Sweden showed that a high neighborhood deprivation (a composite of income, education, unemployment, social welfare assistance) was associated with a 20% increased odds of having sarcoidosis.[104] Additionally, racial discrimination can trigger a "weathering" or accelerated physiologic deterioration in Black Americans and has been associated with chronically high levels of proinflammatory cytokines, increasing the risk for inflammatory and chronic conditions such as cardiovascular disease.[105–113] In a disease that similarly disproportionately affects Black Americans, observational studies of Black female patients with systemic lupus erythematosus (SLE) showed increased frequencies of self-reported racial discrimination or vicarious racism stress were associated with an increased SLE activity and irreversible organ damage.[114–116]

Granuloma Formation

Once both genetic and environment insults occur, a predominantly Th1 immune response, helped by the innate immune system and Th17 response is initiated to drive granuloma formation followed by either persistent or resolving disease. Subclinical inflammation with each exposure begins with the activation of membrane-bound pattern recognition receptors (eg, toll-like receptors). When stimulated, macrophages and other innate immune cells promote transcription factors, resulting in the production of cytokines and chemokines such as CD4+ and CD8+ cells.[14] IL-13, a potentially significant cytokine to target, promotes the differentiation of alveolar macrophage 2 and monocytes into antigen-presenting cells. The mammalian target of rapamycin complex (mTORC1) of the mTOR pathway, a potent repressor of autophagy, is activated, which promotes and sustains further granuloma formation.[117,118] Ongoing hypotheses propose that dysregulation of autophagy may lead to aberrant degradation of cellular byproducts and affect antigenic presentation.[119] Many cytokines are involved in this process including IL-1, IL-2, IL-12, IL-17, IL-18, IL-23 with IFN-γ, and TNF-α playing key roles including activating the previously discussed JAK-STAT pathway.[74] If the antigen can be eliminated, the response will shut down. Conversely, if the antigen persists, granuloma formation occurs through the persistent activation of IFN-γ and TNF-α triggering a complex fibrotic process stimulated by the release of TGF-β and IL-10.[120] Circulating fibrocytes can differentiate into fibroblasts and release collagen and other profibrotic substances.[121] FoxP3-expressing regulatory T (Treg) cells have the ability to aid in granuloma resolution but often are dysfunctional.[58]

Clinical Presentations

Cutaneous disease is often the first sign of systemic sarcoidosis, and commonly, many patients have initially skin-limited disease. Cutaneous manifestations can be divided into 2 major categories: lesions specific to sarcoidosis, with characteristic sarcoidal granulomas, and nonspecific lesions resulting from the systemic immunologic response. Specifically, when evaluating patients with darker pigmented skin, lesions can appear pink, red-brown, yellow-brown, purple-brown, or even gray. Erythema can be more subtle and can seem brown or purple. The various specific sarcoidosis findings are detailed in **Table 1** (selected examples in **Figs. 1–3**). Patients of color are more likely to present with specific manifestations compared with nonspecific lesions. Lupus pernio,[122,123] papule/plaque,[124,125] hypopigmented, verrucous, ulcers, psoriasiform, and scalp sarcoidosis occur more frequently in Black patients than in White patients.[2,122–124,126–133] Certain variants of cutaneous sarcoidosis carry potential prognostic implications and are discussed further below.

Lupus Pernio

The clinical variant, lupus pernio, consisting of violaceous, firm papules, and nodules that may develop scale. It is most often seen on the central

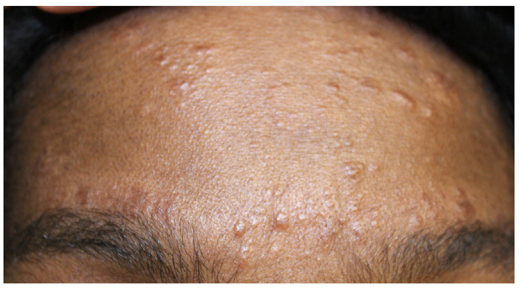

Fig. 1. Papular sarcoidosis: flesh colored papular lesions are shown on the forehead here. Papular sarcoidosis is a very common morphologic subtype.

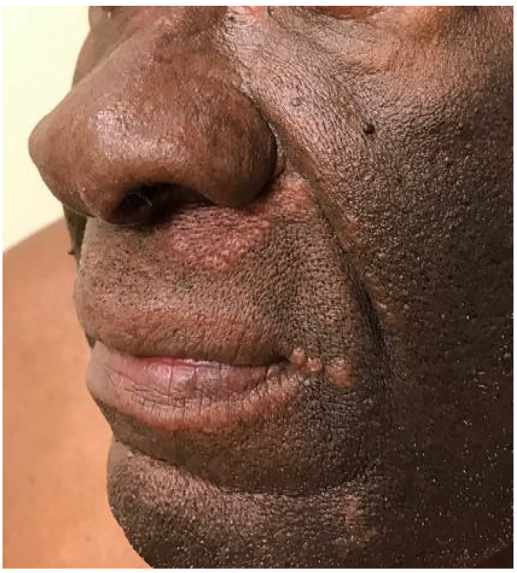

Fig. 2. Erythematous papules and plaques: slightly pink lesions with a vaguely annular architecture are seen in the perinasal area, with additional papules on the lip.

face, especially the distal nose, ears, lips, face, and less seen on hands and feet. It is characterized by a later age of onset and is disproportionately seen in Black and female patients.[123,126] It can present with a few small nodules on the nose, spread insidiously with progressive infiltration and induration into bone and cartilage. Lesions wrapping inward from the alar rim to obliterate the nasal mucosa can be seen on clinical examination and suggest the possibility of additional upper airway involvement. In addition to the standard workup for extracutaneous disease, the evaluation of a patient with lupus pernio should prompt otorhinolaryngology evaluation because sinus disease can be severe in patients with lupus pernio. It can be disfiguring and is associated with a more chronic or refractory course.[134] It can present as an isolated skin lesion but more often is an early systemic manifestation. Lupus pernio is associated with an increased risk of extracutaneous, especially upper respiratory and pulmonary, involvement as well as bone involvement. Lupus pernio warrants a thorough workup and often requires aggressive systemic therapy, specifically including the use of TNF-inhibitors.[122,123,135–137]

Scar Sarcoidosis

Cutaneous sarcoidosis may occur in scar tissue, at traumatized sites, and around imbedded foreign material, such as tattoos.[138,139] This can include scars from surgical incisions, venipuncture, acne, *herpes zoster* virus, and other forms of skin trauma. They can become raised and erythematous to violaceous. Lesions developing in old, chronic scars may be confused with hypertrophic scars or keloids.[140] Tattoo involvement can be mistaken for granulomatous hypersensitivity reactions to tattoo pigment or infections such as syphilis or atypical mycobacterial infections. The appearance of disease in previously inactive scars is thought to herald increased disease activity.[139]

Subcutaneous Sarcoidosis

Subcutaneous sarcoidosis presents as asymptomatic smooth cutaneous nodules located in the deep dermis and subcutis.[140] It is sometimes referred to as Darier-Roussy sarcoidosis.[128,141] They typically present on the trunk and extremities, mainly arms.[142] They can be distributed in a

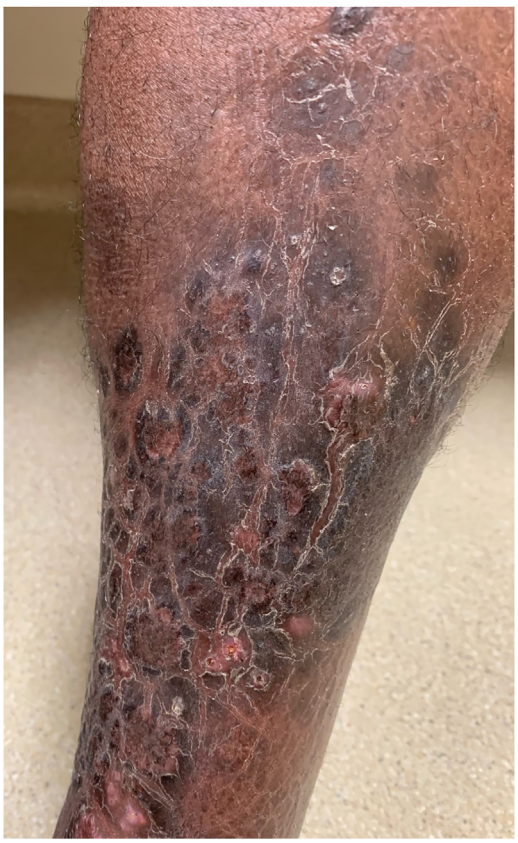

Fig. 3. Ichthyosiform sarcoidosis: this rare morphology is clinically challenging to distinguish from other forms of acquired ichthyosis however, a biopsy would typically show sarcoidal granulomatous inflammation. This patient has also had ulcerative sarcoidosis within the ichthyosiform lesions and has healing ulcers and scars at sites of earlier severe inflammation.

Table 1
Specific cutaneous sarcoidosis manifestations

Common	Papules and nodules	• Red-brown to purple-brown micropapules, papules, and nodules usually located on extensor surfaces or face, particularly the nasolabial folds, periorbital, perioral regions. Can originate within scars
	Plaques	• Red-brown to purple-brown well-demarcated, round to oval infiltrated plaques on the trunk and extremities predominantly but also the scalp and face. Can be annular with peripheral elevation or with white-gray scale • More likely to have chronic or scarring disease compared with papular lesions
	Lupus pernio	• Red-brown to purple-brown smooth indurated papules and nodules present symmetrically on the central face, also ears. Can present with beaded appearance with notching along the nasal rim • Often disfiguring and chronic
Uncommon or rare	Atrophic and ulcerative	• Easily ulcerative depressed plaques with roller borders • May have surrounding yellow-brown plaques with telangiectasias • Favors head and neck • Can originate de novo or in preestablished specific lesions
	Angiolupoid	• Pink to purple-brown papules and plaques with pronounced overlying telangiectasias on face • Commonly diagnosed as lupus pernio but usually more discrete and less extensive
	Erythrodermic	• Indurated red-yellow brown or purple-brown confluent plaques with overlying fine scale or desquamation
	Hypopigmented	• Skin colored to yellow-brown macules on extremities. Can be more noticeable or prominent in darkly pigmented skin • Present in isolation or papules and plaques • Better diagnostic value if biopsy of indurated hypopigmented lesions or associated papule
	Ichthyosiform	• Brown or white-gray polygonal with scale more adherent in center than edge, appearing pasted on • Present on lower legs • High rates of progression to systemic sarcoidosis
	Mucosal	• Can vary from papules, plaques, nodules with localized edema or infiltrative thickening. Located on buccal mucosa, gingiva, hard palate, tongue, posterior pharynx, and salivary glands
	Nail	• Thinning, brittle nails, thickened nails, pitting, ridging, trachyonychia, hyperpigmentation, clubbing or pseudoclubbing, onycholysis, or destruction of the nail plate and scarring (ie, pterygium)
	Psoriasiform	• Red to pink-brown plaques with overlying scale resembling psoriasis primarily on the legs • Unlike psoriasis, heals with scarring and hyperpigmentation
	Scalp	• Scarring or nonscarring alopecia, localized or diffuse • Range in lesions resembling alopecia areata-like macules, seborrheic dermatitis-like scaly plaques to infiltrated plaques and nodules
	Subcutaneous nodules	• Firm, mobile, painless, oval, flesh-colored to purple-brown subcutaneous nodules on the trunk or extremities
	Verrucous	• Hyperkeratotic pink to red-brown wart-like papules and plaques possibly with overlying white-gray scale

Data from Caplan A, Rosenbach M, Imadojemu S. Cutaneous Sarcoidosis. Semin Respir Crit Care Med. 2020;41(5):689-699, Rosenbach, Misha A., et al. "Non-Infectious Granulomas." *Dermatology*, Fourth Edition, 2018, pp. 1644–63 and Heath CR, David J, Taylor SC. Sarcoidosis: Are there differences in your skin of color patients? *J Am Acad Dermatol*. 2012;66(1):121.e1-14.

linear fashion in a lymphangitic or sporotrichoid pattern. It presents more commonly in White patients.[143] Some argue that subcutaneous sarcoidosis is associated with benign systemic disease but this assertion is debated.[128,142]

Erythema Nodosum

Erythema nodosum is the most common nonspecific sarcoidosis lesion, developing in up to 25% of patients.[140] It is a reactive panniculitis that seems as erythematous to violaceous to brown, tender, warm subcutaneous nodules, predominantly located on the pretibial leg. It presents usually with arthralgias, lower extremity edema, and fever. Erythema nodosum has been associated with a favorable prognosis, a pattern most commonly seen in White patients of Scandinavian European descent.[144,145] Of note, a variant called erythema nodosum-like sarcoid has been described in a Japanese cohort, which, by contrast, is a specific cutaneous sarcoidosis manifestation.[146] It resembles erythema nodosum solely in appearance as sarcoid granulomas are seen histologically.

Löfgren syndrome consists of the tetrad of erythema nodosum, bilateral hilar lymphadenopathy, migratory polyarthralgia, and fever.[140] Löfgren syndrome is associated with a good prognosis with spontaneous resolution within 2 years, although it can be very symptomatic.[147,148] It is typically managed with nonsteroidal anti-inflammatory drugs but can demand systemic corticosteroids.

Other nonspecific cutaneous findings of sarcoidosis include calcinosis cutis, clubbing, and prurigo.[140]

DIAGNOSTICS AND EVALUATION

Clinicopathologic Diagnosis

The diagnosis of sarcoidosis is clinicopathologic, ruling out other causes of granulomatous disease in conjunction with a systemic evaluation given the high prevalence of concomitant systemic sarcoidosis. Cutaneous histopathology of sarcoid-specific lesions can present a high-yield source of diagnostic information. Punch or incisional biopsy is preferred over superficial shave biopsy, as granulomatous involvement can be superficial, deep within the dermis, or in subcutaneous tissue.[12,149,150]

Typical biopsies of sarcoid-specific lesions demonstrate “naked granulomas”—noncaseating aggregates of epithelioid histiocytes without inflammatory cells. Multinucleated giant cells—typically of the Langerhans or foreign-body type—are often present. These giant cells at times show asteroid bodies (eosinophilic starburst inclusions) within their cytoplasm or Schaumann bodies (laminated, cytoplasmic calcifications) but neither Schaumann bodies nor asteroid bodies are specific to sarcoidosis.[151] Although naked granulomas are typical, sparse infiltrates of lymphocytes and plasma cells and focal necrosis have been reported. These findings should not preclude a diagnosis of sarcoidosis in the right clinical and pathologic setting.[12,150,151]

The clinical differential diagnosis is broad given the numerous presentations but includes granuloma annulare, leprosy, tuberculosis, lichen planus, SLE, secondary or tertiary syphilis, leukemia cutis, necrobiosis lipoidica, and leishmaniasis. The differential diagnosis of naked granulomas includes cutaneous Crohn disease, orofacial granulomatosis (Melkersson-Rosenthal syndrome), granulomatous rosacea, silica, beryllium, zirconium granulomas, and tuberculoid leprosy. Perineural infiltration of granulomas has rarely been reported in sarcoidosis and cannot definitely differentiate tuberculoid leprosy from sarcoidosis.[151] Foreign body reactions, infections (including deep fungal infections), immunodeficiency disorders, drug eruptions, and other entities may also show granulomas on biopsy.[12,151,152] Therefore, all slides with granulomas should be stained for infections, and tissue culture should be considered based on clinical suspicion. Additionally, all slides should be polarized for foreign material. Notably, up to 25% of sarcoidal granulomas can contain foreign body material, which should not exclude a diagnosis of sarcoidosis.[12,150–153] Clinical correlation and additional workup is required when foreign body material is evident on biopsy.

Uncommonly, patients present with sarcoid-like skin lesions and sarcoidal granulomas on biopsy without other diagnoses to explain these findings and without another organ involvement. These patients can be diagnosed with “sarcoid-like granulomatous disease of unknown significance,” although many refer to them as having “isolated cutaneous sarcoidosis.”[12] It is controversial whether patients with isolated skin findings can be diagnosed with sarcoidosis because strict definitions require involvement of at least 2 organ systems.[12,154]

Workup and Evaluation

Skin involvement can be objectively and systematically evaluated. Clinical assessment tools such as the Cutaneous Sarcoidosis Activity and Morphology Instrument and the Sarcoidosis Activity and Severity Index can be used to measure clinical response to treatment.[155,156] Evaluating a patient with suspected sarcoidosis combines clinical, pathologic, and radiographic analysis to

both establish a diagnosis and evaluate for systemic disease.[12,157] A thorough history must be taken to screen for extracutaneous sarcoidosis and to help eliminate other diagnoses (occupational history, exposures, travel, and family history).[12,158] Collaboration with specialists in pulmonology, cardiology, ophthalmology, otolaryngology, neurology, and endocrinology among others may be necessary to investigate and further manage extracutaneous involvement.[159] Extracutaneous manifestations can include pulmonary (interstitial lung disease, pulmonary hypertension), cardiovascular (palpitations, conduction disease, sudden cardiac death), ocular (uveitis, conjunctivitis), neurologic (nerve palsies, neuropsychiatric symptoms or seizures), among others. Nonspecific or parasarcoid symptoms such as fatigue, exercise intolerance, cognitive impairment, and small fiber neuropathy can greatly affect quality of life and wellness.[29,160–164] Workup includes a chest X-ray, pulmonary function testing to evaluate for interstitial lung disease, ophthalmologic examination, and an electrocardiogram (ECG). Some experts advocate a baseline echocardiogram and 24-hour Holter monitor in all patients with sarcoidosis, and those tests should be considered in patients with any history of palpitations because an ECG may miss cardiac sarcoidosis.[12,31,165] One study found that cardiac sarcoidosis is more likely to occur in Black patients with sarcoidosis as compared with other groups.[31] Although controversy exists, cardiac sarcoidosis may be better imaged with either PET scanning or dedicated cardiac MRI.[14] Laboratory analysis should include a complete blood count, comprehensive metabolic panel, urinalysis (if a history of nephrolithiasis), vitamin D (both 25-hydroxyvitamin-D and 1,25-dihydroxyvitamin D3), and thyroid testing.[12,158] Biomarkers may be more useful as evidence of active inflammation as opposed to pathognomonic tests.[166] For example, the serum angiotensin-converting enzyme is elevated in only 50% to 60% of patients with sarcoidosis, lacking diagnostic specificity with limited use for therapeutic response.[166–168] Other proposed biomarkers, including soluble IL-2 receptor, C-reactive protein, serum amyloid A (SAA), and chitotriosidase, may aid in assessing the disease activity but are either expensive, not available, or lack broad studies demonstrating reliability. FDG PET-computed tomography may be more effective for detecting tissue-specific inflammatory activity and identifying site for diagnostic biopsies[14] and may be an option to track disease activity and response in some patients.

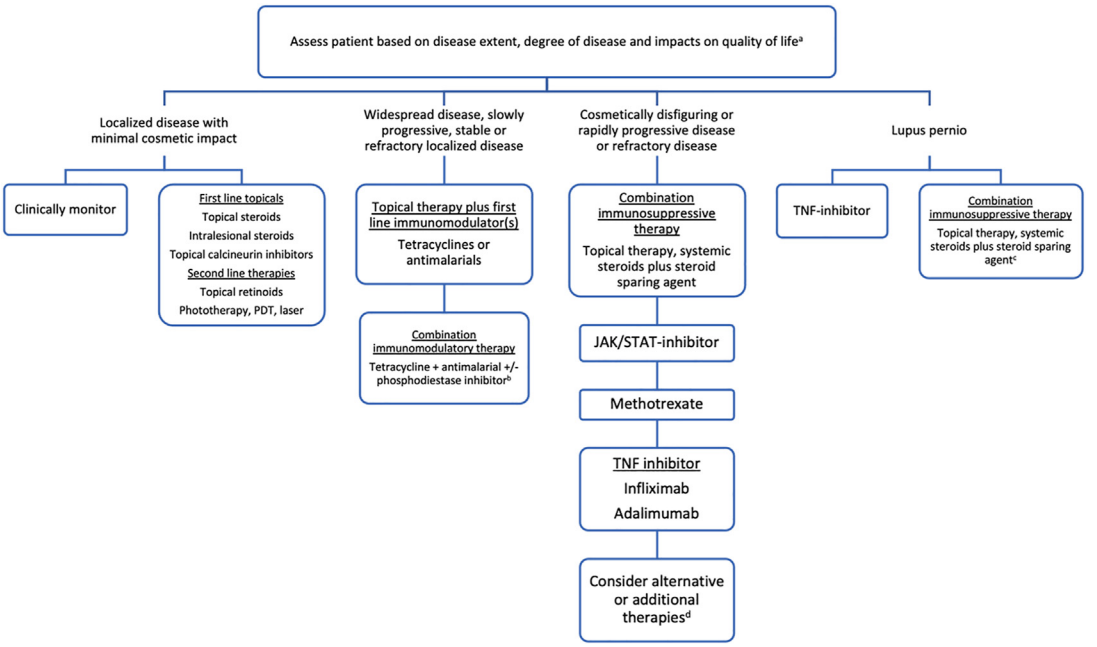

Fig. 4. Cutaneous sarcoidosis treatment algorithm.[140a]Give 3 mo of therapy before assessing treatment efficacy. [b]Second-line immunomodulation: pentoxifylline and isotretinoin. [c]Second-line immunosuppressives: leflunomide, thalidomide, lenalidomide, mycophenolate mofetil, and azathioprine. [d]Additional/alternative therapies include IL-6 inhibitors, rituximab. (*Adapted from* Imadojemu S, Wanat KA, Noe M, English JC, Rosenbach M. Cutaneous sarcoidosis. In: Baughman RP, Valeyre D, eds. *Sarcoidosis, a clinician's guide*. Vol 2019; 127–144.)

MANAGEMENT

Management of sarcoidosis poses significant challenges due to its clinical diversity. For most patients, there is spontaneous resolution without the need for systemic therapies. Because there are no Food and Drug Administration–approved cutaneous sarcoidosis therapies, retrospective case series and expert opinion offer treatment guidance from a range of local therapies, immunomodulatory systemic therapies, and immunosuppressive therapies.

In general, treatment can include topical therapy, systemic immunomodulatory therapy, and systemic immunosuppressive therapy. **Fig. 4** describes a proposed treatment algorithm. First-line therapy for mild local cutaneous sarcoidosis includes a combination topical and intralesional corticosteroids, topical calcineurin inhibitors, along with antimalarials,[6,140,169,170] and doxycycline (minimal risk for hyperpigmentation and autoimmune sequelae).[11,140] Small case series and case reports with post hoc analysis have shown limited benefit in phosphodiesterase (PDE4) inhibitors having a steroid-sparing effect in pulmonary sarcoid but cutaneous effects have yet to be fully studied.[171,172]

For moderate-to-severe disease, refractory, disfiguring, or destructive lesions, systemic corticosteroids and methotrexate are first line[140,173–176] except in patients with thick plaque sarcoidosis or lupus pernio. Those patients should be immediately considered for TNF-inhibitor therapy, which has demonstrated efficacy in multiple studies and case series.[177–184]

Emerging therapies with an increasing evidence base as a beneficial treatment of sarcoidosis include topical and systemic JAK inhibitors,[77,78,185–192] with open-label clinical trials showing improvement in pulmonary and cutaneous sarcoidosis.[190,193] A monoclonal antibody to IL-6 currently in a clinical trial as inhibition has been linked to reduction in SAA and granulomatous formation (ClinicalTrials.gov identifier: NCT04008069). Unfortunately, IL-12/-23 inhibitors have been studied in a randomized control trial and failed to show efficacy and were shown to exacerbate or induce disease in case reports.[194–196] IL-17 inhibitors have been reported to paradoxically induce granulomatous inflammation in early reports.[197]

Box 1
Workup recommendations in patients with cutaneous sarcoidosis

History including full review of systems, occupational/environmental exposures

Physical examination including ophthalmologic examination

Complete blood count

Comprehensive metabolic panel including creatinine, liver function tests, and calcium

Urinalysis if history of nephrolithiasis

Vitamin D_{25} and Vitamin D1, 25

Thyroid function tests

Chest X-ray

Pulmonary function tests including diffusion capacity for carbon monoxide

Electrocardiogram; if palpitations noted, cardiology referral for further testing (transthoracic echocardiogram, Holter monitor/event monitor/EP evaluation, cardiac MRI, cardiac PET)[a]

Can consider:

- Biomarkers such as angiotensin converting enzyme or others[b] for disease activity
- FDG PET-CT for identifying potential biopsy sites or disease activity

[a]Some cardiac experts prefer cardiac MRI or PET to evaluate for cardiac sarcoidosis.[b]Soluble interleukin-2 receptor, C-reactive protein, serum amyloid A (SAA) and chitotriosidase can aid in disease activity assessments but can be expensive or inconsistently available.

SUMMARY

Sarcoidosis is a multiorgan disease with high levels of cutaneous involvement. Although the exact cause is still unclear, it is thought that genetic predisposition combined with an environmental insult triggers granuloma formation. Black Americans are disproportionately affected by this condition with more severe and disfiguring disease as well higher rates of increased morbidity and mortality. This is likely due to ethnic and familial variations in pathogenic genes coupled with environmental triggers that likely include structural and institutional racism. Future studies should specifically look at the role of racism in the development of sarcoidosis. Evaluation of patients with cutaneous sarcoidosis should include workup (**Box 1**) for systemic involvement. Treatment should be focused on severely impacted organs and symptoms negatively affecting quality of life with the use of topical, immunomodulatory, and/or immunosuppressive medications.

DISCLOSURES

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