Cutaneous Sarcoidosis

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KEYWORDS

• Cutaneous sarcoidosis • Erythema nodosum • Lupus pernio • Darier-Roussy • Angiolupoid

KEY POINTS

- About 20% to 35% of patients with sarcoidosis may show cutaneous involvement.
- Skin lesions of sarcoidosis may represent either specific skin involvement by sarcoidal granulomas or nonspecific reactive lesions.
- Common specific skin lesions include lupus pernio, dermally based papules and plaques, and subcutaneous nodules. The most widely recognized nonspecific cutaneous manifestation is erythema nodosum.
- Cutaneous manifestations of sarcoidosis can have a significantly negative influence on patients' quality of life, may lead to scarring and dyspigmentation, and may be a motivation for patients to pursue treatment.
- Treatment strategy depends on the severity and distribution of skin lesions and should incorporate patient preference and treatment considerations for other organs that may be involved.

INTRODUCTION

Sarcoidosis is a multisystem disease that most commonly affects the lungs, lymphatic system, eyes, and skin but any organ may be involved. It has been estimated that 20% to 35% of patients with sarcoidosis have cutaneous involvement.[1,2] Cutaneous sarcoidosis (CS) most commonly presents as pink-red to red-brown papules and plaques (raised lesions) that commonly affect the head and neck. However, CS is often referred to as a great mimicker in dermatology, meaning several other lesion morphologies are possible and a high index of suspicion must be maintained. These varied cutaneous presentations will be reviewed herein. Dermatologic evaluation can provide strong evidence to support a suspected diagnosis of sarcoidosis due to the skin being readily accessible for assessment and biopsy.[3,4] We will also review disease immunopathogenesis and how this relates to current and emerging treatment approaches.

BURDEN OF CUTANEOUS DISEASE

The burden of inflammatory skin diseases on quality of life (QoL) has been extensively documented.[5–8] This encompasses the psychological, social, and emotional consequences of skin diseases on patients' health and wellness. Studies have demonstrated that patients with skin diseases are more likely to have depression, suffer from social isolation or loneliness, and have a lower QoL.[5–8] Furthermore, inflammation in cutaneous diseases such as psoriasis can have direct consequences on health by effects of chronic inflammation on the vasculature, thereby increasing cardiovascular risk. This concept is not as well studied in other inflammatory skin diseases including CS, however, and merits further investigation.[9]

The consequences on QoL specific to CS have not been well described. Compared with other inflammatory skin disorders, CS more commonly involves the face, a particularly cosmetically sensitive area. In addition to active inflammatory lesions, CS

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may also result in postinflammatory dyspigmentation (hyperpigmentation and/or hypopigmentation) and scarring, especially in individuals with darker skin types (Fig. 1). This may be difficult or impossible for patients to conceal and may make things like going out in public a challenge. In our experience, skin involvement may be the patient's primary motivating factor for seeking treatment of their sarcoidosis. Yet, the effects of CS on QoL and how they might be mitigated by successful treatment are not well documented in the medical literature. In our experience, acknowledging how difficult CS may be for patients and giving them the opportunity to openly discuss its effects on their lives can make patients feel heard and may improve compliance with treatment recommendations for their sarcoidosis more generally. Shared decision-making around therapeutic selection and discussing the likelihood it will help their CS is also key.

CLINICAL PRESENTATION

The relationship between cutaneous and systemic sarcoidosis is not well understood. Why some patients develop cutaneous involvement, whereas others do not is not fully clear. Although lupus pernio and angiolupoid presentations (see later discussion, Table 1) may be associated with more chronic disease, the severity of cutaneous involvement in general does not usually correlate with the severity or extent of extracutaneous disease. In fact, most patients with severe systemic sarcoidosis have no skin involvement at all.

In some patients, skin involvement may be the presenting sign of disease. In other patients, cutaneous involvement may develop synchronously with or after internal organ involvement. The evaluation and monitoring of patients with CS is outlined in Box 1. A study by Mana and colleagues noted that approximately 30% of patients who initially had only cutaneous lesions later developed systemic involvement, emphasizing the importance of ongoing screening.[10]

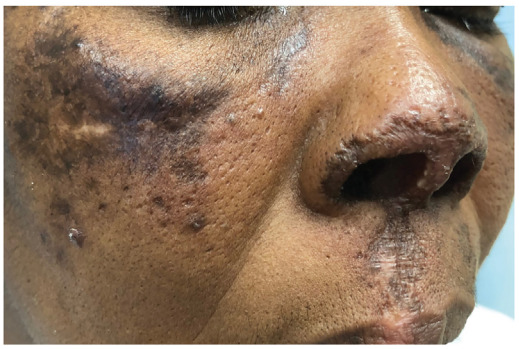

Fig. 1. Atrophic scarring and dyspigmentation in a Black woman with sarcoidosis. Dyspigmentation refers to areas of both hyperpigmentation and hypopigmentation.

Lesion morphology in sarcoidosis may vary but the most common presentation is of dermally based papules and plaques (raised lesions). Common and uncommon presentations of CS will be reviewed in the following section. Hair and nails may also be affected, necessitating a comprehensive mucocutaneous examination when evaluating for CS (Table 2). Classically, skin lesions of sarcoidosis have been divided into 2 categories: specific lesions and nonspecific lesions. Specific lesions reveal noncaseating granulomas (the histologic hallmark of sarcoidosis) when biopsied, whereas nonspecific lesions are thought to be a reactive phenomenon, show different histopathology, and may be seen in settings other than sarcoidosis.[1,2,11] The most commonly recognized nonspecific skin lesion is erythema nodosum (EN; Table 3).[1,11]

Common Morphologies of Specific Cutaneous Involvement

Papules

A common cutaneous morphology in sarcoidosis is papules, which are small, raised lesions less than 1 cm in diameter (Fig. 2).[2] They are characterized as having a pink-red to red-brown color. Erythema may be more difficult to appreciate in patients with darker skin tones. As a dermally based inflammatory process, classic sarcoidosis lesions do not have scale, which reflects epidermal inflammation when present. However, in clinical practice, lesions may have some scale and so its presence does not necessarily exclude sarcoidosis (Fig. 3). Papule-predominant morphology has been described as more common in self-resolving presentations of sarcoidosis.[12,13] Lesions may be present on the face (often peri-orificial), neck, extremities, and/or trunk. Papular sarcoidosis may resolve without scarring.

Plaques

Plaques are larger raised lesions that are 1 cm or larger in diameter. They commonly co-occur with papules and are thought to be similar pathophysiologically. These lesions may commonly involve the face, trunk, extensor surfaces of the arms, scalp, and/or extremities; however, any area of the skin may be involved.[2,14,15] Sarcoidosis plaques (and papules) are frequently but not always annular with raised, prominent edges (see Fig. 3).[14] Plaques, therefore, may be associated with chronic presentations of this disease and often resolve with scarring and/or hyperpigmentation.[2] It is important to note that these secondary changes may be equally bothersome to the patient

Table 1
Commonly used sarcoidosis terms and definitions

Term	Definition
Lofgren syndrome	Lofgren syndrome presents with hilar lymphadenopathy, arthritis, fever, and erythema nodosum.[15,34] This syndrome is generally considered an acute form of sarcoidosis with an excellent prognosis. It is most common in Scandinavian countries
Melkersson-Rosenthal syndrome	"Classic" Melkerson-Rosenthal presents with a triad of orofacial swelling, facial weakness, and fissured tongue.[33] However, most patients do not have the full triad. Granulomatous cheilitis may be used to describe swelling of lips in this setting and may be the only sign present. Orofacial granulomatosis may be a more useful, encompassing term. This constellation of symptoms may be seen in the setting of sarcoidosis, Crohn disease, or may be idiopathic
Blau syndrome	Blau syndrome classically presents with a triad of CS, arthritis, and uveitis in young children.[37] Also known as early-onset sarcoidosis, this is caused by germline *NOD2* mutation and is inherited in an autosomal dominant fashion
Angiolupoid sarcoidosis	Angiolupoid sarcoidosis refers to lesions of sarcoidosis that have prominent overlying telangiectasia. This is most common on the nose and central face in patients with lighter skin tones and is seen in the setting of chronic disease[26,27]
Heerfordt-Waldenström syndrome	A very rare presentation of sarcoidosis that shows parotid gland enlargement, anterior uveitis, fever, and facial palsy.[89,90] All features may not be present, and these findings are not specific to sarcoidosis. Signs of CS may also be present on examination and help with the diagnosis
Darier-Roussy sarcoidosis	Refers to specific involvement of the subcutaneous fat by sarcoidal granulomas (see **Table 3**)[14,15]
Lupus pernio	The most precise and preferred definition refers to papules of sarcoidosis along the alar rims and/or columella of the nose. Lupus pernio is associated with upper airway involvement. A less-specific usage of this term in the literature is to refer to sarcoidosis of any part of the central face
Miescher granuloma	This histologic feature may be seen in erythema nodosum. It refers to radially configured aggregates of histiocytes around a central cleft and is typically present in inflamed septae of the subcutaneous fat, when present.[91] It should not be confused for the granulomas of sarcoidosis
Schaumann bodies	Although this histologic finding may be seen in sarcoidosis, it is neither specific to sarcoidosis nor required for diagnosis. Schaumann bodies are intracytoplasmic inclusions typically found within multinucleated giant cells. They appear as concentric laminated calcifications (purple on hematoxylin and eosin stain)[40,41]
Asteroid bodies	Although this histologic finding may be seen in sarcoidosis, it is neither specific to sarcoidosis nor required for diagnosis. Asteroid bodies are intracytoplasmic inclusions typically found within multinucleated giant cells. They appear as star-like bodies and are pink in color on hematoxylin and eosin[40,41]

as the inflammatory lesions themselves, particularly pigmentation changes in individuals with darker skin tones.

Lupus pernio

In 1889, Ernest Besnier was the first to describe CS in a patient with what was called "lupus pernio."[2] Although ultimately a misnomer because there is no direct relationship to lupus, this nomenclature has persisted. Lupus pernio refers to papules along the alar rims and/or columella of the nose (**Fig. 4**).[2,15] Similarly to papules in other areas of the skin, lesions are often pink-red in color in patients with lighter skin tones and more brown in

Box 1
Initial evaluation and monitoring recommendations for patients with cutaneous sarcoidosis without known sarcoidosis in other organs

Evaluation of patients with a new diagnosis of CS for systemic involvement

History

- Including occupational/environmental exposures
- Comprehensive ROS

Physical examination

Pulmonary evaluation

- At least a screening chest radiograph[a]
- Pulmonary function tests[b]
- Referral to pulmonology

Cardiac evaluation

- At least a screening EKG
- If ROS positive for history of presyncope, syncope, episodic dizziness, or palpitations urgent referral to cardiology is mandatory

Ophthalmologic evaluation

- Consider ophthalmology referral[c]

Other organs

- Consider referral to other specialists depending on ROS and laboratory workup
- Communicate with the primary care provider

Laboratory testing

- Complete blood count
- Comprehensive metabolic panel (liver function tests and basic metabolic panel)
- QuantiFERON
- Thyroid stimulating hormone level
- Vitamin D: 25-hydroxyvitamin D, 1,25-hydroxyvitamin D
- Disease biomarker (soluble IL-2R [CD25][d] level and/or ACE level)

Monitoring of patients with known CS for progression to systemic involvement

- Annual complete physical examination, ROS[e]
- Annual complete blood count (CBC) and comprehensive metabolic panel[e,f,g]
- Consider rechecking disease biomarker if change in symptoms
- Consider re-referral to specialist (or discuss with PCP) if change in symptoms

[a]If positive pulmonary ROS (case-by-case basis) consider starting with high-resolution chest CT

[b]We typically will refer to pulmonology to perform and interpret this testing

[c]Some experts recommend referrals for all patients with CS, others on a case-by-case basis depending on ROS. Referral for baseline examination in patients embarking on hydroxychloroquine therapy in particular, regardless of ROS, is likely judicious.

[d]Although not elevated in all patients with CS/sarcoidosis we find this useful for following disease activity and response of systemic disease to therapy

[e]Therapeutics may require more frequent follow-up and laboratory evaluation

[f]Further diagnostic workup guided by physical examination and ROS

[g]Consider annual EKG

Abbreviations: ROS, review of systems, EKG, electrocardiogram.

Table 2
Elements of a comprehensive mucocutaneous examination in patients with diagnosed or suspected cutaneous sarcoidosis

Site	Example of Clinical Features
Hair	Sarcoid alopecia is an inflammatory and scarring process. Look for inflammatory papules, papules, and/or nodules with overlying loss of hair (and eventually the follicular ostea (or openings) will disappear). This typically occurs in a patchy, asymmetric as opposed to diffuse, symmetric pattern
Face	Nose: look for papules along the alar rims and/or columella of the nose (lupus pernio) Eyes: lacrimal gland hypertrophy may be present and helps support the clinical impression of sarcoidosis Tear trough and nasofacial sulcus: sarcoidosis lesions in these areas may be associated with ocular involvement Neurologic: assess for facial asymmetry (Melkersson-Rosenthal and Heerfordt-Waldenström syndromes)
Oropharynx	Oral manifestations are nonspecific but may include fissured tongue, orolabial swelling, or mucosal cobblestoning
Complete cutaneous examination	Be sure to look everywhere as CS lesions may be very localized. For example, they rarely may be limited to the genitalia
Tattoos	Visually inspect and palpate tattoos for papules and subcutaneous nodules. If present, biopsy may be required to establish the diagnosis. Specific ink colors such as red and yellow may be preferentially involved with visible papules
Scars	Visually inspect and palpate scars for papules and subcutaneous nodules. If present, biopsy may be required to establish the diagnosis
Digits and nails	Nail alterations seen in sarcoidosis include nail plate dystrophy. Dactylitis may or may not be present. Distal digital involvement is associated with underlying bony abnormalities. Evaluate for digital clubbing

patients with darker skin tones. A deep violaceous color may sometimes develop and is evocative of the original "pernio" nomenclature. Patients with lupus pernio have a higher likelihood of upper airway involvement with sarcoidosis.[16] Patients presenting with lupus pernio frequently have involvement of other areas on their face and tend toward more chronic disease. Facial involvement,

Table 3
Features that may help distinguish erythema nodosum and subcutaneous sarcoidosis

	Erythema Nodosum (non-specific)	Subcutaneous Sarcoidosis (specific)
Color	Pink-red	Flesh colored to light pink
Symptoms	Painful, tender	Usually painless, nontender
Size	Larger lesions common, lesions <1 cm uncommon	May have mix of small and large lesions
Number of lesions	May be relatively few	May be numerous
Motility and demarcation	Nonmobile, poorly demarcated	May be mobile, may be sharply demarcated
Distribution	Symmetrically on anterior shins	Extremities (most commonly the arms) and sometimes trunk, may be asymmetric, can occur anywhere on skin
Histologic findings	Septal panniculitis and may have focal granuloma formation (Meischer granuloma)	Epithelioid granulomas within subcutaneous fat ± deep dermis
Diagnostic of sarcoidosis	No	Yes

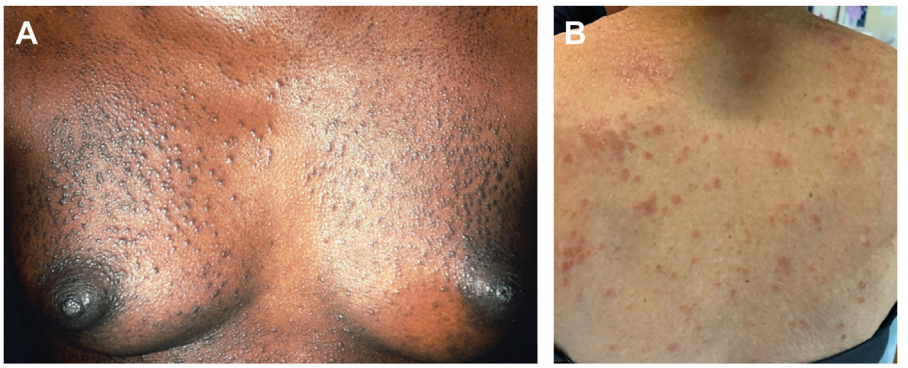

Fig. 2. Papules of sarcoidosis in a Black patient (*A*) and White patient (*B*). In B, some papules coalesce into small plaques. (William D. James, Dirk Elston, James R. Treat, Misha A. Rosenbach. Andrews' Diseases of the Skin. Edition 13, Figure 31.9; Elsevier 2019.)

specifically lupus pernio, has the potential for a devastating impact on patients' QoL; however, studies quantifying these effects have not been performed and are needed.[17]

Subcutaneous sarcoidosis

Subcutaneous sarcoidosis, sometimes referred to as the Darier-Roussy subtype (see **Table 1**), typically presents as subcutaneous nodules. Compared with the papules and plaques of sarcoidosis, nodules of subcutaneous sarcoidosis may have less well-defined borders because the granulomatous inflammation is located deeper in the skin. For this reason, inflammation may be less clinically apparent (light pink to flesh-colored) (**Fig. 5**). Patients may or may not have more typical papules and plaques in addition.[14,15] Histologic evaluation of subcutaneous lesions shows sarcoid granulomas based in the subcutaneous fat (and may also involve the deep dermis).

Subcutaneous sarcoidosis on the anterior lower legs may be confused with EN. Clinical features that may help distinguish between the 2 are summarized in **Table 4** but ultimately evaluation by an experienced dermatologist and a sufficiently deep biopsy are often required. Whereas subcutaneous sarcoidosis shows epithelioid granulomas in the subcutaneous fat on histopathologic examination, EN instead shows septal predominant panniculitis. The septal panniculitis in EN may be focally granulomatous in nature but this so-called Miescher's granuloma (see **Table 1**) of EN should not be confused with sarcoidosis.

Scar and tattoo sarcoidosis

CS is also known to exhibit tropism to tattoos and/or scars. Involvement of tattoos is well documented and was first reported in 1939.[18] Specific ink colors, especially red and yellow, may be preferentially involved and present as induration and/or visible papules (**Fig. 6**).[19,20]

Scars involved by sarcoidosis may appear erythematous and/or indurated (**Fig. 7**).[17,21,22] Patients presenting with concern for sarcoidosis should have their scars and tattoos examined (see **Table 2**). It is also important to consider the

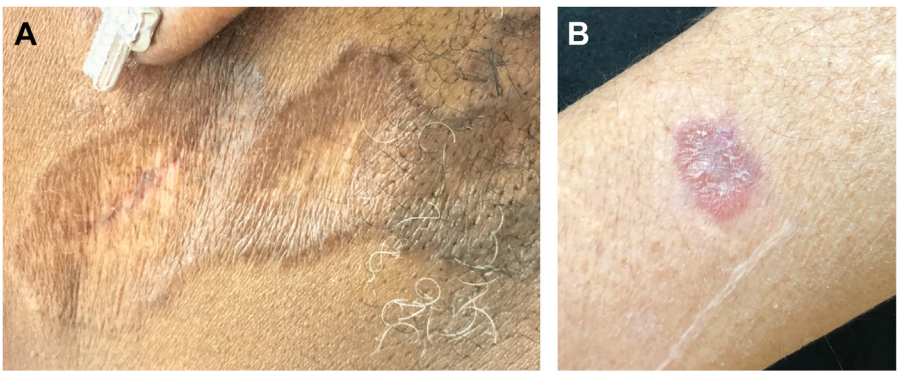

Fig. 3. Plaque of sarcoidosis in a Black patient (*A*) and White patient (*B*). Annular lesions with a raised border are common in sarcoidosis (as in *A*). Some scale may be present and does not exclude the possibility of CS (as in *B*).

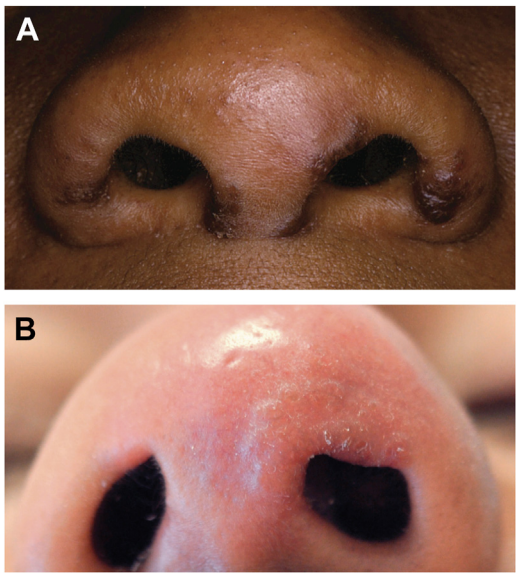

Fig. 4. Lupus pernio in a Black patient (*A*) and White patient (*B*). Although inflammation is dermally based, slight scale may be present (as in B). (Jean Bolognia, Julie Schaffer, Karynne Duncan, Christine Ko. Dermatology Essentials. Edition 2, Figure e78.2; Elsevier 2021.)

possibility of systemic involvement of sarcoidosis even in patients presenting with cutaneous involvement limited to scars and/or tattoos (see **Box 1**).[17,21,22]

Sarcoidal Dactylitis

Dactylitis is the inflammation of one or more fingers and/or toes (**Fig. 8**). Sarcoid dactylitis is a rare manifestation that is observed in approximately 0.2% of cases of sarcoidosis.[23] Involvement of the underlying bones is not uncommon in this setting.[23,24] Radiologically, sarcoidosis dactylitis is characterized by trabecular changes with a honeycomb appearance.[24,25] Sarcoid dactylitis is generally quite resistant to treatment and is mostly seen with chronic forms of sarcoidosis. Dystrophy of the nail plate may or may not be present (see later discussion).

Angiolupoid Sarcoidosis

Angiolupoid sarcoidosis is also a less common manifestation of the disease and typically affects patients with lighter skin tones.[26] Angiolupoid refers to the involvement of the nose and central face with prominent telangiectasia developing over the inflammatory lesions (**Fig. 9**).[26,27] Angiolupoid sarcoidosis is often seen in the setting of chronic disease. The mechanism by which telangiectasias form in this variant is unclear; however, one hypothesis involves the production of vascular endothelial growth factor and other angiogenic factors by activated macrophages.[28]

Other Uncommon Morphologies and Special Sites

Several other cutaneous morphologies have been described in CS. These include hypopigmented, verrucous, ichthyosiform, psoriasiform, and ulcerative; however, they are fairly rare and will not be discussed further other than to state that in order to diagnose one of these other morphologies, a biopsy demonstrating sarcoidal granulomas is required, and in some cases, sterile culture to rule out an infectious process is necessary.[29] Close clinicopathologic correlation by an experienced dermatologist is helpful.

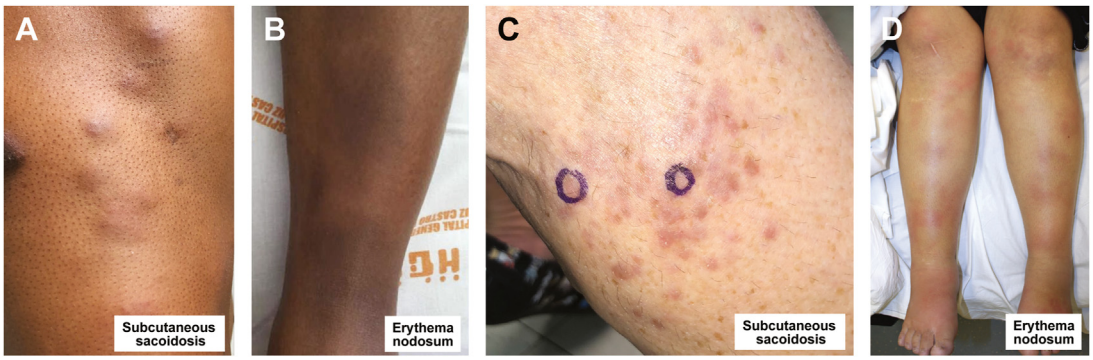

Fig. 5. Subcutaneous sarcoidosis (*A*, *C*) and EN (*B*, *D*) in patients with darker skin tones (*A*, *B*) and lighter skin tones (*C*, *D*). In panel C, typical dermally based papules (pink) and subcutaneous lesions (circled areas) are both present. Clinical features that may help distinguish subcutaneous sarcoidosis and EN are summarized in **Table 3**. (Mariana Montoya Castilloa, Sebastián Herrera Uribeb, Juan David Berlinghieri Péreza. Löfgren syndrome as an acute presentation of sarcoidoisis. 25:2; Figure 1, Elsevier 2018.)

Table 4
List of available therapies for cutaneous sarcoidosis, level of evidence, common adverse effects, and monitoring recommendations

Medication Name	Level of evidence[ref]	Dosing	Adverse Effects	Monitoring
Topical Therapy:				
Topical corticosteroids	IIB[92–94]	Ultrapotent agents intermittently used twice daily, eg, 1 wk on, 1 wk off	Skin atrophy, hypopigmentation, striae, petechiae	None
Intralesional corticosteroids	IA[95,96]	Triamcinolone 2.5–20 mg/mL every 2-3 months	Skin atrophy, hypopigmentation, striae, petechiae	None
Topical calcineurin inhibitors (tacrolimus 0.1% ointment, pimecrolimus 1% cream)	III[67,97,98]	Twice daily	BW: malignancy; also skin irritation, stinging	None
Topical JAK inhibitor (compounded)	III[28,70]	Twice daily	BW: serious infections, mortality, malignancy, major cardiovascular events, thrombosis	None
Systemic Therapy:				
Oral corticosteroids[a]	III[17,99–101]	0.1–0.5 mg/kg/d typically; higher doses may be needed for internal organ involvement	Weight gain, hypertension, diabetes, osteoporosis, mood disturbance, others	Blood pressure, glucose monitoring, DEXA scan if long term
Corticotrophin repository injection[a]	III[102]	80 units/mL (5 mL)	Weight gain, hypertension, diabetes, osteoporosis, mood disturbance, others	Blood pressure, glucose monitoring, DEXA scan if long term
Doxycycline	IIB[77]	100 mg twice daily	Contraindicated in pregnancy, <8 yo; photosensitivity, GI upset, esophagitis	None
Minocycline	IIB[76,77]	100 mg twice daily	Contraindicated in pregnancy, <8 yo; dizziness	None
Chloroquine	IIB[71]	250–500 mg daily	Retinopathy, QT prolongation, myopathy, neuropathy	EKG, fundus examination, CBC and CMP every 3 mo

Hydroxychloroquine	IIB[78,103]	200 mg twice daily	Retinopathy, QT prolongation, myopathy, neuropathy	EKG, fundus examination, CBC and CMP every 3 mo
Methotrexate	IIB[103–105]	10–25 mg po or intramuscular weekly	BW: adverse reactions, hypersensitivity, embryo-fetal toxicity; infection, GI upset, hepatotoxicity, cytopenias, pulmonary fibrosis	CBC, CMP every 3 mo
Mycophenolate	III[106]	500–1500 mg po twice daily	BW: infections, malignancy, embryo-fetal toxicity; GI upset, cytopenias	CBC, CMP every 3 mo
Thalidomide	IIB[81,107–109]	100–200 mg once daily	BW: contraindicated in pregnancy, thromboembolic events; peripheral neuropathy, hypothyroidism	CBC, CMP, and TSH every 3 mo; monitor for neuropathy
Infliximab	III[17,80,83,84,110–112]	3–10 mg/kg every 4–8 wk	BW: serious infections, malignancy; infusion reaction, GI upset, infection	Hepatitis, HIV, and tuberculosis (TB) screening at baseline; annual TB screening
Adalimumab (and other subcutaneously administered TNF-alpha inhibitors)	III[83,113,114]	varies	BW: serious infections, malignancy	Hepatitis, HIV, and TB screening at baseline; annual TB screening
Tofacitinib (or other JAK inhibitors)	III[61,87,115,116]	5–10 mg twice daily (tofacitinib)	BW: serious infections, mortality, malignancy, major cardiovascular events, thrombosis	Hepatitis, HIV, and TB screening at baseline; annual TB screening; CBC, CMP, lipids[b] every 3 mo
Procedural Therapy:				
Pulsed dye laser	III[117–119]	6–14 J/cm2 (585–595 nm, 7–12 mm)	Purpura, bruising, postinflammatory hyperpigmentation	None

Abbreviation: BW, boxed warning; CMP, complete metabolic panel; DEXA, dual-energy X-ray absorptiometry; TSH, thyroid stimulating hormone.

[a] FDA-approved therapy (for pulmonary sarcoidosis).

[b] Monitored annually if stable after 3 mo of treatment.

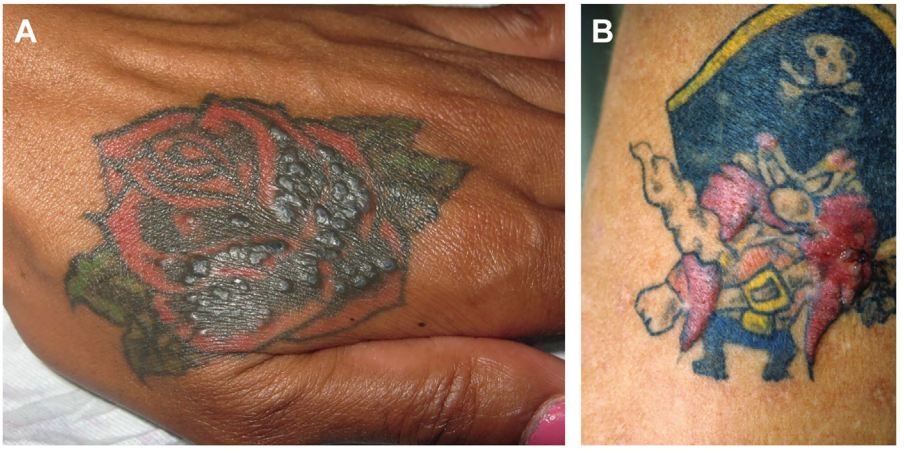

Fig. 6. Tattoo sarcoidosis in a Black patient (*A*) and White patient (*B*). Specific ink colors may be preferentially involved. (Jean Bolognia, Julie Schaffer, Lorenzo Cerroni. Dermatology 2 volume set. Edition 4; Figure 93.2e. Elsevier 2017.)

Involvement of Mucous Membranes, Hair, and Nails

Patients with suspected sarcoidosis should also have careful examination of hair, nails, and mucous membranes because sarcoidosis may also manifest in these areas (see **Table 2**). Scalp involvement may present as cicatricial (scarring) alopecia, usually occurring on a background of more typical sarcoidal inflammatory lesions (**Fig. 10**).[30] Occasionally, sarcoidosis may present as large solitary plaques of the scalp, which may develop alopecia and even ulcerate. A biopsy is required for the diagnosis of sarcoidal alopecia and noncaseating granulomas are expected; other processes may need to be excluded.

Sarcoidosis can also result in alterations to the nail unit including nail dystrophy and subungual hyperkeratosis (see **Fig. 8**).[31] This may occur in the setting of sarcoid dactylitis or in isolation. Nail sarcoidosis is most commonly mistaken as tinea unguium. Definitive diagnosis requires a nail matrix biopsy, which would be expected to demonstrate sarcoidal granulomas. Finally, mucosal changes may be present and are most commonly characterized by localized swelling.[32] In Melkersson-Rosenthal syndrome, there is a triad of facial paralysis, swelling of the face and lips (usually upper lip), and the development of folds and furrows in the tongue.[33] Although not specific, an assessment for lacrimal gland hypertrophy is often performed. Heerfordt syndrome of sarcoidosis may present with facial palsy and parotid swelling (see **Table 1**).

Nonspecific

Nonspecific cutaneous lesions seen in sarcoidosis are thought to be reactive in nature and when a biopsy is performed, sarcoidal granulomas are not seen. The most common nonspecific cutaneous

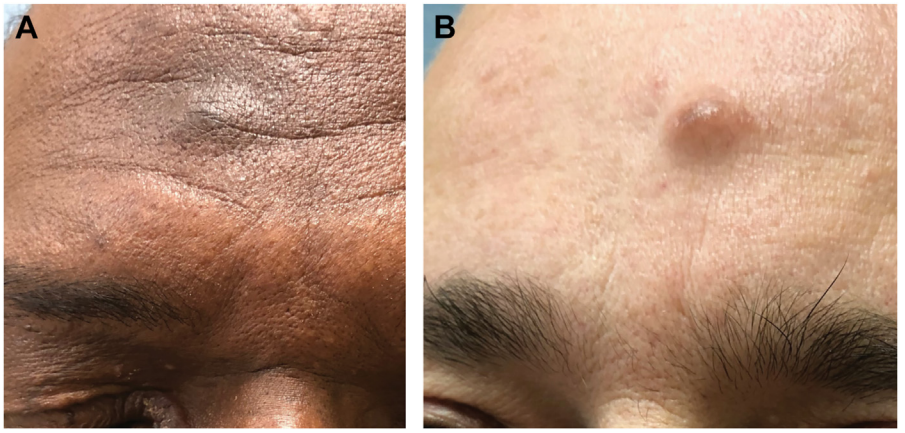

Fig. 7. Involvement of scars in a Black patient (*A*) and White patient (*B*) with sarcoidosis. Involvement in a similar area of the forehead is coincidental.

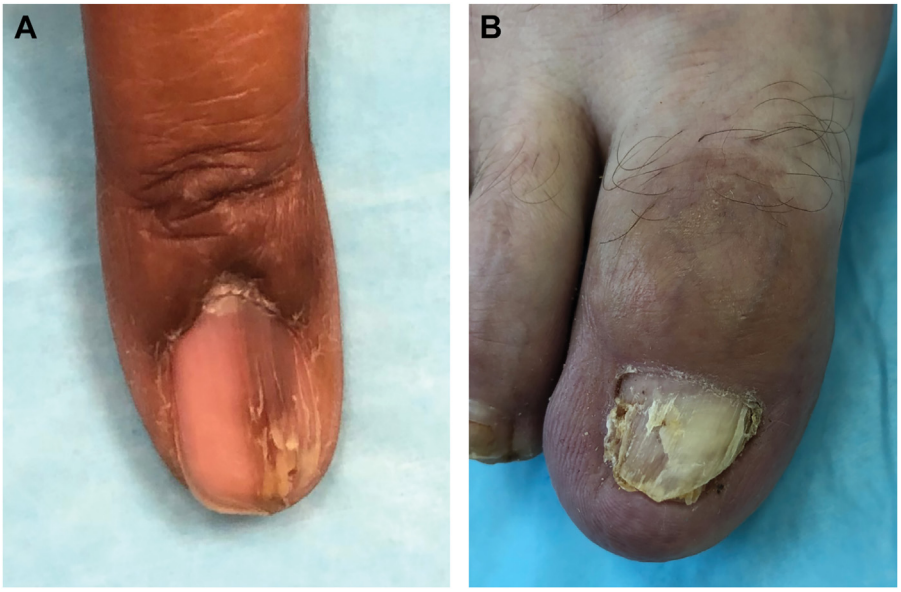

Fig. 8. (*A*) Nail plate dystrophy and hyperpigmentation due to nail matrix involvement by sarcoidosis in a Black patient. Dactylitis is absent. (*B*) Nail plate dystrophy in the setting of sarcoid dactylitis in a White patient. Nail matrix biopsy in patient A showed sarcoid granulomas. Nail dystrophy in both patients improved with treatment of sarcoidosis.

lesion seen with sarcoidosis is EN. EN is not specific to sarcoidosis and is more commonly observed in other settings. EN presents as painful, pink-to-red subcutaneous nodules that are usually symmetrically distributed on the anterior shins.[12] In sarcoidosis, EN is most commonly seen in the setting of Lofgren syndrome, which also includes hilar lymphadenopathy, arthritis, and fever (see **Table 1**).[13,34] This syndrome, which is typically considered an acute form of sarcoidosis, has an excellent prognosis and often does not require steroids.[19,20,34]

Digital clubbing, which is thought to occur in the setting of clinically significant pulmonary disease (of many causes), is a poor prognostic factor when present in sarcoidosis.[35,36]

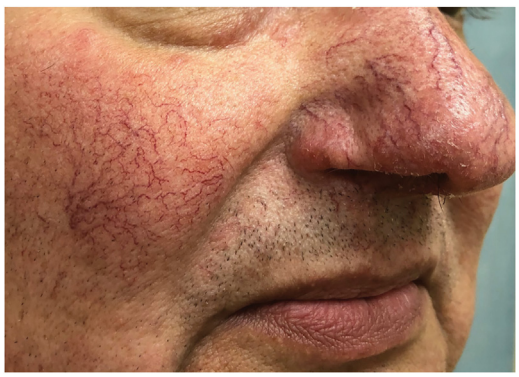

Fig. 9. Angiolupoid sarcoidosis in a White patient. Prominent telangiectasis is present within inflammatory papules and plaques.

Cutaneous Sarcoidosis in Children

Sarcoidosis is very uncommon in pediatric patients. When it does present in children, those aged 9 to 15 years are more commonly infected. Blau syndrome is an early onset form of sarcoidosis due to *NOD2* mutation and usually presents with a triad of CS (which may be the initial presentation), uveitis, and arthritis (see **Table 1**).[37] Sarcoidosis is very rare in children, and cutaneous granulomatous inflammation in this population should raise concern for alternate diagnoses such as immunodeficiency syndromes.[38,39]

Histopathological Features

When CS is suspected, punch biopsy of the cutaneous lesions is generally recommended so the dermis and subcutaneous fat are sampled. Deep sampling is especially important if subcutaneous sarcoidosis is suspected.[40]

The hallmark of sarcoidosis is the presence of noncaseating granulomas that are composed of tightly aggregated epithelioid histiocytes (macrophages) (**Fig. 11**). In the skin, the associated lymphocytic infiltrate may be sparse, and the term "naked granulomas" has been used to describe the histology of sarcoidosis in the skin for this reason.[41,42] Multinucleated giant cells may or may

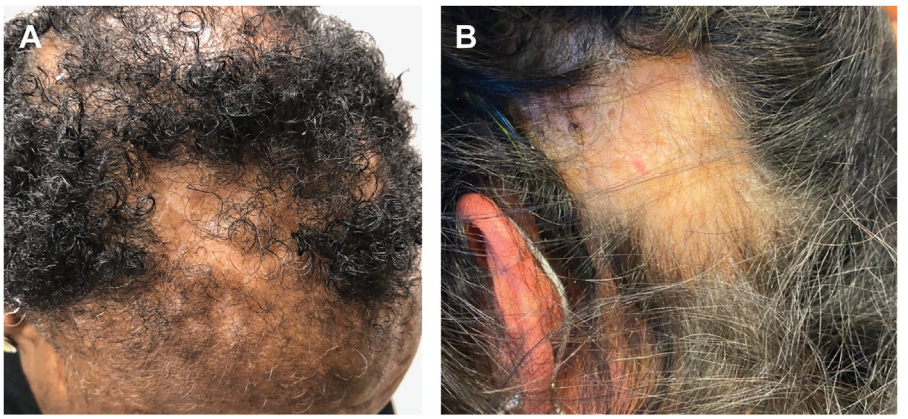

Fig. 10. (*A*) Multifocal plaques of cicatricial alopecia in a Black patient with extensive CS. (*B*) Large solitary plaque of cicatricial alopecia in a White patient with CS; biopsy showed sarcoid granulomas.

not be present, and in some cases, they are prominent. Schaumann bodies and asteroid bodies are also commonly described histologic phenomena; however, they are neither specific to sarcoidosis nor required to make the histologic diagnosis (see **Table 1**).

Even with a typical histologic appearance, establishing a diagnosis of sarcoidosis still requires clinicopathologic correlation. Other causes that can lead to granulomatous inflammation histologically should be considered and excluded: these include foreign body reactions (evaluate for polarizable foreign material) and infection (stain for microorganisms and possibly biopsy for sterile tissue culture depending on the clinical presentation). Polarizable foreign material has been described in 22% to 77% of CS biopsies and does not necessarily preclude a diagnosis of CS.[42] Clinical correlation is also required as granulomatous inflammation may also be seen in the setting of immunodeficiencies (including Rubella granulomas as may occur in patients with common variable immunodeficiency), paraneoplastic syndromes, and with immunostimulatory medications including recombinant interferon alpha and cancer immunotherapies such anti-CTLA-4 and anti-PD1/PD-L1.

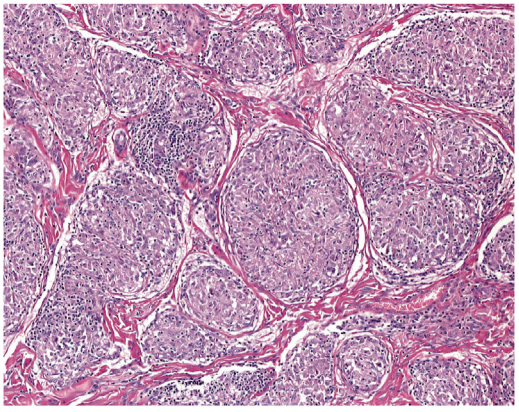

Fig. 11. Hematoxylin and eosin-stained section of CS. Larger pale cells (macrophages) form tight spheroid aggregates (granulomas) in the dermis. Smaller darker cells (lymphocytes) are present but relatively sparse. (Jean Bolognia, Julie Schaffer, Lorenzo Cerroni. Dermatology 2 volume set. Edition 4; Figure 93.6a. Elsevier 2017.)

Molecular Pathogenesis of Cutaneous Sarcoidosis

The pathogenesis of CS (and sarcoidosis in general) is not completely understood. Broadly, inflammation in sarcoidosis is thought to result from a complex interplay among factors including environmental and/or infectious antigens, nonorganic material from the environment, genetics, and the immune system. Possible infectious triggers that have been proposed include *Cutibacterium acnes* (formerly *Propionibacterium acnes*) *and Mycobacterium* spp.[43] Pesticides, herbicides, bioaerosols, beryllium, aluminum, zirconium, agricultural agents, and other environmental agents have also been implicated.[44] The role of genetics is reinforced by observations such as monozygotic twins of patients with sarcoidosis having an 80-fold increased risk of developing sarcoidosis.[45] Genome-wide susceptibility studies have also identified new susceptibility loci.[46–48]

A truly infectious nature to sarcoidosis has largely been disproven and patients improve with immunosuppression. Although CS may rarely respond to treatment with oral antibiotics (see later discussion), most patients do not respond. Antibiotics are also generally not used to treat patients with extracutaneous sarcoidosis and so the true role, if any, of *C. acnes* in sarcoidosis pathogenesis remains unclear. In terms of *Mycobacteria*, an active role for viable organisms also seems unlikely given the negative

results of the CLEAR trial,[49] where patients with pulmonary sarcoidosis were treated with a potent antimycobacterial regimen. Interestingly, CD4+ T cells from patients with Lofgren's sarcoidosis were recently shown to recognize an *Aspergillus nidulans* epitope.[50] The broader implications of this compelling finding, particularly in chronic presentations of sarcoidosis, are not yet clear.

Multiple lines of evidence support that granuloma formation in sarcoidosis is a T cell-dependent process. This includes (1) the observation that genetic variation at major histocompatibility complex (MHC) class II loci is associated with sarcoidosis[51,52]; (2) the observation that *BTNL2*, a B7 receptor family protein involved in T cell receptor signaling (probably acting as a costimulatory molecule) also exhibits genetic variation in sarcoidosis[53,54]; (3) the observed expansion of CD4+ T cell subclones in sarcoidosis, including in CS[55]; and (4) the observation that sarcoidosis can be unmasked or triggered by T cell-stimulating cancer immunotherapies.[56,57]

The infiltrate in sarcoidosis is CD4+ T cell predominant. The exact signals used by CD4+ T cells to recruit monocytes to the skin and promote macrophage activation and granuloma formation are not fully understood. Pulmonary sarcoidosis has been most intensively studied from a molecular standpoint and is characterized by a prominent Th1 polarization, with a possible Th17 precursor and/or hybrid phenotype with concomitant interleukin (IL)-17 production (so-called Th17.1 phenotype).[58] Th2 polarization has also been identified in some studies of pulmonary sarcoidosis and may be more prominent in cases with fibrotic changes.[59]

In 2011, Judson and coworkers evaluated gene expression in 15 cases of CS compared with normal skin from healthy controls.[60] They found that lesional sarcoidosis was characterized by marked upregulation of interferon (IFN)-γ, IL-12, and tumor necrosis factor (TNF). These signals are typical of a Th1 polarized response and make immunologic sense given the importance of these signals in productive granuloma formation such as that which occurs in the setting of true mycobacterial infection. Notably, they did not find significant IL-17 expression.[60] Whether this represents a true biologic difference from pulmonary sarcoidosis or instead reflects differences in methodology is not yet clear.

In 2018, our group showed constitutive activation of the Janus kinase (JAK)-signal transducer and activation of transcription (STAT) pathway in a study evaluating 21 biopsy cases of CS.[61] This finding is highly consistent with persistent IFN-γ signaling. This is also similar to the Judson and colleagues findings in CS, as well as findings in other organ systems of sarcoidosis.[62–65] Using single-cell RNA sequencing (scRNA-seq) and bulk RNA sequencing in CS, our group again found similar signals that centered on activation of Th1 immunity with CD4+ T cell-derived IFN-γ appearing to drive classical macrophage activation. GM-CSF, which has proinflammatory effects on myeloid cells in the tissue, was also upregulated by lesional T cells. IL-12 from dendritic cells seemed to reinforce this inflammatory signal. IL-6 and IL-15 derived from stromal cells may also reinforce the inflammatory milieu.

A recent study by Krausgruber and colleagues that used scRNA-seq as well as spatial transcriptomics in CS similarly identified CD4+ T cells producing IFN-γ and GM-CSF as prominent molecular features in this disease.[66] We have integrated these molecular findings into a working model of CS pathogenesis (**Fig. 12**).

Treatment

Prednisone and corticotropin gel are the only US Food and Drug Administration (FDA)-approved therapies for (pulmonary) sarcoidosis. There are no FDA-approved therapies for CS, or sarcoidosis in other organs. In patients with other organ involvement, collaboration among specialists is necessary for selecting the optimal treatment regimen. A European Respiratory Society (ERS) task force recently developed updated clinical practice guidelines for the treatment of sarcoidosis using GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methods.[67] Prednisone remains the recommended first-line therapy for extracutaneous sarcoidosis. The ERS guidelines have a conditional recommendation for consideration of the use of prednisone for patients with active CS not controlled by local treatment (see further discussion below). However, as stated in the guidelines, the recommendation remains conditional due to very low quality of evidence; there are no randomized trials in this area and recurrence on treatment discontinuation is common. Dermatologists may tend to avoid the use of systemic steroids for the treatment of CS due to the often-chronic nature of the disease and the myriad possible adverse effects of steroids, although in some patients, it may still be an option.

A ladder-like approach is often described for the treatment of patients with CS. However, in clinical practice, in cases for which topical or localized therapy is unlikely to be sufficiently effective, systemic therapy or systemic therapy in combination with topical/localized therapy may be selected as first-line therapy (see **Table 4**).

For localized or minimally bothersome CS, topical therapies may be appropriate. Mid-to-ultra potent topical steroids are commonly used in this

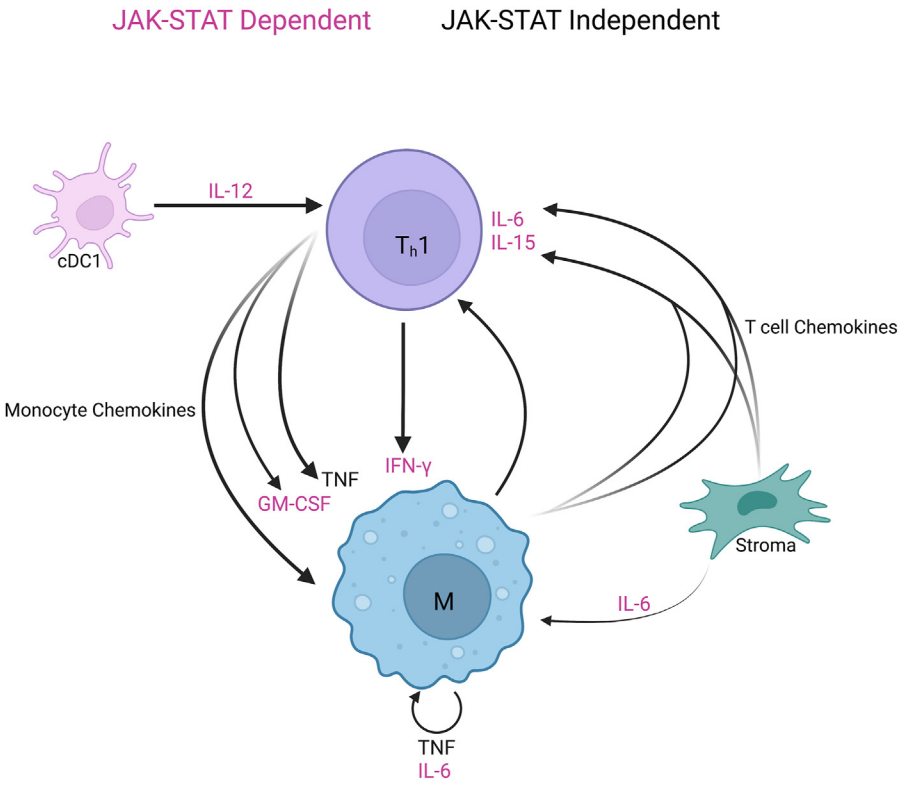

Fig. 12. An overview of the molecular pathogenesis in CS. Th1 polarized CD4+ production of IFN-γ is a pathogenic hallmark of the disease. IL-12 production by classically activated dendritic cells (cDC1) reinforces T cell activation. CD4+ T cells also overproduce GM-CSF, which contributes to the inflammatory activation of macrophages. TNF is produced by both T cells and macrophages and along with IL-6 and IL-15 production from stromal cells maintains an inflammatory milieu supporting granuloma persistence.

setting.[57–60] Although steroids may be effective, problematic local side effects include hypopigmentation, atrophy, and striae. Topical calcineurin inhibitors, which do not have these side effects, may be used; however, the evidence for this approach in CS is limited to case reports,[68–70] and real-world experience suggests the results are often suboptimal. There is anecdotal evidence that topical JAK inhibition may be helpful in some cases.[28,71] Topical medications for subcutaneous sarcoidosis are not generally effective.

Another option for patients with localized involvement is an intralesional injection of steroids (typically triamcinolone suspension at a concentration of 5–10 mg/mL). Intralesional injections deliver the steroid directly to the dermis and/or subcutis and may be very effective in some settings.[60] However, frequent clinic visits for injection may be required and may limit compliance (or ability to comply) with therapy. Adverse effects including hypopigmentation and atrophy are still common with this approach.[61,72,73] Hypopigmentation from steroids may be particularly bothersome in patients with darker skin tones.

There is some evidence for the use of physical approaches. However, these approaches have not been rigorously studied, generally work much better for patients with lighter skin tones, require frequent treatments, and may not be covered by insurance or readily available for many patients. Nonetheless, the use of photodynamic therapy, ultraviolet A light therapy, pulsed-dye laser (PDL), and CO_2 laser have been reported.[74–76] PDL in particular can be effective for telangiectasias in patients with angiolupoid presentations.

For patients with more widespread and/or refractory CS, those who had been treated with systemic glucocorticoids and have continued active CS, other immunomodulatory medications may be used (and often combined with topical or localized approaches). Antibiotics are a commonly used first-line therapy by dermatologists to treat CS. Although there is some evidence that tetracycline antibiotics may be useful,[77,78] in our experience they are often ineffective, and we generally do not pursue this line of therapy in most patients. Antibiotics are generally not used for the management of extracutaneous sarcoidosis.

Other common systemic therapies used by dermatologists for the treatment of CS are antimalarials, including chloroquine (250–500 mg daily) and more commonly hydroxychloroquine (200–400 mg daily). Most of the data for chloroquine is from studies performed in the 1960s, which do include prospective, randomized trials. The consensus from these studies was that CS seemed to respond better to chloroquine than did pulmonary sarcoidosis.[72] Some of the best data for hydroxychloroquine in CS largely comes from a 1990 case series of 17 patients.[79]

Methotrexate and thalidomide/lenalidomide are used for their immunomodulatory effects in sarcoidosis and may be effective in some patients[74,80]; however, a randomized placebo-controlled trial of thalidomide 100 mg daily for 3 months failed to demonstrate efficacy.[81] Neuropathy may limit the duration of therapy with thalidomide/lenalidomide. Methotrexate is commonly used as a steroid-sparing agent in patients with pulmonary involvement who require chronic prednisone therapy.[73,80]

TNF-α inhibitors are also commonly used to treat CS. The ERS guidelines recommend infliximab for patients with CS who have been treated with glucocorticoids and/or other immunosuppressive regimens that have ongoing activity, although this is a conditional recommendation supported by very low quality of evidence. In a double-blind trial by Judson and colleagues, of patients treated with infliximab, there was a promising but not statistically significant trend toward improvement in cutaneous involvement with treatment.[82,83] In a small prospective, randomized study of patients with CS treated with adalimumab 40 mg weekly, 4 of 10 treated patients had clearance or marked improvement in their CS after 12 weeks of therapy.[84] In a retrospective study by Heidelberger and colleagues, of 46 patients treated with various TNF inhibitors, 28.3% had complete skin clearance, whereas another 39% had a partial cutaneous response.[85] Trials with etanercept in sarcoidosis have been disappointing, and this agent should not be used for sarcoidosis.

It is important to consider that in some individuals, sarcoidosis including CS, may develop in the setting of TNF inhibition for another diagnosis. The exact reasons(s) for this phenomenon are not entirely clear but may involve paradoxic immune activation by the TNF inhibitors.[86] TNF inhibitors are also typically avoided in patients with a history of heart failure, which may include patients with advanced pulmonary and/or cardiac sarcoidosis.

One of the newest developments in CS involves the use of JAK inhibitors. JAK inhibitors can simultaneously block the activity of multiple cytokines. In our open-label trial published in 2022, 10 patients with long-standing CS were treated with tofacitinib 5 mg daily for 6 months. All 10 patients had improvement in their cutaneous disease with an average reduction in cutaneous disease activity of 82.7%, with 6 patients experiencing a complete response.[87] Disease control with a tofacitinib-based regimen was superior to the baseline immunotherapeutic regimens in all 10 patients, most of whom were also able to taper or completely discontinue prednisone due to the improvement they had during this 6-month study. Improvement in internal organ inflammation was also seen in a majority of patients with tofacitinib therapy.[87] The central mechanism of action of tofacitinib seems to be suppression of IFN-γ signaling (signals via JAK1/2-STAT1).[87] Inhibition of GM-CSF, IL-6, IL-12, and IL-15 activity by tofacitinib was also apparent and may also contribute to the response. Similar success with JAK inhibitors has been described in case reports and small series.[88] Additional investigation into this approach will be underway soon.

SUMMARY

Sarcoidosis is a multiorgan granulomatous disease with recognizable cutaneous manifestations. Although progress has been made in our understanding of CS, priorities moving forward include expanding our understanding of the QoL influences in sarcoidosis—especially in patients with darker skin tones, further uncovering the molecular pathogenesis of CS and how it relates to other involved organs and developing and evaluating effective and safe therapeutics for CS using rigorous clinical methods.

CLINICS CARE POINTS

- Evaluation of skin for cutaneous sarcoidosis may aide in diagnosis of patients with suspect systemic sarcoidosis.
- Patients with limited skin sarcoidosis (eg, tattoo sarcoidosis) need screening and ongoing evaluation for systemic disease.
- Cutaneous sarcoidosis may have a significant quality of life impact and treatment decision making should take this into account.

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