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Sarcoidosis: A great imitator

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Abstract Sarcoidosis is a chronic multisystemic, inflammatory disease with specific granulomatous cutaneous lesions. The cutaneous form may be considered a "great imitator," due to its extensive clinical morphology that occurs in upwards of 20% to 35% of patients. Cutaneous lesions may have a variety of presentations including papules, plaques, nodules, infiltrative scars, annular, angiolupoid, psoriasiform, hypopigmented, atrophic, ulcerative lesions, scarring and nonscarring alopecia, erythroderma, and ichthyosiform lesions. The dermatopathology is generally the same for all of the clinical presentations; however, variations in the cutaneous findings cause confusion in following a clinical course, therapeutic approach, or prognosis.

Introduction

Sarcoidosis may be defined as an inflammatory, granulomatous chronic disorder that may affect multiple organs.[1] Sir Jonathan Hutchinson (1828-1913) provided the initial description of his patient Mrs. Mortimer (ie, Mortimer maladay) in 1875. Later, Caesar Boeck (1845-1917) presented his own patient to the 3rd International Congress of Dermatology in London in 1896. He considered the entity, "sarcoid," noting the similarity of the lesions to sarcoma and to Hutchinson's patient.[2]

The onset of sarcoidosis shows a bimodal age distribution, peaking in the 30s and again in the 50s age group.[3,4] The disease is quite prevalent in the Scandinavian countries, where the incidence in Sweden is 64 per 100,000. In the United States, African-Americans have an incidence of 35 to 64 per 100,000,[5,6] whereas white patients have an incidence of 10 to 14 per 100,000.[5] The condition is much less prevalent elsewhere, for example, Spain and Japan each have an incidence of 1.4 per 100,000.[7]

The etiology of sarcoidosis has never been confirmed. The notion that pine trees somehow played a role has been disproven. It most likely represents a complex polygenic immune response in genetically predisposed people augmented by appropriate environmental exposure.[8,9] The immunologic response begins with the recognition and phagocytosis of an unknown antigen from an antigen-presenting cell to CD4+ T cells that produces acellular immune response. The granulomatous inflammatory process is characterized by helper T cell type 1 (Th1)-associated cytokines (including interleukin-12 [IL-12], interferon gamma [IFN-γ], IL-15, and IL-18) and molecules regarding chronic granulomatous inflammation (including angiotensin-converting enzyme, tumor necrosis factor alpha [TNF-α], and macrophage inflammatory protein).[10–13] Cutaneous delayed-type hypersensitivity is depressed, along with an increased Th1 immune response. There are also indications of B-cell hyperactivity.[14]

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Clinical features

Sarcoidosis is a multisystemic disease, with cutaneous involvement in 20% to 35% of patients. Although the lungs are most often afflicted, the skin is the second system to be involved, either independent of other organs or along with several other organ systems, thus earning the term of "a great imitator."[15–18]

Whereas cutaneous sarcoidosis can be suspected by its various clinical presentations, the histopathologic findings may be confirmatory; however, there are two distinct observations: noncaseating granulomas–specific and a reactive process–nonspecific.[18–20] Adding to the mix is the fact that noncaseating granulomas can be found in a variety of clinical presentations. The clinical diagnosis may be helped by the use of diascopy, which shows the "apple jelly" color in which pressure induces blanching,[1,21] and dermatoscopy, which reveals translucent yellow to orange globules parts and structureless whitish areas with linear vessels.[1,18,22]

Specific skin lesions and differential diagnosis

Cutaneous sarcoidosis has a variety of presentations ranging from the more specific papules, plaques, nodules, infiltrative scars, and lupus pernio to the less distinctive, including Darier-Roussy disease, annular, angiolupoid, psoriasiform, hypopigmented, atrophic, ulcerative lesions, scarring and nonscarring alopecia, erythroderma, and ichthyosiform lesions.[4] Table 1 shows the differential diagnosis of cutaneous sarcoidosis.

Papular and maculopapular lesions

Papular lesions are the most common specific skin lesions in sarcoidosis, but they often imitate several diseases.[18] These are discrete, 0.1 to 1 cm lesions and are usually observed on the face, eyelids, and nasolabial folds. They decompose with no scarring.[17] The color of all sarcoidal lesions can change from red, brownish-red, and brown to violet. This form is more common in patients with acute disease (Figures 1-4).[23] Acute organ involvement, like the sudden onset of lymphadenopathy, acute arthritis, acute uveitis, and parotid gland enlargement has been connected with the maculopapular eruptions. Without scarring and any treatment, papular sarcoidosis usually resolves within years and is sometimes related to less severe systemic manifestations.[21]

The differential diagnosis may include lichen planus, xanthelasma, xanthomas, syringoma, lupus erythematous, adenoma sebaceum, acne, granulomatous rosacea, lupus miliaris disseminatum faciei, trichoepithelioma, perifollicular fibroma, foreign body reaction, and secondary syphilis.[17,21]

Table 1 Differential diagnosis of specific sarcoidal lesions[15,17,21,26,29]

Papular sarcoidosis	Lichen planus, xanthelasma, xanthomas, syringoma, lupus erythematous, adenoma sebaceum, acne, granulomatous rosacea, lupus miliaris disseminatum faciei, trichoepithelioma, perifolicular fibroma, foreign body reaction, secondary syphilis
Plaque sarcoidosis	Psoriasis, lupus vulgaris, necrobiosis lipoidica, morphea, leishmaniasis, lichen planus, discoid lupus erythematosus, leprosy, granuloma annulare, nummular dermatitis, cutaneous T-cell lymphoma, erythema gyratum, Kaposi sarcoma, secondary or tertiary syphilis
Verrucous sarcoidosis	Keratoacanthoma, squamous cell carcinoma, deep fungal infection, cutaneous Crohn disease, foreign body granulomatous reactions, tuberculosis, leishmaniasis
Angiolupoid sarcoidosis	Plaque sarcoidosis, basal cell carcinoma, rosacea
Lupus pernio	Chilblain pernio, Jessner lymphocytic infiltration, pseudolymphoma, lupus vulgaris, chilblain lupus
Nodular sarcoidosis	Foreign body reactions, granuloma annulare, rheumatoid nodules, lymphocytoma cutis, lipoma, cyst, pseudolymphoma, cutaneous metastasis, dermatofibrosarcoma, reticulohistiocytosis, atypical mycobacterial infections
Darier-Roussy sarcoid	Subcutaneous granuloma annulare, erythema nodosum, foreign body granulomas, lupus panniculitis, lymphomas, lipomas, cysts, other panniculitides
Sarcoidal scar	Hypertrophic scars or keloids, lupus erythematosus, squamous cell carcinoma
Atrophic sarcoidosis	Localized scleroderma, mycosis fungoides
Ulcerative sarcoidosis	Necrobiosis lipoidica, lipodermatosclerosis, squamous cell carcinoma, basal cell carcinoma
Hypopigmented	Mycosis fungoides, leprosy, pityriasis alba, pityriasis lichenoides chronica, tinea versicolor, vitiligo, postinflammatory hypopigmentation, idiopathic guttate hypomelanosis
Sarcoidosis of the scalp	Seborrheic dermatitis, alopecia areata, cicatricial alopecia (discoid lupus erythematosus, lichen planopilaris, pseudopelade of Brocq, necrobiosis lipoidica, morphea, alopecia due to metastatic disease)
Mucosal	*Oral:* Orofacial granulomatosis, Crohn disease, bacterial or fungal infection, Melkerssohn-Rosenthal syndrome, foreign body granuloma, granulomatous cheilitis, malignancy *Genital:* Tuberculosis, Crohn disease, foreign body granuloma, anogenital granulomatosis, malignancy

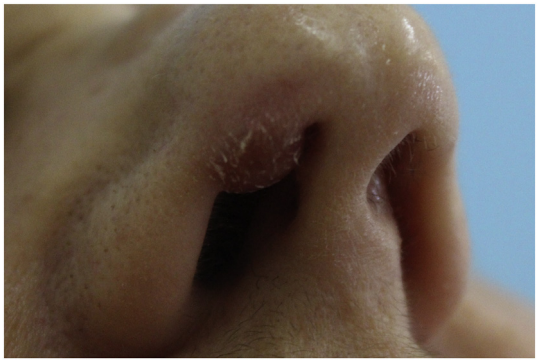

Fig. 1 Smooth, erythematous or violaceous papules involving the nose.

Plaques

Plaque sarcoidosis frequently exists with round, oval, or annular, discrete plaques which are flesh-colored, erythematous, or red-brown. The extensor surface of the extremities, buttocks, face, and back are included in the frequent sites of involvement (Figures 5-7).[17,24] The plaques are indurated and often heal with permanent scarring or pigmentary changes.[19,20] Plaque sarcoidosis is usually related to chronic systemic diseases, such as pulmonary disease, uveitis, and lymphadenopathy.[17]

Many other cutaneous disorders share some clinical features with plaque sarcoidosis, and they may be considered in the differential diagnosis. This could even include the large telangiectatic vessels or thick scaling that can imitate psoriasis. When there is central atrophy and scaling, plaques on the face can mimic discoid lupus.[22] The other examples of disorders, resembling plaque sarcoidosis, are shown in Table 1.[17,22,24–26] Less common types of plaque sarcoidosis are verrucous sarcoidosis, angiolupoid sarcoidosis, and psoriasiform sarcoidosis.

Verrucous sarcoidosis

Verrucous sarcoidosis can be easily misdiagnosed, if a biopsy is not taken appropriately, because it is a very rare cutaneous manifestation of sarcoidosis.[27] Marked verrucous

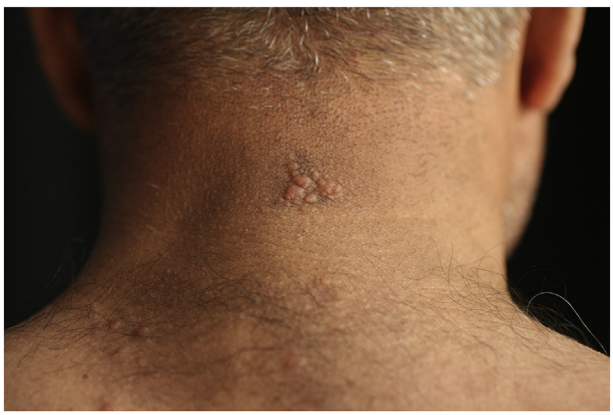

Fig. 2 Skin-colored, sarcoidal papule-like fibroma on the neck.

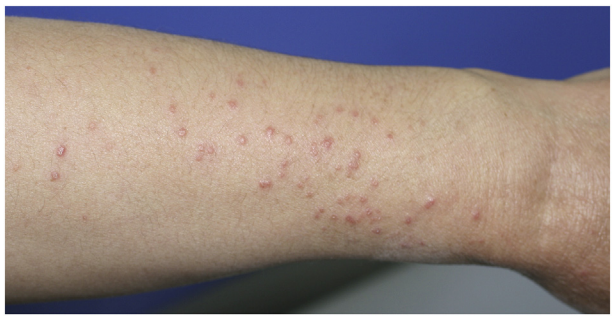

Fig. 3 Erythematous small papules involving the arm.

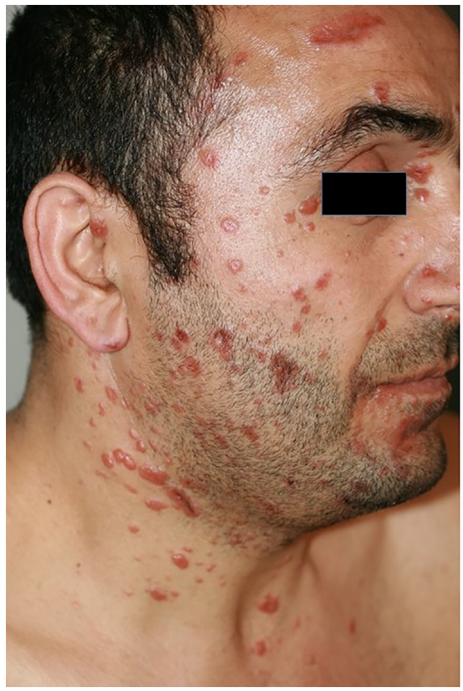

Fig. 4 Multiple, erythematous, typical sarcoidal papules on the face.

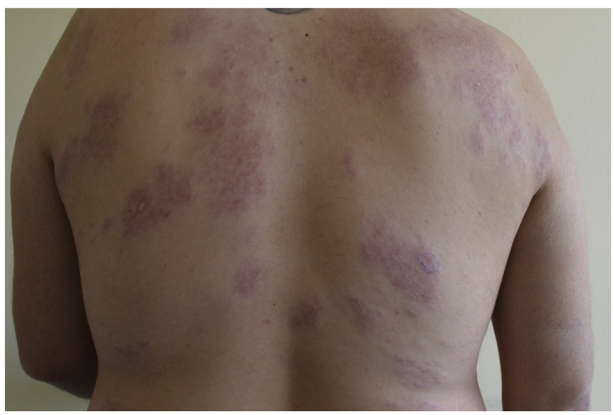

Fig. 5 Erythematous or violaceous, infiltrated plaques on the back.

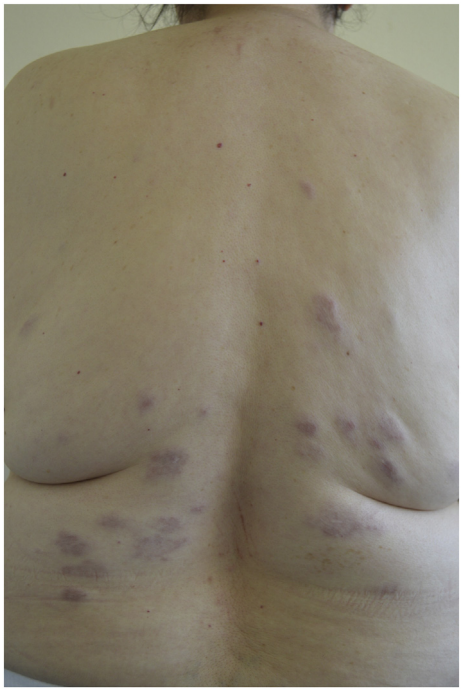

Fig. 6 Sarcoidal plaques on the back.

epidermal hyperplasia with dermal involvement by both typical noncaseating sarcoid granulomas is observed in the histology of these cases. According to Shaffer and Beerman, the verrucous epidermal response altered extremely as a skin reaction to insistent rubbing and scratching which explains hypertrophic localized neurodermatitis.[28] A long-standing systemic disease is usually observed in the patients.

The differential diagnosis includes squamous cell carcinoma on a long-standing lesion especially if the patient had received a long-term immunosuppressant.[28] Other diseases to be distinguished are keratoacanthoma, deep fungal infections, cutaneous Crohn disease, foreign body granulomatous reactions, tuberculosis, and leishmaniasis.[27,28]

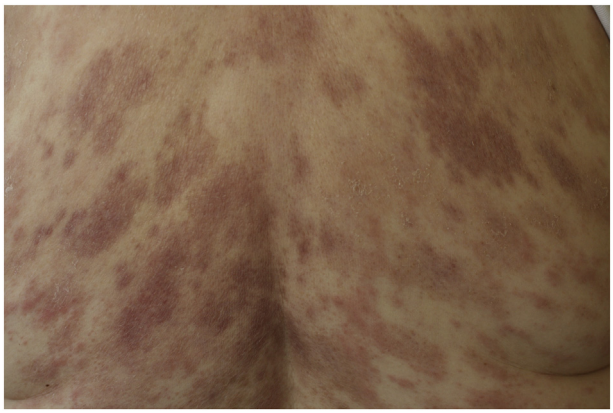

Fig. 7 Generalized erythematous macules and plaques on the back.

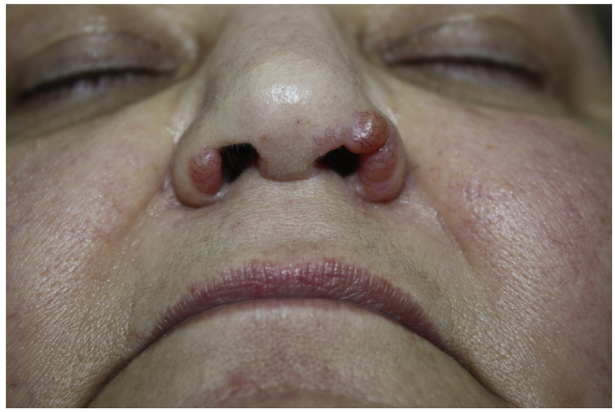

Fig. 8 Angiolupoid sarcoidosis on the nose.

Angiolupoid sarcoidosis (Brocq-Pautrier angiolupoid)

Angiolupoid sarcoidosis is uncommon and appears as one or a few erythematous to violaceous hemispheric papulonodular lesions with telangiectasia, commonly on either side of the nasal bridge close to the inner canthus (Figure 8).[19]

There are different opinions about angiolupoid sarcoidosis, where plaque sarcoidosis may be the subtype of large telangiectasias or lupus pernio. Some authors suggest that this telangiectatic formation is induced by high-potency topical steroid use on the regular plaques.[17,29]

The differential diagnosis for angiolupoid sarcoidosis includes plaque sarcoidosis, basal cell carcinoma, and rosacea.

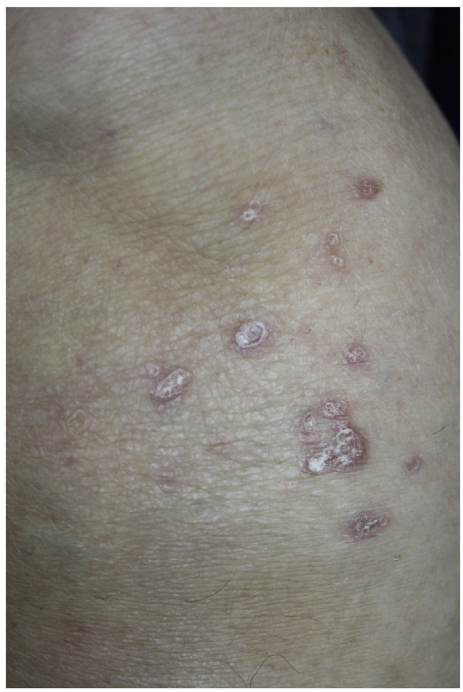

Fig. 9 Psoriasiform plaques on the legs.

Psoriasiform sarcoidosis

Psoriasiform lesions of sarcoidosis are a rare cutaneous manifestation of sarcoidosis. Only 0.9% of patients with sarcoidosis develop this form of the disease, and the majority of these cases have been reported in dark-skinned patients.[10] The plaques may mimic psoriasis, but these resolve with scarring, hypopigmentation, or atrophy (Figure 9).[29]

Psoriasis may occur also in patients with sarcoidosis; yet, the concurrent occurrence is seldom reported in the literature. The coexpression of TNF-α in both entities is a possible explanation for the psoriasiform expression of sarcoidosis.[10,30] Another hypothesis involves the idea of sarcoidosis developing as a Koebner phenomenon on existing psoriasis rather than cutaneous sarcoidosis which clinically presents as psoriasis.[1,8]

Lupus pernio

Papulonodular and plaques characterize lupus pernio that primarily involves areas affected by cold, such as the nose, ears, and cheeks (Figures 10 and 11). Lupus pernio disproportionally affects African-Americans and women.[29,31] The lesions consistently infiltrate and indurate without treatment, and in the end, they erode the underlying cartilage and bone, resulting in massive destruction and disfigurement.[5,29]

There is an increased risk of chronic diseases for patients with lupus pernio that lasts more than 2 years.[17] Even a small papule in this area might be associated with granulomatous infiltration of the nasal mucosa and upper respiratory tract, resulting in masses, ulcerations, or even life-threatening airway obstruction.[22,32] Lupus pernio can rarely occur on the dorsal hands, fingers, and toes, and may be associated with bone cysts, dystrophic nails, and lytic bone lesions.[17] The lesions on the hands can be confused with chilblain pernio. The eruption often does not respond to aggressive systemic treatment.[17]

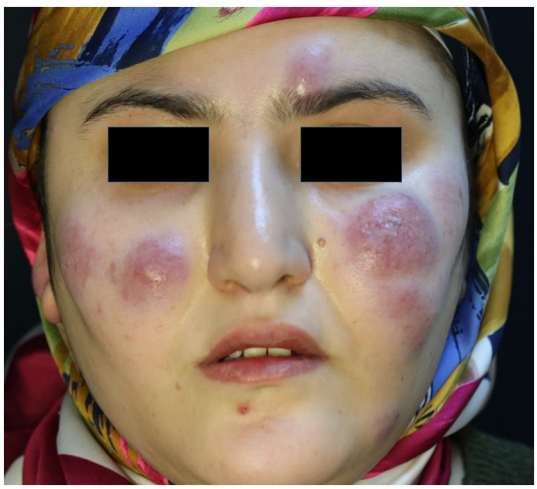

Fig. 10 Violaceous, erythematous papulonodular lesions on the face.

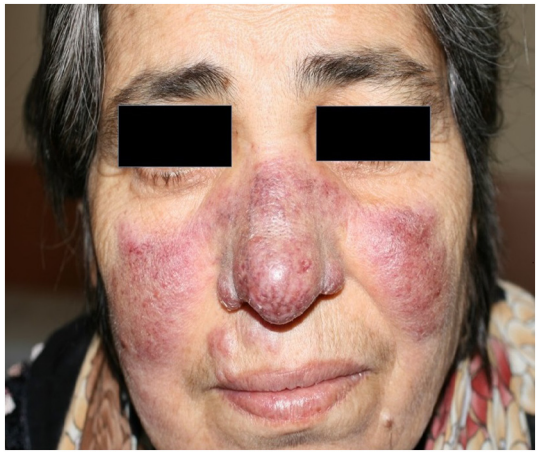

Fig. 11 Lupus pernio with violaceous, infiltrated plaque on the cheeks and nose.

Plaques on the arms, thighs, and buttocks, and sausage-shaped expansion of the phalanges may develop in some cases.[33] Mutilating sarcoidosis is a severe form of lupus pernio, with large centrofacial tumors, extending into the oral and upper respiratory tissue and resembling Wegener granulomatosis and malignant pleomorphic lymphoma.[26,34]

Not all sarcoidosis lesions on the nose are lupus pernio.[32] The infiltrative, chilblainlike form of lupus pernio should not be confused with papular, papulonodular, or nodular sarcoidosis lesions that might include the nose and cheeks, being usually not as destructive and responding better to treatment.[17]

Nodules

The development of sarcoidal granulomas in the dermis or subcutaneous tissue are related to long-standing systemic sarcoidosis.[17,25,35] They can create diagnostic challenges, as foreign body reactions, granuloma annulare, rheumatoid nodules, lymphocytoma cutis, pseudolymphoma, and even cutaneous metastasis may have similar clinical appearances.[17,29]

Subcutaneous sarcoidosis

The terms “subcutaneous sarcoidosis” and “Darier-Roussy sarcoidosis” are used to describe nodular sarcoidosis which primarily involves the subcutaneous tissue. Subcutaneous sarcoidosis exists as single to multiple, asymptomatic to mildly tender, erythematous, flesh-colored, violaceous, or hyperpigmented nodules. Lesions on the forearms usually form a linear distribution, and they even coalesce to form bands (Figure 12).[29,36,37] The skin above the nodules is unchanged. Spontaneous remissions have been seen, and sometimes the subcutaneous form is the first sign of the systemic presentation of the disease. The diagnosis should be reached only after excluding other more

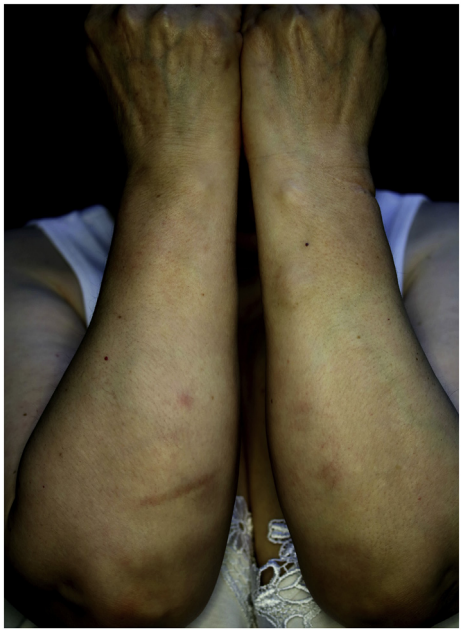

Fig. 12 Skin-colored, subcutaneous nodules on the arms.

common diseases with similar clinical manifestations, for example, subcutaneous granuloma annulare, foreign body granulomas, lupus panniculitis, lymphomas, benign tumor lesions like lipomas, cysts, and panniculitis.[29,36]

Erythema nodosum is a possibility in sarcoidosis patients with nodular lesions, especially if the nodules are on the legs. Opposed to erythema nodosum, the nodules of subcutaneous sarcoidosis predominate on the arms, and they are only mildly tender. A biopsy may be helpful to distinguish these diagnoses.[29,36]

Infiltrative scars

Scar sarcoidosis may appear on a tattoo, incision, or even a lesion of discoid lupus eythematosus.[22] The erythematosus or violaceous scar may indicate reactivation of the underlying sarcoidal process (Figures 13 and 14).[17,29]

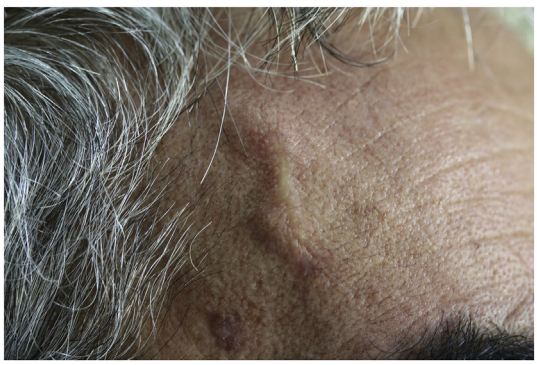

Fig. 13 Sarcoidosis infiltration of an old scar on the forehead.

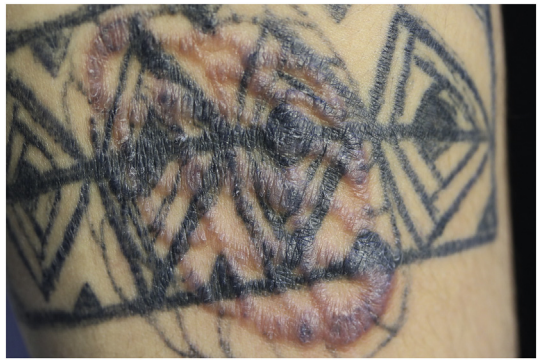

Fig. 14 Tattoo sarcoidosis.

Atrophic sarcoidosis

The atrophic type may be characterized by hypopigmentation, shiny areas, cigarette paper–type of central atrophy, and even a morpheaform presentation plaques (Figure 15).[17] The erythema and poikiloderma may mimic localized scleroderma or even mycosis fungoides (Figure 16). In African-American patients who are diabetic, necrobiosis lipoidica diabeticorum may also mimic this form of sarcoidosis.[24,29]

Ulcerative form of cutaneous sarcoidosis

Ulcerations may occur independent of other cutaneous lesions or due to a worsening of other lesions, such as atrophic or papulonodular ones. Such findings can be confused with

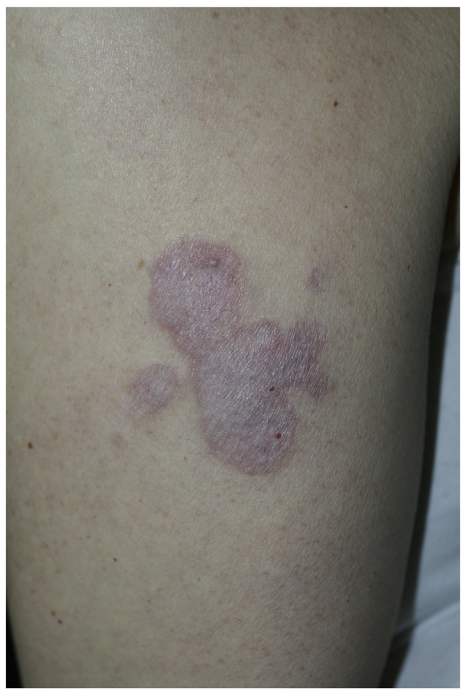

Fig. 15 Well defined, violaceous, atrophic plaques on the arm.

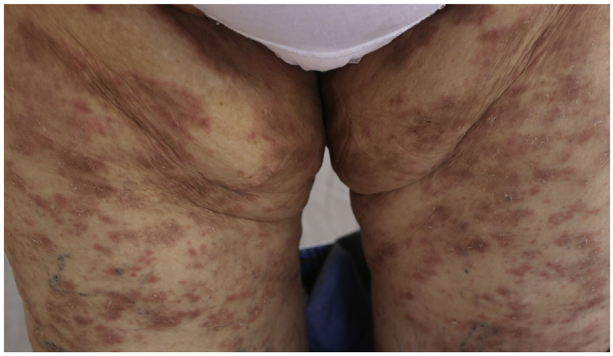

Fig. 16 Generalized, mycosis fungoides-like sarcoidosis.

necrobiosis lipoidica diabeticorum, statis dermatitis with ulceration, or even prurigo nodularis.[17,26,29,38]

Ichthyosiform sarcoidosis

This occurs infrequently on the legs, where there may be scaling that might be confused with xerosis or forms of ichthyiosis. The scale has a more central adherence, giving a "pasted on" appearance. In its extreme presentation, it may become ichthyosiform erythroderma.[26,39,40]

Hypopigmented sarcoidosis

Hypopigmented sarcoidosis, more noticeable in skin that is Fitzpatrick II to VI, may have round to oval plaques that are well-demarcated. Histologic examination may distinguish it from idiopathic guttate hypomelanosis, mycosisis fungoides, and even leprosy.[17]

Erythrodermic sarcoidosis

Erythrodermic sarcoidosis characteristically occurs with slightly infiltrated, erythematous to yellow-brown localized plaques, becoming confluent, and desquamation. Classic exfoliative erythroderma is usually more diffuse,[26,29] whereas ichthyosiform erythroderma would have more scales that are larger.[41] In contrast to generalized exfoliative erythroderma, erythrodermic sarcoid lesions are localized. According to reports, Sézary syndrome has epithelioid granulomas that look like sarcoidosis on a skin biopsy specimen. This condition should be ignored before making a decision on the diagnosis of erythrodermic sarcoidosis.[42]

Scalp sarcoidosis

The involvement of the scalp is uncommon, and it is mostly seen on African-American women.[21] The lesions on the scalp may appear as either localized atrophic, annular, or indurated plaques or as flesh-colored or erythematous nodules. Seborrheic dermatitislike erythematous scaly plaques and alopecia areatalike macular lesions can be considered with early lesions of sarcoidosis.[21,26,32] Local destruction and scarring of the hair follicles may lead to permanent alopecia development, if there is a progression of scalp disease. This condition is often indistinguishable from pseudopelade of Brocq.[29] Sarcoidosis can resemble other causes of scarring alopecia, particularly discoid lupus erythematosus, lichen planopilaris, necrobiosis lipoidica, morphea, or alopecia neoplastica.[21,43] With atrophic or annular scarring alopecia, scalp involvement of sarcoidosis becomes a sign of an underlying systemic disease, and it portends a poor response to therapy.[43]

Mucosal sarcoidosis

Mucosal lesions of sarcoidosis, such as papules, papulonodules, edema, ulcers, gingivitis, gingival hyperplasia, localized swelling, or gingival recession, are rarely reported in the literature. The most common presentation includes localized swelling or nodules.[21,29] The majority of patients with oral sarcoidosis also have visceral lesions (Figure 17).[44] The diagnosis of oral sarcoidosis depends on the clinical presentation on the skin. Orofacial granulomatosis, Crohn disease, infections, Melkerssohn-Rosenthal syndrome, foreign body granulomas, and granulomatous cheilitis must be considered as granulomatous oral disorders.[21] Orofacial granulomatosis is characterized by persistent or recurrent orofacial soft tissue swellings and oral ulceration in the absence of systemic disease. Lymphoedema and the presence of multiple noncaseating giant cell granulomata are the pathologic features of the disease that resemble sarcoidosis.[45]

Genitourinary tract involvement in either women and men is uncommon. Infiltrated plaques on the vulva and perianal region may resemble tuberculosis, Crohn disease, and foreign body granulomas. Masses can be seen in any part of the genitourinary tract, and resemble tumors or abscess formation.[46,47]

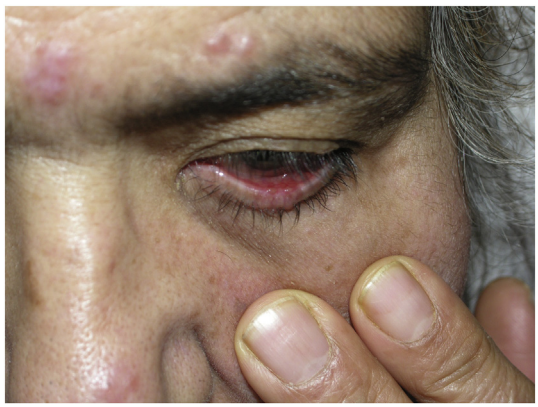

Fig. 17 Sarcoidal papules on the eyelid.

Similarly, anogenital granulomatosis is a rare chronic inflammatory disorder of unknown etiology that resembles sarcoidosis clinically and histopathologically.[48]

Nail sarcoidosis

Although nail dystrophy can develop with sarcoidosis, there are a number of nonspecific findings that can include nail thickening, longitudinal ridging, discoloration, splinter hemorrhages, onychorrhexis, onycholysis, pterygium, subungual hyperkeratosis, lamellar splitting, clubbing, nail pitting, cracking, and brittleness.[49,50] Progressive polycystic osteitis, involving soft finger and toe tissues (Perthese-Jüngling disease), can cause similar nail dystrophy (Figure 18).[26] Bulbous swelling of the fingertips, "drumstick dactylitis," and subsequent distortion of the nails are associated with lupus pernio.[26] When nail sarcoidosis is suspected, radiologic study is indicated to reveal possible boney cysts and pulmonary involvement.[50,51]

Rare variants

The literature is replete with a number of rare forms: perforating, erythema multiformelike, leonine facies, pustular folliculitis, pityriasis rosealike, annular, lichenoid, photodistributed, lympedematous, polymorphous, and palmoplantar erythema.[8,21,26] Whether they can be considered with current diagnostic tools to be variants of sarcoidosis is open to conjecture. For example, photodistributed sarcoidosis is no longer accepted as a common form of sunlight-induced papular sarcoidosis. Negative phototesting of such patients would rule out polymorphous light eruption and lupus erythematosus.[52] A polymorphous variant of sarcoidosis includes different types of lesions, specific and nonspecific, existing in the same patient generally with multisystem disease involvement.[53]

Nonspecific lesions of sarcoidosis

Erythema nodosum, erythema multiforme, prurigo, and calcinosis cutis are the recognized nonspecific lesions of cutaneous sarcoidosis.[15] Erythema nodosum is the most widespread nonspecific cutaneous lesion of sarcoidosis; the others are seen very rarely in patients with sarcoidosis.

Erythema nodosum

Erythema nodosum can occur with sarcoidosis, although it is more likely to be a hypersensitivity reaction to several likely stimuli, such as medications, infections, and inflammatory diseases. Erythema nodosum may be characterized as highly tender, subcutaneous erythematous nodules, usually on the anterior tibia. Histopathologic examination of erythema nodosum will exhibit panniculitis with septal inflammation.[22]

Löfgren syndrome is an acute clinical form of sarcoidosis that is first described by Sven Löfgren (1910-1978) as a constellation of acute onset erythema nodosum, bilateral hilar lymphadenopathy, fever, and migratory polyarthritis, without granulomatous skin involvement (Figure 19). The situation

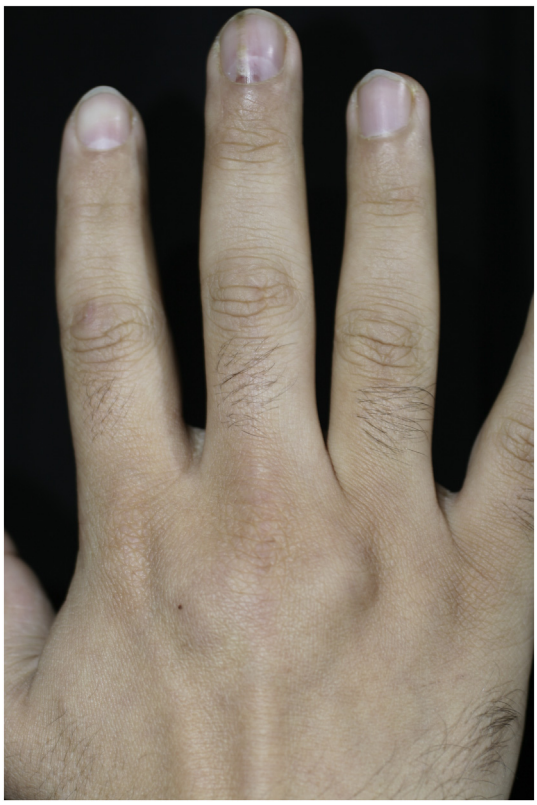

Fig. 18 Nail sarcoidosis (Pertes-Jugling sign).

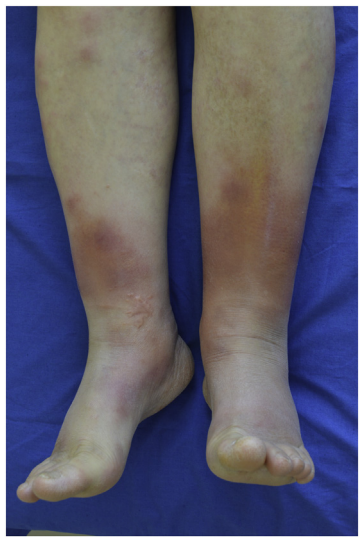

Fig. 19 Löfgren syndrome with erythema nodosum.

can suddenly commence, appearing with systemic clinical manifestations like fever, malaise, and polyarthralgias. A small but significant number of patients (6.4%) present only with ankle swelling without erythema nodosum, which is considered a variant of Löfgren syndrome.[54] This syndrome has some differences in terms of treatment, prognosis, and recurrence compared with sarcoidosis, and it portends a favorable prognosis.[55] The differential diagnosis is broad, including atypical mycobacterial and fungal infections, drug-induced serum sickness, lymphoma, reactive arthritis, crystalline arthritis, and vasculitis.[56]

Ethnicities and sarcoidosis

Sarcoidosis is seen more often in African-Americans than in other races. Some rare variants are seen more in darker skin patients, such as ulcerative, hypopigmented macules, plaques, erythrodermic, and ichthyosiform changes.[57] Lupus pernio is a destructive skin finding which is seen most commonly in pigmented patients, and plaques can create a hypopigmented surface.[58] It can appear at an earlier age in skin of patients of color. The prognosis is worse in African-Americans, who have more extrathoracic disease, especially advanced pulmonary involvement, chronic uveitis, liver involvement, and cystic bone lesions.[8]

Nonspecific erythema nodosum is a sign of good prognosis of the skin finding that is observed more often in whites or Asians. Also, subcutaneous nodules are rarely seen in African-American patients, where the incidence of cardiac disease and death is much lower than in Japanese patients.[59]

African-American women with sarcoidosis have a more chronic and severe disease than other populations, and death rates may be higher. Compared with white patients, the long-term prognosis is poorer with the rate of relapses being higher in African-Americans.[8] In addition, the diagnosis is often not confirmed in African-American patients until sarcoidosis has reached an advanced stage of cutaneous or systemic involvement.[8]

Sarcoidosis: As a systemic disease

Sarcoidosis may affect any organs or systems, so all organs must be included in the medical history and physical examination.[17] The lungs (90%), lymph nodes (90%), eyes (40%), and skin (25%) are the most frequently affected organs. The others are the liver, kidney, parotid gland, bones, joints, heart, and the central nervous system.[15,60,61] Table 2 shows extracutaneous manifestations for patients with sarcoidosis.

Constitutional clinical manifestations of fever, fatigue, and weight loss can be observed in one-third of patients. Ocular involvement, with uveitis, conjunctivitis, optic neuropathy, and lacrimal gland enlargement, can be seen in about 20% to 30% of individuals; yet, there are series with up to 80% of patients having eye disease.[62]

Sarcoidosis causes no significant manifestations of internal organs. This may be related to the fact that the granulomatous inflammation of sarcoidosis is often found in the interstitial parts of various tissues.[63]

Pulmonary involvement is seen in the majority of patients (more than 90%), and its severity ranges from asymptomatic involvement of mediastinal lymph nodes to progressive pulmonary fibrosis and treatment-insensitive chronic respiratory failure.[3,64]

Bilateral hilar adenopathy is the most frequent diagnostic radiographic finding.[8] It may be difficult to diagnose, because it may mimic many other diseases, such as lymphoproliferative disorders and granulomatous infections, and because no specific test for diagnosis is available depending on the relationship of clinical, radiographic, and histopathologic features.[65]

Hepatic involvement in sarcoidosis might be more widespread, whereas sarcoidosis in the liver shows clinically related manifestations in about 10% of patients. It can be present with asymptomatic elevations in serum alkaline phosphatase and serum aminotransferase levels, and a cholestatic picture with pruritus, jaundice, portal hypertension, and potentially liver failure.[66] Cardiac involvement may cause palpitations, heart block, and sudden death, and might be underrecognized and more common than studies have shown.[67] The gastrointestinal tract, sinuses, musculoskeletal (arthritis, arthralgias), hematologic (lymphopenia or hypergammaglobulinemia), endocrinologic (pituitary involvement, Heerfordt syndrome), and renal (hypercalcemia, hypercalciuria, or nephrolithiasis) systems are the other probable organ systems.[15,60]

Up to 25% of patients with sarcoidosis may include the central nervous system, but as few as 10% of patients have the clinical manifestations. Cranial nerve or peripheral nerve palsies, meningitis, neuropsychiatric clinical manifestations, seizures, or neuroendocrine dysfunction most frequently characterize neurosarcoidosis.[68,69]

A variety of other presentations of bone and bone marrow sarcoidosis can cause major diagnostic issues, especially unifocal or multifocal osteolytic and sclerotic forms of the disease. The articular manifestations of sarcoidosis are hard to differentiate from the other inflammatory and degenerative arthropathies.[69,70]

Diagnosis

As sarcoidosis may have varied presentations and include multiple systems, no simple single diagnostic test can be done. There are various diseases that mimic sarcoidosis lesions clinically and histopathologically, so it is not only difficult for the clinician evaluating the patient but also the dermatopathologist evaluating the histologic specimen.[27] In addition, exact diagnosis requires the clinical presentation, pathologic confirmation of noncaseating granulomas, supportive laboratory and radiologic evidence of multiorgan disease, and exclusion of

Table 2 Extracutaneous manifestations of organ involvement in patients of sarcoidosis[22,23]

Organ involvement	Findings
Pulmonary	Bilateral hilar lymphadenopathy
	Mediastinal lymphadenopathy
	Parenchymal infiltrate (especially in the upper lobes)
	Pneumothorax
	Cor pulmonale
	Mycetomas
	Respiratory failure
	Pulmonary hypertension
	Pulmonary fibrosis
Ocular	Uveitis (anterior, intermediate, or posterior)
	Keratoconjunctivitis sicca
	Adnexal (eyelid or conjunctival) granulomas
	Retinal vasculitis
	Retinal periphlebitis
	Vitreous opacities
	Multiple chorioretinal peripheral lesions
	Nodular or segmental periphlebitis
	Optic disc nodules or granulomas
	Solitary choroidal nodule
	Optic neuropathy
Upper respiratory tract disease	*Laryngeal sarcoid:* Supraglottis, subglottis
	Nasal and sinus sarcoid: Rhinosinusitis, nasal obstruction, epistaxis and nasal polyposis, mucosal hypertrophy
Exocrine glands	Painless swelling of the salivary and parotid glands
	Xerostomia
	Keratoconjunctivitis sicca
Cardiovascular	Heart block and arrhythmias
	Ventricular tachycardia
	Heart failure
	Valvular dysfunction
	Simulated infarction,
	Pericardial disease
	Pulmonary hypertension
	Cor pulmonale
	Sudden death
Lymphadenopathy	Hilar or paratracheal mediastinal adenopathy
	Peripheral lymphadenopathy
	Intraabdominal lymphadenopathy
Liver	Liver function test abnormalities
	Hepatomegaly
Spleen	Splenomegaly
	Splenic nodule
	Hypersplenism
Musculoskeletal system	Acute polyarthritis
	Chronic arthritis with periosteal bone resorption
	Diffuse granulomatous myositis
Neurologic system	Cranial neuropathy
	Parancimal lesions
	Cognitive manifestations
	Peripheral neuropathy
	Myopathy
	Meningeal disease
Renal	Nephrocalcinosis
	Nephrolithiasis
	Hypercalciuria
	Chronic renal failure

(*continued on next page*)

Table 2 (*continued*)

Organ involvement	Findings
	End-stage renal disease
	Interstitial nephritis
	Glomerulonephritis
	Membranous nephropathy
	Hypertension
Endocrine	Anterior pituitary involvement
	Thyroid infiltration
Genitourinary tract	Endometrium, ovary, and uterine fibroids
	Testicular involvement

other possible diseases, and, moreover, some diagnostic tools are required for diagnosis. Diagnosis that is generally made by skin biopsy is more convenient than a lymph node biopsy or lung biopsy.[4,27]

Diascopy

It is said that the lesions have an "apple jelly" color upon diascopy in which pressure induces blanching. This method is considered to press out the vascular and inflammatory erythema of sarcoidosis that show epitheloid granulomas.[21] Although it is not a specific finding, apple jelly appearance is a clue for the other granulomatous lesions such as tuberculosis, granulomatous rosacea, lupus miliaris disseminatus faciei, leprosy, and granulomatous periorificial dermatitis.[1,21]

Dermatoscopy

For melanocytic lesions, dermatoscopy is very practical, but for granulomatous diseases, it can provide only supportive findings. Translucent yellow to orange globule parts and structureless whitish areas with linear vessels are dermatoscopically monitored in sarcoidosis and in other granulomatous diseases, and still, no specific pattern observed.[1,18]

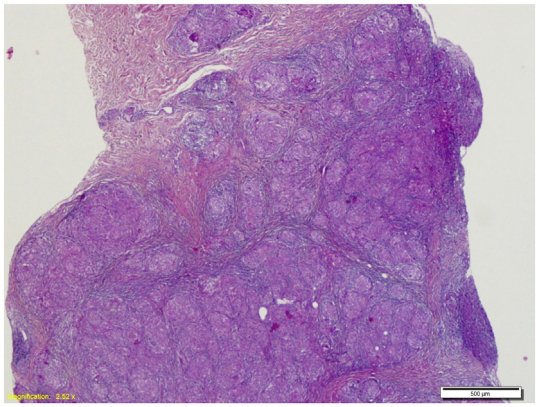

Fig. 20 Hematoxlyin and eosin stain, (4 × magnification). Multiple granulomas in the dermis which similar size.

Histopathology

Superficially shaved biopsies should be avoided, because the key pathologic alterations are frequently within the dermis or even within the subcutaneous tissue, so it is necessary to obtain a sample by punch biopsy from lesions.[4] Naked or sarcoidal noncaseating granulomas are seen on histopathologic examination of the specific sarcoidosis lesions (Figures 20 and 21).[19] The most common infiltrating pattern is an extensive superficial and deep perivascular infiltrate of the dermis.[19]

Biopsy specimens of completely macular lesions may not reveal granulomas as readily as biopsy specimens from other cutaneous forms of sarcoidosis. Repeated biopsies may be required to confirm the diagnosis in such suspicious cases. Multinucleated giant cells are commonly found among the epithelioid cells within the granuloma follicle, and they usually have cytoplasmic inclusions, such as asteroid bodies, Schaumann bodies, and birefringent crystalline particles (calcium oxalate and other calcium salts). Small amounts of central fibrinoid necrosis may be seen, but large amounts of necrosis suggest an alternate diagnosis or necrotizing sarcoid granulomatosis.[71]

Other atypical presentations made within sarcoidosis lesions, including the presence of necrosis, foreign material, periadnexal and interstitial distribution of granulomas, coexis-

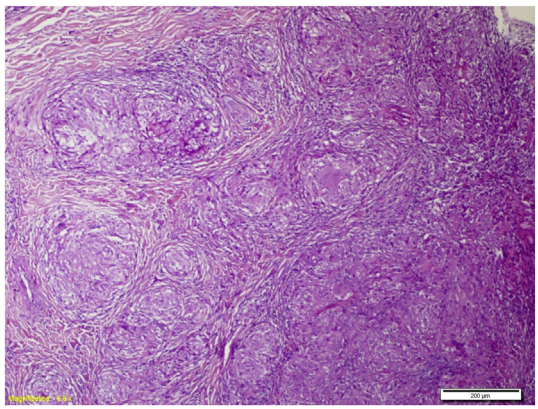

Fig. 21 Hematoxylin and eosin stain, (10 × magnification). Noncaseating granulomas with multiple epitheloid histiocytes and rare Langhans-type giant cells. There are small amounts of lymphocytes surrounding the granulomas.

tence of lichenoid and granulomatous infiltrate, granulomatous vasculitis, and epidermal changes.[72]

Noncaseating granulomas are not specific for sarcoidosis and are observed in response to infectious agents, tuberculoid leprosy, cutaneous Crohn disease, orofacial granulomatous beryllium granulomas, foreign material, immunodeficiency disorders, lymphoproliferative disorders, and drug eruptions.[27,29,73,74] The pathologic differential diagnosis of sarcoidosis would include tuberculosis, atypical mycobacteriosis, fungal infection, foreign body reaction, beryllium, zirconium, tattooing, rheumatoid nodules, leishmaniasis, and Melkersson-Rosenthal syndrome.[1,75]

Laboratory findings

A baseline workup for systemic sarcoidosis should contain a full history and physical examination, baseline laboratory testing (calcium, renal function, hepatic function, complete blood count, serum angiotensin-converting enzyme level), chest radiography and pulmonary function testing, electrocardiography, tuberculin skin test or interferon gamma release assay for latent tuberculosis, and fundoscopic and ophthalmologic evaluation.[22]

The findings that can be seen in laboratory tests are anemia, leukopenia, or lymphopenia, hypercalcemia (as a consequence of the dysregulated production of calcitriol by granulomas, and activated macrophages), elevated liver, and kidney function tests. A moderate elevation in the serum alkaline phosphatase concentration suggests diffuse granulomatous hepatic involvement.[69] The erythrocyte sedimentation rate and C-reactive protein are often elevated. Hypergammaglobulinemia, and there might be a positive rheumatoid factor, yet, not always obtained.[69] Chest X ray shows hilar and paratracheal adenopathy with predominantly upper lobe bilateral infiltrates in pulmonary involvement. Angiotensin-converting enzyme (ACE) serum levels are increased in 60% of patients with sarcoidosis, and thus serum ACE has been claimed a potential diagnostic test for sarcoidosis. Because ACE is produced by epithelioid cells in granulomas, the possibility that increased ACE serum levels in sarcoidosis correlate with the granuloma burden has been proposed. On the other hand, serum ACE cannot be fully used for diagnostic testing to ascertain disease activity due to poor sensitivity (false negative outcome) and insufficient specificity (almost a 10% rate of false positive results).[8,16,76]

Table 3 Recommended screening and advanced laboratory examination for suspected sarcoidosis patients[60,61,63,69]

	Initial screening	Advanced tests
Laboratory tests	Complete blood count Biochemical tests (creatinine, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, calcium) Urine analysis Serum angiotensin-converting enzyme level	24-hour urinary secretion of calcium
Pulmonary	Posteroanterior chest radiography *Pulmonary function testing:* Spirometry, diffusion capacity, total lung capacity	High-resolution computed tomography Bronchoalveolar lavage Fluorine-18-fluorodeoxyglucose-positron emission tomography Gallium-67, thallium-201, and technetium sestamibi single photon emission computed tomography
Cardiac	Electrocardiography	Echocardiography 24-hour Holter monitoring Positron emission tomographic Gadolinium-enhanced cardiac magnetic resonance imaging scans
Ophthalmologic	Fundoscopic and slit-lamp examination Visual acuity Tonometry	Fundus fluorescein angiography Optic coherence tomography
Specific test	Tuberculin skin test or interferon gamma release assay Antinuclear antibodies	Adenosine deaminase Serum amyloid A Soluble interleukin-2 receptor
Radiographic	Gallium-67 scan screen	*For specific involvement:* Laryngoscopy Bone radiography Abdominal computerized tomography Positron emission tomography scan Magnetic resonance imaging

A gallium-67 scan to monitor for lymphadenopathy, detect parotid and lacrimal gland involvement, and to evaluate for evidence of systemic involvement is necessary in addition to the previously mentioned tests.[19] Tuberculin skin test is generally anergic and is useful for distinguishing it from tuberculosis.

During the process of the disease, organs that are previously not involved might develop sarcoidosis, although affected organs can heal or get impaired. No established guidelines are currently available to monitor patients with the disease limited to the skin for the development of extracutaneous sarcoidosis. If new or worsening extracutaneous involvement is suspected on the grounds of clinical manifestations, there may be a need based on the physical examination, or laboratory abnormalities, to refer to an appropriate specialist for further evaluation and management.[16] Table 3 includes the laboratory tests used for initial screening and more advanced tests for special organ involvement.

Prognosis

The prognosis of patients that have cutaneous sarcoidosis depends on the extent of systemic involvement; however, the severity of the skin lesions does not indicate the extent of systemic involvement.[8]

Information on the prognosis and potential extracutaneous involvement can be obtained by the extent of the cutaneous manifestations. Ethnicity can change the lesional morphology frequency and systemic involvement can be related to different lesion types. Lupus pernio, scar sarcoidosis, and subcutaneous variants are mostly associated with lymphadenopathy. Systemic involvement, particularly eye involvement (67%), is more widespread in the angiolupoid variant.[19] Lupus pernio is associated with upper respiratory, lung, or nasal mucosa and possibly with bone cysts. Lupus pernio is associated with a more chronic, refractory course. Erythema nodosum typically accompanies a more acute course but a better prognosis.[8,26,77] A large multicenter study showed that Löfgren syndrome and the presence of mediastinal lymphadenopathy are clinical factors associated with a good prognosis, whereas advanced age, along with pulmonary and splenic involvement, are associated with poor outcomes.[16] Maculopapules and subcutaneous sarcoidosis are more frequently related to erythema nodosum and radiologic stage I, but they may portend a good prognosis. By contrast, plaque-type lesions and lupus pernio are usually associated with improved radiologic stages, recurrence of systemic sarcoidosis activity for >2 years, and the need for systemic corticosteroid therapy, thus giving a poorer prognosis.[23]

Treatment

Corticosteroids remain the treatment of choice for most patients as first-line therapy. Topical or intralesional steroids are used for localized involvement.[22] Patients who have progressive lesions, severely scarring sarcoid, lesions that are refractory to local treatment, or cutaneous and systemic involvement, may require systemic corticosteroids.[8]

Second-line therapy includes antimalarial therapy and cytotoxic agents, such as methotrexate, azathioprine, leflunomide, and mycophenolate.[26,78] Third-line therapy would be a biologic agent, with infliximab being the most studied drug in this class. Alternative therapies include thalidomide, isotretinoin, allopurinol, cyclosporine, and laser therapy. Newer treatments, such as repository corticotropin injections and rituximab, have also been noted as effective treatment.[79–82] Surgically removing inactive sarcoid scars may stimulate reactivation.[8]

Conclusions

Sarcoidosis is one of the great imitators with significant skin findings.

- Sarcoidosis is a multisystemic disease, and the role of the dermatologist is very substantial.
- Cutaneous findings are very important.
  - Eliminate the need for more invasive evaluation.
  - Eliminate the need for more invasive tissue biopsies.
  - Provide clues for discovering asymptomatic systemic findings, clinical course, and prognosis.
- The main diagnostic findings are histopatologically proven noncaseating granulomas. Several diseases may have similar findings, making exclusion of other granulomatous diseases crucial to the diagnosis of sarcoidosis.
- In countries where tuberculosis is common, the differentiation between tuberculosis and sarcoidosis may be difficult due to similar organ involvement and skin manifestations. The histopathology, lung findings, tuberculin skin test, and polymerase chain reaction analyses of the *Mycobacterium tuberculosis* genome may be helpful.
- Dermatologists have an important role in the multisystemic evaluation of patients in recognizing the cutaneous findings of this great imitator.

Acknowledgments

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