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Subcutaneous Sarcoid Nodules: A Dermatologic Presentation of Systemic Sarcoidosis for Primary Care Physicians

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ABSTRACT

Sarcoidosis is a multisystem granulomatous disease primarily characterized by pulmonary manifestations. Extrapulmonary involvement in sarcoidosis is well-documented and common, but isolated extrapulmonary involvement is rare in around 10% of cases at the time of diagnosis. Cutaneous presentations vary significantly, with erythema nodosum being the most common. Since extrapulmonary symptoms most likely suggest systemic involvement, any way to identify sarcoidosis early is paramount. We present a case of a 63-year-old Caucasian female with multiple palpable 0.5-3cm nodules under the skin of the bilateral forearms, left hand, and lower extremities. A lesion biopsy revealed numerous sarcoidal phenotype granulomas without necrosis surrounded by a mild lymphocytic infiltrate. Imaging confirmed calcified mediastinal, hilar, and sub-carinal lymph nodes, and revealed scattered calcified and non-calcified granulomas in the upper lung fields. Treatment is not always required, and this patient's subcutaneous nodules resolved with a single course of steroids. Therefore, primary care providers need to maintain a high index of suspicion for sarcoidosis with various dermatological findings, as it may be the presenting symptom for sarcoidosis and allow early recognition, monitoring, and intervention.

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INTRODUCTION

Sarcoidosis is a granulomatous disease of unknown etiology. It is characterized as an autoimmune entity resulting in non-infectious, non-caseating granulomas that frequently affect the lungs.[1] Though 90% of patients with systemic sarcoidosis present with pulmonary complications, extra-pulmonary involvement of the lymph nodes, skin, eyes, or joints is frequently associated with the disease.[2,3] Dermatologic manifestations of sarcoidosis at the time of diagnosis are relatively uncommon (11.8%-16%), with painful, lower-extremity erythema nodosum most frequently observed.[4]

Rarely, systemic sarcoidosis can manifest within the subcutaneous tissue as non-tender, granulomatous lesions characterized by palpable, mobile nodules on the upper extremities without dermal or epidermal modification.[5,6] While erythema nodosum is most common in Northern European patients, granulomatous skin manifestations can be seen in Black patients, who have a 3 times higher incidence of sarcoidosis in the United States.[7] The peak incidence of these subcutaneous sarcoid lesions is in the fourth or fifth decade of life and is more common in females, especially those with preexisting autoimmune disease.[8] In 1984, Vainsencher and Winkelmann described a specific subset of systemic sarcoidosis with subcutaneous, nodular lesions composed of noninfectious, epithelioid cell granulomas sparsely infiltrated with lymphocytes.[5,9,10] Further evaluation has consistently revealed a systemic component associated with these lesions, making them a specific cutaneous manifestation of systemic sarcoidosis.[11] Since isolated extra-pulmonary manifestation of sarcoidosis is rare (<10%), a clinical presentation of such lesions warrants suspicion of systemic

sarcoidosis.[2] This case presents such a patient with isolated subcutaneous sarcoidosis that with further evaluation led to a diagnosis of systemic sarcoidosis.

CASE PRESENTATION

A 63-year-old white female presented with a 3-month history of "lumps under the skin on my arms and legs." The patient reported the lesions were not painful but increased in both number and size. Her medical history was remarkable for type 2 diabetes with neuropathy, hypertension, moderate persistent asthma, depression, and a remote history of psoriasis. Her medications included: aspirin, biotin, calcium, gabapentin, metformin, hydrochlorothiazide, lansoprazole, losartan, hydrocodone/acetaminophen, pravastatin, albuterol, sertraline, budesonide/formoterol inhaled, trazodone, and tizanidine.

Upon exam, she was well dressed, nourished, and in no acute distress. Vitals were normal with a BMI of 26.8. Her exam was unremarkable except for palpable 0.5-3.0cm nodular lesions under the skin of both forearms and the left outer hand and scattered over the lower extremities with the greatest concentration around the thighs. These lesions were firm without erythema or tenderness. Imaging of the bilateral forearms and left hand with X-ray was unremarkable with no abnormalities found corresponding to the palpable areas. A 5mm punch biopsy was performed on the left wrist lesion revealing numerous sarcoidal phenotype granulomas without necrosis but surrounded by very mild lymphocytic infiltrate (Figure 1). No fungal or atypical mycobacterial microorganisms were detected by PAS-D and Fite stains.

The patient was referred to pulmonology for further workup for systemic sarcoidosis. A chest radiograph was completed showing calcified mediastinal lymph nodes suggestive of a chronic granulomatous process. A follow-up high-resolution computerized tomography (CT) revealed underlying interstitial disease and scattered calcified granulomas and non-calcified upper lung lobe nodules with confirmation of calcified mediastinal, hilar, and sub-carinal lymph nodes (Figure 2). Pulmonary function tests were completed indicating moderate obstructive

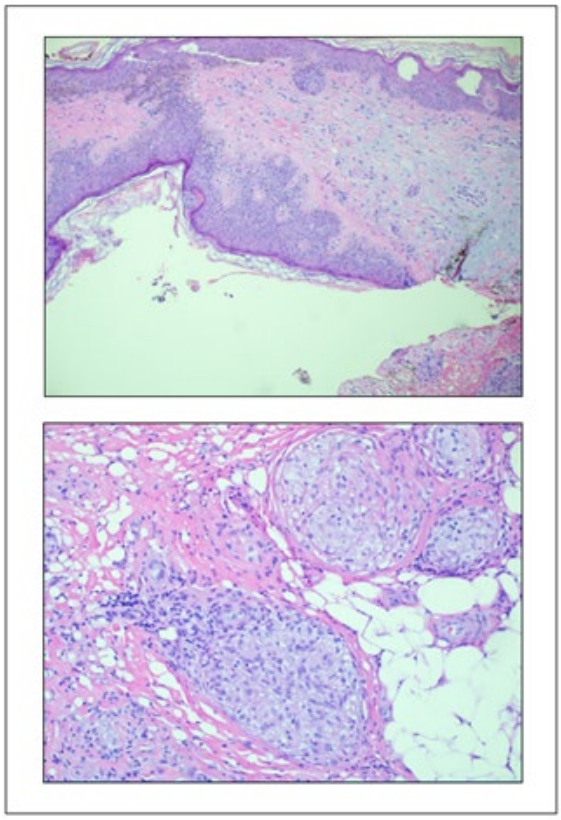

FIGURE 1. Histologic examination of biopsy adjacent to a cyst (top) and at 200x magnification (bottom).

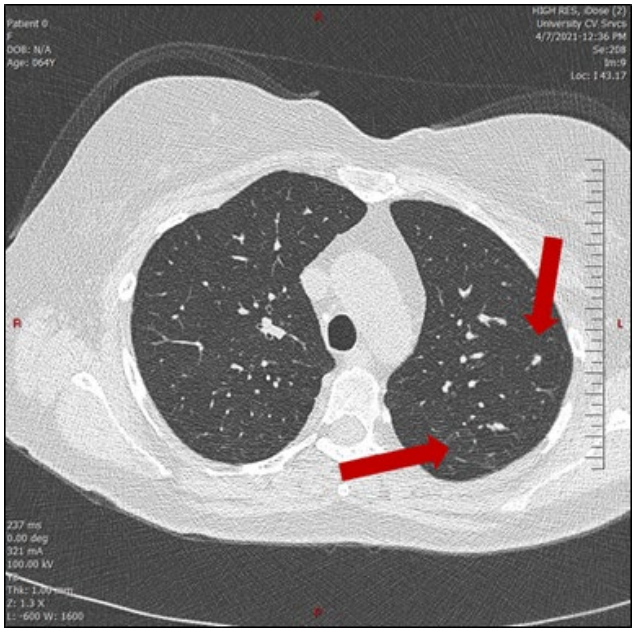

FIGURE 2. High-resolution computerized tomography showing underlying interstitial disease and scattered calcified granulomas and non-calcified upper lung nodules with confirmation of calcified mediastinal, hilar, and sub-carinal lymph nodes.

impairment with severe diffusion limitation. She had no lymphopenia or calcium abnormalities, and her angiotensin converting enzyme level (ACE) was normal at 41 (normal = 14-82). Further follow-up with the pulmonologist was delayed 6 months due to patient concern related to COVID and a month-long hospitalization for acute kidney injury secondary to acute interstitial nephritis, which was treated with steroids. She eventually returned to the clinic for follow-up, and her subcutaneous nodules had resolved.

DISCUSSION

The etymology of "sarcoid" is Greek meaning "flesh."[12] While 90% of sarcoidosis involves pulmonary tissue, nearly one-third of all manifestations of sarcoidosis are cutaneous. Cutaneous involvement of sarcoidosis can present clinically with great variability making the differential diagnosis wide (Table 1).[5,13] Papules are common with acute sarcoidosis, usually occurring on the face, but can appear anywhere on the skin. They usually resolve spontaneously over a couple of years without scarring.[13] Lower extremity lesions (Erythema Nodosum) and complaints of dyspnea should raise suspicion for Lofgren syndrome.[14] Plaques usually target the face, back, buttocks, and extensor surfaces and are associated with chronic sarcoidosis. These plaques, along with papular lesions, are the most common skin manifestations of sarcoidosis.[13] Lupus Pernio lesions are reddish-purple to violaceus-brown, shiny, and indurated plaques that occur in a malar distribution but extend inferiorly to the lips and laterally to the ears. Preferentially affecting the Black population, the scarring can lead to disfigurement and is associated with pulmonary fibrosis, chronic uveitis, and bone cysts.[13] Nodules in sarcoidosis are benign but are associated with chronic systemic disease and include a vast differential.[12] Subcutaneous lesions, also called Darier-Roussy disease, involve adipose tissue and result in single or multiple tender, indurated, skin-colored nodules or plaques leading to panniculitis. They are associated with bilateral hilar lymphadenopathy and non-severe systemic disease.[13] Scar sarcoidosis lesions are non-pruritic, non-painful granulomatous infiltrates arising from any dermatologic trauma (tattoos, piercings, surgical scars, herpes zoster lesions, etc.) and are seldom related to systemic complications.[13]

Differential Diagnosis for Cutaneous Manifestations of Sarcoidosis				
Papular Type Lesions	**Plaque Type Lesions**	**Lupus Pernio Type Lesions**	**Nodular Type Lesions**	**Subcutaneous Type Lesions**
Elevated solid lesion < 1cm in diameter	Elevated solid lesion > 1cm in diameter	Reddish purple to violaceus brown, shiny, indurated plaque	A circumscribed, elevated solid lesion with depth up to 2cm	Involvement of the adipose tissue directly inferior to the dermal layers
Examples				
Acne	2º or 3º Syphilis	Discoid Lupus Erythematous	Atypical Mycobacterial Infections	Cellulitis
Adenomas	Kaposi Sarcoma	Lupus Vulgaris	Cysts	Cutaneous Metastases
Granulomatous Rosacea	Leishmaniasis	Nasal NK/T-Cell Lymphoma	Dermatofibrosarcoma	Deep Mycoses
Sebaceum	Lichen Planus	Nodular Amyloidosis	Foreign Body Reactions	Epidermal Cysts
Xanthelasma	Lupus Erythematous	Nodular Rosacea	Lipomas	Foreign Body Granulomas
Xanthomas	Mycosis Fungoides	Paracoccidiomycosis	Nodular Lymphoma	Lipomas
	Nummular Eczema	Rhinoscleroma	Reticulohistiocytosis	Nodular Lymphoma
	Psoriasis	Superficial Wegner Granulomatosis	Rheumatoid Nodules	Tuberculosis

TABLE 1. Differential Diagnosis for Cutaneous Manifestations of Sarcoidosis with descriptions and examples (not in any order of prevalence).[5,13]

Pathophysiology

Sarcoid granulomas consist of giant cells fused from differentiated macrophages and CD4+ Helper T cells at the center with a surrounding mass of CD8+ and regulatory T cells, fibroblasts, and B cells. This mixture of cells suggests that the innate and adaptive immunity of the patient plays a role in the onset of the disease. The inflammatory granulomatous process that occurs in the progression of the disease is better understood than the causative event or antigen.[1]

Diagnosis

There is no single definitive test to confirm the diagnosis of sarcoidosis, but there are 3 required diagnostic criteria.[1,2] First, since pulmonary manifestations occur in about 90% of those affected with the disease, a chest x-ray followed by a CT scan is necessary to document and characterize bilateral hilar lymphadenopathy and parenchymal disease.[2,6] Second, a biopsy should be obtained to discover if a noncaseating granuloma is present on histopathological review. The biopsy should target the least invasive area of disease, which can include skin, subcutaneous nodules, parotid or lacrimal glands, eye, lymph node, or lung.[2] Third, the clinical manifestations must involve more than 1 organ and not be better defined by another disease process. Exclusion of other diseases is essential, as sarcoidal granuloma histology is not easily distinguishable from other noncaseating granulomas.[2] Adjunctive serological tests could aid the diagnosis but are not conclusive. For example, ACE levels are elevated only 60% of the time, and hypercalcemia or hypercalciuria are present in only 40% of cases or less.[2] Other beneficial serology include lymphopenia (decreased CD4 count), increased β-2 microglobulins, and increased lysozyme.[2] Lofgren's syndrome is particularly difficult to diagnose relative to general sarcoidosis. Defined as bilateral hilar lymphadenopathy with erythema nodosum and/or arthritis, it occurs in up to 34% of sarcoidosis cases, but this definition meets only 2 of 3 diagnostic criteria mentioned above.[2,6]

Treatment and Prognosis

The prognosis for those with sarcoidosis is generally positive.[2] Approximately two-thirds either have spontaneous recovery prior to treatment or following a single course of the first-line therapy of oral steroids. However, one-third suffer from chronic or relapsing sarcoidosis.[2] For this population, oral steroid use from 6 to 24 months was found to improve chest radiographic findings, forced vital capacity, and diffusing capacity of oxygen regardless of baseline disease severity.[15] Second-line treatment is needed if the disease progresses, or the patient is no longer able to tolerate the side effects of the steroids. This includes immunosuppressive agents such as methotrexate, azathioprine, mycophenolate mofetil, or leflunomide, with methotrexate being the drug of choice in this group. Again, if disease progression continues or drug toxicity becomes too great, third-line therapy, including anti-TNFα antagonists like infliximab and adalimumab, may become necessary.1 As every drug used in the treatment of sarcoidosis carries multiple side effects, shared decision-making with detailed goals for treatment is highly important for the success of therapy.

CONCLUSION

Dermatologic symptoms may be the initial presentation of systemic sarcoidosis. Therefore, to assist in early diagnosis and intervention, subcutaneous nodular lesions presenting on the extremities should be considered for biopsy and those found to display non-caseating granulomatous changes should trigger further evaluation for systemic sarcoidosis.

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