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Sarcoidosis with prominent necrosis on histopathology

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Abstract

Sarcoidosis is a multiorgan inflammatory disease with variable clinical presentations and the common histopathologic finding of noncaseating granulomas. The etiology of the disease is not known, but evidence suggests both environmental and genetic contributions to the pathogenesis. Depending on the severity of cutaneous disease and extent of extracutaneous involvement, therapies range from topical and intralesional glucocorticoids to systemic immunomodulatory and immunosuppressive agents. We present the case of a patient with cutaneous sarcoidosis with prominent necrosis on histopathologic examination in the setting of severe pulmonary sarcoidosis.

Case Presentation

PATIENT: 38-year-old man
DURATION: Ten years
DISTRIBUTION: Face, trunk, and extremities

HISTORY: A 38-year-old African-American man presented to the Dermatology Clinic at Bellevue Hospital Center in 2015 for the evaluation of widespread skin lesions that had been progressively worsening since 2006. A diagnosis of pulmonary sarcoidosis was made in 2005, and the patient was treated with courses of systemic glucocorticoids until 2012. The skin lesions initially developed over his elbows and legs and have progressively worsened with time. Intermittent pruritus is associated with the skin lesions. Prior courses of oral glucocorticoids promoted mild improvement of the skin lesions. Application of topical glucocorticoids did not produce appreciable change.

At the time of presentation, the patient denied fever, chills, and night sweats; however, he did report intermittent fever, chills, sweats, weight loss in the recent past. The patient also had a history of persistent coughing, the absence of hemoptysis, and dyspnea on exertion with an inability to walk more than one half of a block comfortably. The patient denied change in vision and joint pain aside from localized traumatic left knee pain.

In the Dermatology Clinic, topical glucocorticoids and calcineurin inhibitors were prescribed for the cutaneous lesions while the histopathologic and infectious evaluations of the skin lesions were

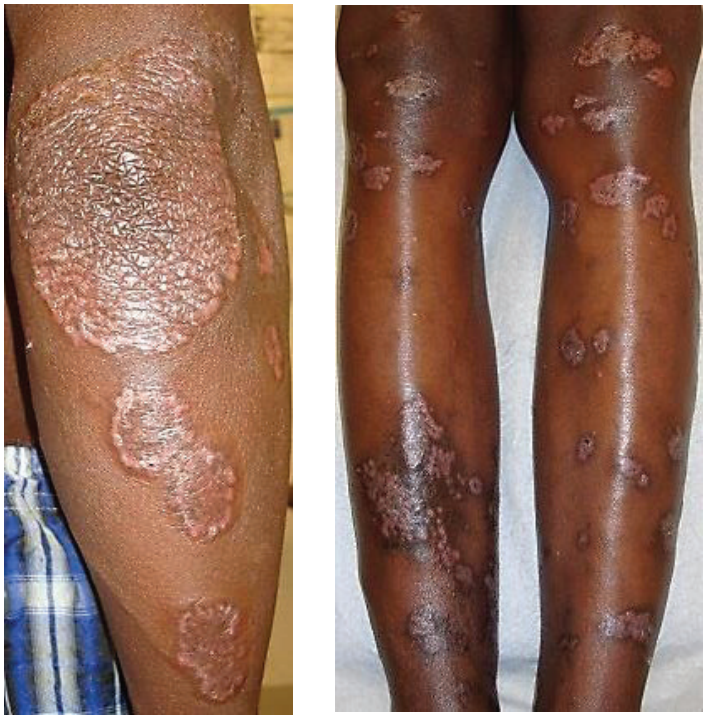

Figure 1. Hyperpigmented-erythematous papule coalescing into plaques on extensor aspect of arm (Left); Erythematous plaques, some with peripheral hyperpigmentation, on legs (Right).

ongoing. Prior to his dermatology visit, the patient had established care with the Pulmonary Clinic at Bellevue Hospital Center and imaging and laboratory studies were performed. He was lost to follow-up until February, 2016, when methotrexate 7.5 mg weekly was prescribed, and the prospect of lung transplantation, considering the severity of the lung disease, was discussed. Most recently, in the Dermatology Clinic, hydroxychloroquine 200 mg daily was prescribed. Upon ophthalmologic evaluation, no evidence of ocular disease was found.

PHYSICAL EXAMINATION: On the conchal bowls were erythematous patches with scale and on the forehead and periocular skin were erythematous, thin plaques. On the posterior aspect of the neck was a hyperpigmented, thin plaque. On the elbows and extensor aspects of the arms were hyperpigmented-erythematous papules that coalesced into plaques, some with an annular appearance with peripheral hypopigmentation. On the legs were erythematous plaques, some with peripheral hyperpigmentation, central scale, and crust (**Figure 1**). On the left chest tattoo were scattered papules. On the buttocks were hyperpigmented, indurated plaques. On the back, chest, and abdomen were a few, small, erythematous-hyperpigmented papules.

LABORATORY DATA: A complete blood count with differential analysis showed a normal white-cell count and hemoglobin of 11.5 g/dL. A basic metabolic panel and hepatic panel were normal. The angiotensin-converting enzyme level was 69 micrograms/liter (reference range 14- to-82). The antinuclear antibody level was elevated, with a titer of 1:160 and a homogeneous pattern. The glucose-6-phosphate-dehydrogenase level was normal. The anti-Ro and anti-La levels were negative. The quantiFERON-TB gold test was indeterminate, but acid-fast bacilli induced sputum cultures and the purified protein derivative tuberculosis test were negative. Tissue culture biopsies from the right forearm and right lower leg showed no evidence of bacterial, fungal, or acid-fast bacillus growth.

HISTOPATHOLOGY: Within the upper dermis, there is a nodular, granulomatous infiltrate with areas of central necrosis. There is slight, irregular, epidermal hyperplasia (**Figure 2**). No foreign material was identified under polarized microscopy. Acid fast bacilli and periodic-acid Schiff-diastase stains fail to show microorganisms.

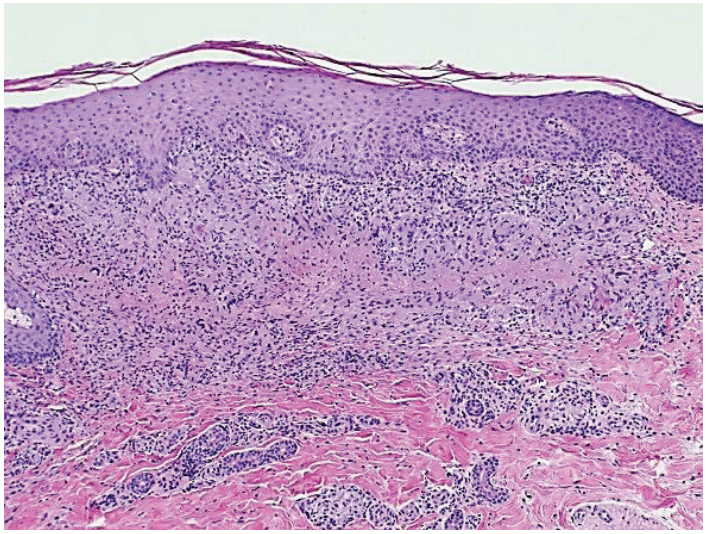

Figure 2. Nodular, granulomatous infiltrate with areas of central necrosis within the upper dermis. There is also slight, irregular, epidermal hyperplasia.

DIAGNOSIS: Sarcoidosis with prominent necrosis on histopathology

Discussion

Sarcoidosis is a multiorgan, inflammatory disease that is characterized by the histopathologic finding of noncaseating granulomas [1]. Sarcoidosis most often involves the lungs, lymph nodes, skin, eyes, with possible involvement of virtually all organ systems [1, 2]. Cutaneous lesions are present in 25 to 30% of patients, may be highly variable, and range from macules to nodules that may be tan-brown, violaceous, skin-colored, erythematous, or depigmented. There also are many classic clinical presentations, with tan-brown, waxy papules being the most common manifestation. Primary cutaneous sarcoidosis can occur in many described forms, which include scar sarcoidosis, violaceous mid-facial plaques of lupus pernio, or, less commonly, the Darier-Roussy subcutaneous nodules. Eruptions secondary to the associated systemic inflammatory response of sarcoidosis also may occur, for example erythema nodosum. These cutaneous presentations may help predict the disease course and prognosis [1, 3].

Sarcoidosis occurs most frequently in African-

Americans and northern Europeans, with a slightly increased prevalence in women. It typically presents in the third-to-fourth decades of life, but, in some populations, there is a bimodal distribution, with a second peak in women greater than 50 years old [4]. Specific disease presentations vary according to demographic group [1, 2].

Although traditionally defined as a disorder of unknown etiology [5], efforts have been made to identify triggers of the disease. As sarcoidosis is a granulomatous disease, there is a predominant theory that the inflammatory response is triggered by persistent antigen exposure [6]. The development of sarcoidosis has been associated with multiple environmental exposures, which include employment in the agricultural industry and exposure to microbial aerosols, among many others [4, 7]. Throughout its history, there has been much discussion regarding a microbial etiology and, most prominently, a mycobacterial etiology for sarcoidosis [5], but the data have not yet been definitive [6]. Familial associations, twin studies, HLA associations, and findings regarding common cytokine signaling pathway polymorphisms have suggested a genetic component to the disease and highlight the likely interplay between genetics and environmental triggers in the pathogenesis of the disease [2, 6].

A typical histopathological feature of sarcoidosis is the naked granuloma, which is a mass of epithelioid histiocytes without prominent infiltration of other inflammatory cells [8]. An atypical feature of our case is the extent of necrosis in the biopsy specimens, which may be suggestive of an infectious etiology. In our patient, tissue cultures for bacteria, mycobacteria, and fungi were negative. A study that assessed histopathologic variants in 31 biopsies of cutaneous sarcoidosis found necrosis in only 6% of cases; other atypical features included the extent and localization of inflammatory infiltrate, periadnexal distribution, interstitial distribution, presence of foreign material, and epidermal changes [8]. Another study assessed features of 28 cutaneous biopsy specimens from 24 patients with systemic sarcoidosis and found focal necrosis in 43% of cases, fibrinoid necrosis in eight cases, focal necrobiosis of collagen around granulomas in four cases, and focal karyorrhexis in six additional cases. In all but one case, the necrosis was focal [9]. While some have suggested that there may be no necrosis [10], rare necrosis [11], or mild necrosis [12, 13] in cutaneous sarcoidosis, others advise vigilance when necrosis is found to rule out an infectious etiology before accepting the diagnosis of sarcoidosis [9]. Another study suggested that caseous necrosis is a sign of a regressing lesion [14]. In approximately 60% of cases, the granulomatous inflammation resolves within five years while the remaining patients develop chronic disease that may produce fibrosis [15].

Once other etiologies of granulomatous inflammation have been ruled out, which include infections and foreign body reactions, assessment for extracutaneous sarcoidosis is indicated [13]. An extensive history, which includes information about environmental exposures, a review of systems, and physical examination are important initial steps in the evaluation for systemic disease [16]. Chest radiographs and pulmonary function tests are important for the assessment of lymphadenopathy and interstitial disease. Ocular disease may be asymptomatic and ultimately lead to blindness, which makes early ophthalmologic evaluation important. To assess for an asymptomatic arrhythmia, an electrocardiogram should be obtained. Laboratory assessment should include a complete blood count, comprehensive metabolic panel, urinalysis [1, 13, 16], thyroid function tests [1, 17], 25-hydroxyvitamin D, and 1,25-hydroxyvitamin D [1, 18]. Although the angiotensin-converting enzyme level often is elevated in sarcoidosis, it is not sensitive or specific enough to determine the diagnosis [13]. Tuberculosis infection must be ruled out considering the similarities in presentation with sarcoidosis [1, 16]. Any positive findings on history or physical examination should prompt additional laboratory studies, imaging, and referral to the appropriate specialist. It is recommended that annual reassessment of the history, physical examination, chest radiographs, pulmonary function tests, ophthalmologic examination, complete blood count, and comprehensive metabolic panel be done [1].

Therapy for sarcoidosis typically targets the

most severely affected organ [1], with the hope of benefiting other involved organs. In limited cutaneous disease, topical and intralesional glucocorticoids and topical calcineurin inhibitors often are prescribed. Initial systemic therapy for cutaneous disease involves treatment with antimalarials, tetracycline antibiotics [2, 19], and immunomodulators, such as phosphodiesterase-4 inhibitors [1, 20]. More severe or progressive disease may require systemic glucocorticoids, methotrexate, thalidomide, tumor necrosis factor inhibitors, or other immunosuppressants [1, 15]. Presenting with impaired pulmonary function, our patient was started on methotrexate, which is the most widely used agent for pulmonary sarcoidosis [21]. Hydroxychloroquine, which is one of the most frequently prescribed systemic medications for cutaneous sarcoidosis [2], was recently added to the regimen by the Dermatology Service. Considering the severity of our patient's pulmonary findings, lung transplantation also has been discussed as it is often necessary in the setting of irreversible, severe disease that has failed medical management. This procedure has shown similar rates of survival compared to non-sarcoid transplant recipients [22].

References

1. Wanat KA, Rosenbach M. A practical approach to cutaneous sarcoidosis. Am J Clin Dermatol 2014; 15:283
2. Haimovic A, et al. Sarcoidosis: a comprehensive review and update for the dermatologist: part I. Cutaneous disease. J Am Acad Dermatol 2012; 66:699
3. Marchell RM, Judson MA. Cutaneous sarcoidosis. Semin Respir Crit Care Med 2010; 31:442
4. Rybicki BA, Iannuzzi MC. Epidemiology of sarcoidosis: recent advances and future prospects. Semin Respir Crit Care Med 2007; 28:22
5. Danbolt N. The historical aspects of sarcoidosis. Postgrad Med J 1958; 34:245
6. du Bois RM, et al. Is there a role for microorganisms in the pathogenesis of sarcoidosis? J Intern Med 2003; 253:4
7. Newman LS, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. Am J Respir Crit Care Med 2004; 170:1324
8. Cardoso JC, et al. Cutaneous sarcoidosis: a histopathological study. J Eur Acad Dermatol Venereol 2009; 23:678
9. Ball NJ, et al. The histologic spectrum of cutaneous sarcoidosis: a study of twenty-eight cases. J Cutan Pathol 2004; 31:160
10. English JC, 3rd, et al. Sarcoidosis. J Am Acad Dermatol 2001; 44:725
11. Rabinowitz LO, Zaim MT. A clinicopathologic approach to granulomatous dermatoses. J Am Acad Dermatol 1996; 35:588
12. Mitchell DN, et al. Sarcoidosis: histopathological definition and clinical diagnosis. J Clin Pathol 1977; 30:395
13. Judson MA. The diagnosis of sarcoidosis. Clin Chest Med 2008; 29:415
14. Kuramoto Y, et al. Subcutaneous sarcoidosis with extensive caseation necrosis. J Cutan Pathol 1988; 15:188
15. Baughman RP, et al. Sarcoidosis. Lancet 2003; 361:1111
16. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. Eur Respir J 1999; 14:735
17. Anolik RB, et al. Thyroid dysfunction and cutaneous sarcoidosis. J Am Acad Dermatol 2012; 66:167
18. Sage RJ, et al. Preventing vitamin D toxicity in patients with sarcoidosis. J Am Acad Dermatol 2011; 64:795
19. Doherty CB, Rosen T. Evidence-based therapy for cutaneous sarcoidosis. Drugs 2008; 68:1361
20. Baughman RP, et al. Efficacy and safety of apremilast in chronic cutaneous sarcoidosis. Arch Dermatol 2012; 148:262
21. Wijsenbeek MS, Culver DA. Treatment of sarcoidosis. Clin Chest Med 2015; 36:751
22. Taimeh Z, et al. Lung transplantation for pulmonary sarcoidosis: twenty-five years of experience in the USA. Thorax 2016; 71:378