

Can Granuloma Annulare Evolve Into Cutaneous Sarcoidosis?

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We report the unique case of a 50-year-old African American female with pulmonary sarcoidosis who presented with a new ichthyosiform eruption symmetrically located on the anterior shins and surrounded by red, translucent, intradermal papules. A skin biopsy of a new red papule showed features consistent with granuloma annulare (GA) with positive mucin staining, and an older hyperpigmented papule showed classic dermal noncaseating granulomas consistent with sarcoidosis.

Recent reports have clearly demonstrated GA occurring in association with sarcoidosis, but this is the first report that suggests that a GA lesion may develop into a sarcoidal granuloma. We propose that GA may act as a precursor lesion to the more mature sarcoidal granuloma. This case further underscores the importance of careful clinicopathologic correlation.

Sarcoidosis is an unusual granulomatous disorder of unknown etiology. It is a multisystem disease with involvement of the lungs, mediastinal and peripheral lymph nodes, bones, liver, spleen, skin, eyes, and parotid glands.¹ Cutaneous findings are reported to occur in 20% to 35% of patients with systemic disease.^{2,3} Cutaneous lesions are variable, but they classically include lupus pernio, infiltrated papules and plaques, macules, subcutaneous nodules, and infiltration of old scars. The most common non-specific cutaneous lesion is erythema nodosum, which is referred to as Lofgren's syndrome when associated with hilar adenopathy.¹

Granuloma annulare (GA) is also a granulomatous disorder of unknown etiology and is clinically



FIGURE 1. Ichthyosiform eruption on the anterior shins.

characterized by flesh-colored or pale erythematous papules and plaques, often in annular or circinate configurations.⁴ The lesions, which tend to be asymptomatic, are frequently seen on the hands and feet of children and young adults. GA can be localized or generalized and has been reported in association with diabetes mellitus.^{4,5}

Case Report

A 50-year-old African American female with a 6-year history of pulmonary sarcoidosis confirmed by transbronchial lung biopsy was seen for a scaly eruption on her lower legs that had been present for 3 months. The patient complained of localized pruritus and a constant superficial burning sensation. On the anterior shins, she developed tender papules that healed with hyperpigmentation. Additionally, the patient complained of fatigue and increasing dyspnea on exertion. She was taking 20 mg of prednisone 4 times a day for her pulmonary symptoms and had been steroid dependent for the past 6 years. Her past medical history was significant for hypertension

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FIGURE 2. Lateral edge of the lower legs with red, intradermal papules surrounding the ichthyotic scale.

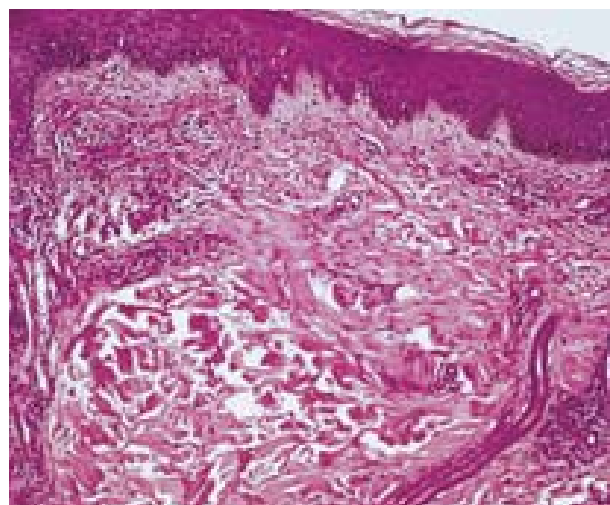


FIGURE 3. Skin biopsy of a new, tender, red papule demonstrating features suggestive of a granulomatous infiltrate with a circular area of necrobiotic collagen and a perivascular infiltrate (H&E, original magnification $\times 20$).

for which she took 20 mg of hydrochlorothiazide 4 times a day.

Physical examination showed the patient to be moderately obese with a symmetric ichthyosiform eruption consisting of polygonal, adherent, brown scales on the lower legs (Figure 1). This eruption was surrounded on both sides of the anterior shins by numerous tender, red to violaceous, translucent, intradermal papules (Figure 2). There were also hyperpigmented macules and papules with slight scale. The remainder of the cutaneous examination was unremarkable.

A skin biopsy of a 2-week-old, erythematous, indurated papule had features consistent with GA. There was a suggestion of a granulomatous infiltrate with a circular area of necrobiotic collagen and a perivascular infiltrate (Figure 3). The central connective tissue was abnormal in appearance, and a colloidal iron stain was strongly positive for mucin, favoring a diagnosis of GA. Special stains, including Gram, acid-fast, and periodic acid-Schiff, were negative.

Because the patient had a 6-year history of sarcoidosis and developed a new ichthyosiform eruption of the lower extremities as an adult, a diagnosis of cutaneous sarcoidosis was highly suspect. A second biopsy was performed on an older hyperpigmented papule that had started as a red, intradermal papule similar to the initial biopsied lesion. This older papule had been present for almost 5 months, and its biopsy was more characteristic of sarcoidosis, with numerous well-circumscribed, noncaseating granulomas of epithelioid histiocytes with a sparse infiltrate of lymphocytes. There was also overlying hyperkeratosis, flattening of the rete ridges, and an atrophic epidermis consistent with ichthyosis (Figure 4).

A recent chest computed tomography demonstrated increased right paratracheal adenopathy but no hilar adenopathy. A chest x-ray showed increased density at the lower bases, consistent with fibrosis. Pulmonary function tests showed a moderate restrictive ventilatory defect with a restrictive flow volume loop and a moderately reduced total lung capacity, which was worse compared with previous studies. A recent angiotensin-converting-enzyme level had normalized at 49 U/L (normal range, 9–67 U/L), but the ery-

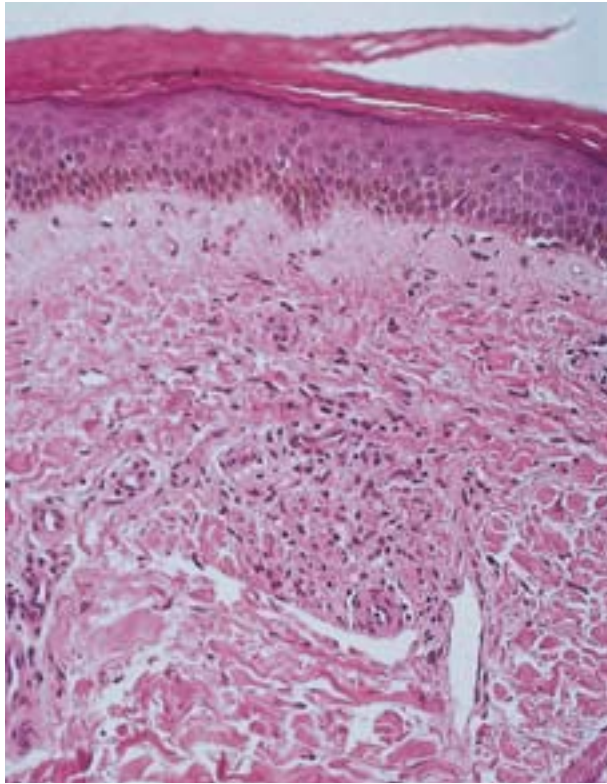


FIGURE 4. Skin biopsy of an older, hyperpigmented papule with a well-circumscribed area of noncaseating epithelioid histiocytes with overlying hyperkeratosis and mild atrophy of the epidermis (H&E, original magnification $\times 20$).

throcyte sedimentation rate was mildly elevated at 45 mm/HR (normal range, 0–30 mm/HR). Other laboratory evaluations demonstrated normal hemoglobin, nonreactive rapid plasma reagin, calcium, and liver function tests.

The patient's dosage of prednisone was increased to 40 mg 4 times a day, and she was started on a high potency topical corticosteroid cream for her legs (betamethasone dipropionate, 0.05%). Her symptoms slowly improved, and she is currently maintained on 20 mg of prednisone 4 times a day for control of both her pulmonary and cutaneous diseases. She has continued, however, to occasionally develop tender, red, intradermal papules on the legs, which become less tender and resolve with hyperpigmentation over several months.

Discussion

There are numerous reports in the literature describing an association between GA and sarcoidosis.⁶⁻⁸ Both are granulomatous disorders of unknown etiologies and their coexistence has been speculated to result from a common underlying pathogenesis.⁵

GA and sarcoidosis have many common features, which may account for their simultaneous occurrence. They both have granuloma formation with epithelioid histiocytes and are probably mediated by similar, but unidentified, antigenic stimuli.^{1,5} The invading lymphocytes in both diseases are of the CD4-activated, helper-T-cell subset⁵ and have similar patterns of neutrophil migration.⁸

In this patient, biopsy of the newer lesions demonstrated features consistent with GA with positive mucin staining. Biopsy of older resolving lesions, however, demonstrated classic dermal noncaseating granulomas with a sparse inflammatory infiltrate most consistent with sarcoidosis.

We propose that some GA lesions may be precursor lesions to cutaneous sarcoidal granulomas. This further underscores the importance of clinicopathologic correlation and the need to take a thorough medical history. If only one biopsy of the newly developed papule had been taken from this patient, there would have been a delay in her diagnosis. When the various antigenic stimuli that cause these 2 disorders are fully known, we may be able to better classify these granulomatous infiltrates. It is possible that some cases previously diagnosed as GA may actually prove to be cutaneous manifestations of sarcoidosis. Our patient's case suggests that GA may be an immature form of disease that can transform after some time into a more classic dermal sarcoidal granuloma. This patient will be monitored to further define the exact timing and progression of her cutaneous lesions and to discover the significance and prognostic importance of these types of precursor lesions.

REFERENCES

1. Mana J, Marcoval J, Graells J, et al. Cutaneous involvement in sarcoidosis. *Arch Dermatol.* 1997;133:882-888.
2. Gawkrödger DJ. Sarcoidosis. In: Champion RH, Burton JL, Burns DA, et al, eds. *Rook's Textbook of Dermatology*. 6th ed. Oxford, England: Blackwell Science; 1998:2679-2702.
3. Wilson NJ, King CM. Cutaneous sarcoidosis. *Postgrad Med.* 1998;7:649-652.
4. Veraldi S, Bencini PL, Drudi E, et al. Laboratory abnormalities in granuloma annulare: a case-control study. *Br J Dermatol.* 1997;136:652-653.
5. Dimitrova J, Obreschkowa E, AlJraivi SS. Follicular lichenoid generalized granuloma annulare. *Z Hautkr.* 1984;59:421-425.
6. Ehrlich E, McGuire J, Kim Y. Association of granuloma annulare with sarcoidosis. *Arch Dermatol.* 1992;128:855-856.
7. Umberto P, Winkelmann RK. Granuloma annulare and sarcoidosis. *Br J Dermatol.* 1977;97:481-486.
8. Gange W, Black MM, Carrington P. Defective neutrophil migration in granuloma annulare, necrobiosis lipoidica and sarcoidosis. *Arch Dermatol.* 1979;115:32-35.