Ichthyosiform Sarcoidosis and Systemic Involvement

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PRACTICE **POINTS**

- Ichthyosiform sarcoidosis is a rare form of sarcoidosis that presents as polygonal adherent scales.
- Ichthyosiform sarcoidosis is commonly associated with pulmonary, neurologic, and hepatic involvement.
- Acquired ichthyosis should warrant further investigation for systemic disease.

Sarcoidosis is a systemic disease that can be suspected based on cutaneous findings and confirmed using diagnostic testing such as biopsy and laboratory or radiographic studies. We report the case of a 66-year-old black woman with ichthyosiform sarcoidosis (IS) on the lower extremities. Ichthyosiform sarcoidosis is a rare variant of cutaneous sarcoidosis that is frequently associated with further internal involvement. We review this uncommon presentation of sarcoidosis along with other cases reported in the literature to determine the organ systems most commonly affected.

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Sarcoidosis is a multiorgan, systemic, granulomatous disease that most commonly affects the cutaneous, pulmonary, ocular, and cardiac organ systems. Cutaneous involvement occurs in approximately 20% to 35% of patients, with approximately 25% of patients demonstrating only dermatologic findings.[1] Cutaneous sarcoidosis can have a highly variable presentation. Ichthyosiform sarcoidosis (IS) is a rare form of this disease that has been described as presenting as polygonal adherent scales.[2] It often is associated with internal organ involvement. We present a case of IS without any organ system involvement at the time of diagnosis. A review of the English-language literature was performed to ascertain the internal organ associations most commonly reported with IS.

Case Report

A 66-year-old black woman presented to dermatology with dark scaly patches noted by her primary care physician to be present on both of the lower extremities. The patient believed they were present for at least 4 years. She described dark spots confined to the lower legs that had gradually increased in size. Review of systems was negative for fever, chills, night sweats, weight loss, vision changes, cough, dyspnea, and joint pains, and there was no history of either personal or familial cutaneous diseases.

Physical examination revealed cutaneous patches of thin white scale with a sharp edge in arciform patterns on the lower extremities. Several of these patches were hyperpigmented and xerotic in appearance (Figure 1). The patches were limited to the lower legs, with no other lesions noted.

A punch biopsy of the skin on the right lower leg was performed. Histopathologic analysis showed epidermal compact hyperkeratosis with deep granulomatous infiltration into the subcutaneous tissue (Figures 2A and 2B). At high power, these granulomas were noted to be noncaseating naked granulomas composed of epithelioid histiocytes surrounded by sparse lymphocytic inflammation (Figure 2C). Special stains including acid-fast bacilli, Fite, and periodic acid–Schiff were negative. The diagnosis of IS was made based on clinical presentation and primarily by histopathologic analysis.

The patient's cutaneous lesions were treated with fluocinonide ointment 0.05% twice daily. Although she

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The eTable is available in the Appendix online at www.mdedge.com/cutis.
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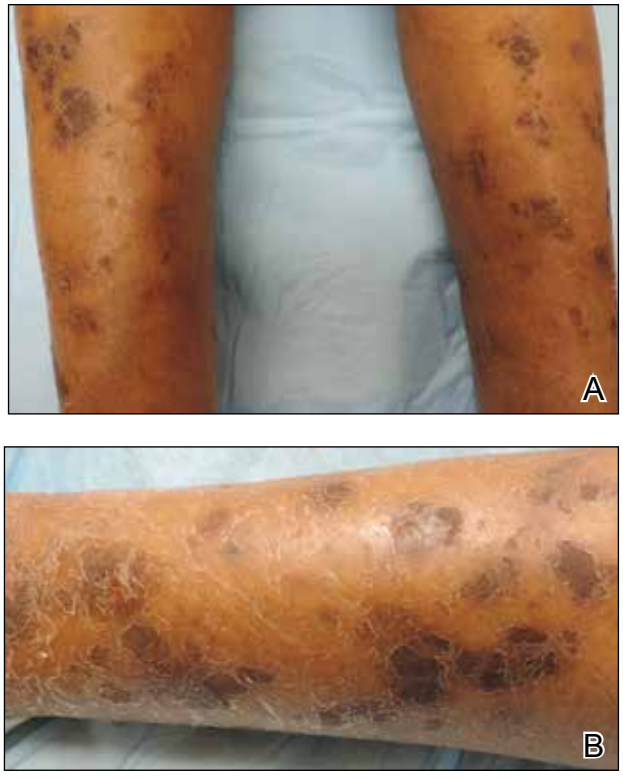

FIGURE 1. Ichthyosis sarcoidosis on the bilateral lower legs with hyperpigmented and xerotic patches (A). Cutaneous patches of thin white scale with a sharp edge in arciform patterns also were present (B).

did not notice a dramatic improvement in the plaques, they stabilized in size. Her primary care physician was notified and advised to begin a workup for involvement of other organ systems by sarcoidosis. Her initial evaluation, which included a chest radiograph and electrocardiogram, were unremarkable. Despite multiple attempts to persuade the patient to return for further follow-up, neither dermatology nor her primary care physician were able to complete a full workup.

Comment

Etiology—Although there are several theories regarding the etiology of sarcoidosis, the exact cause remains unknown. The body's immune response, infectious agents, genetics, and the environment have all been thought to play a role. It has been well established that helper T cell (T_H1) production of interferon and increased levels of tumor necrosis factor propagate the inflammatory response seen in sarcoidosis.[3] More recently, T_H17 cells have been found in cutaneous lesions, bronchoalveolar lavage samples, and the blood of patients with sarcoidosis, especially in those with active disease progression.[3] Infectious agents such as mycobacteria and propionibacteria DNA or RNA also have been found in sarcoid samples.[4] Several HLA-DRB1 variants have been associated with an increased incidence of sarcoidosis.[5]

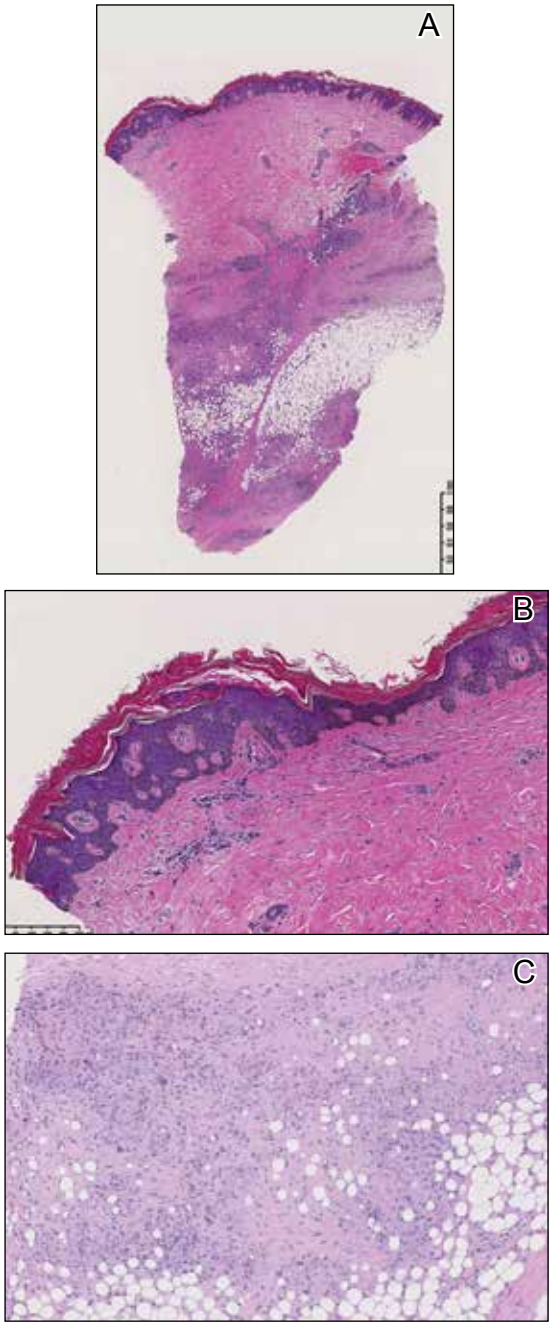

FIGURE 2. Histopathology revealed diffuse, predominantly rounded aggregates of epithelioid histiocytes within the deep dermis and subcutaneous tissue (A)(H&E, original magnification ×25). A dense, compact, orthokeratotic stratum corneum with loss of the normal basket-weave pattern also was present (B)(H&E, original magnification ×100). Noncaseating granulomas composed of epithelioid histiocytes were surrounded by sparse lymphocytic inflammation (C)(H&E, original magnification ×200).

Presentation—Characteristic dermatologic findings of sarcoidosis include macules, papules, nodules, and plaques located on the face, especially the nose, cheeks, and ears, and on the shins or ankles, as well as similar lesions around tattoos or scars. Sarcoid lesions also

have been described as angiolupoid, lichenoid, annular, verrucous, ulcerative, and psoriasiform. Here we present an example of the uncommon type, ichthyosiform. Ichthyosiform sarcoidosis is a rare variant described primarily in dark-skinned individuals, a finding supported by both our case and prior reports. Most reported cases have described IS lesions as having a pasted-on appearance, with adherent centers on the extensor surfaces of the lower extremities, head, and/or neck.[6] Our case follows this descriptive pattern previously reported with adherent patches limited to the lower extremities.

Histopathology—The key histopathologic finding is the presence of noncaseating granulomas on biopsy. Sarcoid "specific" lesions rest on the identification of the noncaseating granulomas, while "nonspecific" lesions such as erythema nodosum fail to demonstrate this finding.[1]

Systemic Involvement—The IS type is believed to be an excellent marker for systemic disease, with approximately 95% of reported cases having some form of systemic illness.[6] Acquired ichthyosis should warrant further investigation for systemic disease. Early recognition could be beneficial for the patient because the ichthyosiform type is believed to precede the diagnosis of systemic disease in most cases by a median of 3 months.[6]

The most common site of internal sarcoid involvement is the lungs, but the lymph nodes, eyes, liver, spleen, heart, and central nervous system also can be involved. Patients can present with nonspecific symptoms such as erythema nodosum in the skin, dyspnea, cough, chest pain, vision changes, enlarged lymph nodes, headaches, joint pain, fever, fatigue, weight loss, and malaise. According to a PubMed search of articles indexed for MEDLINE using the term *ichthyosiform sarcoidosis*, 16 cases have been reported in the English-language literature (eTable).[1,6-14] Of these 16 cases, 3 involved men and 13 involved women. The median age of a patient diagnosed with IS was 37 years. The respiratory system was found to be the most common organ system involved (14 of 16 patients), with hilar adenopathy and restrictive lung disease being the most common findings. Neurologic findings and hepatic involvement also were seen in 3 and 3 patients, respectively. Eight of 16 cases had an elevated serum angiotensin-converting enzyme level. Details of systemic involvement in other cases of IS are listed in the eTable.

Management—Most patients are given topical corticosteroids for their cutaneous lesions, but patients with systemic involvement will likely need some type of systemic immunosuppressive therapy to control their disease. Systemic therapy often is warranted in IS because of reports of rapid progression. Our case differs from these prior reports in the relative stability of the disease at the last patient encounter. Systemic treatment commonly includes oral corticosteroids such as prednisone. Other options, such as hydroxychloroquine, methotrexate, azathioprine, pentoxifylline, thalidomide, cyclophosphamide, cyclosporine, and infliximab, can be considered if other treatments fail.[13] Ichthyosiform sarcoidosis patients should continue to have regular follow-up to monitor for disease progression.

Differential—When evaluating an acquired ichthyosis, dermatologists can consider other associations such as Hodgkin disease, hypothyroidism, multiple myeloma, carcinomatosis, and chronic malnutrition.[1] Skin biopsy demonstrating granuloma formation also is not specific for sarcoidosis. Other etiologies, such as autoimmune diseases, immunodeficiency disorders, infections, foreign body granulomas, neoplasms, and drug reactions, should be considered.[15] All patients with acquired ichthyosis should undergo a thorough evaluation for internal involvement.

Conclusion

We presented a case of IS, a rare type of sarcoidosis commonly associated with further internal involvement of the respiratory, nervous, or hepatic organ systems. Recognition of an acquired form of ichthyosis and its potential disease associations, including sarcoidosis, is important to improve early detection of any internal disease, allowing prompt initiation of treatment.

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eTABLE. Cases of Ichthyosiform Sarcoidosis With Systemic Involvement

Reference (Year)	Age, y	Sex	Location of Lesions	Cutaneous Findings	Histopathology	Internal Involvement
Kauh et al[7] (1978)	31	F	Legs, buttocks, back, and arms	Diffuse hyperpigmented/ hypopigmented, large, adherent scales on anterior aspects of lower legs; multiple erythematous, slightly indurated, 0.5- to 1-cm, coin-shaped lesions over arms, lower back, buttocks, and thighs	Hyperkeratosis with thinning or absent granular layer and mild acanthosis, deeper dermis with noncaseating granulomatous infiltrate, tubercles of epithelioid and giant cells associated with lymphocytes	Pulmonary involvement: CXR revealed bilateral hilar adenopathy, paratracheal node enlargement, diffuse pulmonary parenchymal mottling
Matsuoka et al[8] (1980)	38	F	Lower legs	Fine translucent scales on extensor aspects of lower legs	Absent or marked thinning of stratum granulosum, epidermal atrophy with dovetailing of the rete ridges, noncaseating granulomas present in dermis	Pulmonary involvement: CXR revealed mild perihilar adenopathy, PFTs revealed mild restrictive lung disease
	54	F	Lower legs	Large adherent scales on the anterior tibial aspects of the lower legs	Absent or marked thinning of stratum granulosum, epidermal atrophy with dovetailing of the rete ridges, noncaseating granulomas present in dermis	Pulmonary involvement: CXR revealed bilateral hilar adenopathy, PFTs revealed restrictive lung disease Hepatic involvement: noncaseating granulomas on biopsy
	31	M	Lower legs	Fine scales on anterior aspects of lower legs	Absent or marked thinning of stratum granulosum, epidermal atrophy with dovetailing of the rete ridges, noncaseating granulomas present in dermis	Pulmonary involvement: PFTs revealed mild restrictive lung disease Laboratory studies: increased gamma globulin
Matarasso and Bruce[9] (1991)	33	F	Face, arms, and lower legs	1- to 2-mm waxy, flesh-colored papules around eyes, nose, mouth, and ears; apple green jelly–colored papules on the arms; polygonal, pigmented, adherent scales on pretibial areas	Dermal noncaseating epithelioid granulomas	Pulmonary involvement: CXR revealed diffuse interstitial pattern, possible bilateral hilar prominence Laboratory studies: anemia, hypercalcemia
Feind-Koopmans et al[10] (1996)	60	M	Extensor surfaces of extremities	Erythroderma and large lamellar scales on extensor surfaces of extremities, apple green jelly–colored lesions on diascopy	Multiple noncaseating epithelioid cell granulomas surrounded by a mixed infiltrate of lymphocytes and eosinophils, epidermis was without a granular layer	Hepatomegaly, splenomegaly, adenopathy of the head and neck and axillary and inguinal regions Laboratory studies: eosinophilia, elevated serum calcium, elevated serum ACE

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eTABLE. (continued)

Reference (Year)	Age, y	Sex	Location of Lesions	Cutaneous Findings	Histopathology	Internal Involvement
Gangopadhyay[11] (2001)	25	F	Upper extremities, chest, abdomen, and face	Silver-colored, rhomboidal, scaly plaques	Compact orthokeratosis with diminished granular layer, multiple noncaseating epithelioid cell granulomas in deep dermis, negative PAS and Fite stains	Laboratory studies: elevated serum calcium, elevated serum ACE
Sawhney et al[12] (2003)	36	M	Legs, thighs, arms, shoulders, and abdomen	Well-defined, large, normoesthetic, ichthyotic patches on legs, thighs, arms, and shoulders; grouped erythematous papules on left arm and back; mobile, nontender, subcutaneous nodules on arms and abdomen	Well-defined epithelioid cell granulomas with a mantle of lymphocytes, no giant cells were seen, negative acid-fast stain	Pulmonary involvement: PFTs revealed mild restrictive lung disease Special testing: polyclonal hypergammaglobulinemia, cutaneous anergy to tuberculin testing
Rosenberg[1] (2005)	39	F	Lower extremities (pretibial area)	Polygonal, pigmented, adherent scales	Mixed cell infiltrate composed of histiocytes, lymphocytes, and plasma cells in the papillary and reticular dermis; negative PAS, Ziehl-Neelsen, and Steiner stains	Neurologic involvement: MRI of the brain and orbits revealed multiple enhancing miliary nodules within subarachnoid/pial spaces of the cerebellum and brainstem; small nodules coating tentorium and dura of the inferior temporal lobes, the basal ganglia, the lateral ventricles, and in the right globe Pulmonary involvement: CT chest revealed calcified left hilar node, numerous nonspecific nodules in lung parenchyma Hepatic involvement: low total protein, low albumin, elevated AST and ALT
	36	F	Trunk and thighs	Erythematous nonscaling papules; diffuse, adherent, ichthyosiform scales with some overlying dusky red papules and plaques	Hyperkeratosis, a thinned to absent granular layer, and mild epidermal acanthosis; multiple noncaseating epithelioid granulomas in dermis; negative Grocott-Gomori and Ziehl-Neelsen stains	Pulmonary involvement: mild hilar adenopathy on CXR, PFTs showed a mild obstructive ventilatory defect Ocular involvement: sarcoidal uveitis Laboratory studies: elevated serum ACE; elevated ESR
	36	F	Legs (calves)	Diffuse ichthyotic scaling overlying scattered, discrete, erythematous, nontender nodules	Ichthyotic scale showed hyperkeratosis, a thinned granular layer, mild acanthosis, and dermal noncaseating epithelioid granulomas; negative Grocott-Gomori and Ziehl-Neelsen stains	Pulmonary involvement: hilar adenopathy on CXR Laboratory studies: elevated serum ACE

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eTABLE. (continued)

Reference (Year)	Age, y	Sex	Location of Lesions	Cutaneous Findings	Histopathology	Internal Involvement
Kelley et al[6] (2010)	45	F	Bilateral extensor surfaces of the shins and forearms	Dry scaly patches	Hyperorthokeratosis and patchy parakeratosis without epidermal spongiosis; superficial and deep dermis; nonnecrotizing, well-formed granulomas; negative PAS and Fite stains	Pulmonary involvement: CT of the chest revealed hilar and mediastinal adenopathy, diffuse ground-glass opacities in bilateral lower lungs Lymphatic involvement: CT of the abdomen and pelvis revealed prominent pericaval and retroperitoneal lymph nodes Laboratory studies: elevated serum ACE, elevated serum calcium, depressed parathyroid hormone
Ghosh et al[13] (2013)	35	F	Legs	Xerosis with fine, hyperpigmented, adherent, and rhomboidal scales	Mild hyperkeratosis; thinning of granular layer; focal acanthosis; noncaseating, well-formed epithelioid granulomas; negative Fite and PAS stains	Neurologic involvement: MRI of brain revealed thickened extra-axial tissue symmetrically distributed in cavernous sinuses, sensory loss in the distribution of the left fifth cranial nerve, left sixth cranial nerve palsy, lower motor neuron palsy of left seventh cranial nerve, elevated ACE in the CSF Pulmonary involvement: CT of the thorax revealed reticulonodular pattern and paratracheal adenopathy, CXR revealed upper mediastinal widening and hilar adenopathy Musculoskeletal involvement: swollen and tender ankle joints Laboratory studies: elevated serum ACE

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eTABLE. (continued)

Reference (Year)	Age, y	Sex	Location of Lesions	Cutaneous Findings	Histopathology	Internal Involvement
Miura et al[14] (2016)	69	F	Lower legs, back	Xerotic and lamellar scaly patches on lower legs, yellowish brown indurated plaques on upper back	Nonnecrotizing epithelioid granulomas in the mid to lower dermis with minimal lymphocytic infiltration, granular layers were scarcely detected in the epidermis	Pulmonary involvement: bilateral hilar adenopathy, mediastinal lymphadenopathy, bilateral pleural effusions Cardiac involvement: right heart failure Gallium scintigraphy showed accumulated uptake in the parotid glands Laboratory studies: elevated serum ACE, elevated soluble IL-2R
	59	F	Lower legs	Xerotic changes on bilateral lower legs	Dense sarcoid granuloma in the lower dermis, fewer granular layers in the epidermis	Pulmonary involvement: CT chest revealed bilateral mediastinal lymphadenopathy Ocular involvement: uveitis
	57	F	Lower legs, buttocks, elbows	Ichthyosiform lesions with erythema nodosum–like nodules on the lower legs, subcutaneous nodule on the buttocks, papular lesions on the elbows	Sarcoidal granuloma in the mid to lower dermis and subcutis, fewer granular layers in the epidermis	Pulmonary involvement: CXR and CT chest revealed bilateral hilar adenopathy and bilateral mediastinal lymphadenopathy Neurologic involvement: facial nerve palsy (incomplete Heerfordt syndrome, without parotitis) Laboratory studies: elevated serum ACE

Abbreviations: F, female; CXR, chest radiograph; PFT, pulmonary function test; M, male; ACE, angiotensin-converting enzyme; PAS, periodic acid–Schiff; MRI, magnetic resonance imaging; CT, computed tomography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CSF, cerebrospinal fluid.