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Ichthyosiform sarcoidosis: report of three cases from Japan and literature review

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Abstract. Cutaneous lesions of sarcoidosis present with various manifestations including specific and non-specific cutaneous lesions. Ichthyosiform sarcoidosis is a rare form of cutaneous sarcoidosis, presenting with asymptomatic, adherent, polygonal scales, mainly appearing on the lower limbs. Ichthyosiform sarcoidosis has a predilection for dark-skinned races, and cases affecting Japanese patients have rarely been reported in English literature. We herein describe three Japanese cases of ichthyosiform sarcoidosis on the lower limbs. All of the patients were female, with an age range of 57-69 years old. Histologically, sarcoidal granulomas were located in the mid- to lower dermis. All cases had scar sarcoidosis on the knees. Furthermore, Case 1 presented with papular sarcoidosis on the back, and Case 3 presented with subcutaneous nodules on the buttock as well as erythema nodosum-like lesions on the lower legs. All patients had lung sarcoidosis, but ocular sarcoidosis was seen in only Case 2. Case 3 showed Heerfordt syndrome with facial nerve paralysis. Histological features showed that the granular layers were scarcely detected in the overlying epidermis; however, filaggrin expression was not decreased. Sarcoidal granulomas accumulated around the sweat glands in one case, whereas those features were not detected in the other two cases. In conclusion, ichthyosiform cutaneous sarcoidosis may be overlooked or misdiagnosed as xerotic dry skin which is frequently found in elderly people, and ichthyosiform cutaneous lesions may be more prevalent than previously estimated. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 392-397)*

Key words: sarcoidosis, skin, ichthyosiform

Introduction

Sarcoidosis is a systemic granulomatous disease with various clinical manifestations, including specific and non-specific cutaneous lesions. Ichthyosiform sarcoidosis is a rare cutaneous form, presenting with asymptomatic, adherent, polygonal scales, mainly appearing on the lower extremities. Ichthyosiform sarcoidosis affecting Japanese people has rarely been reported in English literature. We herein describe three cases of ichthyosiform sarcoidosis on the lower limbs in Japanese elderly women.

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Case Reports

Case 1: A 69-year-old female with a history of pulmonary hypertension, respiratory failure, coniosis, asthma, and diabetes mellitus was admitted to our hospital, complaining of pleural effusion, ascites, and generalized edema. A physical examination revealed multiple yellowish brown indurated plaques on the upper back. Furthermore, xerotic and lamellar scaly patches were also seen on the bilateral lower ex-

tremities (Fig. 1a). Chest X-ray showed bilateral hilar lymphadenopathy (BHL) and computed tomography (CT) revealed mediastinal lymphadenopathy. Gallium scintigraphy showed BHL and accumulated uptake in the parotid glands. Serum angiotensin-converting enzyme (ACE) level was increased (42.9 U/L; normal range: 7-25) and soluble IL-2R was elevated (1950 U/ml; normal: 124-460). Tuberculin reaction was negative. Liver and renal functions were normal, but detailed examination revealed bilateral pleural effusion and right heart failure. Pulmonary hypertension was due to cor pulmonale. Ophthalmological examination did not reveal uveitis. Skin biopsies were performed from the upper back and lower leg. In the specimen taken from the lower leg, non-necrotizing, epithelioid granulomas were located in the mid- to lower dermis with minimal lymphocytic infiltration (Fig. 1b), and the granular layers were scarcely detected in the overlying epidermis (Fig. 1c). Of note, some of the granulomas accumulated close to the eccrine sweat glands (Fig. 1d). The upper back specimen also showed sarcoidal granuloma. Based on the presence of pulmonary and skin lesions, the patient was diagnosed with sarcoidosis.

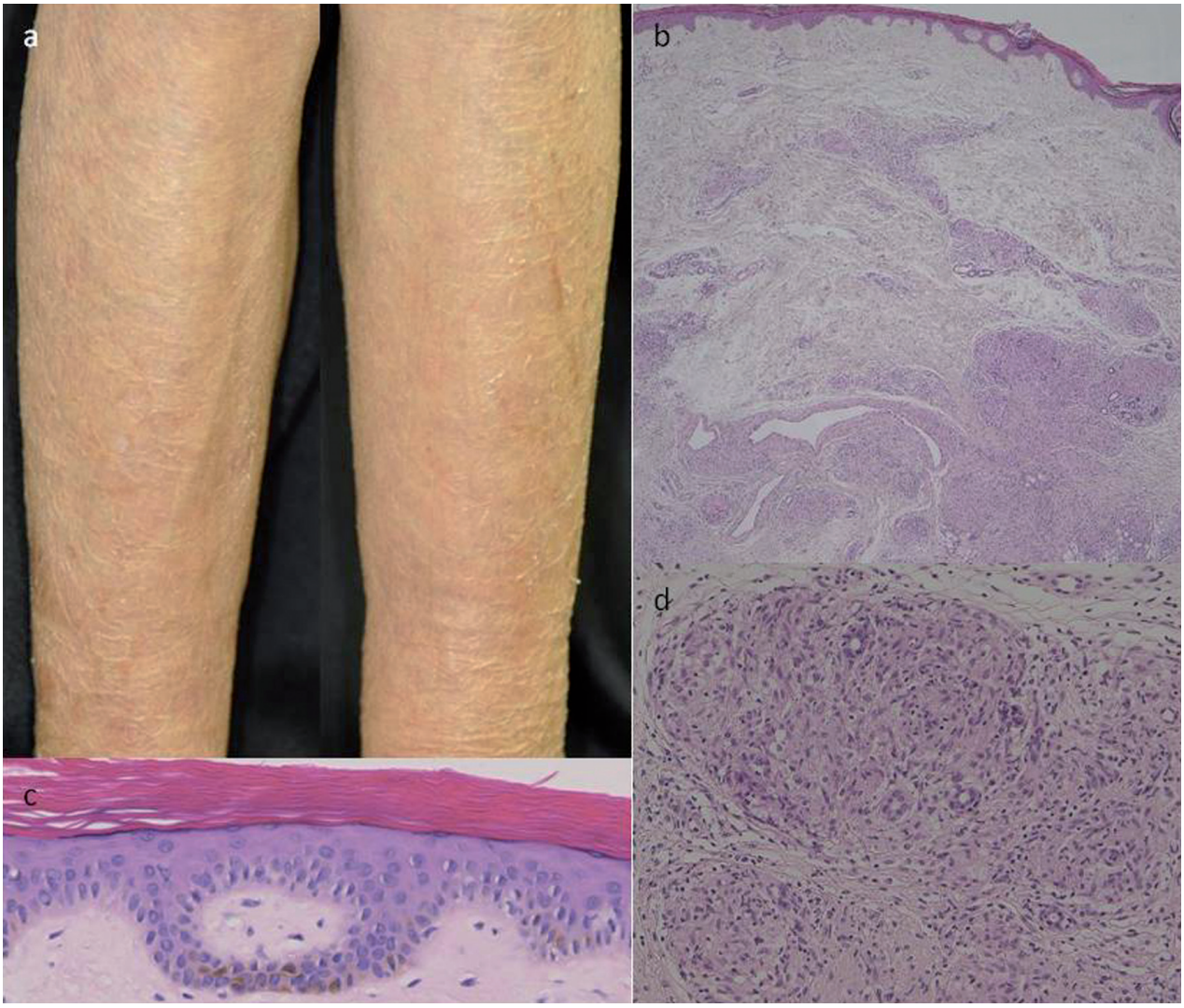

Fig. 1. (a) Ichthyosiform eruption of the bilateral lower extremities. (b) Non-caseating epithelioid granulomas with minimal lymphocyte infiltration in the dermis. (c) Reduction of granular layers in the epidermis. (d) Numerous sarcoidal granulomas around the eccrine sweat glands

Case 2: A 59-year-old female with lung sarcoidosis and uveitis was referred to our department. She complained of misty vision, and ophthalmological examination revealed iris nodules, anterior segment inflammation, and vitreous opacity. Chest CT revealed bilateral mediastinal lymphadenopathy. Laboratory examination showed that serum ACE was within normal range. Tuberculin reaction was negative. Physical examination showed scar sarcoidosis on the knees as well as xerotic changes on the bilateral lower legs (Fig. 2a). A biopsy specimen revealed dense sarcoid granuloma in the lower dermis (Fig. 2b); however, sweat glands in the dermis were not affected by the sarcoidal granuloma. There were fewer granular layers in the overlying epidermis.

Case 3: A 57-year-old female initially presented with a subcutaneous nodule on the buttock, and was diagnosed with subcutaneous sarcoidosis. Chest X-ray and CT revealed BHL and bilateral mediastinal lymphadenopathy (stage II), but she had no ocular sarcoidosis. During the course of her stay at our hospital, she developed facial nerve palsy (incomplete Heerfordt syndrome); however, parotiditis was not observed. Laboratory examination showed increased serum ACE (48.2 U/L). On physical examination at the initial visit to our department, she had scar sarcoidosis on the knee, and papular lesions on the elbow. She later developed ichthyosiform lesions with erythema nodosum-like nodules on the lower legs (Fig. 2c). A biopsy was taken from the xerotic lesion with slight induration, which showed sarcoidal granuloma in the mid-to lower dermis and in the subcutis (Fig. 2d), but not near the sweat glands. There were fewer granular layers in the overlying epidermis.

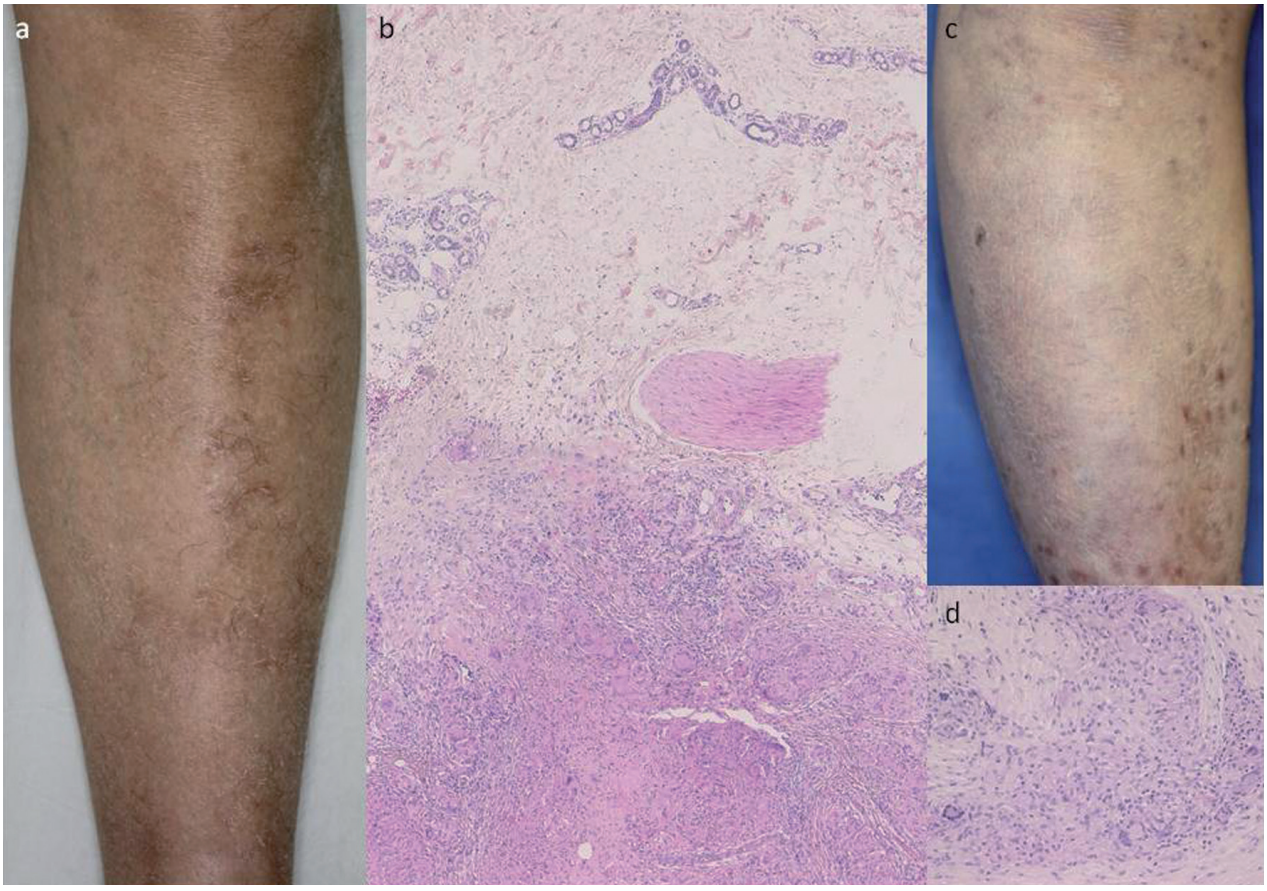

Fig. 1. (a) Clinical features with scales of the lower limb (Case 2). (b) Histological features showing epithelioid granuloma in the subcutaneous tissue. Note that the upper sweat glands are not affected by sarcoidal granulomas. (c) Clinical features of the lower limb (Case 3). (d) Histological features showing sarcoid granuloma with a number of giant cells in the subcutis

Discussion

Ichthyosiform sarcoidosis, first reported by Kauh et al. (1), is a specific lesion and a rare cutaneous manifestation of sarcoidosis. In the majority of patients, it occurs predominantly on the lower extremities without symptoms. The skin lesions typically occur as large, adherent, and scaly, and the microscopic features demonstrate the characteristic findings of both ichthyosis vulgaris and sarcoidosis. Histological examination typically reveals parakeratosis, reduction of the granular layers in the epidermis, and non-caseating granulomas in the dermis.

Skin manifestation associated with sarcoidosis varies depending on race, and the number of reports of in English literature of ichthyosiform sarcoidosis from Japan is currently low. We herein described three Japanese cases of ichthyosiform sarcoidosis. All of the patients were female, and the lower limbs were involved. The three patients presented with other types of cutaneous sarcoid lesions such as scar sarcoidosis, plaques, papular lesions, and erythema nodosum-like lesions. The patients were already diagnosed with or at least suspected as having sarcoidosis at the time of visiting our dermatology department. All of the patients had lung lesions, and one had uveitis. We have been able to find 26 reported cases of ichthyosiform sarcoidosis in English literature (1-15). The appearance of ichthyosiform lesions was preceded by the diagnosis of sarcoidosis in 19 cases (including our three cases), whereas it was followed by the diagnosis of systemic sarcoidosis in seven patients. Systemic features of sarcoidosis were present in 22 of the 26 patients with ichthyosiform sarcoidosis, all of which were associated with pulmonary lesions, especially BHL (Table 1). Although it has been reported that ichthyosiform sarcoidosis is rare in Japan, we have found several cases described in Japanese. To date, 10 cases (six males, four females; mean age of 31 years (range; 16-69 years)) have been reported in Japanese literature. The majority of cases occurred on the lower extremities (seven cases), whole body (two cases), trunk, and back. Six cases exhibited no other cutaneous lesions, whereas four cases also showed other types of cutaneous sarcoidosis, such as alopecia of the scalp, nodular lesions, erythema nodosum-like lesions, and lichenoid lesions. Most of these cases were associated with systemic involvement. Systemic features were BHL (seven cases), multiple lymph node adenopathy (three cases), uveitis (five cases), and neuro-sarcoidosis (one case). Therefore, we suspect that ichthyosiform sarcoidosis is related to systemic sarcoidosis. Our Case 3 developed facial nerve palsy, however, ichthyosiform sarcoidosis associated with neuro-sarcoidosis is rare.

Recently, similar clinical features to those of ichthyosiform sarcoidosis exhibiting asteatosis on the lower extremities, in which histologically sarcoidal granulomas showed syringotropism, have been reported by Hayakawa et al. as syringotropic variants (14). Sweat glands surrounded by sarcoidal granulomas showed a decreased expression of dermcidin and aquaporin 5. In our Case 1, histological examination showed a massive accumulation of sarcoidal granulomas around the eccrine glands, which may have inhibited secretion of sweat. By contrast, in our other two cases, the locations of the sarcoidal granulomas were unassociated with the eccrine sweat glands. Similar to the cases reported by Hayakawa et al. (14), our patients were all females, but older than their patients. The varying degree of sarcoidal granuloma accumulation around the sweat glands may depend on the timing of the biopsy, because cutaneous sarcoid lesions can change spontaneously. Hayakawa et al. (14) speculate that impaired local sweating function may lead to unique clinical features due to sweat duct disruption or mechanical obstruction of the duct. Alternatively, these unique clinical features may also be induced by mechanisms other than impaired sweating. On the other hand, in ichthyosis vulgaris, filaggrin expression is typically diminished in the thin granular layers of the epidermis. However, the immunohistochemistry results in our cases showed that filaggrin expression was not decreased in the epidermis of the lesional skin (data not shown).

In conclusion, ichthyosiform sarcoid appeared at the evolutional phase of systemic sarcoidosis in the present cases. All of the present cases exhibited other types of cutaneous sarcoid at sites other than the lower legs. This rare form of ichthyosiform sarcoid may be a chronic form of cutaneous lesion, but further studies are necessary to elucidate the pathomechanisms of ichthyosiform sarcoidosis.

Table 1. Summary of patients with ichthyosiform sarcoidosis in English literature

Case	Age/ Sex	Site	Other types of cutaneous sarcoidosis	Organs involved	Author (year)
1	31/F	Thighs, abdomen, lower leg, arm	EN-like lesion	BHL	Kauh YC, et al (1978)
2	21/M	Lower extremities	-	BHL, uveitis	Kell AP, (1978)
3	31/F	Lower extremities	-	BHL	Kelly AP, (1978)
4	26/F	Lower extremities	-	BHL, uveitis	Mountcastle EA, et al (1980)
5	38/F	Lower extremities	-	BHL	Matsuoka LY, et al (1980)
6	54/F	Lower extremities	-	BHL, hepatomegaly	Matsuoka LY et al (1980)
7	31/M	Lower extremities, chest, back	-	Restrictive lung disease	Matsuoka LY, et al (1980)
8	31/F	Trunk, buttock, extremities	-	Uveitis, Restrictive ventilatory defect	Griffiths CEM, et al (1986)
9	52/M	Lower extremities	Erythematous plaque	Lung fibrosis	Medalene C, et al (1986)
10	65/M	Shins	-	-	Medalene C, et al (1986)
11	36/F	Lower extremities	EN-like lesion	BHL, uveitis	Banse-Kupin L, et al (1987)
12	36/F	Lower extremities	-	BHL	Banse-Kupin L, et al (1987)
13	44/M	Lower leg	-	BHL, facial palsy	Fred HL, et al (1990)
14	33/F	Lower leg	Papular lesion	BHL	Seth L, et al (1991)
15	60/F	Lower extremities, arms	Erythroderma	BHL, hepatosplenomegaly	Frend-Koopmans AG, et al (1996)
16	68/M	Lower extremities, abdomen	-	BHL	Cather J, at al (1990)
17	52/F	Lower extremities, thighs, chest	Yellowish papule	BHL	Schmuth M, et al (1999)
18	25/F	Upper/lower extremities, chest, arm, back, thighs	-	-	Gragopadhyay AK (2001)
19	36/M	Lower extremities	Erythematous papule subcutaneous nodule	-	Sawhney M, et al (2003)
20	39/F	Lower extremities	-	BHL	Rosenberg B, et al (2005)
21	27/F	Arm and legs	Subcutaneous nodule	BHL, splenomegaly	Zhang H (2009)
22	45/F	Shins, forearms	-	BHL, Multiple lymphadenopathy	Brain PK, et al (2010)
23	35/F	Lower leg and limbs	-	Cranial nerve palsy, paratracheal lymphadenopathy	Ghosh UC, et al (2013)
24	69/F	Lower extremities	Plaque lesion	BHL	Case 1
25	59/F	Lower extremities	Scar sarcoidosis	BHL, uveitis	Case 2
26	57/F	Lower extremities	EN-like lesion Subcutaneous nodule	BHL facial palsy	Case3

EN: erythema nodosum

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