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Subcutaneous sarcoidosis: a report of 13 cases and its association with extracutaneous sarcoidosis

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Introduction

Sarcoidosis is a systemic granulomatous disorder, mainly involving the lung, eye, and skin. Cutaneous sarcoidosis accounts for 20-35% of sarcoidosis patients, with different ratios depending on race (1-3). Cutaneous manifestations of sarcoidosis exhibit specific and non-specific lesions. Specific lesions histologically show non-caseating epithelioid cell granulomas, and the clinical features include papules, nodules, plaques, scars, lupus pernio, as well as various rare forms such as erythema nodosum-like, psoriasiform, ulcerative, and ichthyosiform lesions (3,4). By contrast, a representative of the non-specific lesions, which lack sarcoidal granulomas histologically, is erythema nodosum. Subcutaneous sarcoidosis is one of a rare form of cutaneous sarcoidosis, and studies with large study populations are few (5-8). Herein, we report 13 cases of subcutaneous sarcoidosis which we experienced in our department over a period of ten years.

Materials and methods

The current study was approved by the institutional review board of Fukushima Medical University. All enrolled patients were diagnosed with cutaneous sarcoidosis based on histological findings of non-caseating epithelioid cell granulomas, using the pathology database of the Department of Dermatology at Fukushima Medical University, between 2010 and 2019. Other granulomatous diseases, such as tuberculosis, deep fungal infection, necrobiosis lipoidica, or granuloma annulare, were excluded. Clinical charts were retrospectively examined and the patients' data such as age, gender, types of cutaneous lesion, serum levels of angiotensin converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R), extracutaneous organ involvement, and clinical course were evaluated.

Results

Thirteen cases (3 males and 10 females) developed subcutaneous sarcoidosis, involving the upper extremities (n = 4), trunk (n = 5), and lower extremities (n = 9) (Figure 1). The age range was 28-74 years old, and the mean age was 58.0 ± 15.1 years. A single lesion was observed in two cases, whereas multiple lesions were present in the other 11 cases. The other types of cutaneous sarcoidosis the patients had were scar sarcoidosis (n = 3), erythema nodosum-like lesion (n = 3), plaque-type (n = 3), lupus pernio (n = 1), and ichthyosiform sarcoidosis (n = 2). Histologically, sarcoidal granulomas were densely located in the subcutaneous tissues (Figure 2). Subcutaneous sarcoidosis developed as an initial manifestation in six cases. The lung was involved in all cases, and

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eye sarcoidosis was observed in seven cases. Cardiac sarcoidosis was observed in one case only, and facial palsy was observed in two cases. The other systemic diseases they had were ulcerative colitis (n = 1) and Cushing syndrome (n = 1). Serum levels of ACE were elevated in eight cases (61.5%) (25.4 to 66.2 IU/L, normal; 7-25), and sIL-2R was increased in six cases among eight cases examined (937 to 2730 U/ml, normal; 121-613) (unknown five cases). Regression was observed in seven cases, whereas two cases were resistant to therapies. Follow-up period was less than 1 year in three cases, and one case was not followed. Among the seven cases with resolution, oral prednisolone was used only in one case. Patients' characteristics were summarized in Table 1.

Discussion and conclusions

Subcutaneous sarcoidosis was previously estimated to account for 1.4-6% of the patients with systemic sarcoidosis (9,10); however, recent studies have shown that subcutaneous sarcoidosis was observed in 11.8% of specific cutaneous sarcoidosis cases (5), suggesting that the reported incidence of subcutaneous sarcoidosis may have been underestimated.

To date, there have been some reports on subcutaneous sarcoidosis. Ahmed et al. reported that, in their 21 cases of subcutaneous sarcoidosis, there was a female predominance and frequent involvement of extremities (upper extremity in 21 cases and lower extremity in 16 cases) (6). Other types of cutaneous lesion were observed in 15 cases (71%), which showed plaques (n = 6), papules (n = 4), erythema nodosum (n = 4) and scar sarcoid (n = 1). Systemic evaluation was performed on 20 patients, among whom pulmonary involvement was most common (n = 16), followed by arthritis (n = 3), mucositis (n = 3), peripheral neuropathy (n = 2), kidney sarcoid (n = 2), and uveitis (n = 2). Another study on subcutaneous sarcoidosis from Japan reported on nine patients with subcutaneous sarcoidosis among 35 patients with cutaneous sarcoidosis (7). Among the nine patients, eight were female. The involved sites were the upper extremities (n = 2), lower extremities (n = 7), trunk (n = 1) and hip (n = 1).

In the present study, during the years between 2010 and 2019, 57 cases of cutaneous sarcoidosis were diagnosed in our hospital, among which subcutaneous sarcoidosis was observed in 13 cases (22.8 %). Previous reviews suggest that subcutaneous sarcoidosis is a rare form of cutaneous sarcoidosis (8);

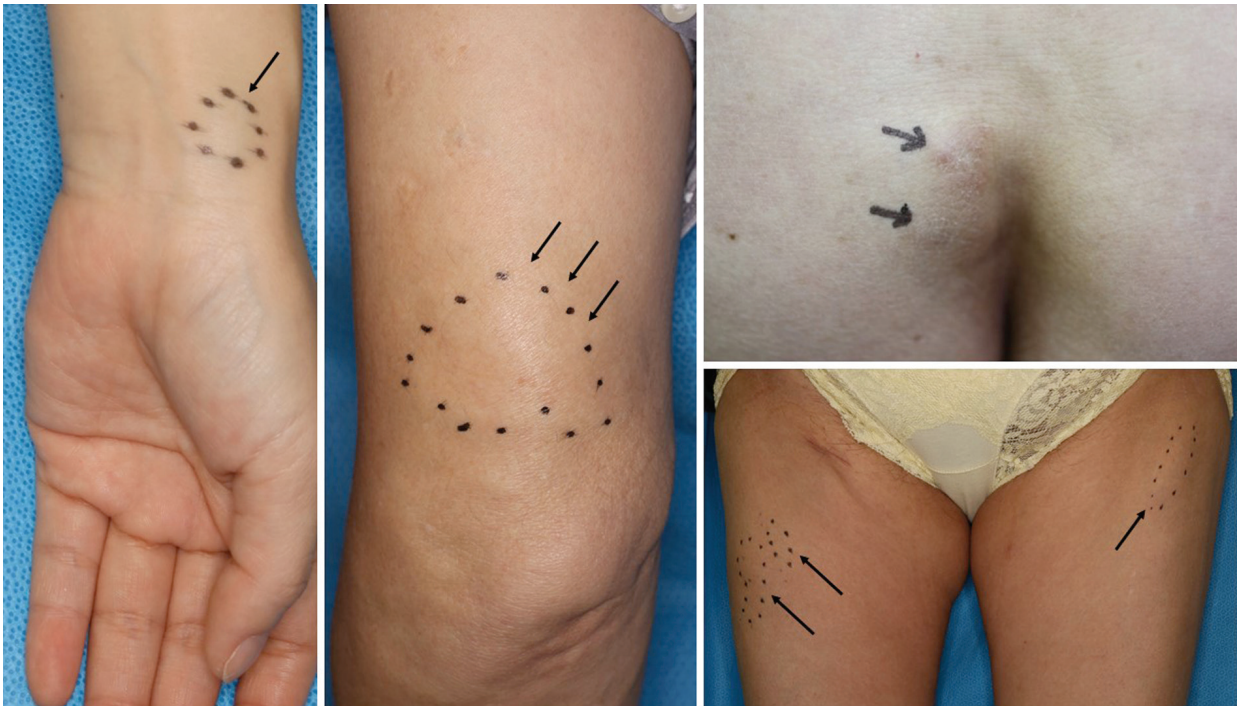

Fig. 1. Clinical features of subcutaneous nodules involving the upper and lower extremities, and buttock (indicated by arrows).

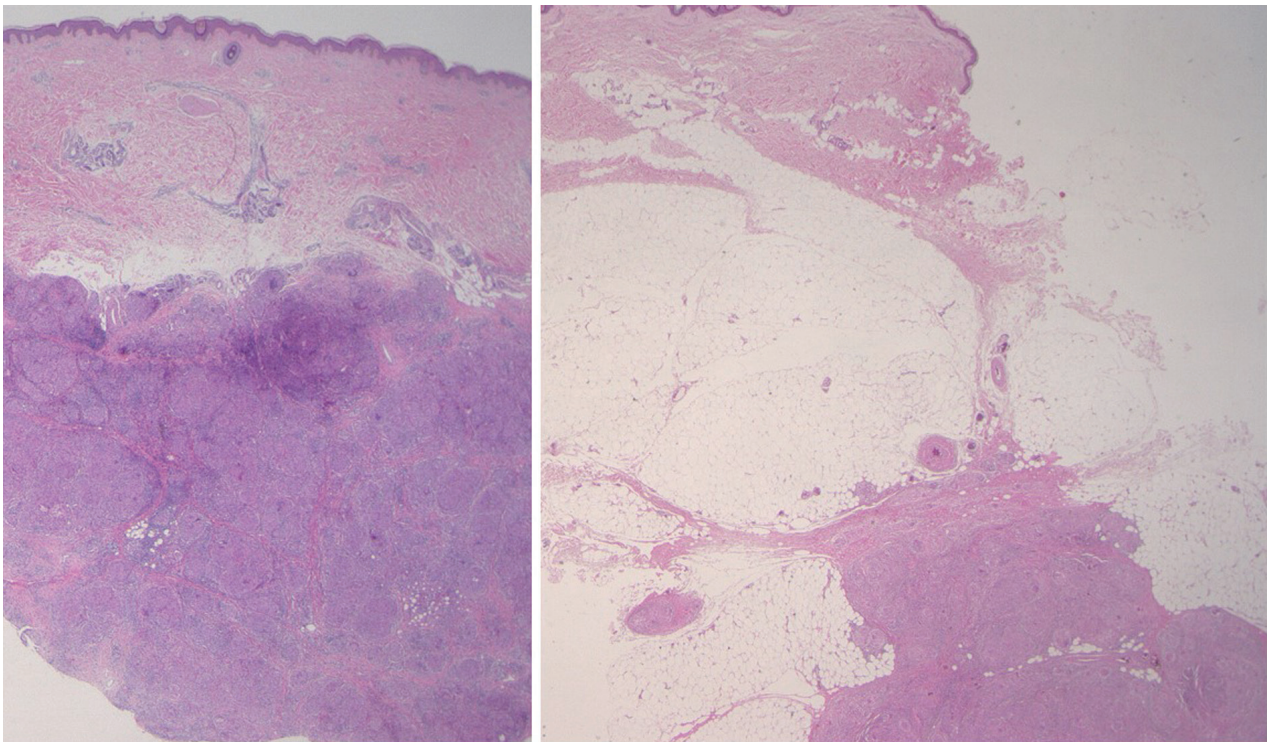

Fig. 2. Histological features showing epithelioid granulomas in the subcutis.

Table 1.

Case	Age/Sex	Location of subcutaneous nodule	Other types of cutaneous sarcoid	Lung	Eye	Heart	ACE	sIL2R
1	28/F	Lower extremity	Scar sarcoid	+	-	-	20.6	n.d.
2	69/M	Lower extremity	-	+	+	+	12	571
3	46/F	Trunk	Scar sarcoid, Erythema nodosum-like, Ichthyosiform	+	+	-	56.8	962
4	52/F	Lower extremity	Plaque	+	+	-	66.2	2730
5	39/F	Forearm, Abdomen	Erythema nodosum-like, Lupus pernio	+	+	-	20.6	1430
6	74/F	Buttock	Erythema nodosum-like	+	-	-	42.2	n.d.
7	73/F	Lower extremity	Scar sarcoid, Plaque	+	+	-	44	2140
8	63/F	Forearm	-	+	+	-	42.5	n.d.
9	65/M	Lower extremity	Plaque	+	-	-	19.6	n.d.
10	70/M	Upper/lower extremity, chest	-	+	-	-	16.8	565
11	69/F	Thigh	-	+	-	-	27.1	n.d.
12	41/F	Lower extremity, forearm, buttock	-	+	-	-	38.2	937
13	65/F	Lower extremity	Scar sarcoid, Ichthyosiform	+	+	-	25.4	1350

Table 2.

	Patient No.	F:M	Age distribution (mean)	Location	Lung(n)	Eye(n)	Heart(n)	Spontaneous regression
Marcoval J, et al. (2005)	10	9:1	29-70 (53 y.o.)	Upper extremity (10) Lower extremity (5)	9	Unknown	Unknown	6
Ahmed I, et.al. (2006)	21	15:6	26-61 (46.3 y.o.)	Upper extremity (21) Lower extremity (16) Trunk(6)	16	2	0	12
Ando M, et al.	9	8:1	23-69 (55.5 y.o.)	Upper extremity (2) Lower extremity (7) Trunk(2)	9	4	0	3
Present study	13	10:3	28-74 (58.0 y.o.)	Upper extremity (4) Lower extremity (9) Trunk(5)	13	7	1	7

however, subcutaneous sarcoidosis may not be so rare as was previously considered. In consistent with the previous data, our results showed a female predominance in Japanese patients, and the lower extremities were most commonly involved. Nearly half of the patients (6/13: 46.1%) in the current study developed subcutaneous lesions as an initial manifestation, which was similar to the results of a previous study (5). Pulmonary sarcoidosis was observed in all cases, and ophthalmological involvement was observed in over 50%. By contrast, cardiac involvement was rare, and peripheral neuronal involvement (Heerfordt syndrome) was observed in two cases. Regression was observed in seven of the 13 cases (53.8 %) in our series, for which systemic corticosteroid was administered in only one case, which suggests that subcutaneous sarcoidosis may be expected to resolve spontaneously. Other reports have shown that regression was observed with a ratio of 33.3-60% (5-8).

A comparison of previous reports is shown in Table 2. Subcutaneous sarcoidosis is closely associated with systemic involvement especially pulmonary sarcoidosis (5,7,8). In conclusion, subcutaneous sarcoidosis is a specific form of cutaneous sarcoidosis that is sometimes observed in Japanese patients with a female predominance, involving the lower leg, and frequently accompanies lung and ocular sarcoidosis. The present study has a few limitations, such as retrospective study and a lack of a long-term follow-up period. Nevertheless, our results may indicate a different frequency of cutaneous types of sarcoidosis patients in Japan compared to other countries.

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