Ulcerative Sarcoidosis: Case Report and Review of the Japanese Literature

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Sir,

Sarcoidosis is a chronic multi-system disease of unknown origin involving the eyes, skin, lungs, heart, bones and nerves. Skin lesions are relatively common, and are classified as either specific or non-specific (1). Specific lesions are those that show the typical sarcoid granulomas, including lupus pernio, infiltrated plaques, maculopapular eruptions, subcutaneous nodules and infiltration of old scars (1). The most typical non-specific skin lesion is erythema nodosum. The patient described here had skin lesions that first suggested a diagnosis of erythema induratum of Bazin, but we ultimately diagnosed sarcoidosis based on other findings, including uveitis, bilateral hilar lymphadenopathy, an increased level of serum angiotensin-converting enzymes (ACE) and a negative response to purified protein derivative of tuberculin (PPD).

CASE REPORT

A 59-year-old man presented with a 6-week history of a progressive, erythematous induration on the legs and arms. He had a medical history of uveitis, but not of tuberculosis. When first seen, he had multiple erythematous induration with tenderness on the arms and legs, linear ulcers and reticulated reddish-blue discoloration mostly on the edge of the erythema on the left leg (Fig. 1). A chest X-ray revealed diffuse changes suggestive of chronic bronchitis. Results from laboratory test, including a full blood count, urinalysis and liver function test, were normal except for elevated ACE (79.8 U/l, normal range: 7–25 U/l), elevated lysozymes (90 μg/ml, normal: 5–10 μg/ml), and slightly elevated CRP (1.36 mg/dl, normal: <0.15 mg/dl). Histopathological examination of the skin biopsy from his leg revealed a granulomatous tuberculoid feature both in the deep dermis and the subcutaneous tissue (Fig. 2a). Caseation necrosis and Langerhans' giant cells were partially seen among the epithelioid granulomas (Fig. 2b). Several small vessels in the deep dermis were involved, with granuloma and disruption of elastic fibre (Fig. 2c). Acid-fast bacilli were not found in the paraffin section of the specimen stained by Ziehl-Neelsen method and by PCR. Skin test with PPD showed no erythema at 48 h. Cultures of sputum and broncho-alveolar lavage (BAL) fluid were negative for acid-fast bacilli and common bacteria. The ratio of helper to suppressor T cells in BAL fluid was 5.8. The lung biopsy specimen obtained by the transbronchial method demonstrated epithelioid granulomas without caseation necrosis. Mediastinal adenopathy was found to be present on computed tomography of the chest. Sarcoidosis was finally diagnosed 8 weeks after the initial presentation. At that time, a daily dosage of prednisolone (30 mg) was prescribed for the uveitis, with a gradual reduction to 10 mg directed by the patient's ophthalmologist. After 6 months of treatment with prednisolone, the erythematous induration with ulcers had healed, leaving scars.

DISCUSSION

The typical histopathological findings for a sarcoid granuloma reveal a non-caseation granuloma with a negative stain for infectious organisms. Our patient showed skin lesions including erythema, induration and ulcers, a negative response to PPD, elevated ACE and lysozyme levels, an elevated T4/T8 ratio in BAL fluid, mediastinal adenopathy, epitheloid granulomas without caseation necrosis in the lungs and uveitis. These findings allowed us to diagnose sarcoidosis. However, our case was considered very rare because of the following two atypical features: the skin lesions were

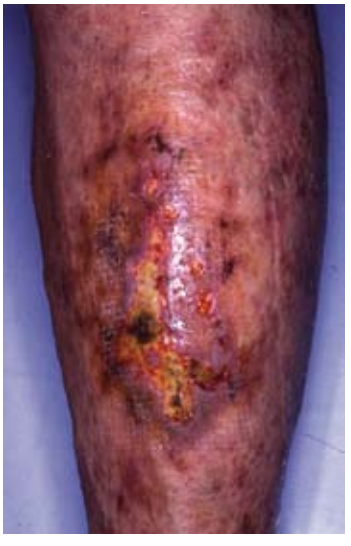

Fig. 1. Clinical manifestations of ulcerative sarcoidosis. Erythematous induration with ulcer and reticulate discoloration on the legs.

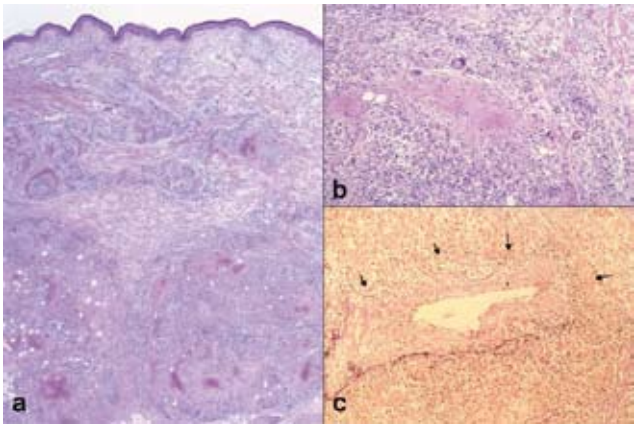

Fig. 2. Histology of a biopsy specimen taken from the induration on the left leg. (a) Granulomatous infiltrate was seen both in the deep dermis and subcutaneous tissue (H&E ×20). (b) Caseation necrosis and Langerhans' giant cells were partially seen among the epithelioid granuloma (H&E ×100). (c) A small vessel in the deep dermis was involved, with granuloma and disruption of elastic fibre (*arrows*) (Elastica van Gieson ×100).

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Table I. *Clinical feature of reviewed cases of ulcerative sarcoidosis in the literature*

Author (ref.)	Year	Number of cases	Race (*n*)	Gender (M:F)	Mean age (years)	Location of ulcer (*n*)	Systemic involvement (*n*)
Albertini et al. (2)	1997	35	Black (18) White (11) Japanese (1) Unknown (5)	12:22	"Young adults"	Leg (29) Arm (4) Trunk (3) Face (1) Penis (1) Multiple (6)	Respiratory (12) Ocular (9) Splenomegaly (8) Hepatomegaly (7)
Yoo et al. (3)	2005	7	Black (7)	2:5	38.6	Leg (7)	Respiratory (3) Mediastinal (4) Sinus (4)
Present study	2008	22	Japanese (22)	8:14	59	Leg (16) Head (2) Buttock (1) Multiple (2) Unknown (1)	Respiratory (15) Ocular (8)

accompanied by ulcers and histological examination revealed granulomas with caseation necrosis.

Ulcerative skin lesions rarely occur in sarcoidosis; they have been reported for only 1% of white patients with sarcoidosis (2). Yoo et al. (3) reported 7 cases of ulcerative sarcoidosis among their 147 cases of sarcoidosis over a period of 14 years (Table I). We gathered 22 cases of ulcerative sarcoidosis, including our case, from the Japanese literature for 20 recent years (4, 5). Of the 22 patients, 15 cases were reported after 1998. All these cases were racially Japanese. Of the patients listed in Albertini's review (2), 18 were black, 11 were white, and one was Japanese. The incidence of ulcerative sarcoidosis among Japanese people seems to be the same as that among black people, and to have increased over the past 10 years. Ulcerative sarcoidosis has been reported to be 1.8–3 times higher in women than in men. We identified a total of 14 women and 8 men in our review. The mean ages for female and male cases in Japan were 62.7 and 52.5 years, respectively. Sixteen patients had leg ulcers, 2 had head ulcers, one had a buttock ulcer, and 2 had multiple lesions. In the review by Albertini et al. (2), 11 of 35 cases presented with ulceration as the earliest manifestation. However, 17 of 19 Japanese patients had previously been diagnosed with sarcoidosis more than one year before the appearance of the ulcerative skin lesions. Evidence of extracutaneous sarcoidosis was found in many of these patients. We found that 15 of the 22 patients had lung lesions, whereas Albertini et al. (2) demonstrated that 12 of 35 cases had respiratory symptoms.

Almost all the cutaneous sarcoidosis showed histopathological features consistent with sarcoidal, non-caseating epithelial granuloma. However, several also showed atypical features including hyaline degeneration, necrotizing granulomas and granulomatous vasculitis. There have been a few reported cases showing caseation or coagulation necrosis (6). Kuramoto et al. (6) reported a case of subcutaneous sarcoidosis with extensive caseation necrosis. In systemic sarcoidosis, organs other than the skin histologically demonstrate necroses. They are also seen occasionally in pulmonary lesions that are described as cases of necrotizing sarcoid granulomatosis (7). The histological finding of necrosis in these lesions does not generally seem to be compatible with sarcoidosis. The lesions can be distinguished from those of other granulomatous disorders, such as Wegener's granulomatosis, because of their benign clinical courses (7). In our case, a lung biopsy did not reveal necrotizing sarcoid granulomatosis. More recently Poonawalla et al. (8) reported a case of ulcerative sarcoidosis with granulomatous vasculitis. Histopathological findings of their case showed focal involvement of medium-sized blood vessel walls, although there was no evidence of caseation necrosis. Saegusa et al. (9) also reported a case of clinically subcutaneous sarcoidosis and speculated that the necrotizing granuloma in dermis was caused by ischaemia due to the rapid increase in epithelioid cells in the granulomas. Our case revealed granulomatous vasculitis histologically in the deep dermis and reticulated reddish blue discoloration clinically.

Corticosteroids have been reported to improve the symptoms of sarcoidosis in all organs, including the eyes, lungs, nerves and skin. However, the indications for the steroid treatment of skin lesions include widespread, progressive, or disfiguring lesions or those that impair function. Our patient showed a good response to prednisolone therapy for his skin lesions and uveitis. Corticosteroids and methotrexate have also been shown to be effective treatment (2). In ulcerative sarcoidosis, treatment failures have been reported with the use of many types of treatment, such as chloroquine, topical corticosteroids, isotretinoin, antibiotics, anti-ulcer cream, X-ray therapy and skin grafts (2). Recently, adalimumab, a human monoclonal IgG1 tumour necrosis factor (TNF)-α antibody, has been reported to improve ulcerative lesions that have not responded to prednisolone or hydroxychloroquine (10). It is generally accepted that TNF-α may play a central role in the formation of granuloma in sarcoidosis (10).

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