A Case of Disseminated Cutaneous Sporotrichosis Mimicking Sarcoidosis, that Required Four Biopsies to Diagnose

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A 69-year-old Japanese woman visited Tokai University Oiso hospital with cutaneous ulcers on her left upper arm that appeared in January 2013, and on her right nose that appeared in December of 2013. Neither the two biopsies and tissue culture from the arm lesion nor the biopsy and tissue culture from the nose lesion detected any organism. In December of 2013, she was diagnosed as cutaneous sarcoidosis at Oiso hospital and treated with oral prednisolone for six months, however, did not show improvement. In June of 2014, third skin biopsy and culture from her left upper arm was done at our hospital, and also could not detect any organism. After six months of continuing treatment with oral steroids and steroid injections, the cutaneous ulcers became enlarged, with purulent exudate, requiring a fourth skin biopsy and culture from left upper arm, which finally detected Sporotrichosis. After one-month administration of itraconazole, in January of 2015, cutaneous ulcers of both the arm and nose shrunk. Sporotrichosis mimics sarcoidosis as well as other skin conditions clinically and histologically, therefore recognizing the importance of carrying out multiple skin biopsies and cultures are imperative to prevent misdiagnosis and improper treatments and possible dissemination.

Key words: Disseminated sporotrichosis, sarcoidosis, mimicking, cutaneous ulcer, multiple skin biopsy

INTRODUCTION

Sporotrichosis is a deep fungus infection caused by the dimorphic fungus *Sporothrix schenckii* species that often arises from traumatic inoculation of inhabited soil and organic debris into skin [1]. However, it is challenging to diagnose when the culture comes back negative. Here, we report disseminated cutaneous sporotrichosis mimicking sarcoidosis that needed multiple biopsies to diagnose.

CASE REPORT

A 69-year-old Japanese woman presented to a nearby dermatology clinic with skin lesion on her left upper arm in January of 2012. The skin lesion was biopsied and cultured twice at this clinic in May and October of 2012. No organism was detected, and she was diagnosed as cutaneous sarcoidosis. She was treated with topical corticosteroid for 11 months, but eventually dropped out of the treatment. She visited Tokai University Oiso Hospital in April of 2013 and was treated with intralesional injection of triamcinolone acetonide. However, after eight months, cutaneous ulcer appeared on her right nose in December of 2013. Skin biopsy and culture from this lesion which sent for bacterial, fungal and mycobacterial culture also came back negative. Treatment was switched to oral prednisolone (30 mg daily) and alfacalcidol for preventing osteoporosis beginning in December of 2013 for six months, but the lesion still did not show improvement. She was referred to our Tokai University Hospital in June of 2014.

Clinical findings showed 1 × 0.5 cm ulcer with yellowish necrotic debris and raised erythematous borders on her right nose, and 3 × 3 cm ulcer with yellowish necrotic debris and erythematous borders with surrounding small satellite ulcerations on her left upper arm (Fig. 1). The third skin biopsy and skin culture were obtained from cutaneous ulcer of her left upper arm and sent for bacterial, fungal and mycobacterial culture. Histopathological finding showed superficial and deep inflammatory cells with histiocytes, granuloma and giant cells infiltrate in the dermis (Fig. 2). No organism was detected in the bacterial, fungal and mycobacterial culture. Laboratory findings were as follows: white blood cell count, 16,700/μL (normal, 4,000–8,000); L-lactate dehydrogenase, 436 U/L (normal, 110–219); Ca, 9.6 mg/dl (normal, 8.6–10.0); C-reactive protein, 0.37 mg/dL (normal, < 0.30) angiotensin converting enzyme, 10.9 IU/L(normal, 7–25); soluble interleukin-2 receptor, 362 U/mL (normal, 145–519). There was no obvious arrhythmia on the electrocardiogram. Ophthalmic examination did not suggest any ocular findings such as uveitis, suggestive of sarcoidosis. Head computed tomography showed a 10 mm nodular lesion, with a non-uniform pale contrast enhancement effect in the base of the right nose, that suggested partial destruction of the nasal bone. Gallium scintigram showed accumulation at the base of the right nose. Chest CT showed linear cord-

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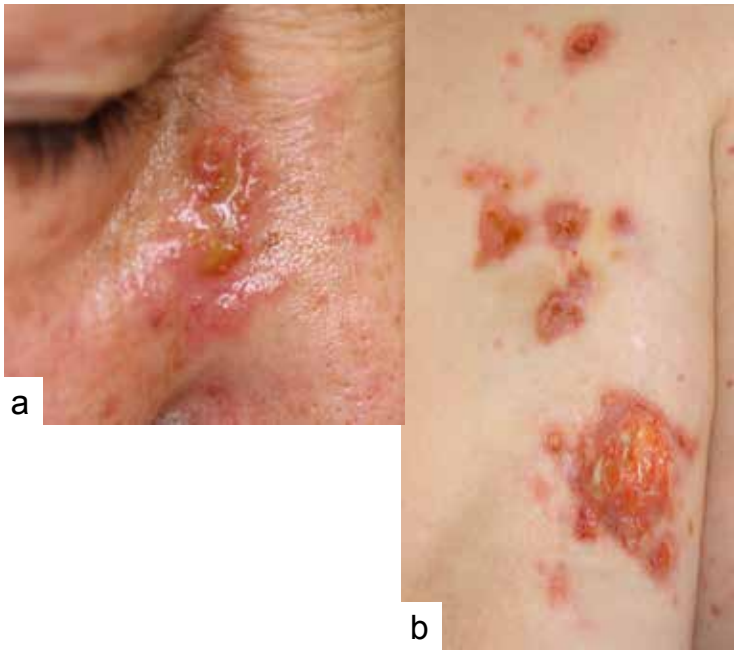

Fig. 1 Physical examination in June of 2014.
(a) 1 × 0.5 cm ulcer with yellowish necrotic debris and erythematous borders on her right side of the nose.
(b) 3 × 3 cm ulcer with yellowish necrotic debris undermined and erythematous borders with surrounding small satellite ulcerations on her left upper arm.

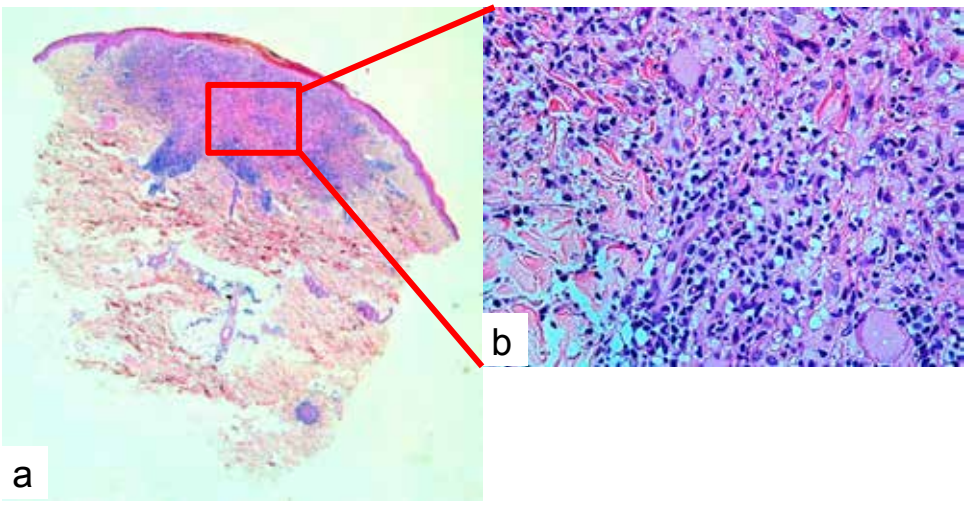

Fig. 2 Histopathological findings on her left upper arm in June of 2014. (the third biopsy)
(a) Superficial and deep mixed inflammatory cells infiltrate in the dermis. (Hematoxylin–eosin [HE], × 20)
(b) Infiltrated cells are numerous histiocytes, granuloma and giant cells. (HE, × 400)

like shadows and reticular shadows along the bronchial circumference in the middle lobe S4 of the right lung and the lingula of the upper lobe of the left lung, but no bilateral hilar-mediastinal lymphadenopathy. Based on these findings, she was diagnosed again as cutaneous sarcoidosis.

Oral prednisolone (30 mg daily) and intralesional injection of triamcinolone acetonide continued, nonetheless, the treatment did not result in any improvement with the lesion. She was also diagnosed with diabetes in August of 2014 and thoracic and lumbar compression fracture in October of 2014, that may have resulted from the long-term effect of prednisolone. After lumber compression fracture, oral alendronate sodium hydrate was added. However, after six months at our hospital, in January of 2015, the ulcer on her left upper arm enlarged and created a new abscess (Fig. 3). The fourth skin biopsy and culture were performed from this fresh lesion. This forth histopathological finding also showed superficial and deep mixed inflammatory cells with numerous histiocytes, granuloma and giant cells infiltrate in the dermis and subcutaneous tissue (Fig. 4), consistent with the prior three biopsies, however, Periodic acid-Schiff and Grocott's methenamine silver stain this time showed oval cigar-shaped yeast forms with single or multiple

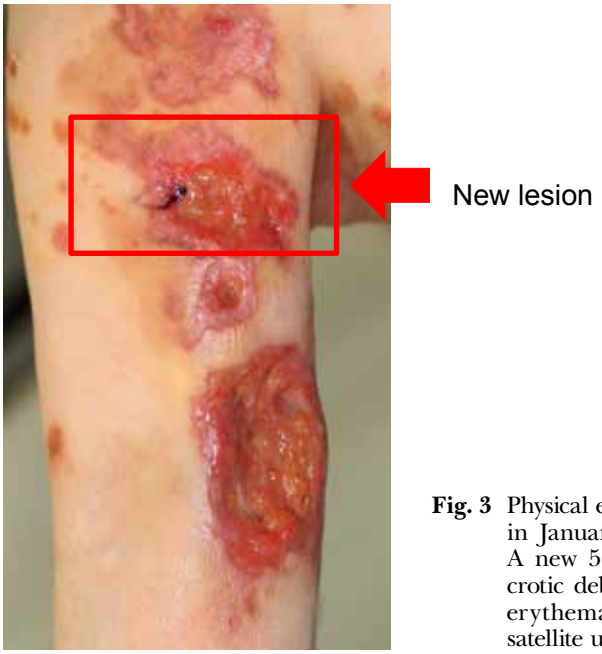

Fig. 3 Physical examination on her left upper arm in January of 2015.
A new 5 × 5 cm ulcer with yellowish necrotic debris and abscess undermined and erythematous borders with surrounding satellite ulcerations on her left upper arm.

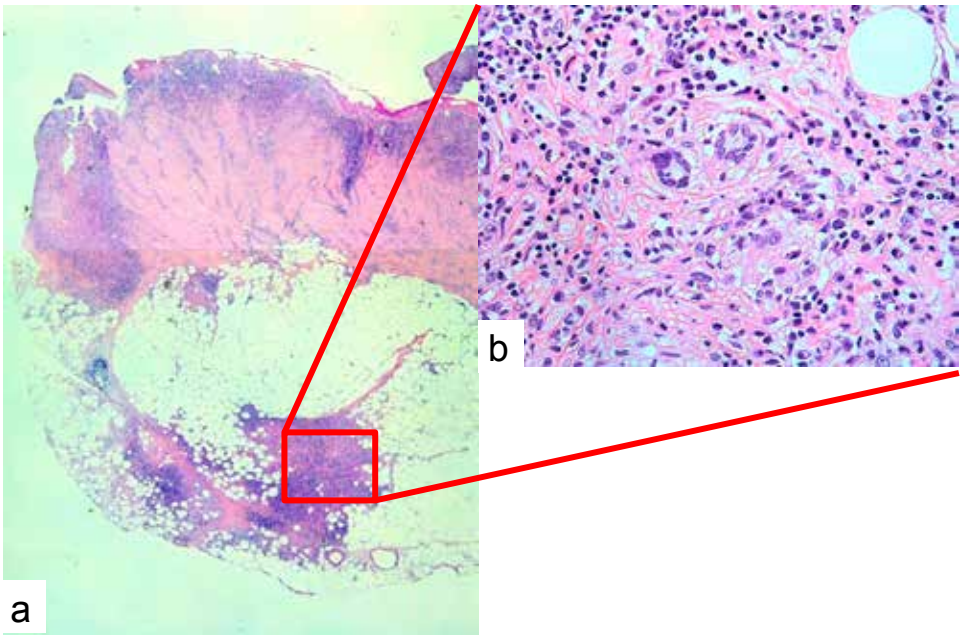

Fig. 4 Histopathological findings on her left upper arm in January of 2015. (Forth biopsy)
(a) Superficial and deep mixed inflammatory cells infiltrate in the dermis and subcutaneous tissue. (HE, × 20)
(b) Infiltrated cells are numerous histiocytes, granuloma and giant cells. (HE, × 400)

budding (Fig. 5). Filamentous and villous mould form of the organism grew on a potato dextrose agar plate at 25–30°C at day 10 and Lactophenol cotton blue preparation of the mould form cells showed delicate branching septate hyphae with slender conidiophores with tapering tips surrounding pyriform conidia (Fig. 6). It was identified as *Sporothrix* species morphologically. From the findings above, she was finally diagnosed as disseminated cutaneous sporotrichosis. After this diagnosis, she proceeded treatment with oral itraconazole (400 mg daily) for 24 days and tapered on the prednisolone. By February of 2015, the cutaneous ulcers gradually epithelized. Her laboratory data after three weeks from initiating oral itraconazole was within normal range including liver function. However, after two weeks, in February of 2015, she was suddenly unconscious and her family called ambulance. When emergency services arrived at her home, she was cardiopulmonary arrest. She was rushed to Oiso hospital by ambulance and her laboratory data showed multiple organ failure as follows; white blood cell count, 4000/μL (normal, 4,000–8,000); sodium, 128 mEq/L (normal, 136–145); potassium, 10.8 mEq/L (normal, 3.5–4.8); aspartate transaminase, 302 U/L (normal, < 30); alanine transaminase, 157 U/L (normal, < 35); blood urea nitrogen, 79 mg/dl (normal, 8–20); creatinine,

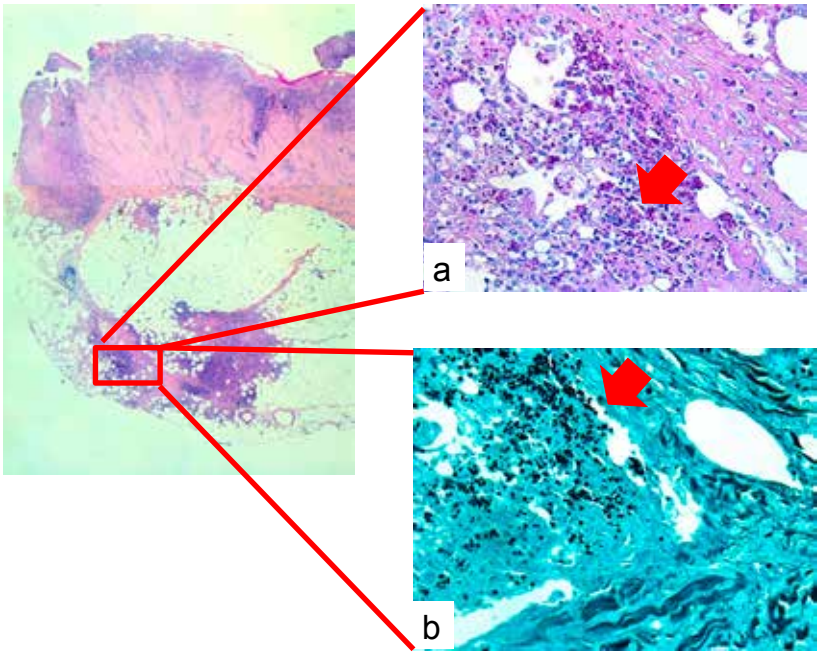

Fig. 5 Immunohistopathological findings on her left upper arm in January of 2015. (Forth biopsy): Oval cigar-shaped yeast forms with single or multiple budding.
(a) Periodic acid-Schiff stain, × 400 from subcutaneous tissue.
(b) Grocott's methenamine silver stain, × 400 from subcutaneous tissue.

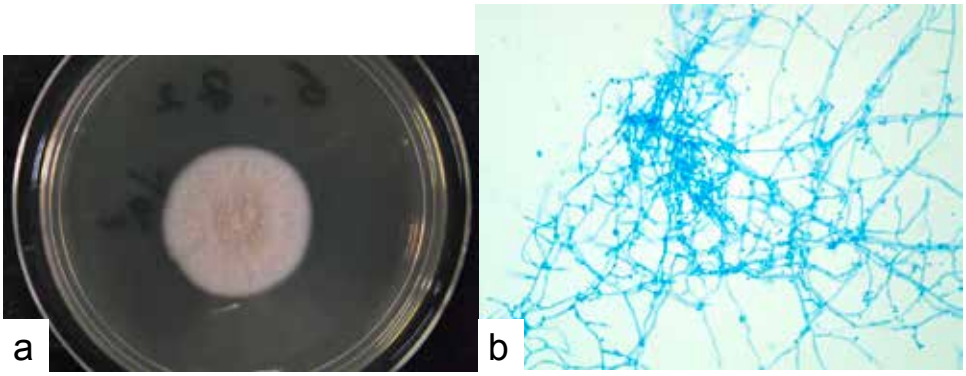

Fig. 6 Skin culture from her left upper arm in January of 2015. (Forth biopsy)
(a) Filamentous and villous mould form of the organism grown on a potato dextrose agar plate at 25–30°C at day 10.
(b) Lactophenol cotton blue preparation of the mould form cells showed delicate branching septate hyphae with slender conidiophores with tapering tips surrounding pyriform conidia.

4.01 mg/dl (normal, 0.5–0.8); C-reactive protein, 51.82 mg/dL (normal, < 0.30). Regardless of chest compression, she was pronounced dead. She was investigated by Oiso police because she was treated as unnatural death. However, the apparent cause of her death was unknown.

DISCUSSION

Sporotrichosis is a subacute or chronic mycosis that often arises from traumatic inoculation of inhabited soil and organic debris into skin [1]. The infection is usually limited to the skin in immunocompetent patients, usually in the form of lymphocutaneous sporotrichosis [1]. Accurate diagnosis rests on clinical data and culture and might be facilitated by biopsy identification of suppurative and granulomatous inflammation with fungal elements [1]. This disease is caused by a dimorphic fungus, previously described as a single species- *Sporothrix schenckii* [2]. The species is now recognized as *Sporothrix schenckii* complex, which comprises of three phylogenetic sibling species, *Sporothrix brasiliensis*, *Sporothrix globosa*, and *Sporothrix luriei*, in addition to *Sporothrix schenckii sensu stricto*, based on phylogenetic studies using DNA sequencing [2]. In Japan, it is reported that 97% were *Sporothrix globosa* and 3% were *Sporothrix schenckii sensu stricto* by DNA sequencing [2]. In our case, the skin culture came back positive for *Sporothrix* species morphologically, but did not perform DNA sequencing. Most patients have a history of agricultural work or hobbies, or exposure to infected animals such as cats [1]. In our case, she might have been exposed to soil because she

regularly gardened for recreation.

There are multiple reports of sporotrichosis mimicking sarcoidosis, making the diagnosis very difficult without a positive culture. Yang *et al.* [3] reported a 40-year-old Caucasian man who had been treated as sarcoidosis in pulmonary lesion and nonhealing ulcers, who was finally diagnosed as disseminated sporotrichosis after a few courses of prednisone treatment. After switching treatments to itraconazole, the skin ulcers healed, and pulmonary lesions also improved. Singh *et al.* [4] also reported that a 49-year-old white man who developed disseminated infection with *Sporothrix schenckii* with cutaneous (subcutaneous nodules of the arms, lower limbs and abdomen), pulmonary, ocular, oral, nasal and articular involvement, was misdiagnosed as sarcoidosis and treated with oral prednisone and intramuscular methotrexate. Similar to the man reported by Yang *et al.*, after switching treatments to oral itraconazole (400 mg daily), the skin lesions, hoarseness, fever and articular complaints disappeared. They pointed out the necessity of several tissue culture for infectious agents, particularly sarcoid-like reactions that do not respond to corticosteroid treatment because cultures for *Sporothrix* are often negative [4].

The similarity between our case and those previously reported cases, are that they were also diagnosed as sarcoidosis and treated with prednisone because first tissue culture could not detect any organisms. Repeated examination was the key to diagnosis of sporotrichosis. The difference between our case and those previously reported cases, was that our patient had no internal organ involvement. Those reported two cases were performed additional skin biopsy due to enlargement of the skin lesion and worsening of symptoms such as hoarseness of his voice, respectively. In our case, she was treated with oral prednisone and later additional injection of triamcinolone acetonide for a few years before the skin lesion enlarged. Therefore, it took us longer to perform the fourth biopsy and tissue culture, which may have been the cause of complications such as diabetes and lumbar fracture. We did not consult internal medicine doctors because our patient had no internal organ involvement including CT scan and Gallium scintigram.

Liver injury was known as the most feared side effects of itraconazole. Her laboratory data after three weeks from initiating itraconazole was within normal range including liver function. When she rushed to Oiso hospital by ambulance, her laboratory data showed multiple organ failure maybe because that blood tests were taken after cardiopulmonary arrest. Therefore, it's difficult to identify whether the abnormal liver function tests were caused by itraconazole or not. However, the possibility of itraconazole induced liver injury was not excluded.

Sporotrichosis often mimics sarcoidosis and pyoderma gangrenosum clinically and histologically, so it is difficult and challenging to diagnose sporotrichosis when the organism is not detected in the biopsy culture. In our case, the three previous skin biopsies couldn't diagnose sporotrichosis because the culture came back negative. We speculated two reasons why *Sporothrix* was detected the fourth time. First, we think there might be a possibility that *Sporothrix* was detected because of oral prednisolone. There might also be a possibility that diabetes caused immunosuppression causing *Sporothrix* to grow in numbers. Secondly, the size of the skin sample might have affected the result. With the fourth biopsy, 1 cm sample was excised, compared to 4 mm sample that was taken with the previous three biopsied. When experiencing cutaneous ulcers that does not respond to treatment, we should always reconsider the possibility of cutaneous mycosis including sporotrichosis. Importance of executing multiple skin biopsies and cultures is crucial in diagnosis of sporotrichosis and prevent prednisolone treatment related side effects such as diabetes and thoracic and lumbar compression fracture. Therefore, physicians taking care of these skin lesions should come up with discontinuing glucocorticoid and performing another biopsy when the patient is worsening as soon as possible.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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