Localized Cutaneous Cryptococcosis: Summary of Reported Cases in Japan

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ABSTRACT

A 68-year-old male plasterer with no history of trauma presented to our clinic in March 2012 with a 16 × 14-mm ulcer that developed following a crushed small papule on the right anterior chest. In April 2012, the patient was referred to another hospital, where cutaneous cryptococcosis was diagnosed based on discharge culture results. The patient was treated with oral itraconazole at a dose of 150 mg/day for 10 weeks; however, the ulcer remained unchanged and he discontinued the treatment. In May 2014, when he revisited our clinic, the ulcer with crust had grown to 29 × 13 mm. No regional lymph node swelling was noted. India ink staining showed a yeast-like fungus with a thick, clear capsule. A cream-colored, viscous yeast-like colony was observed on Sabouraud dextrose agar. Genetic testing identified the isolate as Cryptococcus neoformans serotype A. The patient was negative for serum cryptococcal antigen. Neither chest radiography nor computed tomography revealed any abnormalities. The patient had no underlying disease. Oral fluconazole (400 mg/day for 12 weeks) was prescribed, resulting in scar formation. The patient has remained free of relapse for one year to date, since the end of treatment. Localized cutaneous cryptococcosis is not a commonly used disease name overseas. However, 36 cases of this disease have been reported in Japan (since in 1968). We herein report a new case with localized cutaneous cryptococcosis and summarize previously reported cases in Japan.

Key words: cutaneous cryptococcosis, Cryptococcus neoformans, disseminated, localized

Introduction

Cutaneous cryptococcosis is classified as primary cutaneous cryptococcosis, which manifests as lesions formed by fungi that invade via the transcutaneous route, or as secondary cutaneous cryptococcosis, which manifests as lesions that are attributable to hematogenous dissemination, mainly from the lungs. Cutaneous cryptococcosis localized to the skin with neither visceral lesions nor a history of trauma was first referred to as localized cutaneous cryptococcosis by Geyer et al. in 1984. In Japan, since the report by Tanabe et al. in 1987, localized cutaneous cryptococcosis has been distinguished from primary or secondary cutaneous cryptococcosis (Table 1), and 36 cases have been reported to date. Herein, we report our recent experience with a typical case of localized cutaneous cryptococcosis.
Case

The patient was a previously healthy 68-year-old male plasterer. He kept a Manchurian bush warbler (Horornis borealis) as a pet from 2009 to November 2011. He noticed a small papule (approximately 3 mm) on his anterior chest in September 2011, which eventually formed an ulcer. In March 2012, when he first visited our clinic, physical examination showed a 16 × 14-mm ulcer on the anterior chest (Fig. 1). He was treated with oral minocycline at a dose of 200 mg/day for 14 days and topical silver sulfadiazine; however, the ulcer did not respond to the treatment. Thus, the patient was referred to another hospital in April 2012, where cutaneous cryptococcosis was diagnosed based on a discharge culture, and oral itraconazole (150 mg/day for 10 weeks) was prescribed. However, the ulcer remained unchanged, and he discontinued the treatment on his own judgment. In May 2014, when he revisited our clinic, the ulcer had grown to 29 × 13 mm in size and was accompanied by crust and erythema (36 × 28 mm in size) on the right anterior chest (Fig. 2a). The patient experienced no subjective symptoms. India ink staining of discharge smear showed a yeast-like fungus with a thick, clear capsule with a major axis of 10 μm (Fig. 3a). Cultures of the crust on Sabouraud dextrose agar that were incubated at 25°C for 3 weeks yielded a cream-colored, viscous colony (Fig. 3b). DNA was extracted from the isolate, and homology search was performed with the polymerase chain reaction (PCR) products for the internal transcribed spacer 1 and D1/D2 region of 26S rDNA, resulting to 100% identity to those of Cryptococcus neoformans. In addition, based on a PCR analysis, the isolate was classified as serotype A and mating type a8. The biochemical findings were within normal limits. Complete blood count revealed no abnormalities. The patient was negative for both serum cryptococcal antigen or human T-cell lymphotropic virus type I antibody. Neither chest radiography nor computed

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<th>Table 1. The definition of primary cutaneous cryptococcosis and localized cutaneous cryptococcosis</th>
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<td><strong>Primary cutaneous cryptococcosis</strong>&lt;sup&gt;10&lt;/sup&gt;:</td>
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<td>A solitary skin lesion presenting as a whitlow or phlegmon on an exposed area without simultaneous dissemination. The evidence includes a history of skin injury, participation in outdoor activities, exposure to bird droppings, and isolation of <em>C. neoformans</em> serotype D. All other cases are classified as secondary cutaneous cryptococcosis.</td>
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<td><strong>Localized cutaneous cryptococcosis</strong>&lt;sup&gt;12&lt;/sup&gt;:</td>
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<td>Isolated skin lesion(s) presents without simultaneous dissemination. Neither extracutaneous spread nor antigenemia is found. When positive fungemia or antigenemia, central nervous system involvement, or involvement of at least two non-contiguous organs is present, cases are classified as disseminated or systemic cutaneous cryptococcosis.</td>
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Fig. 1. Clinical features at the first visit. A 16 × 14-mm ulcer can be seen on the anterior chest.

Fig. 2. At the second visit, the ulcer had grown to 29 × 13 mm in size and was accompanied by crust and erythema (a). Clinical features at 4 weeks (b) and 8 weeks (c) after the start of treatment with fluconazole at a dose of 400 mg/day are shown.
tomography revealed any abnormalities. Based on the above findings, localized cutaneous cryptococcosis was diagnosed, although skin biopsy was not available because of the patient’s refusal. The minimal inhibitory concentrations were 1 μg/ml for amphotericin, 4 μg/ml for 5-fluorocytosine, 0.5 μg/ml for miconazole, 4 μg/ml for fluconazole, 0.125 μg/ml for itraconazole, 16 μg/ml for micafungin, and 0.06 μg/ml for voriconazole. However, according to the Infectious Disease Society of America guidelines, oral fluconazole (400 mg/day for 12 weeks) was prescribed. The ulcer healed with scar formation (Fig. 2b and c). The patient has remained free of relapse to date, one year after the end of treatment.

Discussion

Cutaneous cryptococcosis is a rare disease. Many cases are classified as secondary cutaneous cryptococcosis, in which skin lesions are caused by fungi that are hematogenously disseminated from foci of the lungs or central nervous system, particularly in immunocompromised patients. This disease is reported to account for approximately 10% of all cryptococcosis cases. In patients with acquired immunodeficiency syndrome, the skin is the second-most affected organ after the lung. The typical clinical manifestation is molluscum contagiosum-like papules with central umbilication, which commonly occur in the head and neck.

Primary cutaneous cryptococcosis is an extremely rare disease in which lesions are formed by transcutaneously inoculated fungi. Neuville et al. (the French Cryptococcosis Study Group) defined primary cutaneous cryptococcosis as fulfilling at least two of the following criteria: 1) skin lesions are localized to one part of the body with no signs of dissemination; 2) patients have a history of apparent trauma or are engaged in outdoor activities; 3) patients’ jobs or hobbies are potentially associated with risk for trauma; 4) patients have been exposed to something contaminated with fungi; and 5) lesions are located in an exposed area. In Japan, 15 cases of primary cutaneous cryptococcosis have been reported to date since its first description by Fukushiro et al. in 1968. These cases included 5 men and 10 women, with a mean age of 51.3 years. The details of these cases are summarized in Table 2.

In 2012, Biancheri et al. proposed that disease limited to the skin be called “localized cutaneous cryptococcosis,” irrespective of whether the fungus penetrated the skin or spread via the bloodstream, mainly from the lungs, and whether cutaneous lesions are the initial manifestation of pre-existing systemic cryptococcosis. Furthermore, they noted that whether lesions are localized to the skin or disseminated is important with respect to treatment, whereas the route of infection (i.e., whether lesions are primary or secondary) is not important. Eventually, they redefined localized cutaneous cryptococcosis as the opposite of systemic or disseminated cutaneous cryptococcosis.

Although localized cutaneous cryptococcosis can sometimes include primary cryptococcosis, it was defined here as being not due to primary inoculation or secondary dissemination, in that there is no history of a skin injury and no recognizable foci of cryptococcal infection. In Japan, 36 cases with localized cutaneous cryptococcosis, including ours, have been reported since it was first described by Minami et al. in 1968. The details of these cases are summarized in Table 2. There were 14 men and 22 women. These patients were relatively old, with a mean age of 61.5 years. Patients with an underlying disease accounted for 66.7% of all cases, those with serotype A accounted for 81.8%, and those positive for serum cryptococcal antigen accounted for 77.8%. These frequencies may reflect the inclusion of patients with disseminated or syste-
mic cutaneous cryptococcosis. Moreover, it is reasonable to consider a diagnosis of the disseminated type for patients with histologically deep lesions (e.g., subcutaneous nodules, induration, and cellulitis).\(^{15,16}\)

In Japan, cutaneous cryptococcosis is typically classified as localized or secondary cutaneous cryptococcosis; however, localized cutaneous cryptococcosis should be recognized as the opposite of systemic or disseminated cutaneous cryptococcosis. The patient presented herein was previously healthy and developed cutaneous cryptococcosis on the anterior chest. Skin lesions stayed in the same region without disseminated lesions over a 2-year period. The symptoms were consistent with those of cases with localized cutaneous cryptococcosis reported previously. However, the present patient may have asymptomatic lesions that are hidden in the visceras. Therefore, detailed examinations, including measurement of cryptococcal antigen in the serum and spinal fluid, chest radiography, computed tomography, and magnetic resonance imaging, need to be performed periodically. The present case appears to be typical and should be closely followed up.

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### Conflict of Interest

All authors declare no conflict of interest.
References


