Review

Cutaneous Cryptococcosis

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ABSTRACT

Cutaneous cryptococcosis is classified either as primary or secondary based on the route of infection. The disease can also be classified either as localized cutaneous cryptococcosis or cutaneous manifestations of disseminated cryptococcosis. However, from a physician’s point of view, whether lesions are localized to the skin or are disseminated/systemic is more important than the route of infection. The Clinical Practice Guidelines for Diagnosis and Treatment of Cryptococcosis, which was established in 2019 by the Japanese Society for Medical Mycology, adopted the latter classification. Localized cutaneous cryptococcosis is defined as a condition in which lesions are confined within a limited part of the skin, not systemically disseminated at the same time, and are associated with neither cryptococcal fungemia nor glucuronoxylomannan (GXM) antigenemia. In Japan, localized cutaneous cryptococcosis was further classified into primary and secondary cutaneous cryptococcosis. Since the first documented case in Japan in 19875, localized cutaneous cryptococcosis cases reported in Japan.

Key words: Cryptococcus neoformans, cutaneous manifestation of disseminated cryptococcosis, localized cutaneous cryptococcosis, primary cutaneous cryptococcosis, secondary cutaneous cryptococcosis

Introduction

Cutaneous cryptococcosis is classified into primary cutaneous cryptococcosis, which is characterized by traumatic inoculation of Cryptococcus species causing skin lesions, and secondary cutaneous cryptococcosis, which is characterized by hematogenous fungal dissemination primarily from the lungs causing skin lesions5,9. The infection can also be classified into localized cutaneous cryptococcosis and cutaneous manifestations of disseminated cryptococcosis6. However, from a physician’s point of view, whether lesions are localized to the skin or are disseminated/systemic is more important than the route of infection. The Clinical Practice Guidelines for Diagnosis and Treatment of Cryptococcosis, which was established in 2019 by the Japanese Society for Medical Mycology (JSMM), adopted the latter classification. Localized cutaneous cryptococcosis is defined as a condition in which lesions are confined within a limited part of the skin regardless of the route of infection, not systemically disseminated at the same time, and are associated with neither cryptococcal fungemia nor glucuronoxylomannan (GXM) antigenemia. In Japan, localized cutaneous cryptococcosis is defined as cryptococcosis of the skin that is not associated with either visceral lesions or a history of traumatic injury, and the lesions are confined within the skin organ7. Since the first documented case in Japan in 19879, localized cutaneous cryptococcosis was further classified into primary and
secondary cutaneous cryptococcosis. Redefined localized cutaneous cryptococcosis includes almost all cases of primary cutaneous cryptococcosis and a few previously reported cases of localized cutaneous cryptococcosis. Here we describe the clinical features, diagnosis, and treatment of cutaneous cryptococcosis according to the current classification.

Clinical features of cutaneous cryptococcosis

The genus Cryptococcus includes basidiomycetous yeasts and comprises more than 38 species, of which two are considered potentially pathogenic: Cryptococcus neoformans and C. gattii. These two species were previously considered as subspecies (varieties) of C. neoformans but are now classified as distinct species. Although both are found worldwide, they have different primary ecological niches. C. neoformans is ubiquitous in the environment and commonly isolated from pigeon dropping, whereas C. gattii is more frequently isolated from decaying wood and soil. C. gattii has a specific ecological association with Eucalyptus camaldulensis. The global distribution of the tree corresponds to the epidemiologic distribution of cryptococcosis caused by C. gattii.

Serotype D strains were found to occur more frequently than serotype A, AD, B, or C strains among C. neoformans isolates from patients with cutaneous cryptococcosis. Cryptococcus neoformans var. neoformans (serotype D) strains are more susceptible to heat than C. neoformans var. grubii (serotype A) strains and the dermatopism associated with serotype D strains may reflect a preference for growth in the cooler tissue of the skin. In tropical and subtropical regions, C. gattii (serotypes B and C), which is isolated from trees (particularly Eucalyptus), invades wounds and causes localized cutaneous cryptococcosis primarily in immunocompetent individuals.

Cutaneous manifestations of disseminated cryptococcosis account for 5%-15% of all cryptococcosis cases. According to a national survey in Japan, 123 patients with disseminated cryptococcosis were registered during the 51-week study period from 2014 to 2015, and of the 123 patients, 12 (10%) presented with cutaneous symptoms. Overall, 105 (85%) patients had immunodeficiency due to underlying diseases, treatment with immunosuppressant drugs, and/or other reasons, and 8 (7%) patients were infected with the human immunodeficiency virus (HIV). Underlying diseases or other factors associated with cutaneous manifestations of disseminated cryptococcosis include HIV infection, use of systemic corticosteroids, hematologic and solid organ malignancies, CD4 lymphocytopenia, chemotherapy for cancer, immunosuppression after solid organ transplantation, sarcoidosis, diabetes mellitus, and, rarely, hepatic cirrhosis. Of the four patients with cutaneous cryptococcosis complicated by sarcoidosis, two were not treated with corticosteroids.

Cryptococcus species can be found not only in the feces of birds, particularly pigeons, but also in canaries, budgerigars, parrots, cockatoos, chickens, sparrows, and turtledoves. Although birds can carry fungus, they do not usually become sick.

Localized cutaneous cryptococcosis is not a common condition, and it is characterized by lesions that are confined within the skin organ. We searched for case reports in Japanese published from 1968 to August 2018 in the Ichushi Web (Japanese Medical Abstracts Society), and 65 patients presented with such infection in Japan (Table 1). Of these patients, 28 were men and 37 were women (male-to-female ratio: 1:1.3) with a mean age of 59.8 years. Because their diagnoses were based on the conventional classification of localized cutaneous cryptococcosis, our study showed that 23 (35%) patients presented with GXM antigenemia. There is a possibility, however, that this includes patients with disseminated serotype A infections that were initially occult and progressed insidiously during the disease process. Furthermore, 14 (22%) patients with primary cutaneous cryptococcosis had a history of traumatic injury. The isolates belonged to serotype A (55%, 12/22), serotype D (41%, 9/22), and serotype A/D (4%, 1/22). Approximately 68% (44/65) of patients had underlying diseases. Of the 65 patients, 20% (n = 13), 14% (n = 9), and 11% (n = 7) presented with autoimmune diseases (e.g., systemic lupus erythematosus [SLE] and chronic rheumatoid arthritis), hematologic malignancies (e.g., leukemia and myelodysplastic syndrome), and diabetes mellitus, respectively. Moreover, approximately 49% (32/65) of patients used systemic corticosteroids. A history of contact with birds was observed in 15% (10/65) of patients.

Diagnosis of cutaneous cryptococcosis

Cutaneous manifestations predominantly occur on the head and neck, and they are associated with various clinical features, such as acneliform papules, molluscum contagiosum-like lesions (Fig. 1), blisters, pustules, nodules (Fig. 2), granuloma, tumor, draining sinuses, ulcers (Fig. 3a), subcutaneous swellings, abscesses, cellulitides (Fig. 4a), eczematous plaques, and plaques. In patients with HIV, the prevalence rate of cutaneous manifestations of disseminated cryptococcosis is approximately 6% (21). Cutaneous lesions appear as umbilicated papules, nodules, and violaceous plaques, and such lesions frequently mimic molluscum contagiosum and Kaposi’s sarcoma. In some cases, Kaposi’s sarcoma and cutaneous cryptococcosis histologically coexisted in the same lesion. The typical manifestation was umbilicated papules with a tiny central hemorrhagic crust on the head and neck, which were observed in approximately 50% of cases. In Japan, cutaneous
| No | Age | Sex | Serotype | Antigenemia | Underlying conditions / systemic steroids | Trauma | Affected sites (symptoms) |
|----|-----|-----|----------|-------------|------------------------------------------|--------|--------------------------|
| 1  | 36  | F   | (-) / (-) | (-) / (-)  |                                          |        | Rt middle finger          |
| 2  | 41  | F   | (-) / (-) | (-) / (-)  |                                          |        | Lt orbital region          |
| 3  | 33  | M   | (-) / (+) | (-) / (-)  | Scalp (nodule), Lt cheek                  |        | Rt postauricular region    |
| 4  | 27  | F   | (-) / (-) | (-) / (-)  |                                          |        | Rt postauricular region    |
| 5  | 81  | M   | (-) / (+) | (-) / (-)  |                                          |        | Rt postauricular region    |
| 6  | 35  | F   | (-) / (+) | (-) / (-)  |                                          |        | Rt postauricular region    |
| 7  | 37  | F   | (-) / (-) | (-) / (-)  |                                          |        | Rt postauricular region    |
| 8  | 43  | F   | Systemic lupus erythematosus / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 9  | 74  | M   | Rheumatoid arthritis / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 10 | 55  | F   | Diabetes / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 11 | 27  | M   | D / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 12 | 29  | M   | Pilomidal sinus / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 13 | 67  | F   | (-) / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 14 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 15 | 42  | M   | D / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 16 | 43  | F   | Sarcoïdosis / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 17 | 74  | M   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 18 | 74  | F   | D / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 19 | 17  | F   | D / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 20 | 63  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 21 | 49  | M   | (-) / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 22 | 65  | D   | D / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 23 | 57  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 24 | 37  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 25 | 65  | M   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 26 | 42  | F   | Sarcoidosis / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 27 | 43  | F   | Systemic lupus erythematosus, nerosis / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 28 | 37  | F   | D / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 29 | 65  | F   | Diabetes / (+) | (-) / (-)  |                                          |        | Lt postauricular region    |
| 30 | 55  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 31 | 54  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 32 | 52  | M   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 33 | 55  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 34 | 70  | M   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 35 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 36 | 70  | M   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 37 | 42  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 38 | 43  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 39 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 40 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 41 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 42 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 43 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 44 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 45 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 46 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 47 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 48 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 49 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 50 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 51 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 52 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 53 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 54 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 55 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 56 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 57 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 58 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 59 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 60 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 61 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 62 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 63 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 64 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 65 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 66 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 67 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 68 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 69 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |
| 70 | 65  | F   | A / (+)  | (-) / (-)  |                                          |        | Lt postauricular region    |

Lt: left, Rt: right
manifestations of disseminated cryptococcosis with HIV infection have been observed in two patients.\(^{24,25}\)

Cutaneous manifestation of disseminated disease in most individuals who underwent solid organ transplantation (18%, 26/146) preferentially involves the lower extremities (65%, 15/23), and the clinical features were nodules/masses, maculopapular lesions, ulcers/pustules/abscesses, and cellulitides in 35% (8/23), maculopapular lesions in 30% (7/23),
ulcers/pustules/abscesses in 30% (7/23), and cellulitis in 30% (7/23) of patients. In solid organ transplant recipients, cellulitis of the lower limb is a characteristic clinical presentation. The occurrence of cutaneous cryptococcosis mimicking pyoderma gangrenosum has been reported.

In localized cutaneous cryptococcosis in Japan, 6% (n = 5), 23% (n = 20), 25% (n = 21), 19% (n = 16), and 27% (n = 23) of lesions involved the head, face, upper limbs, trunk, and lower limbs, respectively (Table 1). Solitary lesions were observed in 80% (52/65) of patients, and multiple lesions were noted in 20% (13/65) of patients. The clinical manifestations were as follows: ulcers in 38% (32/85), papules/nodules/tumor in 26% (22/85), subcutaneous nodules/induration/cellulitides in 20% (17/85), and localized infiltrative erythema in 16% (14/85) of patients.

To diagnose localized cutaneous cryptococcosis, disseminated cryptococcosis should be excluded by using cultures (14/85) of patients in 20% (17/85), and localized infiltrative erythema in 16% (22/85), subcutaneous nodules/induration/cellulitides in 20% (17/85), and localized infiltrative erythema in 16% (14/85) of patients.

To diagnose localized cutaneous cryptococcosis, disseminated cryptococcosis should be excluded by using cultures with a sufficient amount of blood, spinal fluid, and urine; GXM antigen test; chest computed tomography scan; and sometimes bronchoscopy. Ng et al. have concluded that disseminated cryptococcosis is characterized by the following features: inflammation in the deep dermis or subcutaneous fat, lesion on covered parts of the body, and multifocal skin lesions.

When cutaneous cryptococcosis is suspected, direct microscopic examination is useful. Tzanck smear (Giemsa staining) and India ink method prepared from the base of the vesicles, pustules, acneiform lesions, or ulcers may show the encapsulated yeast form of Cryptococcus. The stamp smear preparation of biopsy specimen is also helpful. Histopathological diagnosis should also be performed to isolate and identify pathogenic fungi in the tissue. Pathogens in the tissue can be identified as fungal elements surrounded by a bright area (polysaccharide capsule) via hematoxylin-eosin staining. They are stained magenta by Periodic acid-Schiff stain and dark brown by Grocott’s methenamine silver stain. Their capsules, either thick or thin, are stained red by mucicarmine stain.

**Treatment of cutaneous cryptococcosis**

The therapeutic strategy for cutaneous cryptococcosis is determined based on severity, treatment response, and immune status of a patient. Regarding therapeutic regimens, patients with fungemia or disseminated cryptococcosis (defined as separated lesions occurring in multiple sites or a serum GXM antigen titer level that is equal to or greater than 512) are treated with antifungal therapy used for cryptococcal meningoencephalitis. Meanwhile, fluconazole is orally administered at a dose of 400 mg (6 mg/kg)/day for 3 months in patients with solitary lesions and are not diagnosed with cryptococcal meningoencephalitis, cryptococcal pneumonia, fungemia (cryptococcemia), or immunodeficiency. Itraconazole with a dose range of 100-400 mg/day for 3-6 months is also a therapeutic option for localized cutaneous cryptococcosis in immunocompetent patients. Itraconazole solution is recommended due to its higher serum drug concentrations and better clinical response rates than the capsule formulation. Moreover, cutaneous manifestations of disseminated cryptococcosis complicated by SLE were treated with an intermittent 3-day on/off cycle of Itraconazole at a dose of 400 mg/day for 5 months. In another case report, the patient was successfully treated with the combination of liposomal amphotericin B, 5-fluorocytosine, and voriconazole for cutaneous manifestations of disseminated cryptococcosis complicated by meningoencephalitis. Surgical resection is useful in some cases. In an 80-year-old woman, a 1-cm nodule located below the breast was removed via a simple resection. Meanwhile, in an 89-year-old man, a 3-cm ulcer developing on the head was removed with a resection margin of 1 cm from the border. Surgical debridement of necrotic tissue is effective in promoting wound healing.

**Conclusion**

In Japan, cutaneous cryptococcosis has been classified as primary, secondary, or localized cutaneous cryptococcosis. In the JSMM Clinical Practice Guidelines for Diagnosis and Treatment of Cryptococcosis 2019, the JSMM Guideline Committee classified cutaneous cryptococcosis into two categories: (1) localized cutaneous cryptococcosis accompanied by solitary lesions but not by fungemia (cryptococcemia) or immunodeficiency and (2) cutaneous manifestations of disseminated cryptococcosis that requires a variety of
treatments. Cryptococcal meningoencephalitis, cryptococcal pneumonia, and fungemia (cryptococcemia) should be excluded to diagnose the infection as localized cutaneous cryptococcosis. At this stage, we recommend the classification and diagnostic criteria adopted in the guidelines for the diagnosis and treatment of cutaneous cryptococcosis. Going forward, we should update the guidelines as needed.

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Conflict of Interest

None declared.

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