

## Cryptococcal Cellulitis in a Patient with Myelodysplastic Syndrome

Yusuke Inoue, Masahito Onoda, Michiko Aihara, Katsuji Koiwa, Yumiko Yamane and Zenro Ikezawa

Department of Dermatology, Yokohama City University School of Medicine, 3-9, Fukuura, Kanazawa-ku, Yokohama-shi, Kanagawa, 236-0004, Japan.

E-mail: yuh-yuh15@hotmail.co.jp

Accepted August 6, 2010.

Cryptococcosis is a rare fungal infection caused by the yeast-like encapsulated fungus *Cryptococcus neoformans*. Cutaneous involvement occurs as an extension of systemic disease after inhalation of fungal spores. However, localized skin involvement has been observed without evidence of disseminated disease. The incidence of primary and secondary cutaneous cryptococcosis is notably increased in immunocompromised hosts. Clinical manifestations vary greatly but include pustules, papules, nodes, ulcers, subcutaneous abscesses and cellulitis (1). We report a case of cryptococcal cellulitis in a patient with myelodysplastic syndrome (MDS).

### CASE REPORT

An 84-year-old man with MDS presented with erythema with subcutaneous induration on the left side of his chest in December 2005. He had been diagnosed with MDS (RA type) without chromosomal abnormalities and was thus deemed to be at low risk of developing leukaemia. During treatment, his peripheral blood was found to contain few blast cells. He had received prednisolone (PSL) (15 mg/day) without chemotherapy. Since his symptoms were not improved with antibiotics, he was referred to our clinic three weeks later.

At his first visit, edematous erythema was observed on the left side of his left chest, together with a 12.5 × 13.5 cm subcutaneous induration (Fig. 1a). He complained of pain when pressure was applied to the lesion. His cutaneous symptom recalled cellulitis but the subcutaneous induration he exhibited was not typical of that condition.

The results of blood tests were as follows: hemoglobin 10.0 g/dl (11.3–14.5 g/dl), platelets 56.0 × 10<sup>4</sup>/μl (18–39 × 10<sup>4</sup>/μl serum

amyloid A 1,195 μg/ml (<8 μg/ml), lactate dehydrogenase 341 U/l (125–225 U/l) and beta-D glucan <6.0 pg/ml (<11.0 pg/ml). Other data were within normal limits. Histopathological examination revealed many spores surrounded by clear zones in the reticular layer of the dermis, as well as in the subcutaneous fat (hematoxylin and eosin stain) (Fig. 2a). An intense inflammatory reaction, with the infiltration of neutrophils and lymphocytes, was observed throughout the dermis and subcutaneous tissue. Periodic acid-Schiff (PAS) stain showed numerous reddish purple stained spores surrounded by wide capsules (Fig. 2b). Grocott stain revealed the presence of multiple budding spores in the subcutaneous fat.

A tissue sample obtained by skin biopsy was cultured with Sabouraud dextrose agar, a procedure that yielded milk-white, creamy colonies. Identification of the culture material, as well as the results of a cryptococcal antigen test performed using the patient's serum – which showed a serum cryptococcal antigen titer of 1:8,192 on admission – led to a diagnosis of *C. neoformans* serotype A infection. General examinations, including a chest examination and a brain CT, revealed no lesions in other organs. Cerebrospinal fluid was not examined. The patient was finally diagnosed with cutaneous cryptococcosis.

The patient was treated with fluconazole (200 mg/day), administered either intravenously or orally. Although his lesion gradually improved after the initiation of fluconazole treatment, local tenderness persisted and a spontaneous rupture occurred three weeks later. After repeating debridement (Fig. 1b), the lesion improved and healed with scarring. The serum cryptococcal antigen titer dropped to 1:128. Fluconazole was administered for seven months.

### DISCUSSION

*C. neoformans* is a soil-dwelling eumycete that is well known to be carried by the feces of doves. It causes opportunistic infections (2–4), although no apparent predisposing immunological factor can be identified in more than half of patients. The primary site of infection is typically the lung, and the disease frequently manifests itself with signs of extrapulmonary dissemination, which in approximately 10–15% of cases involves the

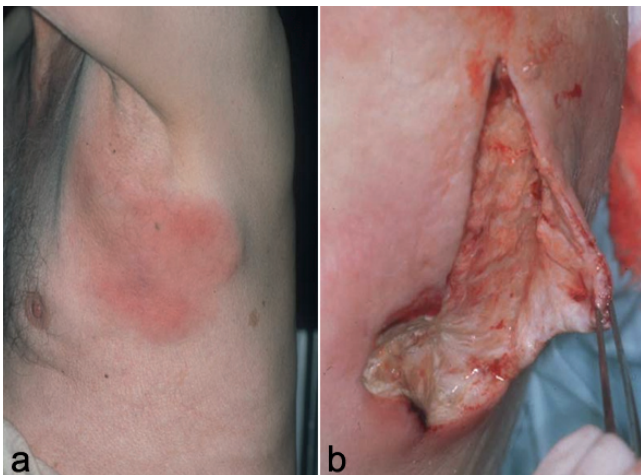


Fig. 1. (a) Clearly-bordered erythema with a 12.5 × 13.5 cm board-like induration on the left side of the patient's chest. These symptoms were accompanied by spontaneous pain and tenderness. (b) Extensive debridement was performed.

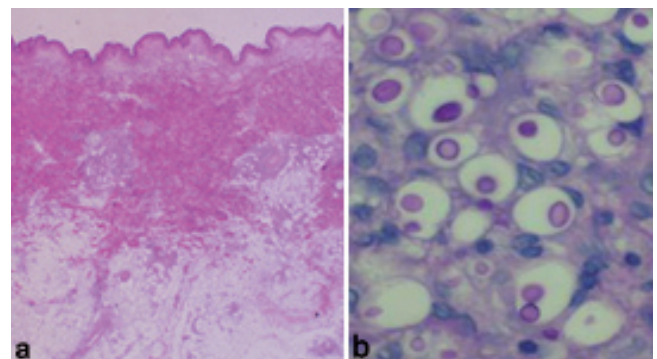


Fig. 2. (a) Large-scale infiltration of cells to the lower dermis and subcutaneous tissue (HE; ×40). (b) Spores stained purple with PAS (×600).

skin (5). In some patients, cutaneous cryptococcosis is observed without evidence of pulmonary disease. However, the existence of isolated cutaneous cryptococcosis is controversial (6).

Cryptococcal cellulitis is a variant form of cryptococcosis that is occasionally limited to the skin. It usually only occurs in immunosuppressed hosts, between whom it spreads rapidly. Our patient was treated for MDS through the long-term administration of a corticosteroid. This may explain the development of his cryptococcal cellulitis. Only two cases of cutaneous cryptococcosis in MDS patients have previously been reported in Japanese-language publications. However, we found 12 cases, reported in English, of patients with haematological malignancies who developed cutaneous cryptococcosis. These included cases of chronic lymphocytic leukemia (7), non-Hodgkin's lymphoma (8) and T-cell lymphoma (9). None reported associations with MDS.

Moore (10) has classified cases of cutaneous cryptococcosis according to their pathological features. Type 1 cases display pronounced tissue reactions involving granulomatous lesions containing histiocytes, giant cells and lymphoid cells. Fungous elements are present in small numbers in the lesions. Type 2 cases exhibit gelatinous lesions with numerous organisms in aggregates and very little tissue reaction. However, it has been suggested that cryptococcal cellulitis displays different histological manifestations – non-specific acute and chronic inflammatory reactions in which the presence of fungi can be demonstrated (11). In our patient's lesion, numerous fungus elements surrounded by gelatinous zones were observed, as well as an intense inflammatory reaction in the dermis and subcutaneous fat. Granulomatous lesions were not observed. This histology is consistent with cryptococcal cellulitis.

*C. neoformans* may be classified into five serotypes – A, B, C, D and AD – by a serological test. In Japan, serotype A is most frequently detected in patients with secondary cutaneous cryptococcosis. In contrast, it has been reported that most cases of primary cutaneous cryptococcosis are caused by infection with *C. neoformans* serotype D (12). Our patient was found to be infected with *C. neoformans* serotype A. In addition, he had not suffered a traumatic injury, or the environmental contamination of a wound, prior to the development of the disease. Taking account of these observations, we cannot exclude the possibility that our patient suffered an undetected asymptomatic lung infection that cleared spontaneously.

Combined therapy with amphotericin B and fluocytosine is recommended as a first-line treatment for disseminated cryptococcosis (13). Because of their low tissue toxicity at effective concentrations, triazole antifungal agents including fluconazole have been used in the treatment of cutaneous cryptococcosis. (14, 15). Fluconazole was used safely in our patient, despite his age and history of MDS. The combination of fluconazole

administration and debridement seems to be useful for intractable cutaneous cryptococcosis, which is most often accompanied by deep invasion in high-risk patients. However the risk of relapse is very high in patients with MDS at this dose level, and our patient will need to be followed up for a year or more.

#### ACKNOWLEDGEMENTS

We thank Prof. Reiko Ikeda (Meiji College of Pharmaceutical University Dept. of Microbiology) for performing *C. neoformans* serotype test and Prof Yoshiaki Inayama (Pathological department, Yokohama City University School of Medicine, Yokohama, Japan) for performing pathological examination.

#### REFERENCES

1. Sampaio RN, Medeiros B, Milfort M. Systemic cryptococcosis with solitary cutaneous lesion in an immunocompetent patient. *Int J Dermatol* 1999; 38: 773–775.
2. Wilson ML, Sewell LD, Mowad CM. Primary cutaneous cryptococcosis during therapy with methotrexate and adalimumab. *J Drugs Dermatol* 2008; 7: 53–54.
3. Moosbrugger EA, Adams BB, Kralovic SM. Cutaneous cryptococcosis in a patient on corticosteroid therapy for rheumatoid arthritis. *Int J Dermatol* 2008; 47: 630–632.
4. Christianson JC, Engber W, Andes D. Primary cutaneous cryptococcosis in immunocompetent and immunocompromised hosts. *Med Mycol* 2003; 41: 177–188.
5. Cawley EP, Grekin RH, Curtis AC. A review of the cutaneous and adjoining mucous membrane manifestations. *J Invest Dermatol* 1950; 14: 327–344.
6. Sanchez-Albisua B, Rodriguez-Peralto JL, Romero G, Alonso J. Cryptococcal cellulitis in an immunocompetent host. *J Am Acad Dermatol* 1997; 36: 109–112.
7. Dilhuydy MS, Jouary T, Demeaux H, Ravaud A. Cutaneous cryptococcosis with alemtuzumab in a patient treated for chronic lymphocytic leukaemia. *Br J Haematol* 2007; 137: 490.
8. Blanco P, Viallard JF, Beylot-Barry M, Faure I, Mercié P, Vergier B, et al. Cutaneous cryptococcosis resembling molluscum contagiosum in a patient with non-Hodgkin's lymphoma. *Clin Infect Dis* 1999; 29: 683–684.
9. Frieden TR, Bia FJ, Heald PW, Eisen RN, Patterson TF, Edelson RL. Cutaneous cryptococcosis in a patient with cutaneous T cell lymphoma receiving therapy with photopheresis and methotrexate. *Clin Infect Dis* 1993; 17: 776–778.
10. Moore M. Cryptococcus with cutaneous manifestation four cases with a review of published reports. *J Invest Dermatol* 1957; 28: 159–182.
11. Elder DE, Elenitsas R, Johnson BL, Murphy GF. *Lever's Histopathology of the skin*. 9th edition. Philadelphia: Lippincott Williams & Wilkins, 2005: 621–623.
12. Ikeda R, Shinoda T. Mycological and serological diagnosis of Cryptococcosis. *Jpn J Med Mycol* 2000; 41: 241–244.
13. Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, et al. Practice guidelines for the management of cryptococcal disease. *Infectious Diseases Society of America. Clin Infect Dis* 2000; 30: 710–718.
14. Ebara N, Kobayashi N, Asaka H. Localized cutaneous cryptococcosis in a patient with chronic myeloproliferative disease. *J Dermatol* 2005; 32: 674–676.
15. Diaz M, Negroni R, Montero-Gei F. A pan-American 5-year study of fluconazole therapy for deep mycoses in the immunocompetent host. *Pan-American Study Group. Clin Infect Dis* 1992; 14: 68–76.