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**Cutaneous cryptococcosis due to *Cryptococcus neoformans* with the formation of a giant subcutaneous nodule**

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**RUNNING HEAD:** Giant subcutaneous nodule due to *Cryptococcus neoformans*

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**ABBREVIATION:** MALDI-TOF MS, Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

**KEY WORDS:** *Cryptococcus neoformans*, cutaneous cryptococcosis, nodule, MALDI-TOF MS

27 **AUTHORS' CONTRIBUTIONS:** A.A., T.F., S.I., K.O., M.N., S.H., H.N., and A.K. analyzed  
28 the data and drafted the manuscript. All authors have read and approved the final manuscript.

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33 publication of their case details.

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36 ***Dear Editor,***

37 *Cryptococcus* is a common cause of infection in immunosuppressed patients.<sup>1</sup>

38 *Cryptococcus* species are encapsulated yeasts that are found in a variety of environments.

39 Infections can occur by inhalation of contaminated dust or by direct entry through trauma.<sup>1,2</sup>

40 Direct entry through a wound can cause various types of skin lesion.<sup>3</sup> Herein, we report a case

41 of cryptococcosis in a patient on long-term oral steroids who developed a giant subcutaneous

42 nodule on the thigh.

43 A 70-year-old man with minimal change nephrotic syndrome due to IgA-type membranous

44 nephropathy presented with a subcutaneous nodule on the right thigh, which he had noticed 2

45 months previously. He was taking prednisolone (10 mg/day) and cyclosporine (90 mg/day) for

46 his nephropathy.

47 Physical examination revealed a 14 × 8 cm well-defined elastic hard subcutaneous mass on

48 his right thigh with an erythema on the surface (Fig. 1a). Magnetic resonance imaging (MRI)

49 revealed a well-demarcated subcutaneous signal suggesting inflammation or edema (Fig. 1b,c).

50 Histopathology of a hematoxylin and eosin-stained biopsy specimen showed no abnormalities in

51 the epidermis or dermis, and revealed a colorless fungus with a thick, clear capsule in the

52 subcutaneous fatty tissue (Fig. 1d-g) which stained red using mucicarmine (Fig. 1h,i). Gram

53 (Fig. 1j), and India ink staining (Fig. 1k) of a smear also showed the presence of a fungus. The

absence of a red color reaction on glycine-cycloheximide-phenol red agar suggested that the organism was *Cryptococcus neoformans*, not *Cryptococcus gattii*. The isolate from the subcutaneous nodule was extracted using ethanol-formic acid and identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Japan, Kanagawa, Japan) as *C. neoformans* at the species level (score: 2.05). To further characterize the organism, fungal DNA was amplified using polymerase chain reaction (PCR) using primer sets targeting the IGS1 gene. Amplified PCR product was sequenced on an ABI Prism 3100 PCR Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The IGS1 gene sequence showed a 100% match with the corresponding regions of *C. neoformans* var. *grubii*. It was deposited in the International Nucleotide Sequence Database through the DNA Databank of Japan under accession number LC770308. A nodule with a cavity was found in the apex of the right lung, and *Cryptococcus* was detected on histopathological examination of bronchoscopic biopsy tissue. The patient was thus diagnosed with systemic cryptococcal infection of the lungs and skin. He was treated with fluconazole 400 mg/day. The nodule was barely palpable at the 2-month follow-up visit. Antifungal treatment was continued for one year.

Most cases of disseminated cryptococcal skin lesions in patients without a history of trauma occur as two or more lesions.<sup>4</sup> Unusually, this patient had a single large skin lesion without a history of trauma. It is not possible to detect the port of entry. The immune status of

72 this patient may make the unusual clinical presentation. MALDI-TOF MS can identify species  
73 faster, in fewer steps than conventional methods.<sup>5</sup> In immunosuppressed patients with rapid-  
74 growing skin lesions, considering cryptococcosis in the differential diagnosis can facilitate early  
75 diagnosis.

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94 **FIGURE LEGEND**

95 **FIGURE 1. Clinical and histopathological manifestations of the giant skin nodule.**

96 **(a)** A 14 × 8 cm infiltration of a relatively well-defined elastic hard nodule on the medial side of  
 97 the right thigh with an erythema on the surface. **(b, c)** Magnetic resonance imaging (MRI) short  
 98 tau inversion recovery (STIR) image showing an area of borderline clear signal change in the  
 99 subcutaneous region of the medial right thigh. The arrows indicate the location of the mass. **(d-**  
 100 **g)** Hematoxylin and eosin staining showing no abnormalities in the epidermis or dermis on low  
 101 magnification (×20; scale bar = 1000 μm) **(d)**, or the epidermis on high magnification (×400;  
 102 scale bar = 50 μm) **(e)**, and showing dense cellular infiltration between fat lobules (×20; scale  
 103 bar = 500 μm) **(f)**, and round or ovoid yeast cells in areas of fatty tissue, lacking cellular  
 104 components (×400; scale bar = 20 μm) **(g)**. **(h, i)** Mucicarmine staining showing a light red  
 105 stained cluster of cells in the fat tissue (×20; scale bar = 500 μm) **(h)**, and multiple light-red  
 106 stained circular fungal bodies (×400; scale bar = 20 μm) **(i)**. **(j, k)** Gram staining showing a  
 107 large gram-positive fungus (×1000; scale bar = 10 μm) **(j)**. India ink staining showing thick  
 108 capsules (×400; scale bar = 25 μm) **(k)**.

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Revised Figure1, Ariyoshi et al.

