Rapidly Progressive Skin Lesions Requiring Admission in a Young, HIV-Infected Man

*(See page 117 for the Photo Quiz.)*

**Diagnosis:** Disseminated Cryptococcosis With Prominent Skin Involvement

The patient’s serum cryptococcal antigen was strongly positive (titer >1:1024). After 96 hours of incubation, both blood and synovial fluid grew *Cryptococcus neoformans*. Cerebrospinal fluid (CSF) analysis showed no pleocytosis, and CSF cultures and cryptococcal antigen were negative. Skin biopsies revealed evidence of a granulomatous inflammation (arrow) in the dermis and subcutaneous tissue (Figure 1A). Round fungal organisms (arrowheads) were seen within the cytoplasm of histiocytes and multinucleated giant cells (Figure 1A-insert). Grocott’s methenamine silver stain demonstrated abundant budding yeasts ranging in size from 5 to 15 μm in diameter (Figure 1B). The budding cells (arrowhead) had a narrow base (Figure 1B-insert). Mucicarmine stain revealed the characteristic pink-red capsule of *Cryptococcus neoformans*. (Figure 2)

The patient was treated with amphotericin lipid complex B and flucytosine. His highly active anti-retroviral therapy (HAART) regimen and trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis were continued. He was eventually discharged in overall better condition and with improved skin lesions, with plans to complete the induction phase of antifungal therapy with oral fluconazole.

The final diagnosis was disseminated cryptococcosis with fungemia, joint and prominent skin involvement, and possible pulmonary involvement, but sparing the meninges, as well as an underlying HIV (human immunodeficiency virus) infection with a low CD4 cell count.

Skin lesions in the setting of human immunodeficiency virus (HIV) infection often present a diagnostic challenge, and newly found nodules and/or ulcers can be the dermal manifestation of infectious and non-infectious diseases. Among the latter, drug reactions, neoplasms (including but not limited to Kaposi’s sarcoma), and vasculitides should be considered. Potential infectious agents include viruses such as *Molluscum contagiosum*, bacteria that include *Treponema pallidum* as well as non-tuberculous mycobacteria such as *Pseudomonas*.
aeruginosa (and associated echyma gangrenosum) and Barto-nella spp. (causing bacillary angiomatosis), and fungi, including endemic fungi, and, as shown in our case, Cryptococcus neoformans [1, 2]. Roughly 1 million new cases of cryptococcal meningitis occur annually worldwide, with the majority in the setting of HIV infection [3]. The incidence of disseminated cryptococcosis, ie, when the organism is found in organs other than the meninges or lungs, is less well known. The recommended antifungal treatment is identical to that for meningitis [4]. Skin lesions, seen in 10%–15% of disseminated cases, are classically described as umbilicated nodules, but can vary in appearance and sometimes resemble plaques, abscesses, sinus tracts, deep ulcers, and even cellulitis. At time of admission, our patient displayed the more typical lesions on his arms while more dramatic ulcerations were found on his face. The appearance of deep confluent ulcers in our patient was unusual. It was likely due to a strong immune response to a high organism burden in the setting of immune reconstitution inflammatory syndrome (IRIS). IRIS typically occurs in younger patients with low pre-treatment CD4 cell counts and after the initiation of HAART. In the setting of C. neoformans infection, it can manifest in 2 ways [4, 5], one of which is the paradoxical worsening of a patient’s clinical status with recurrence of symptoms and signs resembling those of the initial opportunistic infection despite adequate antifungal therapy. This occurs 1–3 months after HAART has been initiated and during maintenance treatment for cryptococcus. Our patient’s rather dramatic presentation with fungemia, joint involvement, and rapidly worsening facial lesions was likely due to the second variant of IRIS. In this less common syndrome, unveiling of subclinical cryptococcal disease occurs within weeks of initiating treatment with HAART. The World Health Organization recommends serum cryptococcal antigen screening in resource-limited settings for all HIV-infected patients with a CD4 cell count less than 100 cell/mm³ (regardless of skin findings) and subsequent pre-emptive treatment if the test is positive [6]. We believe that such a strategy would have helped prevent dissemination and IRIS-related, severe, ulcerating, facial skin lesions in our patient. We speculate that for certain high-risk populations (ie, younger patients with critically low CD4 cell counts), screening would be a cost-effective approach even in the developed world because it may allow treatment with oral agents and obviate the need for hospitalization. Regardless of screening strategies, newly developing, progressive skin lesions seen in patients with low CD4 cell counts have a broad differential diagnosis, and disseminated cryptococcosis should always be considered, especially when HAART has been recently initiated.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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