Disseminated Cryptococcal Infection in Rheumatoid Arthritis Treated with Methotrexate and Infliximab

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Cryptococcal infection has been associated with low dose methotrexate (MTX) therapy for rheumatoid arthritis (RA)[1,2], chronic corticosteroid use[3], and diabetes mellitus[4]. We describe a patient with RA who developed pancytopenia complicated by disseminated *Cryptococcus neoformans* while receiving low dose MTX and infliximab.

A 69-year-old white man with a history of longstanding RA and type-2 diabetes mellitus was referred for arthritis management. He had been receiving intramuscular gold until 1998 when therapy was changed to 10 mg weekly oral MTX. Corticosteroid therapy had ranged from 10 to 20 mg daily over many years. He had received 5 infliximab infusions at a 3 mg/kg dose at the time of initial evaluation. Examination revealed limited range of motion in the wrists and ankles and mild synovitis in the metacarpophalangeal joints.

Eight weeks after the fifth infliximab infusion, he was found to have a leukocyte count of 2000/μl, hematocrit 22%, platelet count 74,000/μl, and serum creatinine 2.0 mg/dl. He was admitted for blood transfusion. The day after admission, he developed fever and a pulmonary infiltrate on chest radiograph that was treated with antibiotics. Computerized tomographic evaluation revealed multiple bilateral lung nodules and right lower lobe airspace disease (Figure 1). Biopsy of a pulmonary lesion and blood cultures identified *C. neoformans* (Figures 2 and 3). Cerebrospinal

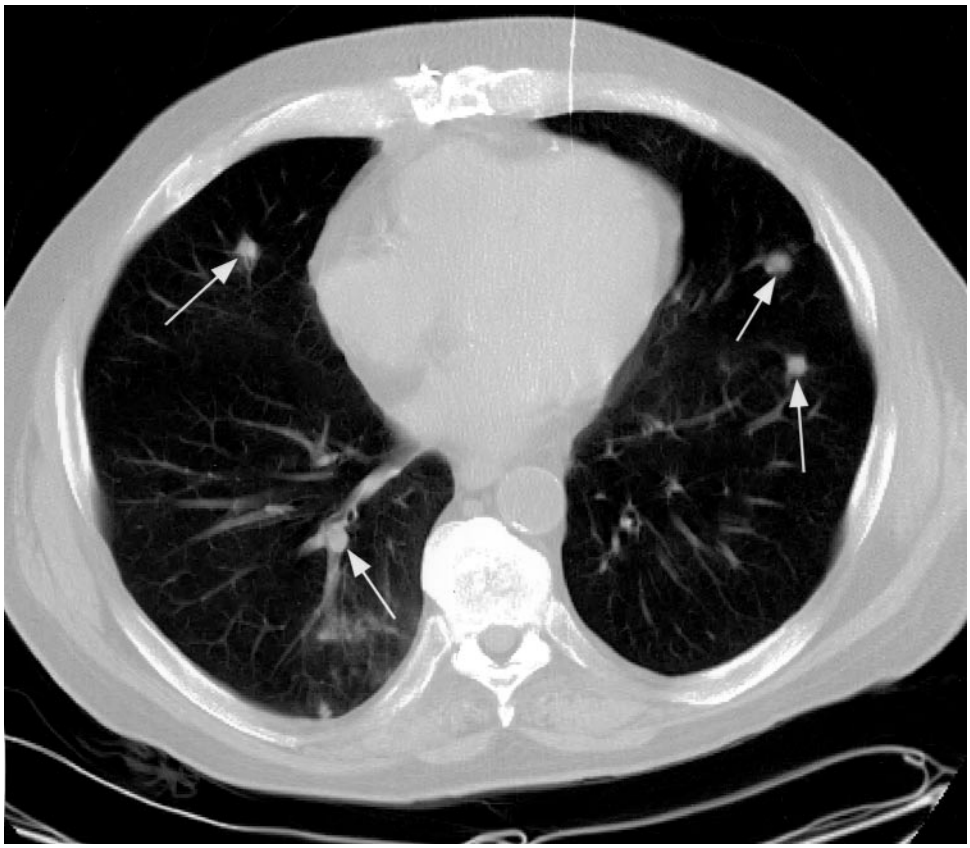

Figure 1. Axial section of chest CT scan without contrast reveals multiple subcentimeter pulmonary nodules without associated hilar or mediastinal lymphadenopathy (arrows).

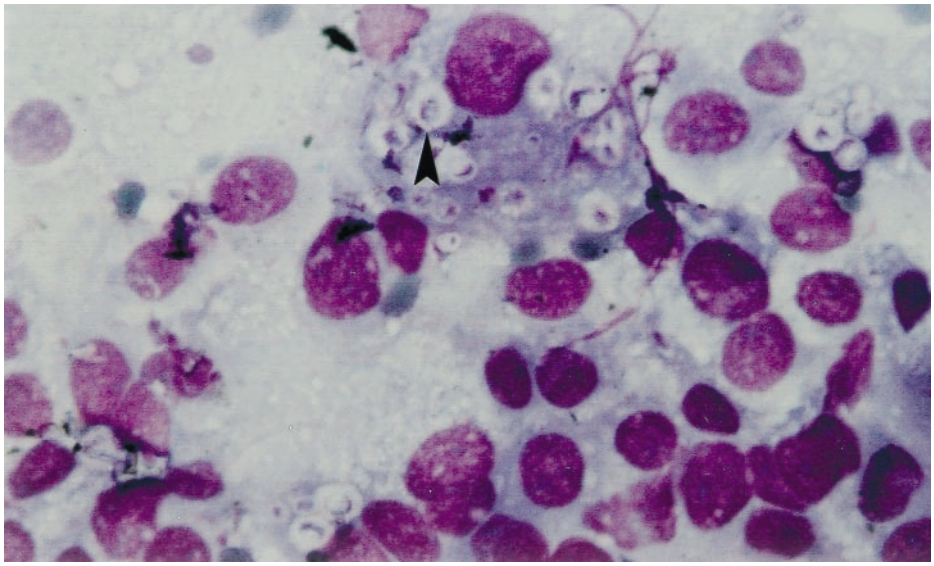

Figure 2. Touch preparation from core biopsy of lung lesion shows multiple variable size encapsulated yeasts of *C. neoformans* (arrow) within a macrophage (Diff-Quik stain, ×400).

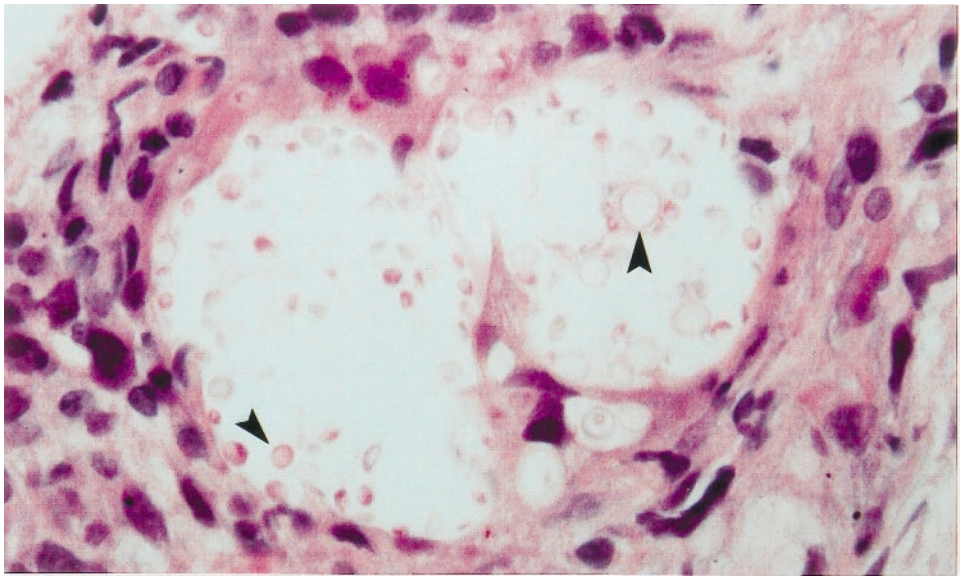

Figure 3. Hematoxylin and eosin stained section of core biopsy of lung lesion. Multiple variable size encapsulated yeast cells are present (arrows) (×400).

fluid analysis was normal. MTX and infliximab were discontinued. He was intolerant of amphotericin B, but responded well to fluconazole.

C. neoformans is infectious to both immunocompromised and immunocompetent hosts, with impaired T lymphocyte function imparting the greatest risk[4]. Cryptococcus may be a primary infection or reactivation of latent infection. The polysaccharide capsule is essential for virulence. It may block antibody binding and complement activation, reduces cell–cell interactions via electrostatic repulsion, impairs leukocyte diapedesis and production of tumor necrosis factor-α (TNF-α), interleukin 1ß (IL-1ß) and IL-6, and increases levels of IL-10, inducing a Th-2 type immune response[5].

Cryptococcal virulence factors, which impair other host defences, impart greater dependence upon TNF-α to mount a sufficient host response[6]. Temporally, the addition of infliximab provided the additional degree of immunosup-

pression required to allow cryptococcal dissemination. Renal failure and leukopenia may also have contributed in this case.

More widespread clinical indications for TNF-α antagonists may increase the incidence of cryptococcosis in rheumatic disorders. Continued vigilance will be required to identify actual clinical risk of opportunistic infections associated with TNF-α inhibition.

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