Anthony Amoroso, Section Editor

A 53-Year-Old Woman With an Unusual Etiology of Joint Pain

(See page 76 for the Photo Quiz.)

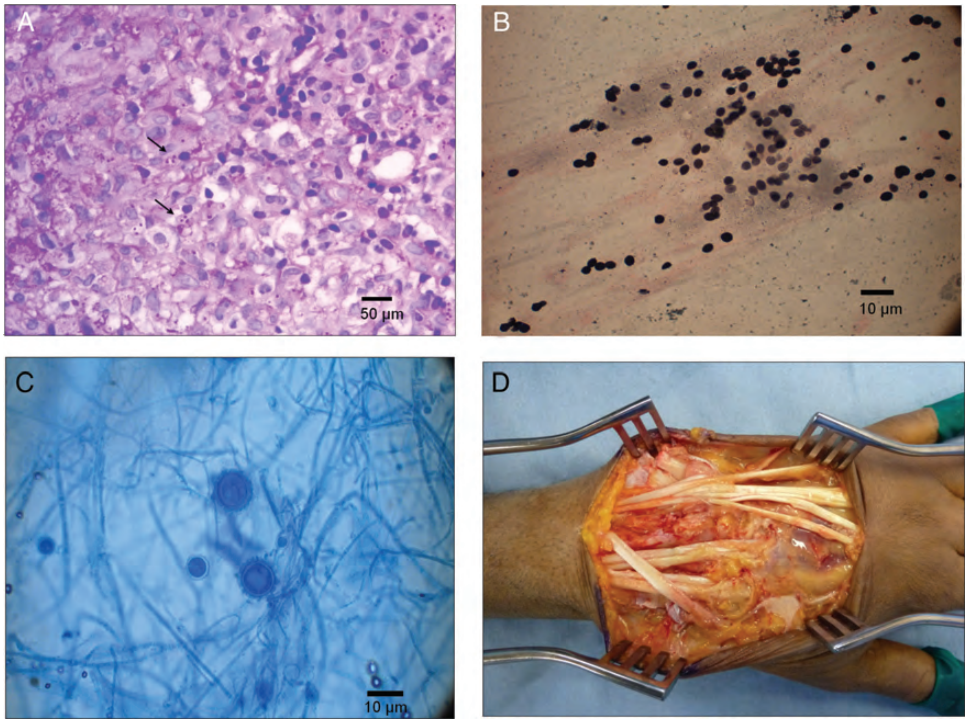

Figure 1. *A*, Necrotizing granulomatous lymphadenitis, with encaspulated yeast cells (arrows) (periodic acid-Schiff coloration). *B*, Grocott methenamine silver staining of lymph node biopsy showing numerous yeasts and the "figure 8" budding typical of *Histoplasma capsulatum* var. *duboisii* (n = 83; mean length [major axis], 3.5 µm; SD, 0.5; range, 2.4–5.0). *C*, Dimorphic fungus culture: *H. capsulatum* var. *duboisii* (lactophenol cotton blue coloration). *D*, Status during surgical procedure: diffuse synovitis that extended to the common extensor III and IV.

Diagnosis: Disseminated *Histoplasma capsulatum* var. *duboisii* infection (African histoplasmosis).

Silver staining of lymph node biopsy showed several yeasts (Figure 1*A* and 1*B*). Broad-range fungal polymerase chain reaction (PCR) targeting the 18S ribosomal RNA gene was positive but failed to distinguish *Histoplasma capsulatum* from *Blastomyces dermatidis*. The polymorphisms detected in the *OLE* gene (delta-9 fatty acid desaturase) allowed the differentiation between the 2 dimorphic fungi as well as the identification of the variety *duboisii* of *H. capsulatum* (Figure 1*C*). Clinical involvement of liver and bone marrow was suspected because of elevated liver enzymes and leukopenia. The patient was treated with liposomal amphotericin B (3 mg/kg daily) for 2 weeks, followed by itraconazole (200 mg 3 times daily for 3 days, then 200 mg twice daily), with blood concentrations >1 µg/mL. Prednisone was reduced to 10 mg daily and the immunosuppressive treatment was substituted for hydroxychloroquine. On antifungal treatment, the patient became afebrile, with marked improvement of shoulder pain and swelling. Liver enzymes and white blood cell count returned to normal values. In contrast to the general favorable outcome, painful swelling of the left wrist persisted. Magnetic resonance imaging (MRI) of the left hand showed osteomyelitis of carpal bones, wrist arthritis, and wrist extensor tenosynovitis. One month after hospitalization, a left wrist synovectomy and proximal row carpectomy was performed. On surgery, severe synovitis involving the extensor tendons was observed (Figure 1*D*). Because of persistent wrist swelling with limited range of motion, a second synovectomy

was performed 3 months after start of antifungal treatment. Silver staining showed several yeasts, but fungal cultures were sterile. On the last follow-up 6 months after start of antifungal treatment, the patient had no signs of active infection but had severe sequelae on both hands with rupture of several extensor tendons (third and fourth extensor of the left wrist, subluxation of the second metacarpophalangeal joint of the right hand).

This case is an example of the triple tropism (lymphadenopathy and skin and bone involvement) of *H. capsulatum* var. *duboisii* [1, 2], an organism prevalent in West Africa and Madagascar, in contrast to *H. capsulatum* var. *capsulatum*, which occurs commonly in the southern and midwestern United States and in Central America [3] and more frequently affects internal organs. Three hundred cases of African histoplasmosis are described in the literature [4], but its true prevalence is unknown. Disseminated disease is associated with poor immunologic status in patients infected with human immunodeficiency virus (HIV) (CD4 count <50 cells/μL). Patients typically present with fever, weight loss, pancytopenia, lymphadenopathy, lung infiltrates, hepatosplenomegaly, and cutaneous and mucosal lesions. Mortality is high, up to 80% in septic shock with multiple organ dysfunctions [5, 6].

African histoplasmosis is transmitted by inhalation of microconidia found in soil containing bird or rat droppings, although a primary pulmonary infection has not been reported. Although *H. capsulatum* var. *duboisii* yeast cells are generally larger (8–15 vs 2–4 μm) [7], the mean diameter of yeast in the present case and in a previously published case [6] was <4 μm. *Histoplasma capsulatum* var. *duboisii* is often seen in the cytoplasma of giant cells, with a thicker wall that can prevent neutrophilic phagocytosis; well-organized granulomas with caseous centers, characteristic of *H. capsulatum* var. *capsulatum*, are not observed [4]. Diagnosis is performed by direct examination and fungal cultures, which is considered to be the gold standard. PCR identification of the variety *duboisii* is possible by sequencing of the polymorphic gene *OLE*, and its use can shorten the time to the diagnosis [6].

Standard treatment with amphotericin B, followed by maintenance therapy with itraconazole, should be given by analogy with *H. capsulatum* var. *capsulatum* disseminated infections [8], but there are no specific recommendations for antifungal treatment of osteoarticular histoplasmosis. A recent review of the literature reported 10 cases of tenosynovitis (4/10) and carpal tunnel syndrome (6/10) caused by *H. capsulatum* (var. *capsulatum*) [9]. The best response to treatment was achieved with the combination of surgical debridement and antifungal therapy with liposomal amphotericin B.

We reviewed 18 published cases of *H. capsulatum* var. *duboisii* bone infections [10–18]. All patients came from West Africa, the median age was 28 years (range, 2–65 years), and 9 were female. HIV coinfection was reported in 3 cases. The majority had disseminated disease, and only 4 patients presented localized (bone) infection. Eight patients had a favorable outcome, 2 died, 3 recovered with severe sequelae, and 2 had an unfavorable evolution under treatment (cutaneous extension and possible immune reconstitution inflammatory syndrome). Only 6 cases required surgery (debridement, bone reconstruction), probably because of limited access to surgical procedures and loss to follow-up. In our opinion, surgery should be recommended in osteoarticular involvement in cases of insufficient response to antifungal treatment and should be guided by osteoarticular imaging (eg, MRI), with the aim of decreasing fungal load, removing necrotic foci, and preserving joint function.

Note

Potential conflicts of interest. S. G. G. has received travel grants from Gilead Sciences and Merck and has served as an advisory board member for Merck. P. M. H. has received personal fees from Merck. All other authors report no potential conflicts.

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