Myositis Resulting from Disseminated Cryptococcosis in a Patient with Hepatitis C Cirrhosis


Rheumatology Division and Division of Infectious Diseases, Department of Medicine, and Departments of Pathology and Radiology, Mount Sinai Medical Center, and Department of Medicine, Beth Israel Medical Center, New York

We report a case of myositis that resulted from disseminated cryptococcosis in a patient with hepatitis C cirrhosis. One year after cessation of treatment, the patient remains symptom free with negative results of serum cryptococcal antigen tests and negative culture results.

Infectious myositis, also known as “pyomyositis,” is characterized by an acute infection of the skeletal muscle. Prior to the AIDS epidemic, infectious myositis was virtually limited to children and adolescents who resided in tropical climates [1]. The most common infecting organisms in these cases were staphylococcal and streptococcal species. In recent years, an increased incidence of infectious myositis has been noted in more-temperate climates, primarily as a result of the growing HIV-infected population. In this immunodeficient population, the infection is not limited to bacterial pathogens but can also result from infection caused by parasites, viruses, or fungi [2]. We present a unique case report of an HIV-negative patient with hepatitis C cirrhosis who developed myositis secondary to disseminated cryptococcal infection.

Case report. A 53-year-old Hispanic woman was admitted to Mount Sinai Medical Center, New York, with chief complaints of increasing abdominal girth, nausea, vomiting, and fever. Her medical history included type 2 diabetes mellitus, hepatitis C cirrhosis, and a remote history of alcohol abuse and injection drug abuse (both types of abuse had ended 5 years prior to admission). A transjugular intrahepatic portosystemic shunt had been placed 2 years prior to this admission. The patient was on the waiting list to receive an orthotopic liver transplant, and she had tested negative for HIV infection 3 years prior to admission, when she was first evaluated at the Mount Sinai Medical Center liver transplant clinic. Her medications included furosemide, omeprazole, and insulin. She had taken no corticosteroids.

Physical examination done at the time of admission revealed a temperature of 38°C, a blood pressure of 115/60 mm Hg, a pulse rate of 82 beats/min, and normal respiration. The patient was anicteric, and her lungs were clear bilaterally. Her heart rate was regular, and there was a grade 2/6 systolic murmur at the left upper sternal border. Abdominal examination was remarkable for the presence of mild ascites and splenomegaly. Peritoneal signs were absent. There was edema of grade 2+ in the lower extremity bilaterally, and asterixis was noted.

The values obtained during initial laboratory examination were as follows: WBC count, 5500 cells/mm³; hemoglobin, 12 g/dL; hematocrit, 34.2%; and platelet count, 145,000 cells/mm³. Serum levels of electrolytes and creatinine, and prothrombin and partial thromboplastin times were all within normal limits. Liver function tests revealed the following values: alkaline phosphatase, 135 IU/L; alanine aminotransferase, 22 IU/L; aspartate aminotransferase, 45 IU/L; total bilirubin, 1.0 mg/dL; total protein, 5.0 g/dL; and albumin, 1.7 g/dL. The chest radiograph did not show evidence of cardiopulmonary disease. Paracentesis performed at the time of admission revealed an RBC count of 10,000 cells/mm³ and a WBC count of 470 cells/mm³ (32% polymorphonuclear leukocytes, 9% lymphocytes, 17% monocytes, 25% macrophages, and 17% mesothelial cells). No organisms were seen on Gram stain. Cultures of blood, urine, and ascitic fluid samples were performed. Administration of iv cefotaxime was begun for treatment of presumed spontaneous bacterial peritonitis.

Within 36 h of admission to the hospital, the patient developed severe bilateral calf pain and swelling. On examination, the patient remained febrile. The circumference of the right calf was 38.5 cm, and that of the left calf was 37.5 cm. No erythema or cord was noted in either lower extremity; however, on palpation, marked tenderness was noted bilaterally, and a Homans’ sign was noted on the left. Bilateral Doppler ultrasound of the lower extremity was done and revealed no evidence of deep venous thrombosis. Creatine kinase and aldolase levels were mildly elevated at 128 IU/L and 10.2 IU/L, respectively. Cryoglobulins were present in blood, but at levels that were too low to quantify. The erythrocyte sedimentation rate was elevated at 135 mm/h. C3 and C4 levels were within normal...
limits. After 7 days of incubation, cultures of blood and ascitic fluid samples obtained at the time of admission yielded yeast. Treatment with a lipid formulation of amphotericin B was begun as a result of increases in blood urea nitrogen and creatinine to levels of 40 mg/dL and 2.4 mg/dL, respectively.

To further evaluate calf pain and tenderness, MRI was performed. Increased signal intensity was noted in the gastrocnemius muscles bilaterally on T2-weighted images (figure 1), a finding consistent with myositis. There was no involvement of the soleus muscles. A muscle biopsy of the right gastrocnemius muscle was performed, and the biopsy specimen showed atrophic muscle. Special stains of the muscle biopsy specimen demonstrated the presence of intracytoplasmic cryptococcal organisms (figure 2). Inflammatory cells were not identified in the biopsy specimen. The yeast yielded by the blood and ascitic fluid cultures done at the time of admission was identified as *Cryptococcus neoformans*. Urine cultures done at the time of admission and cultures of muscle biopsy specimens done 1 week after treatment with a lipid formulation of amphotericin B was begun continued to show no growth. Performance of lumbar puncture was contemplated, but the test was not done because of concerns about an increased risk of bleeding in this patient, who had cirrhosis and worsening renal insufficiency (the creatinine level peaked at 3.2 mg/dL). Calf pain and swelling gradually diminished, and repeated cultures of blood and ascitic fluid samples remained sterile. Repeated serological tests confirmed that the patient remained HIV negative.

After completing a 20-day course of treatment with an iv lipid formulation of amphotericin B, 300 mg/day (dose, 4 mg/kg/day), the patient was discharged from the hospital while taking oral fluconazole, 400 mg/day. One year after discharge, the patient remained free of infection. Soon thereafter, she self-determined to discontinue fluconazole therapy. Nearly 1 year after discontinuation of fluconazole therapy, the patient remains free of recurrence of symptoms and tests negative for serum cryptococcal antigen. The results of multiple cultures of blood and ascitic fluid samples that have been done since dis-continuation of treatment have been negative. The patient’s azotemia resolved, and her current creatinine level is 1.0 mg/dL.

**Discussion.** *C. neoformans* is an encapsulated yeast that is found ubiquitously in soil. Despite the high prevalence of the organism in the environment, human cryptococcal infection is rare except in patients with disorders of cell-mediated immunity, such as AIDS or lymphoreticular malignancy, or in patients with immunosuppression after corticosteroid therapy or organ transplantation [3, 4]. Liver dysfunction occasionally has been reported to be a risk factor for cryptococcosis [5–9]. Although T cell–mediated immunity is thought to be the predominant mechanism for combating cryptococcal infection, intact phagocytosis and complement-mediated mechanisms also are thought to be important in the prevention of cryptococcal disease [10]. Cirrhosis may increase the risk of cryptococcal infection because of its association with elevated levels of chemotactic inhibitors and reduced complement levels [11]. Hepatitis C cirrhosis was our patient’s only apparent risk factor for cryptococcal disease.

The 3 organs that are most commonly affected by *Cryptococcus* species are the CNS, the lungs, and the skin. The lung is thought to be the common portal of entry for cryptococcal disease, although it is not uncommon for infected patients to have no evidence of pulmonary disease, as was the case for the patient who we describe. When lung disease is detectable, its presentation may vary from a subacute respiratory illness with fever to asymptomatic pulmonary infiltrates, subpleural masses, solitary nodules, or effusions. Rare case reports of cryptococcal peritonitis [5, 6], arthritis [12], and olecranon bursitis [7] also have been described. In patients with hepatic dysfunction, cryptococcosis has been reported to manifest primarily as peritonitis or disseminated disease [6]. Rare cases of cryptococcal infec-

---

**Figure 1.** Postgadolinium T2-weighted MRI of the distal lower extremities of a patient with cryptococcal myositis. Note the high signal intensity within the gastrocnemius muscles bilaterally.

**Figure 2.** Mucicarmine staining of gastrocnemius muscle shows capsules of *Cryptococcus* species in the interstitium of muscle fibers.
tions that involve the colon have been described in patients with cirrhosis [6].

Cryptococcal myositis is an extremely rare condition. In only a handful of cases has cryptococcal myositis been reported in skeletal muscle at the time of autopsy [13, 14]. Only 4 case reports of cryptococcal myositis that was identified prior to autopsy have been described previously in the literature. One case was identified in a patient who had received corticosteroids for 3 years after undergoing kidney transplantation [15]. A second case of cryptococcal myositis presented atypically as proximal muscle weakness in a patient with chronic lymphocytic leukemia who previously had undergone prolonged immunosuppressive therapy [16]. A third case was described in a patient with AIDS (CD4 cell count, 120 cells/mm³) who presented with a 3-day history of pain, swelling, and a sensation of warmth in the right thigh [17]. The fourth case was reported in a man who had been taking immunosuppressive agents for years after undergoing an orthotopic heart transplantation prior to his presentation with increased left lower-extremity swelling, erythema, and pain [18].

Outcomes for patients who have been given a diagnosis of cryptococcal myositis have been poor. Three of the 4 previously described patients with cryptococcal myositis died despite having received therapy with amphotericin B, although the causes of death (brain hemorrhage or cardiac arrest) suggest that the poor outcomes may have reflected the severity of the patients’ comorbidities rather than a failure of antifungal therapy. Both our patient and the HIV-positive patient who had cryptococcal myositis remained free of infection while they received maintenance treatment with fluconazole after having received initial treatment with amphotericin B.

The majority of recent studies that have identified optimal treatment strategies for cryptococcal infections have been of patients with AIDS and cryptococcal meningitis. These studies suggest that initial treatment with amphotericin B, with or without fluocytosine, allows for more rapid sterilization of CSF than does fluconazole and that it may also yield a lower failure rate [21]. The addition of fluocytosine to treatment with amphotericin B may improve efficacy [22], but it increases the prevalence of drug-induced cytopenias, which is a special concern for patients with AIDS [23]. Maintenance therapy has also been studied most extensively in patients with AIDS who have cryptococcal meningitis. Oral fluconazole was found to be less toxic than amphotericin B, and it led to fewer relapses than did weekly injections of amphotericin B [24]. Fluconazole has also been shown to be more effective than maintenance therapy with itraconazole for AIDS-associated cryptococcal meningitis [25]. Determination of the best regimen for treatment of cryptococcal myositis requires that additional cases are recognized and treated promptly and that outcomes are reported in the literature.

Because infectious myositis can lead to death in the absence of prompt diagnosis and treatment, it is imperative that the presenting symptoms of this disorder be recognized. Most patients present with a localized and asymmetric area of swelling of a single muscle group [2, 19]. Extreme muscle pain often accompanies the swelling. In 80%–90% of cases, large muscles in the buttock, thigh, or calf are involved. A recent minor injury to the affected area frequently has been noted. Our case differs from the most classic presentation in that symmetrical muscle involvement was seen and no antecedent trauma was experienced. Patients with infectious myositis may also have intermittent fever, leukocytosis, and an elevated erythrocyte sedimentation rate. Results of cultures of blood samples are negative in as many as 70% of patients, and muscle enzyme levels are often within normal limits. As a result, the condition may be confused with deep venous thrombosis or cellulitis, and the correct diagnosis may be delayed. The radiological study that is most useful for the diagnosis of pyomyositis is MRI [2, 20]. T1-weighted images show increased muscle size. T2-weighted images show increased signal intensity within the affected muscle. Although MRI is useful in establishing the diagnosis, tissue biopsy is necessary to find the specific pathogen and to determine the most appropriate treatment.

This case report confirms the existence of cryptococcal myositis. In patients who are at risk for cryptococcal infection, C. neoformans should be considered among the pathogens that cause infectious myositis. Patients who are at risk include those who have T cell–mediated defects. Patients with liver cirrhosis may also have an increased risk. A thorough evaluation to establish the diagnosis of infectious myositis can lead to prompt recognition of the disease and implementation of lifesaving therapy.

References