Introduction

Infection with Cryptococcus neoformans is a universal problem of increasing importance. The incidence of recognized clinical cases is increasing, as immunosuppression becomes more widespread, and as clinical awareness of this disease increases. Immunosuppressed patients with disseminated cryptococcosis usually present with either pulmonary or central nervous system involvement. In addition, cutaneous involvement is a rare but important feature of disseminated cryptococcosis, and has a poor outcome if unrecognized and untreated. We present a case of cryptococcal cellulitis in a patient with rheumatoid arthritis who was receiving long-term steroid treatment. Reviewing the literature, this is the first report of rheumatoid arthritis with disseminated cryptococcosis initially presenting as cellulitis.

Case Report

This 76-year-old male was diagnosed with RA and diabetes mellitus (DM) and was on methylprednisolone and hypoglycemic treatments since 4 years before this presentation. The dose of methylprednisolone he was using at admission was 12 mg/day. His RA was initially diagnosed by subcutaneous rheumatoid nodules, a high serum level of rheumatoid factor, morning stiffness of bilateral upper extremities and typical X-ray findings in the juxta-articular bones of both hands.

In March 2006, he was hospitalized with a 1-month history of progressive swelling, erythema, induration, tenderness and ulceration on the medioposterior aspect of the left lower leg (Figure 1). The patient denied fever, shaking chills, night sweating, cough, sputum production, chest pain, or dyspnea. There was no history of pigeon exposure, antecedent bronchitis, pharyngitis, otitis, visual difficulty, or headache. Abnormal laboratory tests included white blood cell count 10,000/mm³ with 94% polymorphonuclear leukocytes, C-reactive protein 3.20 mg/dL and creatine kinase 35 U/L. General biochemistry tests including liver and renal functions were normal. Urinalysis was unremarkable. Antibody to human immunodeficiency virus was negative. The initial chest X-ray revealed a normal finding.
Left lower leg X-ray disclosed only soft tissue swelling, but no bone destruction. Immediately, the patient was treated parenterally with oxacillin, and the methylprednisolone was discontinued simultaneously for fear of immunosuppression. Nevertheless, the area of cellulitis progressed gradually. So, an ultrasound of the lower limb was performed, which showed no evidence of arterial insufficiency or deep vein thrombosis. Three-phase osteomyelitis scan of the left lower leg showed a negative result.

On the 5th day after hospitalization, a newly developed round rubbery mass on the medial aspect of the left upper arm was noted (Figure 2). Skin biopsy and culture of the left upper arm mass and left leg lesion were done. These 2 lesions proved to be infected with Cryptococcus neoformans (Figure 3). Meanwhile, the blood culture also grew Cryptococcus neoformans, which was sensitive to fluconazole and amphotericin-B. Fluconazole was added because of its lower nephrotoxicity than amphotericin-B. Due to productive cough with yellowish sputum, chest X-ray was taken 16 days after admission. It revealed a new patch lesion over the right lower lung field. Under the suspicion of disseminated cryptococcosis, lumbar puncture was performed, and the cerebrospinal fluid culture was also positive for Cryptococcus neoformans. Furthermore, latex agglutination to cryptococcus in serum was positive, with a titer > 1:1,024. Under the diagnosis of disseminated cryptococcosis, amphotericin-B was prescribed to replace fluconazole 4 weeks after admission. We prescribed amphotericin-B 16 mg as the test dose on the 1st day and increased the dose to 20 mg every night over the following 7 days. Thereafter, amphotericin-B 25 mg every night was applied over the following 15 days until we discontinued amphotericin-B. The patient’s left leg cellulitis improved significantly. Meanwhile, 2 sets of blood culture 6 weeks after admission grew no fungus or bacteria. Thus, amphotericin-B was stopped after a total of 8 weeks of treatment with amphotericin-B and fluconazole.

However, fever and comatous consciousness occurred 3 days after we discontinued amphotericin-B. The patient did not take opiates or alcohol. There was no electrolyte imbalance or trauma. The repeated blood glucose levels were within normal limits. Brain computed tomography showed only periventricular arteriosclerotic encephalopathy. Hence, we speculated that sepsis was the main cause of comatous consciousness. Empirical treatment with ceftazidime was given immediately. Unfortunately, he suffered acute respiratory failure and septic shock. His sputum culture then grew yeast, Pseudomonas aeruginosa and Klebsiella pneumoniae. So, we prescribed amphotericin-B again, as well as shifted ceftazidime to maximipine and...
vancomycin. We used amphotericin-B 20 mg every night for 9 days until the patient died. The total accumulated amphotericin-B dose was 711 mg.

During his admission, persistent anorexia and painful oral ulcers were noted. Although nasogastric feeding and intravenous albumin supplement were given, he still had a very low serum albumin level (1.5 g/dL in the 8th week of admission, initial serum albumin was 4.1 g/dL). Finally, he expired in the 10th week of admission.

**Discussion**

Impaired lymphocyte response to cryptococci, especially in immunocompromised hosts with T cell dysfunction, is noted in most patients with cryptococcal infection. The depletion of CD4+ T lymphocytes may decrease the ability to eliminate them and increase the possibility of dissemination. This may explain the increased incidence of cryptococcosis in immunocompromised hosts. RA is a chronic inflammatory disease of the synovium, which is associated with many phenotypic and functional T lymphocyte defects, including abnormal clonal expansions and suppressed proliferative responses, suggesting a defect in T lymphocyte differentiation. Additionally, RA patients usually need prolonged immunosuppressive treatment, which also increases the risk of infection. So it is little wonder to find *Cryptococcus neoformans* infection in our RA patient with long-term steroid treatment.

*Cryptococcus neoformans* is a non-mycelial encapsulated budding yeast. The most common exposure sources are inhalation of aerosolized infectious yeast from pigeon, avian excreta, contaminated soil, milk, fruits, and wood products. Patients usually present with pneumonia, and *Cryptococcus neoformans* consequently spreads to the central nervous system. However, our case did not have symptoms of pneumonia, such as cough, sputum production, chest pain or dyspnea. His initial chest X-ray was unremarkable. Conversely, his initial infection site was cellulitis of the left lower leg.

Cutaneous cryptococcal disease usually represents the hematogenous dissemination of cryptococcosis. Cryptococcal skin involvement usually manifest as ulcers, acineform papules or pustules, subcutaneous swellings or tumors, ecchymoses, granulomata, gummas, abscesses, vesicles, palpable purpura, papules, or cellulitis. We performed a MEDLINE search of the literature from 1966 to the present and found no case of RA with disseminated cryptococcosis that initially presented as cellulitis.

The cryptococcal skin infection of our case was specifically diagnosed with a combined Alcian blue–periodic acid-Schiff stain and skin culture. Patients with cryptococcal cellulitis should be treated as those with disseminated cryptococcosis. A prolonged course (6–10 weeks) of intravenous monotherapy with amphotericin-B can be used. Actually, fluconazole and itraconazole, which are as effective as amphotericin-B but with fewer adverse effects, can also be used in cases with systemic and cutaneous cryptococcal diseases. Although intravenous amphotericin-B was replaced by fluconazole in our case due to negative blood cultures and worry about deterioration of renal function after a 4-week treatment, we kept on using fluconazole and amphotericin-B alternately throughout his admission (> 8 weeks) due to his high serum level of cryptococcal capsular antigen.

With appropriate systemic antifungal therapy, the majority of patients (> 80%) with cryptococcal cellulitis can be expected to survive in immunocompetent status. However, our case was immunocompromised with RA, DM and a history of long-term steroid treatment, and he finally expired due to septic shock. A previous study showed that hypoalbuminemia was correlated with high mortality in patients with pneumonia. The hypoalbuminemia of our case came from chronic severe inflammation, sepsis and malnutrition. Also, we repeated urinalysis several times in the whole treatment course. The initial urine survey revealed negative results. However, urine protein loss (spot urine protein, 100 mg/dL) was confirmed by urinalysis after septic shock took place, which coincided with progressive deterioration of renal function and exacerbated the hypoalbuminemia. Our case had painful oral ulcers and anorexia during admission. Nasogastric feeding and intravenous albumin supplement were given, but the patient had persistent malnutrition, which worsened his prognosis. In such circumstance, more aggressive nutrition with total parenteral nutrition should have been considered for our patient as early as possible.

In conclusion, cryptococcal cellulitis is uncommon and indistinguishable in presentation and appearance from acute bacterial cellulitis. Furthermore, disseminated cryptococcosis without treatment is nearly uniformly fatal, and appropriate systemic antifungal therapy can significantly improve the outcome. Thus, the physician must search for an unusual cause early if the cellulitis fails to respond to routine antibiotic treatment. Skin biopsy should be undertaken promptly in such instances. A diagnostic skin culture or biopsy may show characteristic organisms, as well as make an immediate diagnosis and early treatment possible.
References