Disseminated cryptococcosis presenting as cutaneous cellulitis in an adolescent with systemic lupus erythematosus

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Abstract

We report here the case of a 17-year-old girl from Pelotas, Brazil, with systemic lupus erythematosus and disseminated cryptococcal infection. Prior to diagnosis, she was a chronic user of corticosteroids and other immunosuppressive drugs. Her first symptoms were skin lesions that simulated bacterial cellulitis. Upon suspicion, we performed a biopsy and fungal infection was confirmed. Appropriate therapy was established, and the patient was discharged after 42 days of treatment in complete remission.

Introduction

Cryptococcus neoformans is encapsulated yeast, which can be commonly found in bird feces, plants, dust, soil and contaminated food.^{1,2} It is an important pathogen that causes opportunistic infections in immunocompromised individuals [kidney transplant recipients, HIV-positive patients, patients with systemic lupus erythematosus (SLE), and patients on prolonged corticosteroid therapy and immunosuppressants].¹⁻³

Disseminated cryptococcosis can affect lungs, central nervous system (CNS) and skin.^{4,5} Skin involvement, which occurs in 10-20% of patients, presents different clinical morphologies including ulcers, acneiform papules, subcutaneous nodules, and, rarely, cellulitis.^{4,6} Cryptococcal cellulitis is indistinguishable from bacterial forms, and its delayed diagnosis has a worse outcome.^{4,5,7}

Case Report

Our patient is a 17-year-old Caucasian female student from Pelotas, Rio Grande do Sul, Brazil, who was diagnosed with SLE 2 years before admission. In January 2014, SLE evolved to grade IV lupus nephritis and thrombotic microangiopathy; therefore, she was required intermittent hemodialysis and was receiving prednisone (40 mg/day), hydroxychloroquine (6 mg/kg/day) and mycophenolate mofetil (2 g/day).

She was admitted to Santa Casa de Misericórdia Hospital (Brazil), in June 2014, after the appearance of nodular lesions in the right upper extremity and right lower extremity (RLE). These lesions were well-demarcated, erythematous, painful on palpation, non-pruritic, and featured local edema. One day after admission, these lesions spread to all the extremities. No lesion appeared on her face and trunk, and fever was not present.

Initial laboratory findings revealed: hemoglobin 8.6 g/dL, white blood cell (WBC) count of 7710/mm³, platelet count 89.000 cells/mm³, serum aspartate transaminase (AST) 10 U/L, serum alanine transaminase (ALT) 16 U/L, C-reactive protein (CRP) 18.35 mg/L and erythrocyte sedimentation rate (ESR) 58 mm.

On the fourth day after admission, fever appeared, and the lesions on the RLE worsened; therefore, we opted for empirical treatment with amikacin and cefepime, and decreased the dose of prednisone to 30 mg/day. Due to the lack of improvements of the skin lesions, we added vancomycin one week later, upon suspicion of bacterial cellulitis.

Results of blood culture (the samples were collected on the day of admission) initially indicated *Candida* sp. upon direct examination. We assumed that the focus of candidemia was inside the intravenous catheter in her right internal jugular vein. Therefore, intravenous (IV) fluconazole (200 mg/day) was initiated and the catheter removed.

A nodular lesion on her RLE was biopsied on the fourth day of hospitalization; pathology of the fibro-fatty tissue fragment was positive for fungi by Grocott's method, and Hematoxylin and Eosin staining showed collections of spores without a strong inflammatory reaction or evidence of hyphae (Figure 1). Direct mycological examination of the biopsy showed various yeasts with a gelatinous capsule, and the culture in Sabouraud's medium and Mycosel agar indicated the presence of *C. neoformans* in intensive growth. Direct examination of the blood culture obtained upon admission was repeated, and it was also positive for *C. neoformans*.

Based on these results, treatment for disseminated cryptococcosis was initiated; prednisone was further decreased to 20 mg/day and

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fluconazole was discontinued. The patient was treated with amphotericin B (0.7 mg/kg/day, IV) with an infusion time of 6 hours, since the patient had repeated reactions (fever, chills and nausea) with a shorter infusion time. Flucytosine, which could also be indicated in this case, was not used due to its unavailability in our hospital and the difficulty to find it in Brazil.

We further tested our patient for cryptococcal meningitis and pneumonia. She had no respiratory symptoms, and chest X-rays upon admission were normal. The patient, however, complained of headache and altered memory. We performed a cranial computed tomography with contrast, which showed findings within normal limits. Lumbar puncture revealed a clear, colorless and slightly cloudy cerebrospinal fluid (CSF), with a protein level of 16 mg/dL, glucose levels of 51 mg/dL and WBC count of 4 cells per mm³. It was not possible to perform the cytological analysis, due to the low number of WBC. However, direct microbiological examination of the CSF with clarification

and Indian ink staining showed the presence of *C. neoformans*.

Two weeks after the first lumbar puncture, the procedure was repeated: the CSF was clear and colorless, with protein levels of 28 mg/dL, glucose levels of 38 mg/dL and WBC count of 8 cells per mm³. Mycological examination of CSF did not reveal any growth of microorganisms.

During antifungal treatment, the patient developed neutropenia (966/mm³) and was transferred to an isolated unit. Mycophenolate mofetil was discontinued. Ten days later, the patient's condition improved, and she left the isolation unit with neutrophils levels of 4011/mm³, elevation of CRP levels with a maximum peak of 141.44 mg/L, ESR of 75 mm and no other significant laboratory abnormalities.

Soon after leaving this unit, the patient had fever for seven consecutive days; her RLE lesions simultaneously worsened, and the nodes spread to the chest and abdomen.

Bacterial cellulitis was suspected due to the worsening of the lesions, which were blistered, painful upon palpation, and showed signs of inflammation (Figure 2A). Treatment with ceftriaxone and vancomycin was initiated. Four days later, purulent secretion began to drain from these lesions (Figure 2B). This material was collected and analyzed: there was no bacterial growth, and *C. neoformans* was identified by direct examination. *C. neoformans* grew in culture. Therefore, fluconazole (400 mg/day, IV) was added to amphotericin B therapy. During the last week of hospitalization, her RLE lesions improved (*i.e.* pus draining and swelling disappeared); also the pain ceased. Clinically, the patient improved without any neurological or pulmonary sequelae. Laboratory tests previous to hospital discharge revealed hemoglobin levels of 9.2 g/dL, a WBC count of 16.700 cells per mm³, platelet count of 303.000 cells per mm³, AST 10 U/L and ALT 4 U/L, and CRP levels of 6.88 mg/L and ESR of 53 mm. The patient was discharged after 42 days of IV treatment with amphotericin B. She was instructed to continue fluconazole (400 mg/day) at home for 8 weeks and then reduced its dose to 200 mg/day for 1 year.

Discussion and Conclusions

Cryptococcosis, which is common in severely immunocompromized hosts, has a low incidence in HIV-negative patients, approximately 1:100.000.^{4,8} In the reported case, however, the risk factors were due to the underlying disease (SLE), which was treated by prolonged corticosteroid therapy and immunosuppressants.

C. neoformans generally causes three types of infections: pulmonary cryptococcosis, cryptococcal meningitis and cutaneous cryptococcosis.⁷ The dissemination of this disease

occurs when at least two noncontiguous sites are affected, which is unusual and mostly observed in HIV-positive patients.^{3,9} In our case, only pulmonary involvement wasn't present. Some studies support the importance of lumbar puncture in patients with cryptococcosis, even when CNS symptoms are not observed, because asymptomatic meningitis represents a possible early diagnosis for the disease.¹⁰

Skin involvement is rare, but it is nearly all the time a sign of disseminated disease; it may precede the systemic symptoms even eight months before.^{4,7} It is important to stress the rarity and polymorphism of the skin condition, with the possible development of vesicles or blisters and the potential progression to ulceration.^{1,4} The initial presentation of the lesion in our patient was the presence of subcutaneous nodules, which became extensive and spread widely throughout the body over time. These lesions later became blisters that drained pus, from which we identified the intense parasitism of the fungus.

Cryptococcal cellulitis is a specific variety of skin involvement, and our patient had exhibited it in more than one occasion. Similarly to our case, which we initially suspected to be bacterial, further reports have shown that, generally, cellulitis is initially treated with antibiotics until their failure shows the presence of a fungal infection.⁴ Although rare, reported cases of cryptococcal cellulitis seem to be restricted mainly to the lower body, particularly to the lower extremities, as observed in this case report.^{1,6} Cryptococcal cellulitis, in this kind of infections, is uncommon and undistinguishable from acute bacterial cellulitis for appearance and presentation.⁵ More than 80% of the patients with cryptococcal cellulitis are expected to survive in immunocompetent status when they receive the appropriate anti-fungal therapy.⁵ According to the current guidelines of the American Society of Infectious Diseases, for disseminated cryptococcosis, amphotericin B combined with flucytosine is recommended as the primary therapy, followed by fluconazole as a consolidation therapy.^{3,7} Flucytosine is not yet exploited in the Brazilian Unified Health System. It is expensive and not widely available in Brazil, and was therefore not considered for treatment in this case. Our patient received single treatment with amphotericin B, with subsequent addition of fluconazole.

Pappas *et al.* described the high variability in the therapeutic management of cryptococcosis, depending on the anatomical location and severity of the disease.¹¹ The prolonged course (6-10 weeks) of IV amphotericin B monotherapy, together with the reduction of chemotherapy to improve immune status, is a target that is set forth during the treatment of cryptococcosis.^{3,5} Recent evidence also sup-

ports the requirement for maintenance therapy with fluconazole administered as an indefinite secondary prophylaxis, since the rate of recurrence exceeds 50% after apparently successful treatment.¹²

The mortality rate of cryptococcal cellulitis is high, and in case of renal involvement nearly all deaths occur within 2 weeks from diagnosis with or without treatment, indicating an aggressive and fulminant course of the disease.^{4,7} Our patient had a second lumbar puncture that did not show the presence of *C. neoformans*; this was the test that determined the success of the fungal induction therapy.³

Another relevant aspect in this case was the rapid worsening of the patient's clinical status and skin lesions after leaving the isolation

Figure 1. Biopsy of the subcutaneous tissue in Hematoxylin & Eosin (40x magnification). Fungal spores without inflammatory reaction.

Figure 2. A) Right lower extremity lesions, which were blistered, painful upon palpation, and showed signs of inflammation. B) Purulent secretion draining from the lesions.

unit, when the number of neutrophils reached more than four times the previous count in a short period of time. For this reason, we considered the immune reconstitution inflammatory syndrome (IRIS), which manifests as an exuberant tissue inflammation in patients undergoing rapid improvement of cellular immunity.³ In our case, together with autoimmune restoration there was also a concomitant decrease in immunosuppressive therapy, a condition that is predisposing to IRIS.^{3,7} This condition is also probably more common than believed by clinicians, and severe manifestations can be lethal if it is not considered.³

References

1. Dinato SM, Dinato MM, Nakanishi CP, et al. Disseminated cutaneous cryptococcosis in a patient with AIDS. *Rev Inst Med Trop São Paulo* 2006;48:353-58.
2. Probst C, Pongratz G, Capellino S, et al. Cryptococcosis mimicking cutaneous cellulitis in a patient suffering from rheumatoid arthritis: a case report. *BMC Infect Dis* 2010;10:239.
3. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2010;50:291-322.
4. Hall JC, Brewer JH, Crouch TT, et al. Cryptococcal cellulitis with multiple sites of involvement. *J Am Acad Dermatol* 1987;17: 329-32.
5. Lu HC, Yang YY, Huang YL, et al. Disseminated cryptococcosis initially presenting as cellulitis in a rheumatoid arthritis patient. *J Chin Med Assoc* 2007; 70:6.
6. Chaya R, Padmanabhan S, Anandaswamy V, et al. Disseminated cryptococcosis presenting as cellulitis in a renal transplant recipient. *J Infect Dev Ctries* 2013;7:60-3.
7. Ni W, Huang Q, Cui J. Disseminated cryptococcosis initially presenting as cellulitis in a patient suffering from nephrotic syndrome. *BMC Nephrol* 2013;14:20.
8. Mehrabi M, Bagheri S, Leonard J, et al. Mucocutaneous manifestation of cryptococcal infection: report of a case and review of the literature. *J Oral Maxillofac Surg* 2005;63:1543-9.
9. Sathyanarayanan V, Bekur R, Razak A, et al. Clinical profile of disseminated cryptococcal infection - a case series. *Asian Pac J Trop Med* 2010;1:818-20.
10. Kiertiburanakul S, Wirojtananugoon S, Prachartam R, et al. Cryptococcosis in human immunodeficiency virus-negative patients. *Int J Infect Dis* 2006;10:72-8.
11. Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis* 2001;33:690-9.
12. Lee YA, Kim HJ, Lee TW, et al. First report of *Cryptococcus albidus*-induced disseminated cryptococcosis in renal transplant recipient. *Korean J Intern Med* 2004;19:53-7.