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Spondylodiscitis associated with skin lesions caused by *Rhizopus* in a patient with systemic lupus erythematosus

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SUMMARY

Mucormycosis is a serious and rare fungal disease caused by opportunistic fungi of the zygomycete class, order *Mucorales*. The main clinical presentations are rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated infections. There are few reports in the literature of spondylodiscitis caused by mucormycosis. We report a 53-year-old male patient presenting with subcutaneous nodules and severe low back pain radiating to the lower limbs. The patient had systemic lupus erythematosus (SLE) for 8 years and corticoid-induced diabetes. He had been using 60 mg/day of prednisone in the last year, with a recent pulse therapy regimen with methylprednisolone and cyclophosphamide to control the renal dysfunction. Nuclear magnetic resonance (NMR) of the spine showed spondylodiscitis. The patient underwent spinal arthrodesis and lesion biopsy. The histopathological study of the vertebra reported a necro suppurative inflammation with numerous fungal structures described as a wide range of hyaline hyphae. The histopathology of the cutaneous nodule exhibited an extensive suppurative lesion centered on the subcutaneous tissue, associated with a large amount of hyphae, similar to that found in the spinal lesion, suggestive of mucormycosis. The fungal culture showed the growth of *Rhizopus spp.* Treatment was performed with amphotericin B lipid complex 5 mg/kg/day for 60 days. After antifungal treatment, there was a progressive reduction in the number of subcutaneous nodules and total improvement of the patient's low back pain, with recovery of his gait. At the 18-month outpatient visit follow-up, the patient was stable and without recurrence. In our case, timely diagnosis enabled the removal of the osteoarticular focus and the targeted therapy resulted in a satisfactory clinical response, without sequelae or complications, despite the patient's underlying immunosuppressed status.

Keywords: spondylodiscitis, mucormycosis, *Rhizopus*, systemic lupus erythematosus.

INTRODUCTION

Mucormycosis is a serious and rare fungal disease caused by opportunistic fungi of the zygomycete class, order *Mucorales*. In mucormycosis, the most frequent fungal genus is *Rhizopus.* However, other genera can also cause diseases in humans, such as Mucor, Rhizomucor, Absidia, Apophysomyces, Saksenaea, Cunninghamella, Cokeromyces, and Syncephalastrum [1]. These fungi are present in the soil and air. The main transmission route is through the inhalation of spores, but transmission can also occur by ingestion or direct inoculation [2]. The disease occurs predominantly in immunocompromised individuals, such as patients with decompensated diabetes or neutropenia, and in situations that generate iron overload. The main clinical presentations are rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated infections [1]. There are few reports in the literature of spondylodiscitis caused by mu-

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cormycosis [3]. The diagnosis is challenging, and the gold standard is the visualization of fungi in the anatomopathological specimens and their growth in cultures [4]. Treatment success depends on early diagnosis, the possibility of reversal of comorbidities, early initiation of antifungal therapy, and surgical debridement [5, 6].

CASE REPORT

The case description follows the norms established by the Declaration of Helsinki. The patient signed a Free Informed Consent Form authorizing the publication of the case report and related photos.

The patient is a 53-year-old Caucasian male. He worked as a corrections officer. The patient was diagnosed with systemic lupus erythematosus (SLE) 8 years prior. The case occurred right before the beginning of the COVID 19 pandemic and by the end of the treament the first cases of COVID19 started being notified in Brazil. He was admitted to the hospital with anasarca, fever, oliguria, and the presence of subcutaneous nodules (Figure 1), which appeared 20 days before admission. He had laboratory and clinical evidence of SLE, with skin, joint and renal involvement (diffuse proliferative glomerulonephritis), requiring hemodialysis. He had been undergoing a pulse therapy regimen with methylprednisolone and cyclophosphamide to control the renal dysfunction. During hospitalization, he presented with uncontrolled glycemic control, with a diagnosis of corticoid-induced diabetes. The patient also had necrotizing pneumonia, which resolved after antibiotic therapy. The patient became clinically stable, with improvement in renal function, and was discharged from the hospital. Biopsy of the subcutaneous nodules was performed, although no results were available at the time of discharge. After 2 months, the patient developed severe low back pain radiating to the lower limbs and was readmitted for investigation. He was taking 60 mg/day of prednisone. On examination, the patient was hemodynamically stable, afebrile, with severe low back pain that worsened on palpation, which was controlled only with morphine. The patient's ability to walk was limited. Upon examination, hyperchromic nodules, measuring approximately 1 cm were noted on the right thigh, left leg, and right arm. His laboratory test results included: hemoglobin 8.67 g/dL; hematocrit 28.2%; leukocytes, 10,700 cells/mm^3, rods 3%; segmented 87%; lymphocytes 6%; platelets 184,000 cells/mm^3; C-reactive protein 5 mg/dL; lactate dehydrogenase 174 U/L; gamma glutamyl transferase 139 U/L; alkaline phosphatase 82 U/L; urea 42 mg/dL and creatinine 1.2 mg/dL. Tests for HBsAg, anti-HBc IgM, HBeAg, anti-HCV antibodies and anti-HIV antibodies were non-reactive, while tests for anti-HBc IgG and anti-HBs antibodies were reactive. Fluorescent antinuclear antibody (FAN) was positive at 1/640 dilution (homogeneous nuclear pattern).

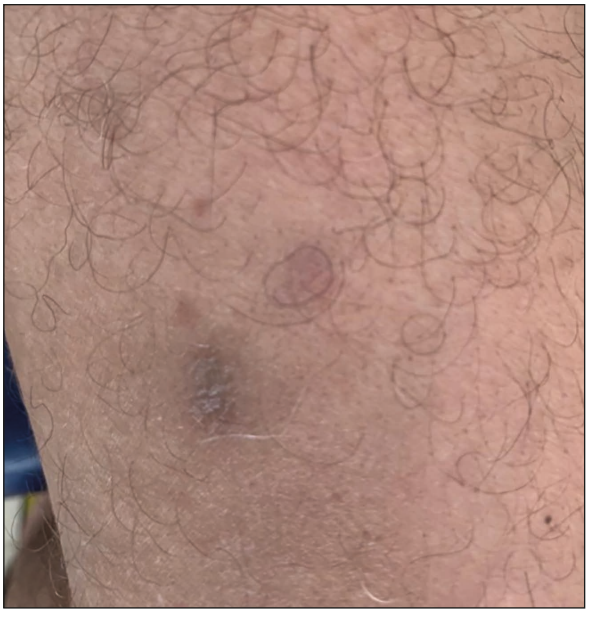

Figure 1 - Subcutaneous nodules on the thigh.

Nuclear magnetic resonance (NMR) of the spine showed a diffuse change in signal intensity, characterized by a marked hypointense signal in the vertebral bodies of L1 and L2 in T1 and T2 sequences, associated with exuberant cortical irregularity, destruction of the epiphyseal plates, with an inflammatory pattern and enhancement after contrast infusion (Figure 2). The patient underwent spinal arthrodesis and lesion biopsy. The histopathology report showed a necrosuppurative inflammation with numerous fungal structures with wide hyaline hyphae, a "rosary bead" sporangium with branching at right angles without evident septations (Figure 3a). The fungal culture of the bone fragment did not have microbial growth. In the histopathological evaluation of the subcutaneous nodule, a picture similar

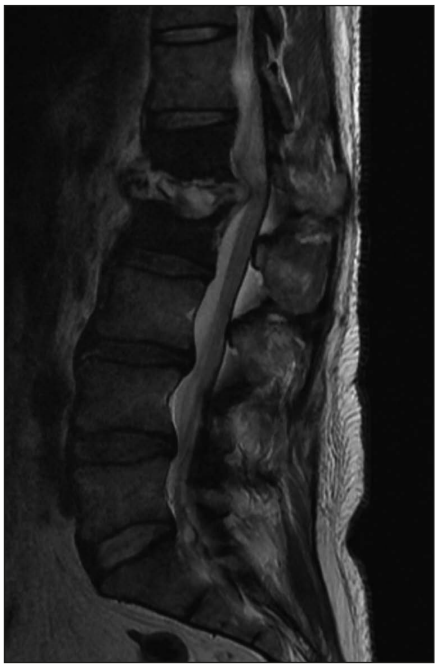

Figure 2 - Nuclear magnetic resonance of the spine. Destruction of the adjacent L1-L2 epiphyseal plates, with increased intradiscal signal suggesting an inflammatory component related to spondylodiscitis. There is also marked hyposignal on T2 in the vertebral bodies.

to that found in the spinal lesion was observed, with an extensive necrosuppurative lesion centered on the subcutaneous tissue, associated with a large amount of fungi, suggestive of mucormycosis (Figure 3b). The fungal culture in Mycosel and Sabouraud agar dextrose media showed the growth of a cottony filamentous colony, identified through microscopy as coenocytic hyphae with straight angle ramifications, compatible with *Rhizopus spp*. Treatment with amphotericin B lipid complex 5 mg/kg/day was initiated and maintained for 60 days, guided by clinical improvement. After antifungal treatment, there was a progressive reduction in the number of cutaneous nodules and total improvement of the patient's low back pain, with a recovery of his gait. There was also partial regression of the inflammatory lesion in the spine NMR performed after 40 days of treatment with amphotericin B. At the 18-month follow-up outpatient visit, the patient was stable and without recurrence.

DISCUSSION

Mucormycosis is a rare invasive fungal disease. Treatment requires a combination of surgical in-

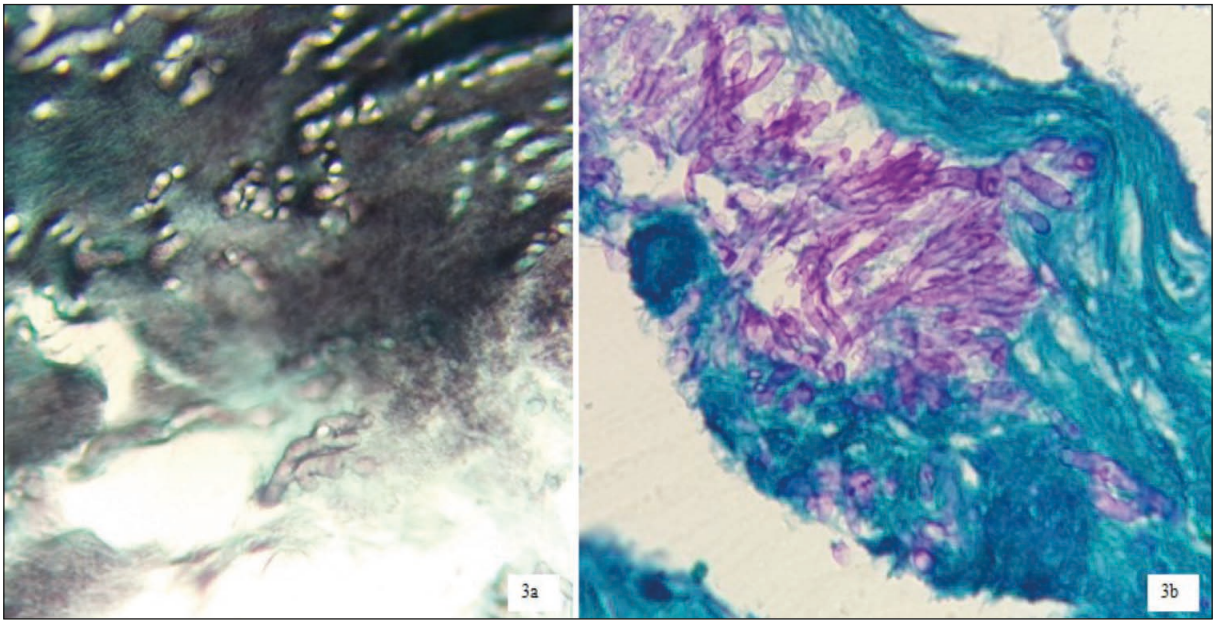

Figure 3 - a. The histopathology of the bone biopsy specimen (Grocott): necrosuppurative inflammation with numerous fungal structures with wide hyaline hyphae, a "rosary bead" sporangium with branching at right angles. b. The histopathology of skin biopsy (PAS = periodic acid-Schiff Fungi): extensive necrosuppurative lesion centered on the subcutaneous tissue, associated with a large amount of fungi, suggestive of mucormycosis.

tervention and antifungal therapy to reduce the high morbidity and mortality (which affects almost 50% of the cases). A recent systematic review described 851 cases of mucormycosis. The median age was 51 years. The rhino-orbital infections were the most frequent (34%), followed by cutaneous (22%) and disseminated infections (15%). Diabetes mellitus was the most common underlying condition (40%), and corticosteroid use at the time of presentation was reported in up to 33% of the patients with mucormycosis [7]. Our patient is in the most common age group and has the main risk factors associated with this condition. Cutaneous infection is commonly found in individuals with trauma and was an undocumented antecedent in this case.

Our patient was diagnosed with the cutaneous and musculoskeletal manifestation of the fungal infection, and the causative agent was identified in culture and histopathology. Despite the classic description of the hyphae of the order Mucorales being broad, aseptate or pauciseptate, and branching at a right angle, the irregular presentation is the one that best represents them. As in this case, the description can be combined with other manifestations due to interstitial pressures exerted on the fungi by tissues and changes in tissue architecture during processing.

Osteomyelitis caused by Mucorales is rare, with few cases described in the literature [3, 8, 9]. The occurrence of spondylodiscitis is extremely rare. Fei Chen et al. reported a case of an immunocompetent patient with low back pain, fever, paresthesia in the lower limbs, and weakness, starting after a lumbar puncture [3]. Fungal cultures collected from the lumbar spine fragments showed growth of *Rhizopus rhizopodoformis*. The patient was treated surgically, with drainage of the exudate, and received 8 weeks of antifungal therapy (amphotericin B and flucytosine) for 3 weeks, which was subsequently replaced by liposomal amphotericin B due to worsening of the renal function. She completed a regimen with itraconazole for 8 months, which was suspended due to gastric intolerance. The clinical course was favorable, with clinical and radiographic improvement. The treatment time in our case was 2 months, with favorable clinical and radiographic responses. We did not continue treatment with itraconazole because it has not active against Mucorales, and the patient did not have access to posaconazole [10]. However, the duration of antifungal therapy is not congruent in the literature, with a variable duration among the cases described, from 6 to 8 weeks. There were also discrepancies in the definition for clinical and radiological improvement and resolution of the basic immunosuppression [11]. Another limitation is the access to drugs to continue outpatient therapy. Posaconazole has been evaluated in the treatment of these cases. However, its high-cost limits access to this drug, especially for outpatient therapy [12, 13].

It is important to consider fungal infections as a differential diagnosis of osteoarticular infections. This is especially important because of the potential disruption to the patient's quality of life when the outcome is not fatal. Complications related to mucormycosis infections that resulted in severe sequelae or death have been reported [11, 14, 15]. In our case, timely diagnosis enabled the removal of the osteoarticular focus. Along with the targeted therapy, it resulted in a satisfactory clinical response, despite the patient's underlying immunosuppressed status.

Conflict of interest
All authors have no conflict of interest to be stated.

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