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**CASE REPORT**

# Spondylodiscitis by *Aspergillus nidulans*: A Diagnostic Challenge

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## ABSTRACT

Fungal infections are significant causes of morbidity and mortality in immunocompromised patients. Aspergillus spondylodiscitis is an uncommon manifestation of invasive aspergillosis and a significant cause of death and frailty.

We report a case of spondylodiscitis caused by *Aspergillus nidulans* section in an HIV patient with Burkitt's lymphoma, who presented with long-term lower back pain and weakness of the lower limbs. Initial MR imaging missed the lesion. Emergent decompression surgery was performed. Fungal culture on the vertebral disc revealed the agent that was later confirmed by sequencing the ITS region of ribosomal DNA genes. Voriconazole was the chosen treatment, and the patient improved. This case demonstrates how difficult a diagnosis can be if we are not considering it. *J Microbiol Infect Dis 2021; 11(3): 162-165.*

***Keywords:*** *Aspergillus nidulans section, Spondylodiscitis, Voriconazole*

## INTRODUCTION

*Aspergillus* species are ubiquitous molds present in compost, air ducts, and air dust. Inhaling *Aspergillus* spores causes aspergillosis, and the lung is the most affected organ. The chance of infection increases if the immune system is compromised since many people inhale these spores every day without being affected. The significant risk factors for invasive aspergillosis include prolonged and/or profound neutropenia, steroid use, solid organ or stem cell transplant, HIV/AIDS, and chronic granulomatous disease [1]. *Aspergillus fumigatus* is the most prevalent species, with *A. flavus, A. terreus*, and *A. niger* [2] coming next in frequency. Among extrapulmonary locations, bone is rarely involved, and vertebral osteomyelitis is the most common form [3], leading to poor clinical outcomes and a 25-95% fatality rate [4-6].

*Aspergillus nidulans* section is an uncommon bone pathogen, even in immunocompromised patients. However, it can be associated with osteomyelitis [7].

We report a case of prolonged lower back pain and weakness of the lower limbs caused by *A. nidulans* spondylodiscitis and consider the importance of proper diagnosis.

## CASE

A 56-year-old man from Guinea-Bissau was admitted into the Infectious diseases department in October 2019 with a history of lower back pain for the last five months and escalation with lower limbs weakness and paresis. For eight months, he was in Portugal and was diagnosed with diabetes, hypertension, Burkitt lymphoma with gastric, intestinal, hepatic, pancreatic, ganglion, and bone involvement, and an HIV-1 infection C2

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CDC Atlanta stage. He started antiretroviral therapy resulting in an important control of the infection at the first month (Lymphocytes CD4+ T 226 cell /uL (60%), ratio CD4+/CD8+ 2.1, HIV RNA 221cp/mL (2.35 Log10) decrease of 3 Log10). Burkitt lymphoma was in remission after five cycles of R-Da-EPOCH (dose adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, and Rituximab). During this time, he presented with multiple infectious complications, having had to complete numerous cycles of antimicrobials, such as Piperacillin-Tazobactam, Vancomycin, Ceftazidime-Avibactam, Meropenem, Amikacin, Fluconazole, a 78-day course of Amphotericin B for a Candida glabrata gastritis, and Ganciclovir.

In May 2019, the patient developed lower back pain. In July, a computed tomography (CT-scan), a magnetic resonance (MR) imaging study of the spine, and a PET-scan showed osteosclerosis compatible with an infiltrative disease, giving the notion of a recurred lymphoma. Unfortunately, the patient was not re-evaluated until October as he missed all his appointments.

He was admitted to the emergency room in October with backache irradiating to both legs and a grade 3 paraparesis with 3-4 days of evolution. A CT scan showed destruction of D12 and L1 vertebral bodies and an epidural mass with paravertebral extension, suggestive of an infectious process. Emergent surgery was performed with decompression and fixation. Bone biopsy showed an inflammatory infiltrate and fungal hyphae without acid-fast bacilli nor suggestion of lymphoma. Immunophenotyping was also negative for malignancy cells. Bacteriological and *Mycobacterium tuberculosis* cultures were negative. Fungal culture revealed the growth of *Aspergillus* isolates belonging to the Nidulantes section, identified by morphological methods. Antifungal susceptibility was determined with resistance to Amphotericin B (MIC=24µg/mL) but susceptibility to Voriconazole (MIC=0.032 µg/mL) and Posaconazole (MIC=0.0625 µg/mL). Molecular methods further confirmed species identification. Total genomic DNA was extracted from purified colonies. The internal transcribed spacer (ITS) region of this isolate's ribosomal DNA (rDNA) was amplified. Sequencing was performed, and nucleotide sequences were edited using Chromas2 and aligned using CLUSTAL X2. These sequences were compared with those deposited in the GenBank and CBS-KNAW Fungal Biodiversity Centre databases, revealing 98% homology with *Aspergillus nidulans*. The amplification of beta-tubulin and calmodulin genes failed after various attempts.

Laboratory analyses were unremarkable apart from a C-reactive protein of 2.47 mg/dL and erythrocyte sedimentation rate of 51 mm/h.

The patient started Voriconazole IV 6mg/kg as a loading dose, followed by 4mg/kg twice daily. Therapy was then switched to oral formulation after one month. At discharge, he was better, his back pain improved, and he could walk with a Jewett vest and the help of a third person. Imaging revaluation in the first month showed a slight improvement, and C reactive protein and erythrocyte sedimentation rate normalized.

At 7-months of therapy, the patient is still waiting for a new image evaluation since the COVID-19 pandemic delayed the one scheduled. Nevertheless, he can walk and almost doesn't need painkiller pills. There's no Burkitt lymphoma relapse, and the HIV infection is controlled.

## DISCUSSION

A minority of spondylodiscitis cases (0.5%) have fungal etiology, [8] and Aspergillus osteomyelitis is a severe, uncommon form of invasive disease. The vertebra is the principal bone involved, especially the lumbar vertebra [1]. Back pain is the most common manifestation, and it is associated with neurologic deficits secondary to cord compromise or kyphosis [3,4].

*Aspergillus nidulans* is a rare etiological agent of cutaneous aspergillosis, maxillary sinus and pulmonary disease, cerebral abscess, and osteomyelitis. In what spondylodiscitis is concerned, it is a common agent in children with chronic granulomatous disease [7]. In those cases, *A. nidulans* has higher virulence, higher ability to invade and disseminate, and lower susceptibility to antifungals than A-fumigatus [6]. In adults with other types of immunosuppression, this is a rare infection. Only 3 and 4 cases of *A. nidulans* spondylodiscitis were reported respectively between 1965-2012 and 1947-2013 [3,9]. Given its low frequency as an etiological agent

of spondylodiscitis and its high resistance rates to Amphotericin B, we must be aware of it, especially in a prolonged case of back pain, immunosuppression, and antibiotic pressure, as was our case.

The diagnosis of spondylodiscitis must include an image evaluation, and spine MR imaging is the gold standard in patients with neurological symptoms [10]. At first evaluation, our patient completed a CT scan and MR imaging, which showed no alteration consistent with spondylodiscitis. However, less than three months later, a new MR imaging study showed abnormal intradiscal signals between the T12 and L1 vertebral bodies consistent with disc space infection, collapse, and adjacent vertebral osteomyelitis. The accelerated course of bone destruction of aspergillosis in immunocompromised patients [11] may explain this event.

Along with the microbiological diagnosis, fungal isolation in culture may be complex, primarily if yeasts compete for growth. A combination of histopathology and fungal culture was the gold standard for diagnosing aspergillosis [1]. Still, in December 2019, amplification of fungal DNA by PCR combined with DNA sequencing was included as criteria for proven invasive fungal disease [12]. In this case, only the combination of histopathology and culture methods followed by species confirmation by DNA sequencing made the diagnosis possible.

The management of fungal spondylodiscitis should include antifungal therapy and surgery [1,11,13]. In a review by Koehler et al., the combination of surgical and antifungal treatment resulted in a survival rate of 78% vs. 60% compared to patients treated with antifungals only [10]. In the absence of surgical resection, recurrence of Aspergillus osteomyelitis seems familiar after discontinuation of therapy [3,9]. In the presented case, surgery was performed since the patient already had a neurologic compromise.

The Infectious Diseases Society of America (IDSA) guidelines recommend voriconazole to treat Aspergillus osteomyelitis. The length of antifungal therapy for vertebral aspergillosis has not been established but is recommend a minimum of 8 weeks with longer courses of >6 months frequently necessary. In our case, voriconazole was initially administered intravenously due to the severity and extent of the infection and the lack of comparative efficacy studies. Once the patient's vertebral condition was stabilized, the switch to an oral formulation was done. The perfect timing to do so has not been clarified. Voriconazole combines satisfactory systemic antifungal effect, high oral bioavailability, and good bone penetration, being preferred for the treatment of invasive aspergillosis instead of Amphotericin B [1].

Timely intervention with medical and surgical management combined has led to a favorable clinical outcome. At 7-month therapy, our patient maintains weakness of the lower limbs but can walk again, his reactive C protein and erythrocyte sedimentation rate normalized. However, Studemeister et al. reported residual effects following antifungal therapy, including back pain, kyphosis, and limb weakness [14].

The major limitation of our case was the inability to measure voriconazole-blood concentration to deduce its efficiency. However, having proved clinical, laboratory, and imageology improvement without signs of toxicity reassured us of the effective patient's outcome.

## Conclusion

Fungal spondylodiscitis by Aspergillus species is a debilitating infection that may occur in immunocompromised patients. Thus, it should be considered in the differential diagnosis of a patient with prolonged lower back pain even if the MR imaging is unremarkable, especially when bacterial cultures are negative. Also, as helpful as histopathology may be, the diagnosis based on culture and molecular techniques is essential for the fungal species identification and the beginning of proper medication. Our case demonstrates how complex a diagnosis process can be if we are not considering it and how important the combination of surgery and correct antifungal therapy is for a favorable outcome. Nonetheless, further studies are required to fully characterize *Aspergillus nidulans* strain, virulence traits, and pathogenicity.

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