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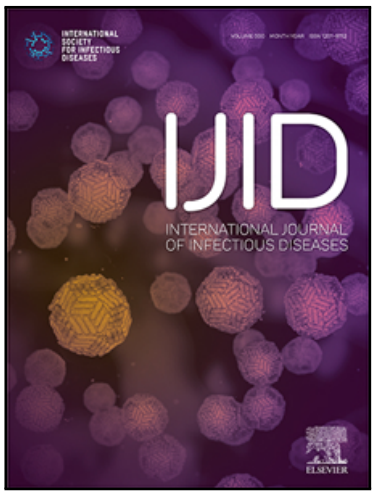

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HIGHLIGHTS

- Black-grain eumycetoma can present with coexisting tuberculosis
- Treatment is challenging with complex drug interactions and overlapping toxicity
- Eumycetoma often requires surgical treatment and prolonged oral antifungal therapy

A case of tuberculosis and black-grain eumycetoma co-infection in a non-endemic country: clinical presentation and therapeutic management

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Running title: TB and black-grain eumycetoma coinfection

Abstract

We report a case of black-grain eumycetoma co-localized with *Mycobacterium tuberculosis* infection, presenting as a painless leg abscess and associated with vertebral tuberculosis. The rare association of these two pathogens raises several challenges regarding foreseeable drug interactions, side effects, the most appropriate management and the potential link between these two diseases.

Introduction

Mycetoma is a neglected tropical disease, caused by bacteria (actinomycetoma) or fungi (eumycetoma). It is associated with low socioeconomic status (Zijlstra et al., 2016) and is unusual in Europe, even less in association with tuberculosis (TB).

Eumycetoma is a chronic granulomatous infection of subcutaneous tissues with possible bone involvement (Zijlstra et al., 2016). Treatment is challenging, long, with poor response to antifungal agents and surgery is often needed (Zijlstra et al., 2016, Suleiman et al., 2016).

We are reporting a case of TB and black-grain eumycetoma presenting as a co-infected subcutaneous leg abscess.

Case report

A 59 year-old Senegalese male presented with L5-radicular pain progressing for two months, without other associated symptoms. This patient, without medical history, except an active, recently treated, B hepatitis, under tenovofir, without significant hepatic injury. He had been

living in France since 2002 and had low socio-economic status. His physical examination revealed a painless 5cm pretibial lesion of the left leg with a purulent discharge, persistent for several months, despite local and antibiotic treatment.

A CT-scan was performed, revealing multiple retroperitoneal lymphadenopathies and a L5 vertebral lesion with cortical rupture, hypermetabolic on PET-scan. The MRI showed L5-spondylitis associated with epiduritis and contiguous pre-vertebral soft-tissues and psoas enhancement (Figure 1A).

CT-guided fine-needle spinal aspiration biopsy was performed. Microscopy, as well as extended-duration bone microbiological culture was negative, both for standard bacteria, as well as for TB. *Mycobacterium tuberculosis* PCR on the vertebral specimen was also negative. Vertebral histological analysis was negative for necrosis or granuloma, but samples were of poor quality.

Incision and drainage of the leg abscess unveiled superficial black grains, 1 mm in diameter (Figure 1B). Fungal culture of these grains led to the identification, by molecular biology, of *Falciformispora senegalensis* (formerly *Leptosphaeria senegalensis)*. Microscopy of the leg abscess was negative for acid-fast bacilli and standard bacteria. However specific culture and PCR revealed the presence of multi-sensible *Mycobacterium tuberculosis* co-localised with the fungal infection in the same leg subcutaneous lesion.

Leg PET-scan revealed multiple subcutaneous collections, with soft tissue and muscle extension, without bone involvement (Figure 1D). The MRI showed typical "dot-in-circle" lesions, highly suggestive for mycetoma (Figure 1E) (Jain et al., 2012).

There was no HIV coinfection or associated pulmonary tuberculosis. Blood protein electrophoresis and immunofixation electrophoresis showed a profile compatible with moderate inflammation. No specific immune deficiency was documented.

Upon re-enquiry, the patient had not returned to Senegal since 2002. The only history of leg trauma was a cycling accident at the age of 12, with skin injury.

Antituberculous quadritherapy by Isoniazid, Rifampin, Pyrazinamide and Ethambutol, at standard dosages, was initiated with good clinical and biological tolerance. After two months of antituberculous treatment, Pyrazinamide and Ethambutol were stopped, Rifampin was replaced by Rifabutin 150 mg/day, Isoniazid was continued at the same dose and Posaconazole was introduced (300 mgx2/day the first day, followed by 300 mg/day).

Biological monitoring consisted of liver function testing, blood count twice a week and drug-concentration monitoring of Rifabutin and Posaconazole trough on day 10, 15 and then monthly. The target values for trough concentrations were, respectively, 0.05-0.10 mg/L and 0.5-2.5 mg/L (Sekar et al., 2010).

Three weeks after Posaconazole initiation, biological monitoring revealed the onset of hepatic cytolysis (3xULN) and neutropenia (500 neutrophils/mm^3). Hepatitis B virus viral load was undetectable. Drug concentrations showed increased concentrations of Rifabutin (0.20 mg/L) and Posaconazole (3 mg/L). Rifabutin was reduced to 150 mg/48h and Posaconazole to 200 mg/day, allowing cytolysis and neutropenia remission. After normalization of biological tests, drug monitoring was performed monthly and was on-target. TB treatment was continued for a total duration of 9 months. MRI at 6 months showed spinal tuberculous lesions remission, but poor response of mycetoma leg lesions. After 10 months of Posaconazole, the leg MRI

revealed radiological progression with increase in size of the lesion. Posaconazole was switched to Voriconazole. However, because of progressing soft tissue lesions, surgery was performed at 13 months of antifungal treatment. Histology showed numerous black-grain mycetomas, overrunning striated muscle, without tuberculous lesions. After surgery, Voriconazole was maintained for 18 months with good tolerance, clinical and radiological remission (MRI and PET-scan).

Discussion

The association between mycetoma and tuberculosis is known but uncommon. In the largest case series published to date, among 6792 patients with mycetoma, 9 also had tuberculosis, without information regarding localization (Fahal et al., 2015). Eumycetoma and TB coinfection simultaneously occuring in the same lesion is extremely rare. Such a clinical form has never been described in a non-endemic country.

Thus, concomitant diagnosis of these two pathologies co-localised in a subcutaneous leg abscess and associated with vertebral lesions was surprising in an African patient living in France for more than sixteen years. Despite a low socio-economic situation, the patient had a good general status and initially presented with a seemingly standard lumbosciatica and a neglected persistent leg lesion. Mycological analysis was triggered by the discharge upon incision of the leg lesion of macroscopic black grains (Figure 1B) and led to the identification of *Falciformispora senegalensis*. Indeed, the patient was originary from Senegal, a mycetoma endemic region. Systematically performed culture on standard and tuberculous specific mediums and PCR allowed TB diagnosis based on the leg abscess sample. In this context and despite the negative vertebral biopsy, the clinical and radiological association of spondylitis,

epiduritis, contiguous involvement of psoas muscle and lymphadenopathy, was very suggestive of Pott's disease. Complete remission of lymphadenopathies, spinal and psoas lesions under TB treatment also supported this diagnostic. Concerning the leg abscess, it is likely that the mycetoma preceded TB infection. A probably dormant mycetoma might have been revealed in a context of secondary tuberculous infection. Interestingly, TB and mycetoma, also a granulomatous inflammatory disease, may share some common features regarding cytokic pathways and adaptive immune responses (Willcocks et al. 2014, Nasr et al., 2016).

Mycetoma lesions are usually painless and hence the majority present late with advanced disease (Zijlstra et al., 2016). The entry point is usually minor trauma with implantation of soil fungi. Our patient had suffered leg trauma in Senegal, 40 years earlier. Indeed, mycetoma is usually described as slow progressing over many years. The classic diagnostic triad is painless subcutaneous swelling, multiple draining sinuses and grain discharge [5], which were all present in our patient, even though grain discharge was visible only after incision of the abscess (Figure 1B). The foot is the most common site; the leg and hand are less frequently affected (Zijlstra et al., 2016, Fahal et al., 2015).

Grain culture is the gold standard for mycetoma diagnosis. Identification often requires molecular techniques. More than 70 microorganisms are incriminated, secreting black, white, yellow or red grains (Zijlstra et al., 2016, Fahal et al., 2015). *Falciformispora senegalensis, (*formerly *Leptosphaeria senegalensis)* (Ahmed et al., 2014) belongs to a family of marine fungi, endemic in tropical areas of West-Africa, mostly Senegal (Fahal et al., 2015). Even though phenotypic antifungal susceptibility could not be assessed in our case, based on

literature in vitro results voriconazole and posaconazole seem more predictably effective in inhibiting *F. senegalensis* growth compared to other azoles (Ahmed et al., 2015)

In the context of concomitant TB infection, treatment of both entities raised several challenges regarding drug interactions and the risk of overlapping therapeutic toxicity. Indeed, antifungal and antituberculous agents share common metabolic pathways and present both potential hepatotoxicity, requiring close monitoring (Krishna et al., 2007). For these reasons and taking into account the slow-progressing course of mycetoma, introduction of antifungal therapy was postponed for two months, at the time of switch from TB quadri to bitherapy. However, the patient developed hepatic cytolysis, which required dose adjustments in both TB and mycetoma treatments.

Rifampin is a powerful enzyme inducer of cytochrome P450, while azoles are strong inhibitors. When used together, this may lead to treatment failure. In order to diminish drug interaction, Rifabutin replaced Rifampin at the time of azole initiation (Krishna et al., 2007). Regarding antifungal treatment, Posaconazole was chosen because of its potential for fewer drug interactions and good tolerability (Herbrecht et al., 2004). Moreover, Posaconazole was reported to be associated with higher cure rates, even in patients with eumycetoma refractory to standard antifungal therapy (Negroni et al., 2005). Nevertheless, a drug-drug interaction between posaconazole and rifabutin was suspected which led us to adapt the rifabutin dosing regimen to 150mg thrice a week.

Regarding treatment response, despite remission of TB lesions after 9 months of therapy, the leg lesion persisted and progressed. Randomized trials have shown that even 6 months of antituberculous treatment were as effective as longer courses for bone TB in the absence of

neurological involvement (Nene et al., 2019). For mycetoma, however, prolonged administration of antifungal therapy (more than one year) and surgery is often necessary (Suleiman et al., 2016). Sometimes limb amputation is reported to avoid potential, but rare, fatal dissemination (Mohamed et al., 2016). Indeed, in our patient, despite optimally dosed antifungal treatment, surgery was needed and allowed remission. Post-operative antifungal treatment is usually maintained for 12 to 24 months (Crabol et al., 2014). However, recurrence after adequate medical and surgical treatment is common (Suleiman et al., 2016, Fahal et al., 2015) and requires close monitoring after the end of treatment.

Coexisting TB infection and eumycetoma represent a rare and challenging occurrence. While tuberculosis usually progresses well under treatment, eumycetoma often requires surgical management. Complex interactions between specific treatments and superposed toxicities, with a risk of antifungal treatment failure, bring forward the need for close clinical, biological and drug-concentration monitoring.

Conflict of Interest

No conflicts of interest to be declared.

Funding Source

No funding to declare. This work was carried out as part of our usual activity.

Ethical Approval Statement

Appropriate written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Figure 1. Evidence of tuberculosis and mycetoma infections. A: Spinal MRI (T2 STIR) showing L5 spondylitis (arrow) posterior and lateral epiduritis with extension to pre-vertebral soft tissue in contact with the psoas muscle. B: Subcutaneous leg abscess after incision showing black grains (arrow). C: Culture of the grains. D: PET/TDM FDG showing multiple contiguous hypermetabolic subcutaneous collections (circles) extending on 16 cm located in front of the anterior face of the left tibial shaft without argument for bone extension (SUV max 11.09, mean SUV 0.38). E: Leg MRI (T1W postcontrast) showing multiple subcutaneous collections extended on the anterior and internal face of the left leg in front of the ipsilateral tibial shaft with partial muscle extension. Arrow showing « dot in circle » sign.