Case Report

Disseminated *Scedosporium apiospermum* infection with leprosy responsive to voriconazole

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Introduction: *Scedosporium apiospermum* is a significant emerging fungus causing potentially life-threatening infections in poor immune responders. Scedosporiosis may complicate chronic diseases such as leprosy rarely presenting with fungaemia and extensive cutaneous lesions resistant to treatment.

Case presentation: An elderly female presented with numerous red, painful, pustules over distal extremities spanning 2 months. Fever and numbness of hands and feet were associated features. A past history of a fall 3 years previously traumatizing the lower back followed by joint pains and self-medication with steroids were antecedent factors as well as uncontrolled diabetes. She was a case of lepromatous leprosy released from multidrug therapy, the period ahead of which was interspersed with episodes of erythema nodosum leprosum. Examination revealed multiple erythematous nodulo-plaques, pus-filled bullae and hyperpigmented verrucous plaques over limbs with black skin discoloration and puckered scars over the right thigh and buttocks. Imaging showed sclerosis of pelvic bones and wedge compression of the lumbosacral spine. Direct microscopy of pus demonstrated branched, septate, hyaline hyphae and closely septate swollen cells in periodic acid–Schiff-stained tissue sections. *S. apiospermum* isolated in cultures of pus and blood depicted fungaemia and this was further substantiated by echocardiographic visualization of echogenic nodules on the anterior mitral leaflet. A transient favourable response on itraconazole 200–400 mg daily was followed by the emergence of new lesions. Parenteral voriconazole at 4–6 mg kg⁻¹ followed by oral treatment at 400 mg daily showed satisfactory improvement. The final outcome remained obscure as the patient was lost to follow-up.

Conclusion: Therapy-resistant cutaneous lesions in chronic diseases such as leprosy should be evaluated for rare opportunistic fungal infections.

Keywords: cutaneous; itraconazole; leprosy; *S. apiospermum*; voriconazole.

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Introduction

Scedosporium apiospermum is an environmental saprophyte (Lavinge *et al.*, 1999; Munoz *et al.*, 2000; Uenotsuchi *et al.*, 2005). The disease in immunocompetent individuals ranges from asymptomatic pulmonary colonization to post-traumatic cutaneous infection and mycetoma. It is becoming an increasingly significant opportunistic agent of potentially life-threatening infection in poor immune responders (Cortez *et al.*, 2008; Kiraz *et al.*, 2001; Munoz *et al.*, 2000). Various malignancies, chronic granulomatous

diseases, organ transplants, therapy with corticosteroids, immunosuppressants, antimicrobials and human immunodeficiency virus-positive state constitute the main risk factors (Barbaric & Shaw, 2001; Castiglioni *et al.*, 2002; Husain *et al.*, 2005; Lavinge *et al.*, 1999; Schaenman *et al.*, 2005). Clinically, scedosporiosis simulates other fungal infections (Cardoso *et al.*, 2009; Kiraz *et al.*, 2001; Schaenman *et al.*, 2005). It exhibits resistance to multiple antifungal agents (Barbaric & Shaw, 2001; Castiglioni *et al.*, 2002; Munoz *et al.*, 2000). Voriconazole promises to be effective with reports of therapeutic success (Cardoso *et al.*, 2009). We report the case of a diabetic woman with previous leprosy, self-medicating with steroids, presenting

Abbreviation: ENL, erythema nodosum leprosum

with multiple skin lesions due to fungal dissemination, evidenced by endocarditis and fungaemia. Initial success with itraconazole and subsequent resistance followed by a favourable response to voriconazole were observed.

Case report

A 50-year-old female housewife sought consultation in the Dermatology Department for multiple cutaneous lesions involving all four extremities. Two months previously, the patient noticed red, raised, painless pus-discharging lesions on her left forearm and wrist. She observed similar lesions on the right arm, left leg and both ankles. The lesions gradually increased in size, discharged pus, became painful and itchy, and a few healed spontaneously with remniscent black discoloration. There was associated fever, joint pain and numbness of bilateral hands and feet. Her medical history suggested hypertension and diabetes. She was self-medicating with low-dose steroids to relieve her joint pain, which she developed subsequent to a fall 3 years previously when she injured her lower back. In March 2007, she was diagnosed with lepromatous leprosy and treated with multidrug therapy and was released from treatment in April 2009. An episode of lepra reaction/erythema nodosum leprosum (ENL) associated with red, tender, cutaneous lesions with neuritis was documented in November 2009.

Mucocutaneous examination showed multiple erythematous nodulo-plaques of size 2×2 to 7×10 cm with overlying pus-filled bullae on the right distal forearm, left hand and forearm, and right ankle. The left distal forearm, hand and ankle had well-delineated hyperpigmented verrucous plaques with erythematous borders and a few bullous lesions. Their size varied from 1×1 to 7×7 cm. Numerous hyperpigmented puckered scars were present on the right thigh and buttocks.

Neurological examination revealed decreased sensations bilaterally over the extremities. Radiography of the chest was non-contributory. X-rays of limbs showed soft-tissue swellings with normal underlying bones. A magnetic resonance imaging scan of the pelvis showed sclerosis of the right ischial tuberosity, irregularity at the right sacroiliac joint, a wedge compression fracture of the lumbosacral spine (L3–L5) with degenerative changes and reduced height from D12 to L5 vertebrae with bilateral neuroforamen compression at multiple levels.

Blood sugar levels ranged from 129 to 335 mg dl^{-1} over a week and glycosylated haemoglobin was 10.6 %. Serology for human immunodeficiency virus and rheumatoid factor were negative. Other haematological and biochemical parameters were within normal ranges.

The clinical possibilities of disseminated cutaneous tuberculosis consequent to probable caries spine, lepra reaction (ENL) or deep mycosis were considered in differential diagnosis. Pus was aspirated from bullous skin lesions and

Fig. 1. Sabouraud's dextrose agar slant showing fluffy, grey colonies with water droplets characteristic of *S. apiospermum*.

subjected to Ziehl–Neelsen staining and a 10 % KOH wet mount. Ziehl–Neelsen-stained smears did not show the presence of acid-fast bacilli. KOH wet mounts revealed characteristic, septate hyphae with acute-angle branching. Pus and skin-punch biopsy samples were cultured on Sabouraud dextrose agar (SDA) with chloramphenicol and incubated at 25°C . Both samples showed growth of fluffy, grey colonies after 5 days of incubation (Fig. 1). Lactophenol cotton blue wet mounts revealed thin, septate, branching hyphae with *Scedosporium* and its synanamorph, *Graphium*, conidial forms with absence of cleistothecia corroborating *S. apiospermum* (Fig. 2). Considering the possibility of haematogenous dissemination, two samples of blood, 10 ml each, were cultured in two sets of brain–heart infusion broth with a 1-week interval and incubated

Fig. 2. Photomicrograph of lactophenol cotton blue wet mount showing *Graphium* and *Scedosporium* morphology of *S. apiospermum*. Magnification $\times 400$.

at 25 and 37 °C. Subcultures were done on SDA slants after turbidity appeared in the broth. There was growth of *S. apiospermum*, which was identified by lactophenol cotton blue tease mounts. The histopathology showed a chronic granulomatous infiltrate and closely septate hyphae seen as swollen cells on periodic acid–Schiff staining. Echocardiography showed a tiny echogenic nodule on the anterior mitral leaflet with minimal pericardial effusion. The left ventricular global systolic function was normal. Ultrasonography of abdominal organs demonstrated normal anatomy and function.

We successfully diagnosed disseminated scedosporiosis presenting with multiple scattered cutaneous lesions, fungaemia and endocarditis from laboratory work-up by direct microscopy and colony characteristics of isolates from pus, skin biopsy and blood cultures.

Management of ENL was started with steroids in tapering doses. Itraconazole 100 mg twice daily was escalated to 400 mg day⁻¹ in two divided doses after 15 days (Kiraz *et al.*, 2001; Schaenman *et al.*, 2005). Anti-hypertensive and anti-diabetic treatment was continued. The steroids were increased after 2 weeks as the patient developed another episode of ENL with the appearance of erythematous lesions. A favourable response was obtained within 3 weeks. Pustular lesions healed with remnant hyperpigmentation and verrucous lesions showed flattening with a perceptible decrease in size. No new lesions appeared during these 3 weeks. Steroid use was tapered off and the patient was discharged on oral itraconazole 200 mg twice daily. Despite strict treatment compliance, fresh cutaneous lesions appeared on her extremities after 3 weeks. Repeat samples of pus and blood were cultured and *S. apiospermum* was re-isolated. The patient did not respond to oral itraconazole. A repeat echocardiography revealed a freely oscillating echogenic nodule over the anterior mitral leaflet without mitral regurgitation, aortic stenosis, or regurgitation or effusion. Voriconazole was started intravenously in a loading dose of 6 mg kg⁻¹ every 12 h for 2 days followed by 4 mg kg⁻¹ twice daily as continuation therapy. Therapy was well tolerated with no observable drug interactions. The lesions regressed over 10 days. The patient was discharged on oral voriconazole 400 mg daily in two divided doses and advised to have a monthly review.

Discussion

S. apiospermum is an environmental saprobe (Jayamohan & Ribes, 2006). A depressed immune response puts patients at continual risk of fungal infections, accounting for an upsurge in the number of cases. Patients with malignancies, long-term corticosteroid use (Enshaieh *et al.*, 2006; Matsumoto *et al.*, 2009; Munoz *et al.*, 2000; Schaenman *et al.*, 2005) and transplant recipients are at heightened risk. Ours was a known case of treated Hansen's disease having episodes of ENL and was self-medicating with steroids leading to immune impairment.

Medical literature reports few cases of leprosy with fungal infection. An adult male with borderline tuberculoid leprosy treated with dapsone monotherapy developed chromoblastomycosis due to *Cladosporium carionii* in a residual anaesthetic patch, which was treated effectively with oral ketoconazole (Pavithran, 1988). Co-occurrence of subcutaneous phaeohyphomycosis due to *Pyrenochaeta romeroi* with leprosy has been reported (Girard *et al.*, 2004). An Indian male with lepromatous leprosy treated with multidrug therapy developed recurrent ENL. While on prednisolone, he developed an erythematous cystic swelling on the hand, which showed ulceration. The pus aspirate revealed fungal hyphae and cultures grew *Exophiala jeanselmei* (Kar *et al.*, 2005). Hansen's disease with chromoblastomycosis due to *Fonsecaea pedrosoi* has been documented from Japan (Miyagi *et al.*, 2008). Another patient with borderline lepromatous leprosy with recurrent type II lepra reaction on azathioprine prescription has been reported from the Bombay Leprosy Project. He presented with verrucous, crusted papules at the site of a tattoo. Direct microscopy of samples revealed sclerotic bodies and an isolate of *Cladosporium carrionii* was obtained. A reduction in the size of lesions followed after 3 months of therapy with 400 mg itraconazole (Apte *et al.*, 2011). None of the previously reported cases demonstrated dissemination or widespread involvement as in the present case. Cutaneous infections due to *Scedosporium* spp. occur in immunocompromised states other than leprosy. A foot ulcer in uncontrolled diabetes and a case of post-traumatic mycetoma have been reported in the Indian literature (Gupta *et al.*, 2013; Vijaya *et al.*, 2013). The fungus is also implicated in systemic abscesses of the thyroid and brain, in chronic suppurative otitis media and in keratomycosis (Vijaya *et al.*, 2013).

Rare cutaneous manifestations of scedosporiosis in immunosuppressed subjects include widespread pustular skin lesions with erythematous margins, bullous or verrucous lesions, necrotic, purpuric, localized ulcerations and lesions in sporotrichoid pattern (Lavinge *et al.*, 1999; Munoz *et al.*, 2000; Enshaieh *et al.*, 2006; Cardoso *et al.*, 2009). In our case, pustular, bullous and verrucoid lesions were distributed distally on the extremities.

The fungus may establish infection following a trivial trauma, remain latent or disseminate haematogenously after reactivation. Bone and vertebral involvement due to fungi has been documented previously, and *Scedosporium* exhibits a predilection for joints (Enshaieh *et al.*, 2006; Guarro *et al.*, 2006; Matsumoto *et al.*, 2009). In the present case, there were hyperpigmented, puckered scars overlying the gluteal region with extensive underlying bone involvement apparent on radiological imaging. In contrast, there was no history of hospitalization or orthopaedic consultation subsequent to the fall. This rejects the severity of bone damage solely due to physical trauma. In the absence of any other probable cause, we attribute the bone and skin involvement in the gluteal region to fungal pathology triggered by possible traumatic implantation of *Scedosporium* during the fall. A clinical

quiescence may have been followed by reactivation and dissemination subsequent to immune suppression due to leprosy, diabetes and steroid therapy.

Rarely, fungal endocarditis may complicate cardiac surgery presenting with thickened, friable, lobulated vegetations on heart valves. The fungus has been retrieved from blood samples (Guarro *et al.*, 2006). In this case, the cardiologist suggested the presence of vegetation on mitral valves as the result of infection as there was an absence of other cardiac anomalies. *S. apiospermum* was isolation from blood samples, amply supporting our diagnosis of fungal endocarditis.

The molecular techniques are still in the experimental stage and the diagnosis of scedosporiosis is based on a combination of clinical, microbiological and histopathological findings (Schaenman *et al.*, 2005; Cortez *et al.*, 2008). Isolation of *S. apiospermum* as characteristic flucanase, grey colonies with its synanamorph *Graphium* and absence of cleistothecia (Cortez *et al.*, 2008; Kwon Chung & Bennett, 1992; Munoz *et al.*, 2000) from repeated pus and blood samples and corroborating histopathological evidence was confirmatory (Figs 1 and 2).

Treatment is challenging due to resistance to antifungal therapies with fluconazole, amphotericin B, ketoconazole, itraconazole and terbinafine. Itraconazole and miconazole have shown variable success (Lavinge *et al.*, 1999; Munoz *et al.*, 2000; Castiglioni *et al.*, 2002; Schaenman *et al.*, 2005; Enshaieh *et al.*, 2006; Matsumoto *et al.*, 2009). In the absence of uniform recommendations, therapy is based on clinical profile, reported antifungal efficacies and cost. Treatment with itraconazole 200 mg twice daily exhibited an initially favourable response (Kiraz *et al.*, 2001; Schaenman *et al.*, 2005). The appearance of fresh cutaneous lesions indicated refractoriness to itraconazole. Subsequent voriconazole 4–6 mg kg⁻¹ at 12 h intervals intravenously followed by oral 400 mg daily in two divided doses proved efficacious with satisfactory improvement in cutaneous lesions and negative blood culture after a month (Husain *et al.*, 2005; Matsumoto *et al.*, 2009; Munoz *et al.*, 2000; Schaenman *et al.*, 2005). From our experience, we advocate initiation of therapy with voriconazole in cases of intractable infections. Furthermore, in cases of leprosy, although ENL remains the single commonest cause of recurrent cutaneous lesions, co-occurrence of fungal infections must nevertheless be suspected and investigated. Unfortunately, the patient was lost to follow-up and the final outcome remained unknown.

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