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Talaromyces *(Penicillium)* species infection in the central nervous system

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Abstract

Talaromycosis typically occurs as an opportunistic infection among immunocompromised individuals. Infection caused by species other than T. marneffei is uncommon. While most reported cases describe infection in the lungs, we report an extremely rare intracranial Talaromyces species infection. This 61-year-old with end-stage renal disease who was unwell for the previous two months, presented with fever and worsening confusion lasting for three days. Lumbar puncture was suggestive of meningitis. Cerebrospinal fluid (CSF) culture was later confirmed to be Penicillium chrysogenum. The patient was co-infected with Group B Streptococcus sepsis. He improved with amphotericin B and ceftriaxone and was discharged with oral itraconazole for four weeks. However, he died of unknown causes two weeks later at home. Talaromyces species infection in the central nervous system is uncommon. This case highlighted a rare but life-threatening fungal meningitis. Among the four reported cases worldwide, none of the patients survived.

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Introduction

Invasive fungal infections have become increasingly common during the last two decades. This is attributed to the increase of chemotherapy, bone marrow transplantation, immunosuppressive agents, invasive catheters and AIDS. As a result, there is a gradual rise of a rare fungal infection among patients in these high risk groups. Talaromycosis, caused by *Talaromyces marneffei*, is the third most common opportunistic infection in HIV-infected Southeast Asian patients.[1] However, it is rare to find non-*marneffei* infection among non-HIV patients. While most cases reported in the literature describe infection in the lungs, we report an extremely rare *Talaromyces* species infection in the central nervous system confirmed by CSF culture.

Case presentation

A 61-year-old male with end-stage renal disease on regular haemodialysis was unwell for the previous two months. He presented to Pulau Pinang hospital with fever and altered mental state associated with neck pain for three days. On examination, he was confused and his Glasgow Coma Scale (GCS) score was E3 V5 M5. Neck stiffness and a positive Kernig's sign were present. Other neurological signs were normal. On the first day, the patient went into septic shock requiring inotropic support. He was treated for meningoencephalitis with IV ceftriaxone and IV acyclovir.

Initial blood investigations showed a white blood cell (WBC) count of 13.8 (neutrophil 92.1%) and a high C-reactive protein (CRP) count of 304.1 mg/l. A CT of the brain showed a minimal right parasagittal subarachnoid bleed and cerebral atrophy. Lumbar puncture performed on the second day revealed a high opening pressure of 45cmH^2O. The CSF cell count could not be interpreted due to blood staining. CSF biochemistry was suggestive of meningitis (CSF protein 1.42g/l, CSF/serum glucose ratio 39%). The CSF gram stain was negative for organisms and pus cells. After 48 hours' incubation on Sabouraud dextrose agar (SDA) plate, fungal growth was present. IV amphotericin B was started immediately.

After two days of amphotericin B treatment, the repeated lumbar puncture showed normal opening pressure and improving CSF biochemistry. There was no CSF and blood fungal culture growth after that. A total of five aerobic blood cultures and one fungal blood culture were sent for analysis. Only the first blood culture taken on the day of admission grew Group B *Streptococcus* (GBS). HIV test was non-reactive.

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Figure 1 Two colonies of *Talaromyces* species grew on the inoculated Sabouraud dextrose agar (SDA) plate. The small white colonies seen on top were due to contamination.

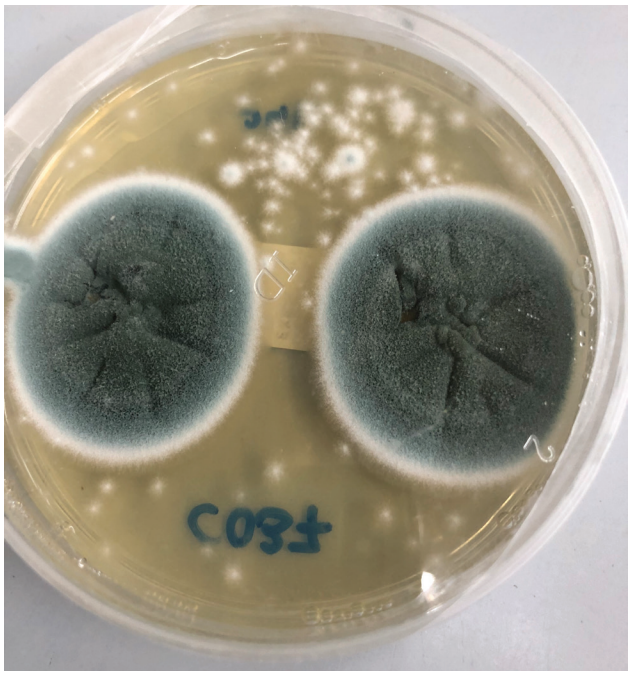
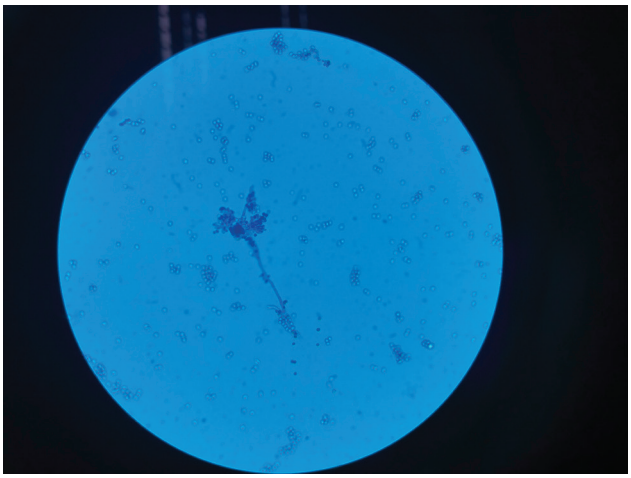


Figure 2 Microscopic view of *Talaromyces* species showing hyphae with conidiophores, and the characteristic 'brush' appearance.



CSF bacterial antigen detection was negative for GBS and other common organisms. CSF for bacterial culture and mycobacterium tuberculosis culture showed no growth. CSF fungal polymerase chain reaction (PCR) later showed *Penicillium chrysogenum*. Fungal meningitis was diagnosed with superimposed GBS sepsis.

After three days of antifungal therapy, the patient's consciousness level improved. He was orientated and able to follow instructions. The fever resolved and the inotrope was discontinued. The patient was well and ambulatory. The treatment with amphoterin B was continued for two weeks, followed by oral suspension of 200 mg itraconazole daily for another four weeks. The patient was discharged after IV treatment with amphotericin B was completed. He was well upon discharge and was scheduled for a follow-up in the Infectious Diseases clinic after one month. However, he died of unknown causes at home two weeks later.

Mycological examination

Talaromyces species are found worldwide and are potential mycotoxin producers. The initial gram stain of the CSF was negative for organisms and pus cells. The colonies grew after three days' incubation on the Sabouraud dextrose agar (SDA) plate (Figure 1). The surface of the colony was powdery with a bluish-green border. The reverse was white. No diffusible pigment was seen. Microscopic examination of the lactophenol cotton blue stain showed the presence of hyphae with conidiophores that have secondary branches known as metulae (Figure 2). On the metulae there were flask-shaped phialides that bore round conidia. The entire structure formed the characteristic 'brush' appearance. These features were consistent with *Talaromyces* species.

Discussion

Invasive disease due to *Talaromyces* species other than *T. marneffei* is uncommon. Over the last 50 years, a total of 34 cases of invasive infection have been described in the literature, many of which were in non-immunocompromised patients.[2] There have been descriptions of lung infection, endocarditis, peritonitis in continuous ambulatory peritoneal dialysis (CAPD), urinary tract infection, endophthalmitis, oesophagitis and intracranial infection. In contrast to other sites of infection, infection in the central nervous system is very rare. To date, there have been only four cases of intracranial infection reported for non-*marneffei Penicillium* infection.[3] Two of them were in immunocompromised patients. The outcome was poor as none of them survived.

In the first case, reported in 1963, intracranial *Penicillium* infection followed primary lung involvement in a patient with acute leukaemia. No treatment was given. Diagnosis was made after autopsy.[4] In the second case, reported in 1970, intracranial infection was the result of local spread from primary orbital-sinus infection causing a mycotic cerebral aneurysm. The patient died despite surgery and treatment with amphotericin B.[5] In the third case, reported in 2002, intracranial infection was reported in a non-immunocompromised middle-aged Pakistani patient. Diagnosis was delayed as brain biopsy was done six weeks after admission. The patient died despite being treated with amphotericin and flucytosine.[2] In Brazil, a fourth case was reported in 2005 with multiple brain abscess due to *Penicillium* species infection in a patient with Child-Pugh C liver cirrhosis.[3] The patient was treated with amphotericin B and showed gradual improvement. However, he later died from oesophageal variceal bleeding.

Talaromyces species is far more commonly associated with superficial infections e.g. dermatitis and onychomycosis, and allergic diseases e.g. asthma and hypersensitivity pneumonitis. Several types of occupational hypersensitivity pneumonitis attributable to *Talaromyces* species are cheese worker's lung,[6]

salami worker's lung[7] and malt worker's lung.[8] However, non-*marneffei* species are being increasingly recognised as emerging opportunistic pathogens causing invasive fungal infections worldwide, with most reports involving *P. citrinum, P. digitatum*, and *P. chrysogenum*.[9] Among the 34 invasive cases reported, nine occurred in immunocompromised patients and 25 in patients not known to be immunocompromised.[2] It appears that this infection can occur in both immunocompromised and immunocompetent patients.

End-stage renal disease is a well-recognized immunocompromised state leading to serious infections. Infection is just second to cardiovascular disease as the leading cause of death in patients with end-stage renal disease.[10] Among dialysis patients, the most common fungal infection is candidiasis (79%), followed by cryptococcosis (6.0%) and coccidioidomycosis (4.1%).[11] Uraemia is associated with a state of immune dysfunction characterised by immunodepression that contributes to the high prevalence of infections among these patients.[12] In addition, fungal infections may occur after a broad-spectrum antibiotic prescription.[13]

P. chrysogenum, which was discovered by Alexander Fleming in 1929, has been cited as an emerging pathogen.[14] These organisms are ubiquitous in nature and can be found in soil, decaying matter, sewage plantations, and construction sites. Our patient, who previously worked as a renovation contractor, may have been at risk. In this case, the fungal growth was significant, both inoculated sites on SDA grew the same colonies, there was no bacterial growth in CSF, bacterial antigen detection was negative for *Group B Streptococcus* and other common organisms, and at the same time there was no other SDA plates growing *Talaromyces* species in the laboratory to suggest contamination.

Standard treatment for non-*marneffei* species is not well established. Treatment with amphotericin B, flucytosine, and azoles has been described in the literature. However, treatment with amphotericin B and surgery failed to prevent death in all intracranial infection cases treated to date. Consistent with the previous experience, our patient did not survive despite early treatment. In a recent study of 118 clinical isolates, mainly from respiratory tract and bronchoalveolar lavage, terbinafine and echinocandins showed the best in vitro activity against *Talaromyces* species.[15] More data on responses to therapy is required before recommendations can be made.

Conclusion

This case highlights a rare but life-threatening fungal meningitis. Based on the reported cases of intracranial *Talaromyces* species infection, the prognosis is poor, and it can occur in both immunocompromised and immunocompetent hosts. More data is needed to recommend treatment.

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