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Multiple cerebral abscesses in a renal transplant recipient: Two swords in one scabbard!

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ABSTRACT

Although rare, both *Cladophialophora bantiana* (*C. bantiana*) and *Toxoplasma gondii* have been known to be associated with brain abscess in renal transplant recipients (RTRs), however co-infection has never been reported till date. In the present case, 40 years old renal transplant recipient on curtailed immunosuppressive therapy presented with progressive headache and altered sensorium. The computed tomography of head showed multiple ring-enhancing discrete lesions in the left frontal lobe, with moderate perilesional oedema. Left frontal craniotomy and aspiration revealed thick yellowish brown pus, which on culture showed the growth of dematiaceous fungal hyphae "*C. bantiana*" and co-infection with "Toxoplasma" was confirmed by PCR as well as serology (both IgM and IgG – Toxoplasma) positivity. Stereotactic aspiration/open craniotomy and drainage is imperative to arrive at microbiological diagnosis and provide timely therapy to the patient.

1. Introduction

Opportunistic infections are well known to occur in the renal transplant recipients (RTRs) [1]. Central nervous system (CNS) complications are a significant cause of morbidity and mortality. Around 30% of RTRs develop some neurological complications [2]. CNS infection manifesting as meningitis is a common complication, but a brain abscess is rare [3]. In general the immunocompetent individual may develop bacterial brain abscess but however the RTRs often acquire opportunistic infections including fungal (*Aspergillus*, *Cryptococcus*), atypical organisms (*Listeria*, *Nocardia*) and *Mycobacterium tuberculosis*. Brain abscess in RTRs is usually due to hematogenous spread from a primary site either lungs or skin.

C. bantiana is a highly neurotropic dematiaceous fungus [4] and a rare cause of cerebral abscess both in immunocompetent and immunocompromised patients, with a mortality of up to 70% despite immediate neurosurgical intervention along with antifungal treatment. *Toxoplasma gondii* is also a rare but significant cause of brain abscess in RTRs [5]. Lack of clinical suspicion and difficulties in establishing an early diagnosis contribute to high mortality.

2. Case

A 40 years old male, who underwent emotionally related (Donor: Wife) renal allograft transplant in 2012, with history of multidrug resistant pulmonary tuberculosis diagnosed in 2016 based on bronchoalveolar lavage fluid GeneXpert positivity with Rifampicin resistance, on second line antitubercular regime (Ethambutol, Pyrazinamide, Levofloxacin, Ethionamide, Amikacin) and curtailed immunosuppression (mycophenolate mofetil withheld) with stable graft function (serum creatinine of 1 mg/dL). Patient presented to emergency (day of admission, day 0) with global, severe headache of 3 days duration and altered sensorium (irrelevant talks and not recognising relatives) for 1 day. There was no history of fever, vomiting, seizures, loss of consciousness, ear discharge or head injury. On evaluation, the patient was drowsy with Glasgow Coma Score (GCS) of 13/15. His pulse rate was 76/minute, and blood pressure was 120/76 mm of Hg. He had bilateral papilledema, with no other localising focal neurological deficits. Rest of the physical examination was unremarkable except for a single ulcerative plaque measuring 4 × 3 cm over the outer aspect of right thigh (Fig. 1a). His initial hemogram was normal (Hemoglobin-12.6 gm/dL and total leukocyte count-7800cells/mm^3), viral markers including HIV1 and 2 by ELISA were negative. Patient was euglycemic, had acute allograft dysfunction with creatinine of 2.3 mg/dL, however, urine

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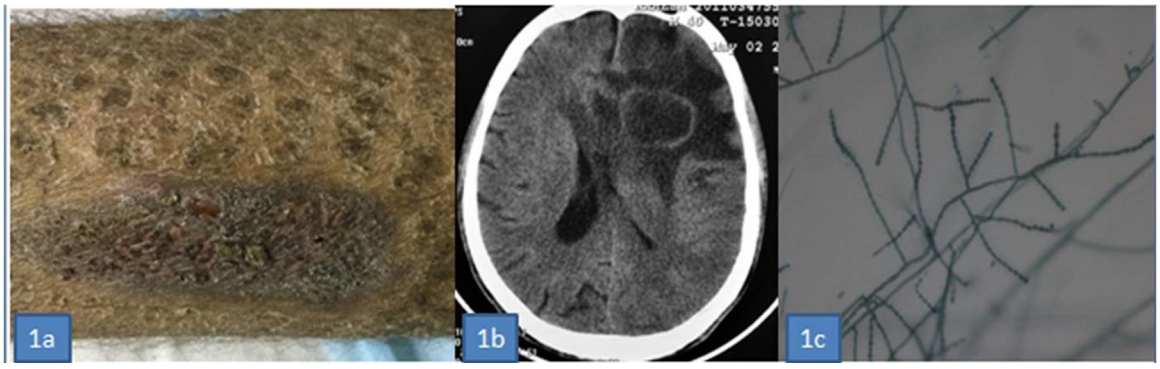

Fig. 1. a- Plaque like lesion with blackish discolouration of skin over outer aspect of right thigh. 1b-Computed tomography of brain showing multiple ring-enhancing lesions in the left frontal lobe, with moderate perilesional oedema. 1c- Slide culture of *Cladophialophora bantiana* showing branched conidiophore with long chains of lemon-shaped, dark conidia on lactophenol cotton blue mount.

routine microscopy was normal with no pus cells and RBC. Whole blood trough level of tacrolimus was 5.7 ng/mL. Computed Tomography (CT) scan of brain revealed multiple ring-enhancing discrete lesions in the left frontal lobe, the largest measuring 26 × 16 mm with moderate perilesional oedema causing mass effect inform of an effaced left frontal horn and minimal midline shift(Fig. 1b). Search for a para-meningeal focus of infection including an ear, nose and throat endoscopic evaluation was negative. On day + 2, he got deteriorated with new-onset progressive left hemiparesis, aphasia and status epilepticus requiring ventilatory support, anti-cerebral oedema measures, anti-epileptic drugs and empirical broad-spectrum antibiotics. On day + 3, Urgent stereotactic left frontal craniotomy revealed tense and pulsatile dura with an abscess about 2 mm beneath the cortex, approximately 20 mL of thick yellowish brown pus was aspirated. Microscopic examination (Gram, Calcofluor white and Grocott silver stain) revealed brown septate hyphae suggestive of dematiaceous fungus, and he was started on empirical liposomal amphotericin (3 mg/kg/day, 150 mg/day). Later fungal culture grew mould which appeared velvety olive grey colour on the obverse and black on reverse. The slide culture showed long, sparsely branched conidiophores bearing wavy chains of oval conidia (Fig. 1c). Based on the morphological features and its ability to grow at 42 °C the mould was identified as C. bantiana and the identity was confirmed by sequencing internal transcribed region of rDNA. The isolate was deposited in the National Culture Collection of Pathogenic Fungi, India (NCCPF- 350068). On day + 7, following culture report, oral flucytosine (75 mg/kg/day, 1 gm QID) and voriconazole (200 mg BD) was added as triple antifungal regimen for *C. bantiana*. To our surprise, Toxoplasma PCR of pus aspirate was also positive, and subsequently Toxoplasma IgM and IgG was positive, thereby confirming the possible co-infection of toxoplasmosis, requiring initiation of pyrimethamine (75 mg OD) with folinic acid (5 mg OD) and sulfadiazine (1 gm QID) for toxoplasmosis. Skin biopsy from right outer thigh also revealed fungal elements with brown septate hyphae demonstrating possible portal of entry or another metastatic lesion. On Day + 12, he developed nosocomial pneumonia, later complicated by cytopenia and septic shock requiring dual ionotropes. In view of progressive worsening of sensorium, repeat CT brain revealed massive intracranial haemorrhage possibly due to severe thrombocytopenia secondary sepsis-related disseminated intravascular coagulopathy. Repeat neurosurgical intervention couldn't be contemplated owing to the absence of brainstem reflexes. The patient succumbed to his illness on day + 15 and family didn't give consent for autopsy.

3. Discussion

We report an unusual case of multiple brain abscesses secondary to co-infection by *C. bantiana* and *Toxoplasma gondii*. Besides novelty, this case-report attempts to re-emphasis need of early tissue diagnosis in RTRs with brain abscess, which may surprisingly reveal relatively rare aetiologies either in isolation or co-infection, with an otherwise fatal outcome, if not diagnosed and intervened early.

Brain abscess in immunocompromised individual can be caused by various organisms. Cerebral phaeohyphomycosis (dematiaceous fungi – pigmented due to melanin in cell wall) appears to be an exception with predilection for immunocompetent patients as well, aptly evident in a review of 101 patients with cerebral phaeohyphomycosis, where over 50% had no apparent risk factors and *C. bantiana* was the most common aetiological agent, found in 48 cases [4]. Chakrabarti et al. [6], reported that *C. bantiana* brain infection was nearly equally distributed in immunosuppressed and immunocompetent individual with higher mortality in former group. Cerebral cortex (usually frontal or parietal regions) is the most common site of infection, although it can involve cerebellum, brainstem or spinal cord. Indeed, symptomatic localised infection due to dematiaceous fungi at other locations (sinus, lung or skin) is sporadic [7]. Inhalation and hematogenous spread to CNS from a primary sub-clinical pulmonary focus can be presumed to be the portal of entry [8]. Neurotropism of *C. bantiana* may be due to its ability to convert various phenolic compounds available in the human brain [9]. On the contrary, Toxoplasma related brain abscess in a RTR can be the result of either a primary infection [10] (seropositive donor kidney transplanted into a seronegative recipient) which usually occurs within the first post-transplant year (median, 60 days) or from reactivation of latent infection (described up to 7 years [5] after transplantation).

Most patients with brain abscesses present with insidious onset headache and slowly evolving focal neurologic deficits and/or generalized seizure. It is important to stress that fever may not always be present and infection parameters can be normal on admission, particularly in a post-transplant setting as was evident in the index case. The abscess can be single or multiple and require CT or MRI [11] for identification.

Radiologically, abscesses caused by rare fungi such as *C. bantiana* cannot be differentiated with certainty from bacterial aetiology, primary cerebral neoplasia or metastasis. Differential diagnosis is even broader in an immunocompromised host and includes a battery of opportunistic infections. CNS toxoplasmosis has typical deep-seated ring-enhanced lesions with an asymmetric target sign, with variable signal intensity on T2-weighted MRI images. Atypical multiple miliary lesions have also been described in bone marrow transplant patients and AIDS patients but so far not in RTRs [12].

Tissue diagnosis with exhaustive microbiological cultures for bacteria, mycobacteria and fungiis considered the gold standard for diagnosis and should always be performed. Definitive diagnosis of cerebral toxoplasmosis requires demonstration of the tachyzoites in biopsy samples, but identification of anti-T gondii antibodies by ELISA and specific nucleic acid amplification by PCR assay is a sensitive and specific method for documenting infection. In immunocompromised

patients, the absence of particular antibodies does not exclude active disease. In our case, PCR assays of aspirate and plasma samples were positive.

Cerebral phaeohyphomycosis is a rare condition; therefore there are no guidelines as to accepted therapy and no clinical trials comparing regimens. It is generally accepted that the best outcomes are seen in patients who receive both complete surgical clearance of the abscess and systemic antifungal triple drug regime comprising of amphotericin, flucytosine and itraconazole [4]. Voriconazole [13] was preferred over itraconazole in index case because of better bioavailability (96% vs. 55%), high volume of distribution and better cerebrospinal fluid penetration (90% vs. 50%). CNS toxoplasmosis requires pyrimethamine, folinic acid along with sulfadiazine. For patients with sulfa allergy, desensitisation or alternatives (clarithromycin, azithromycin, atovaquone) should be considered.

Overall mortality due to cerebral phaeohyphomycosis is around 70% signifying the virulence of *C. bantiana*, attributable mainly to melanin production and thermotolerance above 40 °C. Melanin [14], as an antioxidant metabolite, scavenges the free radicals produced by phagocytic cells and makes the fungus resistant to oxidative and nitrosative stress, which reduces the pathogen's susceptibility to killing by host antimicrobial mechanisms.

4. Conclusion

CNS abscesses in a RTR due to *C. bantiana* and *Toxoplasma gondii* co-infection has never been reported till date. CT guided stereotactic aspiration/open craniotomy and drainage is imperative to arrive at the microbiological diagnosis. We reiterate that in tropical countries, where local epidemiology may suit two or more infections, a possibility of co-infection should always be considered, particularly in immunocompromised patients.

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Conflict of interest

There are none.

Ethical form

Signed Ethical form has been attached.

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