

Brain abscess in patients with chronic kidney disease: A case-based approach to management in resource-limited settings

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SUMMARY The management of patients with brain abscess poses a significant challenge to clinicians in patients with chronic kidney disease. Obtaining a biopsy sample from the affected area is the mainstay in the diagnosis, but it is often unavailable. In most cases, therapy is guided by clinical findings and imaging alone. We discuss three cases of brain abscess- each with a different scenario and discuss the issues faced in management. The first case was a 32-year-old post-renal transplant male patient with a brain abscess due to dematiaceous fungi and was treated with amphotericin. The second case was a 42-year-old female patient with stage 5 chronic kidney disease on maintenance hemodialysis who presented with a brain abscess due to suspected fungal infection based on imaging findings and was managed with antibiotics and voriconazole. The third case was a 42-year-old post-renal transplant male patient who presented with a brain abscess due to nocardiosis and was managed with cotrimoxazole, meropenem and linezolid. We also summarize the approach to the management of brain abscess in resource-limited settings.

Keywords Fungal, dematiaceous, *Cladophialophora*, nocardiosis

1. Introduction

Brain abscess is a focal, intracerebral infection that begins as a localized area of inflammation and develops into a collection of pus surrounded by a rim (1). A total of 8% of intracranial mass turn out to be brain abscess in developing countries compared to 1-2% in developed countries (2). It can be a result of direct contiguous or hematogenous spread or a complication of trauma or neurosurgical procedures. Identifying the cause and source of infection may help select antibiotic therapy for the patients. The definitive diagnosis of brain abscess requires invasive techniques and therefore, more often than not, diagnosis is established based on clinical findings and imaging. For example, multiple abscesses on imaging in middle cerebral artery distribution points towards bacteremia from another source, abscess in frontal lobe indicate a contiguous dental or sinus source and abscess in temporal lobe/cerebellum indicates an otogenic source. Similarly, in patients with immunosuppression, tuberculosis, toxoplasmosis, nocardiosis and fungal etiologies should be kept in

the differential. There are no definite guidelines on the management of brain abscess in resource-limited settings. We report three cases of brain abscess and discuss the challenges and approach to the management of such cases in resource-limited settings.

2. Case report

2.1. Case 1

A 32-year-old male patient from Bihar (a state in northern part of India) presented one year after renal transplant with two episodes of sudden onset tonic-clonic posturing followed by clonic movements of all four limbs. He was admitted to a local hospital where he was stabilized and given intravenous antimicrobials (details unknown). The patient was referred to our centre for further management. At presentation, he was conscious and co-operative without any focal deficits on detailed neurological examination. A magnetic resonance imaging (MRI) was done, which showed a lobulated lesion of 2.7 × 2.5 × 2.5 cm showing restricted

diffusion in the right anterior and basi-frontal lobe. He underwent right frontal craniotomy and excision of the right basi-frontal abscess. Histopathological examination showed pigmented septate hyphae with acute angle branching (Figure 1). He was started on liposomal amphotericin B (3 mg/kg) for the fungal brain abscess. He was incidentally detected to be positive for anti-hepatitis C antibodies. Hepatitis C virus (HCV) genotype was 1a with ribonucleic acid (RNA) levels of 38,237 IU/mL. He was started on sofosbuvir and ledipasvir for this. He was discharged in a stable condition and was advised to complete four more weeks of amphotericin B at a hospital near his home.

2.2. Case 2

A 42-year-old female patient from Bihar, a known case of stage 5 chronic kidney disease on maintenance hemodialysis for the last one year presented with complaints of intermittent high-grade fever with chills and rigours for one month. It was associated with a diffuse, throbbing headache of severe intensity and frequent episodes of non-bilious, non-projectile and non-blood stained vomiting. The patient developed insidious onset progressive weakness in the right half of the body for the past seven days, which started in the lower limbs and progressed to involve the entire right half of the body. She had a history of provoked thrombosis in internal jugular vein due to multiple double-lumen jugular catheter insertions. She also had a history of contact with a tuberculosis patient (husband, diagnosed one year back, completed treatment). On examination, she was conscious and oriented. She had increased tone and power of 0/5 grading in both the right upper and lower limbs. Her right biceps, triceps, supinator and ankle jerks were exaggerated. Plantar on the right side was extensor. Examination in the left half of the body was essentially normal. Sensory exam was normal. Rest

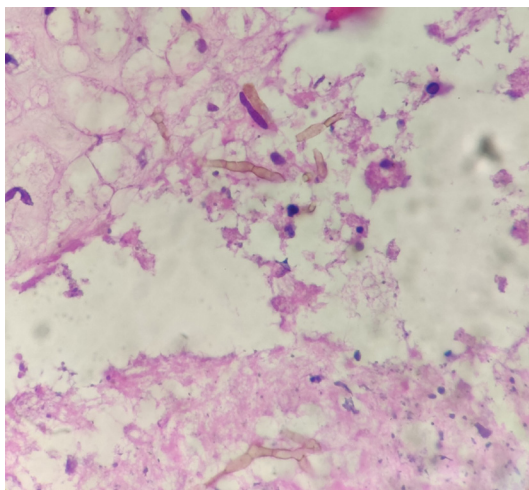


Figure 1. Histopathological examination showing pigmented narrow septate hyphae with acute-angled branching.

of the systemic examination was essentially normal. Non-contrast MRI revealed a well-defined lesion with crenated margins and intra-cavitary projections measuring $2.4 \times 1.6 \times 2$ cm having T2 hypointense rim with a hyperintense core in the periventricular location on the left side with extensive perilesional oedema (Figure 2). The features were consistent with a fungal abscess. She was empirically started on ceftriaxone, metronidazole, linezolid, voriconazole and steroids. Cerebrospinal fluid examination (CSF) showed neutrophilic predominant pleocytosis. CSF cryptococcal antigen was negative, but galactomannan was raised with an optical density value of 2.08. Transthoracic echocardiography was normal. Positron emission tomography (PET) scan was done, which showed isolated uptake in the abscess region only. Anti-tubercular drugs were not started because of isolated brain abscess, no meningeal enhancement and no uptake in any other part of the body. The patient started improving gradually and power improved to 3/5 in right upper limb and 2/5 in the right lower limb after two weeks of therapy. Non-contrast computed tomography (NCCT) head was done on follow up, which showed a significant reduction in the size of abscess and oedema. Brain biopsy was deferred from the neurosurgery side because of improving power. The patient developed in-hospital thrombocytopenia after which linezolid was continued. The patient was discharged on ceftriaxone, metronidazole and voriconazole after three weeks of intravenous therapy in a stable condition and was advised to continue these drugs from a local hospital. She was advised to follow up after four weeks of therapy but was lost to follow up.

2.3. Case 3

A 42-years-old male presented with a history of fall while after which he complained of weakness in the

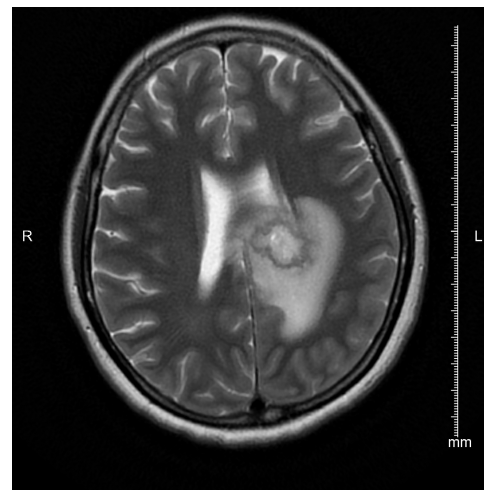


Figure 2. T2 weighted axial image showing a well-defined crenated lesion with a T2 hypointense rim in a left periventricular location with extensive perilesional oedema suggestive of a fungal abscess.

right half of the body and deviation of angle of the mouth towards the left side. He also had a history of low-grade fever and generalized weakness along with loss of appetite and loss of weight for one month. He was a diagnosed case of type 2 diabetes mellitus and hypertension with stage 5 chronic kidney disease and underwent a heterotopic renal transplantation (unrelated matched donor) one year back. Examination revealed features of right hemiplegia with right-sided upper motor neuron facial weakness. A NCCT of the head was suggestive of a left-sided brain abscess. A brain biopsy could not be arranged for him. On re-examination, soft, fluctuant swelling of size 3 × 3 cm with poorly defined margins was noted over the right 9th and 10th intercostal spaces in the mid-axillary line. Contrast-enhanced CT of the abdomen revealed a hypodense collection in the right sub-diaphragmatic and the right sub-hepatic space communicating with the superficial collection. Gram stain of the aspirated pus from the collection revealed gram-positive thin filamentous branching structures that were acid-fast on modified Ziehl Neelsen stain (Figure 3). With a diagnosis of nocardiosis, he was started on cotrimoxazole, meropenem and linezolid and his immunosuppression were reduced. He improved significantly on treatment.

3. Discussion

All three cases of brain abscess highlighted different challenges in diagnosis and management. The first case was relatively stable as he had already undergone a renal transplant, received some empirical antifungals and had no neurological deficits at presentation. The availability of brain abscess in resource-limited settings is a matter of concern. Ours was a referral care centre where the facility of brain biopsy is available, but the procedure is often delayed because of the heavy burden of such cases. Antimicrobial therapy in this patient could be deferred until a brain biopsy was performed because of his stable condition. A definitive diagnosis of fungal brain abscess due to fungal aetiology was established.

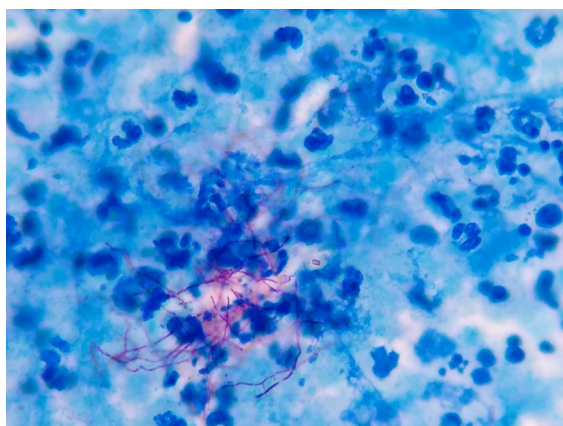


Figure 3. Modified Ziehl Neelsen stain showing long branched filamentous acid-fast bacilli suggestive of nocardiosis.

The likely organism was a dematiaceous fungus because of the pigmented nature of hyphae, and he was started on amphotericin. Voriconazole was avoided in this patient because of possible drug-drug interactions with the immunosuppressants.

In the second patient, the patient was on alternative day maintenance hemodialysis, and since brain biopsy could not be urgently arranged for her, she was started on empiric antimicrobials. Although MRI findings and CSF galactomannan pointed towards a possible fungal aetiology, the patient was initiated on both anti-bacterial and antifungals. Voriconazole was chosen as the anti-fungal of choice as amphotericin was avoided because of its nephrotoxicity.

Fungal abscesses are less common compared to other causes but are very difficult to manage. The optimal therapy for fungal brain abscesses usually requires a combined medical and surgical approach; surgery involves either excision or drainage of the abscess. The therapy in fungal brain abscess is guided by the type of fungus involved. In cryptococcal brain abscess, basal ganglia are commonly involved. CSF shows mild cellularity (predominantly lymphocytic) and raised protein. CSF may be positive for India ink, cryptococcal antigen or culture. Liposomal amphotericin B, along with flucytosine, is used for induction therapy followed by fluconazole for consolidation and maintenance therapy. If the initial KOH or biopsy shows septate hyphae (*Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., dematiaceous fungi including *Cladophialophora bantiana*), the patients should be started on voriconazole. On the other hand, if initial microscopy shows hyaline aseptate hyphae (mucormycosis), liposomal amphotericin B should be used at high doses (at least 5 mg/kg once daily) with close monitoring of renal function and electrolytes. After stabilization of the initial condition, step down therapy with oral posaconazole can be tried.

In the third patient, the patient was post-transplant, and the microbiological diagnosis could be established by sampling from an accessible site (superficial skin collection). Brain biopsy was, therefore, not needed in this case, and with a diagnosis of disseminated nocardiosis, the patient was adequately treated. Diagnostic and therapeutic aspiration is essential in patients with nocardial brain abscess, but aspiration or biopsy of other accessible sites may be tried if available. Modified acid-fast stain shows branched filamentous bacilli. Isolated nocardial brain abscess is treated with initial inpatient parenteral therapy consisting of cotrimoxazole (15 mg/kg *i.v.* of the trimethoprim component per day in three or four divided doses) along with a carbapenem (imipenem or meropenem). After the initial six weeks of parenteral therapy and improving clinical and imaging profile, patients can be shifted on oral therapy (cotrimoxazole +/- amoxicillin/clavulanic acid for one year at least). In patients with brain abscess

Table 1. Radiological features of Brain abscess

MRI features	Pyogenic	Tubercular	Fungal	Toxoplasmosis
Morphology	T1 hypointense, T2 hyperintense, smooth/lobulated thin-walled margins	T1 hypointense, T2 hyperintense, smooth/lobulated thin-walled margins	T1 isointense, T2 hypointense rim, crenated margins, Intra-cavitary projections not showing contrast enhancement	Eccentric target sign on post-contrast images, concentric target appearance on T2-weighted images, multiple abscesses in varying stages
Diffusion-weighted imaging	Central diffusion restriction	Central diffusion restriction	Diffusion restriction in-wall and intra-cavitary projections only. No central diffusion restriction	No central diffusion restriction
MR Spectroscopy	Amino acid peak (0.9 ppm)	Lipid lactate peak (1.3ppm)	Trehalose peak (3.6-3.8 ppm)	Non-specific
Associated features		Infarcts in tubercular vasculitis	Infarcts in angioinvasive fungal infection	Perilesional haemorrhage Basal ganglia location

*MRI, magnetic resonance imaging; MR, magnetic resonance; ppm, parts per million.

and multi-organ involvement (*i.e.*, at least one other site), initial inpatient parenteral therapy can also be supplemented with a third drug, amikacin.

Patients with brain abscess usually present with fever, headache, and focal neurologic deficits. However, this classical presentation is observed in less than half of the patients. In immunocompromised patients, the clinical symptoms are even more non-specific due to diminished inflammatory response in these patients (3). In the presence of focal symptoms & signs or features suggestive of increased intracranial pressure, lumbar puncture should be performed only after imaging. MRI with Magnetic Resonant Spectroscopy (MRS) is the preferred diagnostic modality. The imaging finding of brain abscess due to different etiologies has been summarized in Table 1. In those patients where MRI cannot be done, computed tomography can be used for diagnosis.

Stereotactic brain biopsy/aspiration should ideally be done in all lesions greater than 2.5 cm (4). In resource-limited overburdened settings, it is challenging to obtain brain biopsy in most cases. The treatment of brain abscess without diagnosis has to be empiric in such cases taking clues from radiological findings and other supportive investigations. The empiric regimen is further complicated in patients with renal impairment because of nephrotoxicity of certain antibiotics, need for dosing modifications and possible drug-drug interactions.

The approach to empirical management of brain abscess in resource-limited settings is summarized below based on the available literature and our experience. The empiric management of patients with brain abscess from contiguous sources should consist of ceftriaxone and metronidazole (5,6). This would cover for the most common organisms responsible for brain abscess in Indian studies, *i.e.* *Streptococcus* spp. and anaerobic organisms (7,8). Vancomycin may be added if there is a history of trauma or neurosurgery as these brain abscesses are often caused by methicillin-resistant

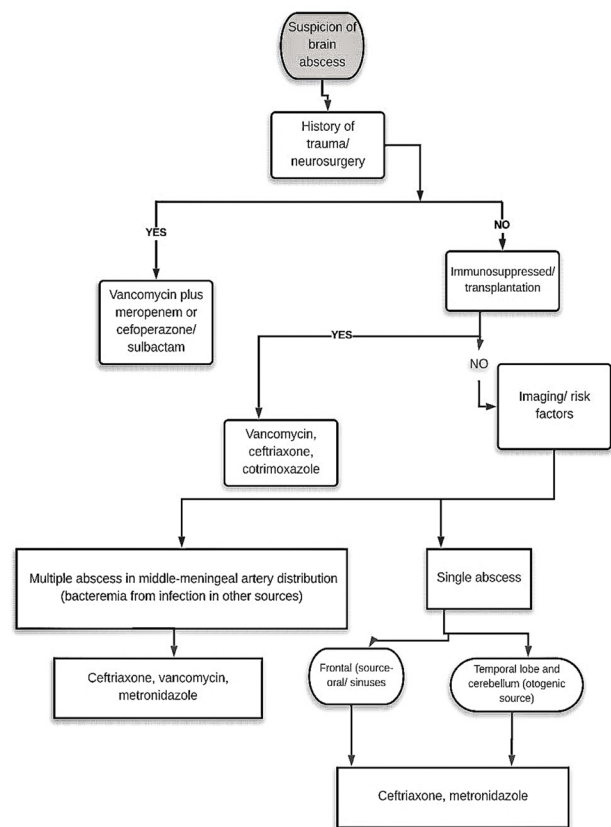


Figure 4. Flow chart showing approach to empirical management of brain abscess.

Staphylococcus aureus (MRSA). In these patients, meropenem or sulbactam containing combinations should replace ceftriaxone and metronidazole to cover for the multi-drug resistant gram-negative organisms, including *Acinetobacter* spp.

In patients with immunosuppression (especially HIV/AIDS and solid organ transplant), cotrimoxazole should be added to cover for toxoplasmosis. The empiric management has been further summarized in a flow chart (Figure 4). The minimum duration of

treatment is six to eight weeks. Duration of therapy beyond that period is primarily individualized depending upon response. Contrast-enhanced CT Scans or MRI can be repeated every two weeks to see the response to treatment. The therapy has to be eventually narrowed down based on the microbiological diagnosis. In patients living with HIV/AIDS (PLHA) having low CD4 count ($\leq 100/\text{mm}^3$), toxoplasmosis is a strong differential (9). Positive toxoplasmosis serology (IgG) positive and response to cotrimoxazole point towards the diagnosis of toxoplasmosis. Tuberculosis may be one of the most common causes of brain abscess in India, according to some earlier reports (2). Characteristic CSF picture (high protein, increased cellular response with lymphocytic predominance and higher values of adenosine deaminase) with microbiological evidence by cartridge-based nucleic acid amplification test or liquid culture from CSF is used for making the final diagnosis. The patients should be treated with at least nine months of anti-tubercular therapy with at-least four weeks of steroids (10-12).

Brain abscess is an important cause of morbidity and mortality in developing countries like India. Besides surgical management, prompt initiation of empirical or microbial directed therapy should be initiated. There is an urgent need for the development of evidence-informed local guidelines based on the epidemiology.

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