Uncommon presentation of intracranial cryptococcal infection mimicking tuberculous infection in two immunocompetent patients

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ABSTRACT

Cryptococcal infection of the brain is commonly seen in immunocompromised patients but rarely considered as the differential diagnosis in immunocompetent patients. We present two cases of cryptococcosis involving the brain in immunocompetent patients, which strongly mimicked tuberculous infection in both conventional as well as advanced magnetic resonance (MR) imaging, and the disease was only confirmed after histopathological /cerebrospinal fluid serological study. One patient was a 52-year-old woman, and the second patient was a 23-year-old man. These two cases highlight the need for workup of fungal infections in immunocompetent patients from the tuberculous endemic regions, even when the imaging is highly suspicious of tuberculous lesions. The imaging findings in advanced MR imaging techniques such as diffusion, perfusion, susceptibility-weighted imaging and MR spectroscopy are discussed.

Keywords: brain infections, central nervous system infection, cryptococcosis, fungal infection, tuberculosis

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INTRODUCTION

Cryptococcus (*C.*) *neoformans* is the most common fungal infection of the central nervous system (CNS).[1] It is one of the most common opportunistic infectious agents in human immunodeficiency virus (HIV)-positive and other immunocompromised patients, but less commonly seen in immunocompetent patients.[2] The conventional computed tomography (CT) and magnetic resonance (MR) appearances of neurocryptococcosis have been described previously for both immunocompetent and immunocompromised patients.[1-4] We present two cases of intracranial cryptococcal infections in immunocompetent patients, with varied presentations on conventional MR imaging and other newer sequences like diffusion, perfusion, susceptibility-weighted imaging (SWI) and MR spectroscopy; where most of the features mimicked intracranial tuberculous infection. Both these cases highlight the need to considering the possibility of fungal infections, even in immunocompetent patients, from regions which are endemic for tuberculosis (TB). Even on newer imaging techniques, cryptococcal lesions have similar MR characteristics as tuberculous lesions.

CASE REPORTS

Case 1

A 52-year-old female patient presented with occasional giddiness and tinnitus in the right ear, holocranial headache and non-projectile vomiting. MR imaging of the brain, done elsewhere, reported an extra-axial right cerebellopontine angle lesion, and the patient was referred to our institute for further management. General examination of the patient was normal. Neurological examination revealed bilateral papilloedema, right V1 and V2 sensory impairment, and right sensory neural hearing loss. Laboratory investigations showed raised erythrocyte sedimentation rate at 99 mm/1st hour. Chest radiograph showed no significant abnormality. The patient underwent a detailed MR imaging evaluation with newer sequences. This revealed an intra-axial mass lesion in the flocculus of the right cerebellar hemisphere, appearing isointense on T1-weighted images and profoundly hypointense on T2-weighted images, with a surrounding hypointense rim. Moderate oedema was noted around the lesion. The lesion was abutting the right VIIth and VIIIth cranial nerves. There was an irregular, lobulated ring-like enhancement and enhancing adjacent tentorial dura (Fig. 1).

The centre of the lesion showed isointensity on diffusion imaging and hypointensity on the apparent diffusion coefficient (ADC) map with the margin of the lesion appearing hypointense on both diffusion and ADC maps. On T2* dynamic susceptibility contrast perfusion imaging, the lesion showed decreased perfusion (rCBV) in the centre with mild increase in the periphery. SWI of the brain revealed hypointensity in the periphery of the lesion. Multivoxel MR spectroscopy with TE of 30 msec demonstrated a large lipid, lactate peak with evidence of reduced N-acetylaspartate (NAA) and choline (Fig. 2). Based on the above imaging findings, tuberculoma and

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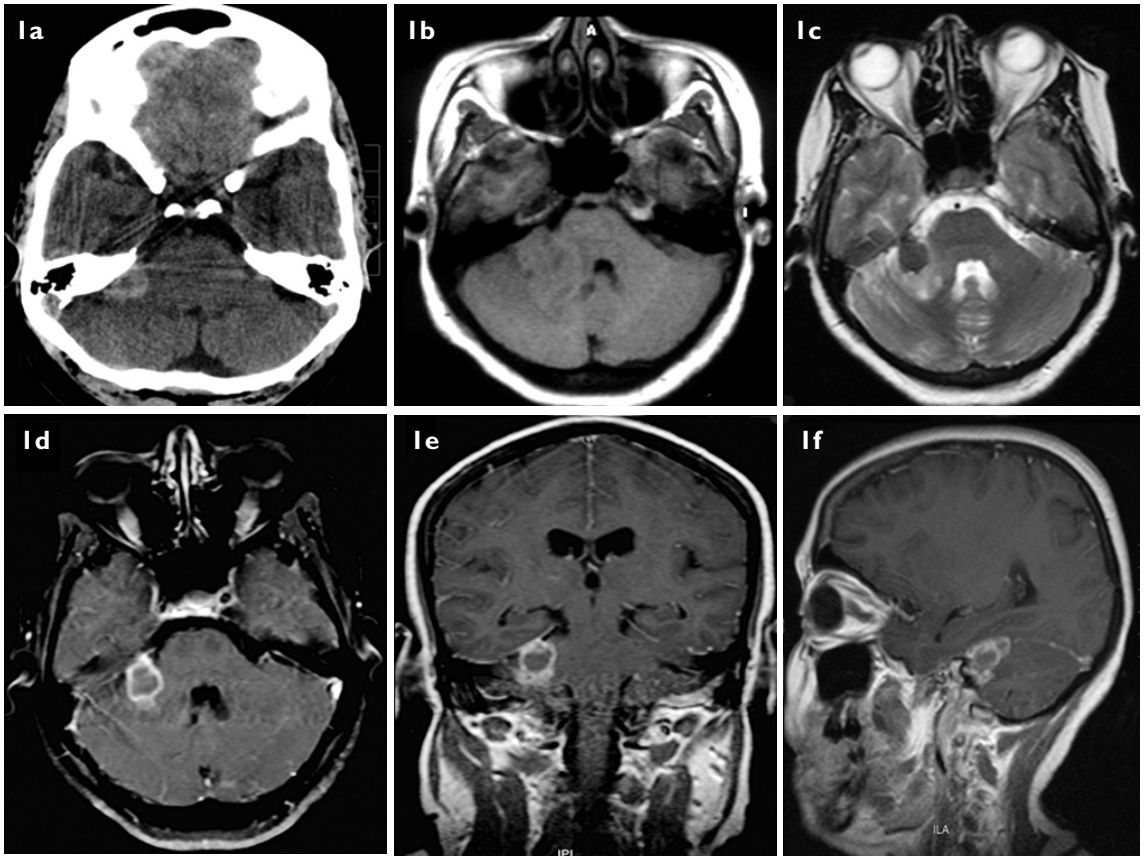

Fig. 1 (a) Axial CT image of the brain shows a round hyperdense lesion in the flocculus of the right cerebellar hemisphere. (b) Axial T1-W MR image of the posterior fossa shows an intra-axial isointense lesion with a mild hypointense peripheral rim in the flocculus of the right cerebellar hemisphere. (c) Axial T2-W MR image shows that the lesion appears profoundly hypointense with surrounding moderate perilesional oedema. (d) Contrast-enhanced axial T1-W MR image shows a ring-enhancing lesion in the right cerebellopontine angle region. (e) Contrast-enhanced coronal T1-W MR image shows the irregular lobulated margin of the ring-enhancing lesion with minimal enhancement of the adjacent tentorium. (f) Contrast-enhanced sagittal T1-W MR image shows a ring-enhancing lesion with an irregular lobulated margin.

metastasis were the two diagnostic possibilities. The patient underwent surgery, which confirmed the intra-axial nature of the lesion, and histopathology revealed granulamotous lesion, with Grocott gomoris stain showing the presence of numerous cryptococcal yeasts in the lesion. Her cerebrospinal fluid (CSF) was also India ink positive for cryptococcus (Fig. 2). Postoperatively, the patient developed cryptococcal meningitis but recovered fully with antifungal treatment.

Case 2

A 23-year-old male student presented with a three-month history of double vision and headache, followed by slurred speech. There was no fever or features of raised intracranial pressure. Examination revealed bilateral 6th and left 12th cranial nerve palsies. The differential diagnosis of polyneuritis cranialis was considered. His CSF study was normal except for marginally elevated proteins. His imaging showed mucosal enhancement of the sphenoid sinus and retroclival pachymeninges. Culture and histopathological examinations of the sphenoid sinus aspirate and mucosal biopsy were found to be negative for fungus, especially aspergillosis. Extensive studies done to rule out lymphoma were negative. The patient was put on empirical antituberculous treatment, but the symptoms progressed, and he additionally developed right 12th cranial nerve palsy. Repeat imaging showed an increase in the size of the thickened retroclival pachymeninges, compressing the cervicomedullary junction and associated adjacent thickened tentorial dura. The thickened pachymeninges showed isointensity on T1-weighted images, hypointensity on T2-weighted images, and intense enhancement. CSF revealed elevated proteins with pleocytosis; cultures (for fungus, bacteria and TB) were negative, and there were no malignant cells. CSF cryptococcal antigen was positive. The patient was treated with amphotericin (liposomal) and flucytosine, added later on. The patient showed gradual improvement, and follow-up imaging after one year demonstrated complete resolution of the retroclival lesion (Fig. 3).

DISCUSSION

C. neoformans, an encapsulated yeast, is the most common CNS mycotic infection.[1] It ranks third after HIV and toxoplasmosis, among the infectious agents causing CNS disease in acquired immunodeficiency syndrome (AIDS).[2,4] It has two varieties: *C. neoformans*

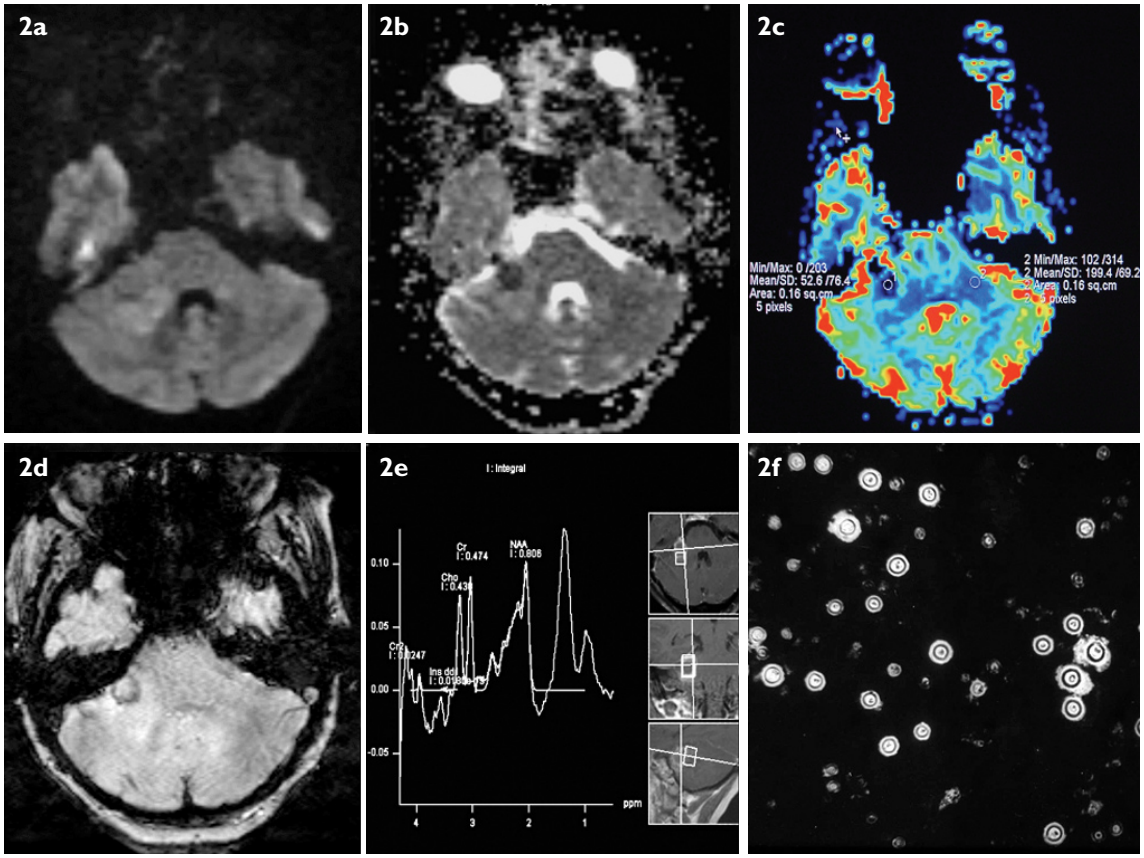

Fig. 2 (a) Axial diffusion-weighted imaging, and (b) apparent diffusion coefficient map at the level of lesion show T2 wash-out effect in the centre and T2 blackout effect in the periphery. (c) rCBV map taken at the level of lesion in the cerebellum shows decreased perfusion inside the lesion with minimal increase at the periphery. (d) Susceptibility-weighted imaging shows hypointensity in the periphery of the lesion suggestive of susceptibility changes. (e) MR spectroscopy with TE of 30 msec shows large lipid-lactate peak with decreased NAA and choline inside the lesion. (g) Photomicrograph of the CSF shows cryptococcal yeasts resembling a starry sky (India ink, × 400).

and *C. gattii*.[2] The *C. neoformans var neoformans* is the most common variety throughout the world, causing infection in immunocompromised patients, including patients infected with HIV. It is found in aged pigeon droppings. *C. neoformans var gattii* grows in a litter around certain species of eucalyptus trees and infects immunocompetent patients, producing intracerebral mass lesions such as cryptococcomas.[2,5] The organism is primarily transmitted via the respiratory route with subsequent spread to different organs through the haematogenous route.[6]

Patients with CNS cryptococcal infection commonly present with features of meningoencephalitis and raised intracranial tension.[7,8] Lumbar puncture is the single most useful laboratory investigation. There is evidence of increased CSF pressure with mild to moderate leucocytosis, decreased glucose and increased protein content. India ink preparation of CSF smear demonstrates the yeast. Infected patients may have elevated cryptococcal antigen titres in the serum or CSF.[3] Organisms may also be detected by microscopical examination and culture. From the imaging standpoint, both CT and MR imaging are very informative, with the latter having very high sensitivity for the detection and characterisation of lesions. Tien et al described four patterns of CNS cryptococcosis on MR imaging, viz. parenchymal mass in the form of cryptococcoma or toruloma; dilated Virchow robin spaces (pseudocysts); multiple miliary enahancing parenchymal and leptomeningeal-cisternal nodules; and mixed pattern.[4]

Meningitis is the most common manifestation, involving the leptomeninges, mostly the base of the brain with distension of the subarachnoid spaces by mucoid gelatinous exudates.[1,2,6] Contrast enhancement is absent or minimal in patients with AIDS, due to impaired cell mediated immunity and inhibition of phagocytosis by the mucoid capsule.[8] Our second patient, an immunocompetent patient, showed enhancing nodular pachymeninges without involvement of the basal subarachnoid spaces; which is very unusual. To the best of our knowledge, this has not been described previously. The enhancement can be explained by the presence of cell-mediated immunity in our patient, and the pachymeningeal involvement could be a direct spread from sphenoid sinusitis without involving the leptomeninges. Hydrocephalus often develops as a result of acute meningeal exudates or chronic meningeal scarring, which is not evident in our case, due to sole

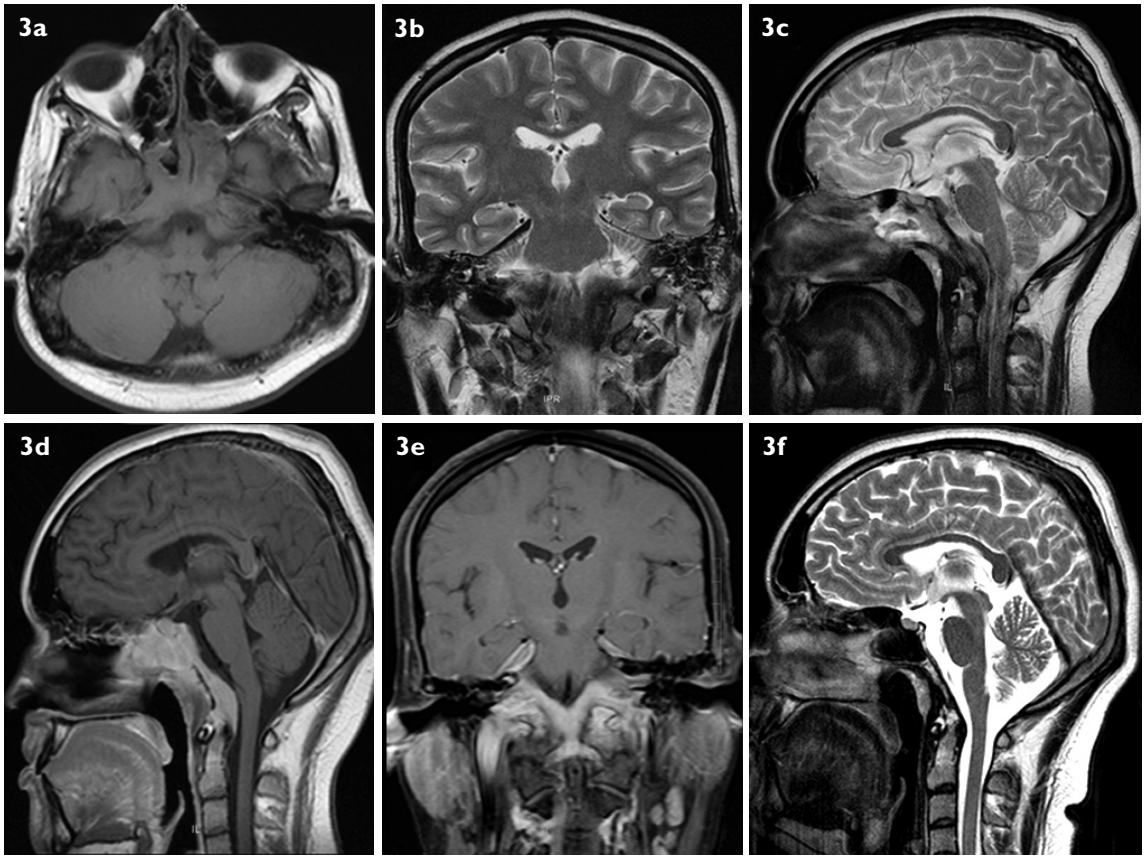

Fig. 3 (a) Axial T1-W MR image of the brain basal shows isointense mucosal thickening of the phenoid sinus and retroclival pachymeninges. (b) Coronal T2-W MR image taken at the level of the tentorium shows thick hypointense tentorial thickening. (c) Midline sagittal T2-W MR image shows thick lobulated retroclival pachymeningeal thickening. (d) Contrast-enhanced sagittal T1-W MR image taken in the midline shows an enhancing sphenoid sinus and lobulated retroclival pachymeningeal thickening. (e) Contrast-enhanced coronal T1-W image taken at the tentorium level shows a thick enhancing tentorium. (f) Post-treatment follow-up sagittal T2-W image does not show retroclival pachymeningeal thickening and sphenoid sinusitis.

pachymeningeal involvement.[1] Based on the imaging features, tuberculous meningitis, lymphoma and fungal meningitis were considered in the differential diagnosis. This case illustrates that cryptococcosis should also be considered in the differential diagnosis of pachymeningitis in an immunocompetent patient.

Once the organism involves the meninges, it spreads through the perivascular spaces to the deeper brain parenchyma, such as the basal ganglia, thalamus, brainstem, cerebellum, dentate nucleus and periventricular white matter, forming gelatinous pseudocysts and soap-bubble-like lesions.[1,7,8] On MR imaging, the lesions commonly show CSF intensity in both T1- and T2-weighted sequences.[1,7] The enhancement of the lesions depends on the host immune response.

Cryptococcomas are the true parenchymal form of cryptococcal infection of the brain, resulting from a chronic granulomatous reaction.[7] The development of these granulomatous lesions depends on the host immune response, and it is uncommon in AIDS patients. On imaging, CT of intracerebral cryptococcal granulomas has been reported as low-density lesions with or without homogeneous contrast enhancement or as isodense lesions with ring enhancement.[7,9] In our first case, the lesion appeared predominantly hyperdense in its periphery with central isodensity on CT. The enhancement pattern was not studied because only non-contrast study was done. Different authors have described differently the conventional MR imaging appearances of cryptococcoma. Miszkiel et al, in their study of 25 patients with AIDS, displayed cryptococcomas as having high signal on T2-weighted and intermediate to low signal on T1-weighted images.[10] None of the lesions enhanced after contrast. Ho et al, in their case report of cryptococcoma in an immunocompetent patient, showed the lesion to be hypointense on T1- and hyperintense on T2-weighted images, with ring enhancement.[6] However, in Gultasli et al's case report, intramedullary spinal cryptococcomas appeared iso- to hyperintense on T1- and hypointense on T2-weighted imaging.[5] The contrast enhancement noted in cryptococcoma usually depends on the host immune response, with immunocompetent patients showing ring enhancement.

The various imaging characteristics described in a cryptococcal granuloma may be due to various stages, as seen in tuberculous infection of the brain. The tuberculous infection can occur as caseating or non-caseating granuloma, or a tuberculous abscess.[11] Our

case resembles the case report of Gultasli et al,[5] with the lesion in the right cerebellum appearing iso- to mildly hyperintense on T1- and predominantly hypointense on T2-weighted sequences. The capsule of the lesion appears hypointense on both T1- and T2-weighted imaging. As our case is an immunocompetent patient, the margin of the lesion showed irregular lobulated contrast enhancement with perifocal oedema. There was also the presence of adjacent dural enhancement. The imaging appearance resembled a caseating tuberculoma.

There are very few reports describing the imaging characteristics of cryptococcoma in advanced MR imaging sequences.[6,12] In this case report, we highlight some of the imaging characteristics of cryptococcoma in newer MR sequences. One interesting finding noted on SWI, not previously described, is the hypointensity of the capsule. These susceptibility changes can be explained by the inflammatory reaction producing paramagnetic free radicals in the capsule. The diffusion characteristics of cryptococcomas may resemble necrotic brain tumour, with the centre of the lesion showing no restricted diffusion. However, Gologorsky et al demonstrated moderate hyperintensity on diffusion imaging and hypointensity on the corresponding ADC map.[2] In our patient, the core of the lesion appeared isointense on diffusion imaging and hypointense on the corresponding ADC map, suggesting some amount of restricted diffusion probably due to the viscous content, which was later confirmed on surgery. The peripheral hypointensity in both diffusion and ADC map could be due to the susceptibility effects produced by the paramagnetic substance in the capsule of the lesion.

The MR spectroscopy of cryptococcoma typically shows decreases in all the major cerebral metabolites like NAA, creatine, choline, myo-inositol, and the presence of a moderate amount of lipids in comparison to normal brain parenchyma. Lactate is rarely observed in cryptococcoma. Compared to toxoplasma and lymphoma, cryptococcoma shows a lesser amount of lipid and lactate.[12] It is particularly difficult to differentiate cryptococcoma from tuberculoma, as tuberculoma also shows high lipid content, decreased NAA, and may or may not show an increase in choline.[13] However, the demonstration of cytosolic disaccharide alpha and alpha-trehalose confirms the diagnosis of cryptococcoma. An *in vitro* study by Himmelreich et al showed a high concentration of alpha, alpha-trehalose in cryptococcomas, and similarly, an *in vivo* MR spectroscopy study by Luthra et al specifically demonstrated trehalose in the fungal abscess wall.[14,15] In our first case, we could find a large lipid peak in the lesion but were unable to get the alpha, alpha-trehalose peak, which may be due to the presence of a lower concentration of metabolite, too insensitive to be detected by the MR spectroscopy. Compared to normal brain parenchyma, perfusion MR imaging of the lesion in the first case showed a decrease in rCBV in the centre and mild increase in the periphery. This appearance is again similar to that noted with tuberculoma.[16]

In conclusion, the presentation of cryptococcal CNS infection in immunocompetent patients may differ from the usual presentation seen in immunocompromised patients. The appearances in both conventional and advance MR imaging strongly mimic tubercuoma, which is also evident in our case. MR spectroscopy detection of alpha, alpha-trehalose, which is specific but less sensitive, could help in differentiating cryptococcoma from tuberculoma. It is strongly recommended to consider cryptococcosis as a differential diagnosis of granulomatous infections of the brain in tuberculous endemic regions.

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