

Balamuthia Mandrillaris Meningoencephalitis associated with Solid Organ Transplantation - Review of Cases

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ABSTRACT

We report the first identified transmission of *Balamuthia mandrillaris* through solid organ transplantation. Kidneys were transplanted from a donor with presumptive diagnosis of autoimmune encephalitis. Shortly after, the recipients developed neurologic symptoms. Magnetic Resonance Imaging of the brain from the donor and both kidney recipients demonstrated multiple ring enhancing lesions with surrounding edema and adjacent leptomeningeal extension. In addition most of the lesions demonstrated signal changes suggesting central hemorrhagic foci. Specimens were tested locally and at the Centers for Disease Control and Prevention. Histopathology revealed *B. mandrillaris* in either brain tissue and/or cerebral spinal fluid in the donor and recipients.

CASE REPORT

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A 4 year old male presented with fever, focal seizure, and a normal neurologic exam after having a recent febrile illness approximately two weeks prior which was diagnosed as Influenza A by a rapid influenza test. After conservative treatment, his symptoms soon progressed to include agitation, multiple seizures, and recurrent low grade fever. Initial cerebral spinal fluid (CSF) studies revealed an elevated white blood cell count (WBC) of 170 cells/cm² (normal 0-20) with normal CSF protein and glucose. CSF cultures were negative. CSF WBC was persistently elevated on subsequent studies.

Initial magnetic resonance imaging (MRI) of the brain demonstrated multiple scattered areas of parenchymal enhancement with surrounding signal changes representing edema involving the supratentorial brain bilaterally. Gyral thickening was noted in the regions of enhancement. The enhancement pattern of the most prominent lesions was of ring-type with poorly defined margins (fig 1). Subsequent MRI imaging performed six days later demonstrated extensive

bilateral areas of abnormal leptomeningeal, cortical, and subcortical signal changes and enhancement. New T1 shortening effects on precontrast images in the areas of abnormality suggested either cortical/laminar necrosis or developing hemorrhagic foci (fig 2). The patient began treatment for a presumptive diagnosis of acute disseminated encephalomyelitis which was largely based on his history of recent viral illness. However, his condition continued to worsen and on day 10, he lapsed into a coma. A computed tomography (CT) scan of his brain at that time revealed diffuse subarachnoid hemorrhage with complete effacement of the basal cisterns and evidence of cerebellar tonsil herniation. Increased attenuation was present within the cortex and subcortical white matter corresponding to the parenchymal signal abnormalities seen on MRI, confirming the suspicion of hemorrhage (fig 3). The patient did not develop hydrocephalus. Brain death was declared the following day and multiple organs were harvested for donation. There were two kidney recipients which were transplanted at our institution. In addition, the patient's heart and liver were transplanted to recipients at outside hospital facilities.

Approximately one month later histopathologic examination of the donor's brain tissue at the Center for Disease Control and Prevention (CDC) revealed the presence of abundant amoebae morphologically suggestive of *Balamuthia* (fig 4). Immunohistochemical and indirect immunofluorescent stains revealed antigens of free-living amoebae in the donor's brain tissue and polymerase chain reaction (PCR) results confirmed *Balamuthia* infection.

The first kidney recipient was a 31 year old female that developed symptoms including right leg twitching, neck spasms, numbness, headache, nausea, and visual disturbances on post-transplant day (PTD) 20. Two days later she became unresponsive and developed generalized seizures. Initial CSF studies revealed elevated glucose and mildly elevated protein with subsequent CSF studies demonstrating an elevated WBC at 507 cells/cm² (normal 0-5) and increased CSF protein.

Initial MRI revealed innumerable poorly defined ring-enhancing lesions with surrounding edema bilaterally throughout the cerebral hemispheres with involvement of the brainstem, cerebellum, and right thalamus. Many of these lesions demonstrated central low T2 signal with associated gradient echo (GRE) blooming artifact, suggesting internal hemorrhage. Mildly restricted diffusion and mild localized mass effect were associated with some of the lesions (fig 5). Subsequent imaging performed three weeks later demonstrated slight increase in the number of lesions as well as the degree of associated edema. She did not develop hydrocephalus.

The patient underwent a brain biopsy with histopathologic examination of the brain tissue at the CDC revealing amoebae. Immunohistochemical stains detected antigens of free-living amoebae, and PCR confirmed *Balamuthia* infection. Despite antimicrobial therapy and neurosurgical intervention, the patient's condition deteriorated and brain death was pronounced on PTD 75.

The second kidney recipient was a 27 year old male that developed symptoms of nausea on PTD 20 which progressed to mental status changes and seizures later that day. CSF studies demonstrated mildly elevated protein at 74mg/dl (normal 12-60) and mild pleocytosis at 19 cells/mm² (normal 0-5).

Initial MRI demonstrated a small ring enhancing focus with surrounding edema involving the peripheral right cerebellar hemisphere and superior right occipital lobe with associated leptomeningeal enhancement (fig 6a). These lesions progressed in size and number on subsequent MRIs with spread to the cerebral hemispheres (fig 6b). The enhancement pattern remained ring-enhancing with poorly defined lesional margins. Many of these lesions again demonstrated central low T2 signal with associated blooming on GRE sequences, consistent with central foci of hemorrhage (fig 7). No hydrocephalus was noted. This patient was found to have a mycotic aneurysm involving the left cavernous/supraclinoid carotid artery measuring greater than 1cm. He also developed diffuse subarachnoid hemorrhage, similar in appearance to what was seen in the donor brain imaging (fig 8).

Balamuthia mandrillaris was confirmed by PCR assay performed at the CDC from a CSF sample obtained on PTD 39. The patient had a prolonged hospital course including two months in a coma, but eventually showed significant recovery of cognitive and motor function from a combination of antimicrobial therapy and neurosurgical intervention for elevated intracranial pressures. He was discharged to rehabilitation on PTD 159 with neurologic sequelae including residual right arm paralysis, bilateral leg weakness, and intermittent vision loss.

The donor's heart and liver were also transplanted with the recipients being 2 and 7 year old children respectively. Both of these recipients have undergone workup for *B. mandrillaris* including MRI of the brain and biopsy with PCR analysis of the transplanted organs. All workup has returned as negative. Both patients underwent prophylactic courses of antimicrobials and remain asymptomatic as of nine months post transplant.

DISCUSSION

Balamuthia mandrillaris is a free-living species of amoebae which was first isolated in 1986, from fragments of brain tissue of a mandrill baboon that died of a neurological disease at the San Diego Zoo [1]. Previously known as leptomyxoid amoeba, it was later renamed in honor of protozoologist, Dr. William Balamuth [1-3]. Representing the sole member of its genus, *B. mandrillaris* has been historically difficult to isolate, but has been recently isolated from soil and cultured using specialized media [1]. The life cycle of *B. mandrillaris* has two stages, cysts and trophozoites. The trophozoites can gain entry to the body through the respiratory tract or through a skin defect. Trophozoites are then capable of hematogenously disseminating to the central nervous system [1,4]. This pathogen is capable of producing a granulomatous amoebic encephalitis (GAE) which is a very rare cause of fulminant life threatening meningoencephalitis. Approximately 200 cases have been reported since 1991 [1-2,5-7]. The organism possesses various virulence factors that aid in binding to and penetrating the blood brain barrier. It is capable of causing cell death via direct phagocytosis as well as through the release of various toxins and proteases capable of destroying the extracellular matrices [1]. GAE typically has a lengthy clinical course followed by rapid deterioration. It has been noted in both healthy as well as immunocompromised patients. However, there does appear to be an increased incidence in young, elderly, and immunocompromised patients [1-3,6-9]. It has been demonstrated that the healthy human population does possess antibodies to this amoebae, suggesting that environmental exposure is common [1]. GAE carries a mortality rate of approximately 90% [5], which is in part due to lack of effective treatment as well as difficulty of diagnosis. The differential diagnosis based on imaging finding includes various ring-enhancing entities such as a parenchymal abscess, toxoplasmosis, and metastatic disease. Clinical history as well as development of central hemorrhage within the parenchymal lesions can help narrow the differential. Diffuse subarachnoid hemorrhage late in the disease course is also a somewhat

unique feature of GAE and was demonstrated in 2 of the 3 cases we present. *B. mandrillaris* can be identified using real time PCR. However, this test is not readily available and the diagnosis is typically made post mortem.

We are reporting the first cases of human to human transmission of *B. mandrillaris* via solid organ transplantation which occurred at our institution in 2009 [5,6]. Two additional cases of transplant related *B. mandrillaris* infection have since been reported in Arizona in 2010 [10]. The goal of this case series is to raise awareness of *B. mandrillaris* and provide a basis to raise suspicion of GAE from diagnostic imaging findings, particularly in the setting of potential organ transplantation. Special care must be taken when considering organ harvesting from potential donors with encephalitis of uncertain etiology as it is possible to transmit unusual infections to recipients with devastating consequences.

TEACHING POINT

Balamuthia mandrillaris has recently emerged as an increasing relevant pathogen capable of producing a highly lethal granulomatous amebic encephalitis in both immunocompromised as well as healthy host. The consistent pattern of poorly defined ring enhancement and adjacent leptomeningeal enhancement with focus of central hemorrhage on radiological imaging should be especially viewed with caution as this may suggest fulminant angioinvasive GAE, particularly in the setting of recent solid organ transplantation.

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FIGURES

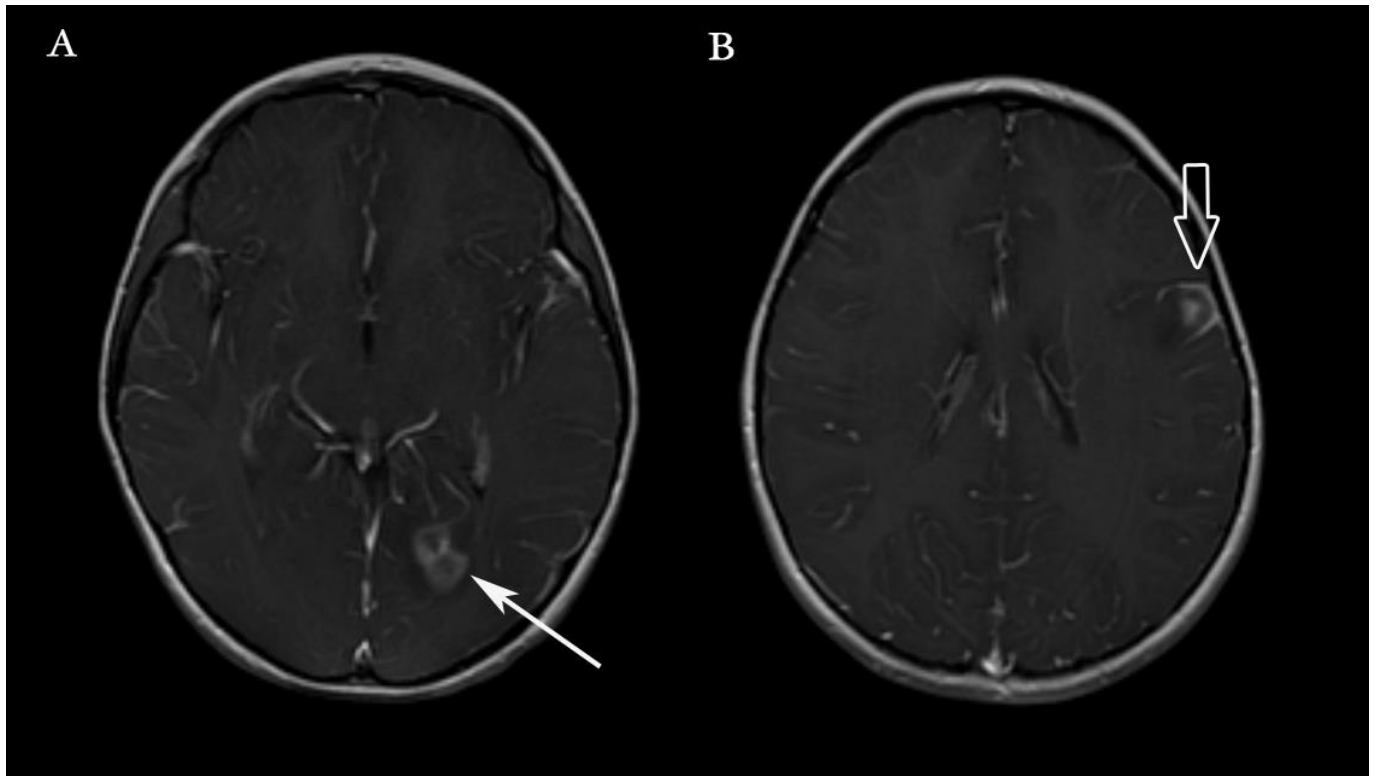


Figure 1 4 y.o male donor with Balamuthia mandrillaris meningoencephalitis. T1W+C SE (TR 416.7/TE 20) axial images demonstrating an ill defined area of ring-enhancement in the left occipital lobe (arrow) (A) and left frontal cortex (B) with enhancement of the adjacent leptomeninges (open arrow). Images were obtained on a 1.5T magnet using 4cc of IV Optimark

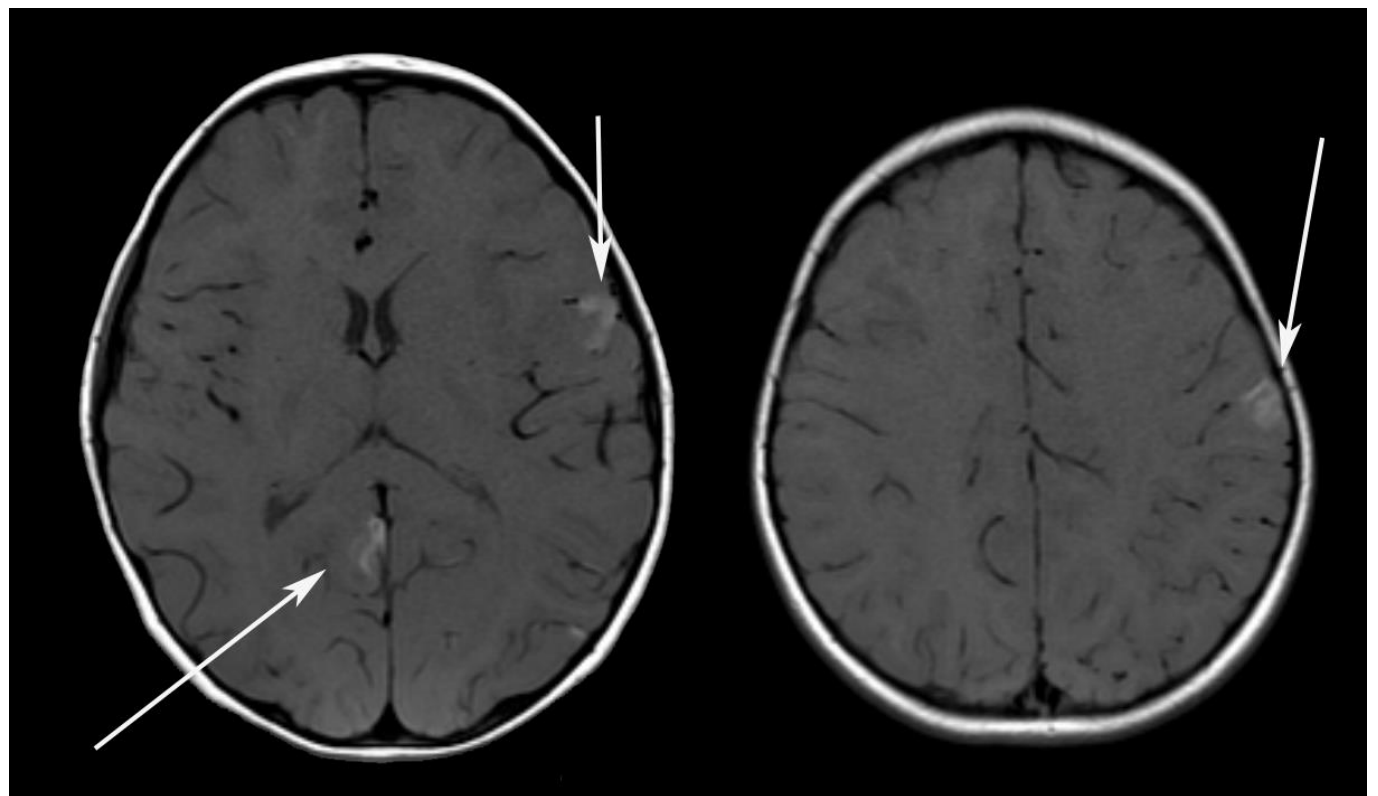


Figure 2. 4 y.o male donor with Balamuthia mandrillaris meningoencephalitis. T1W SE (TR700/TE13 on a 1.5T magnet) axial images demonstrating newly increased cortical signal (arrows) in the right occipital and left frontal lobes, suggesting development of hemorrhage.

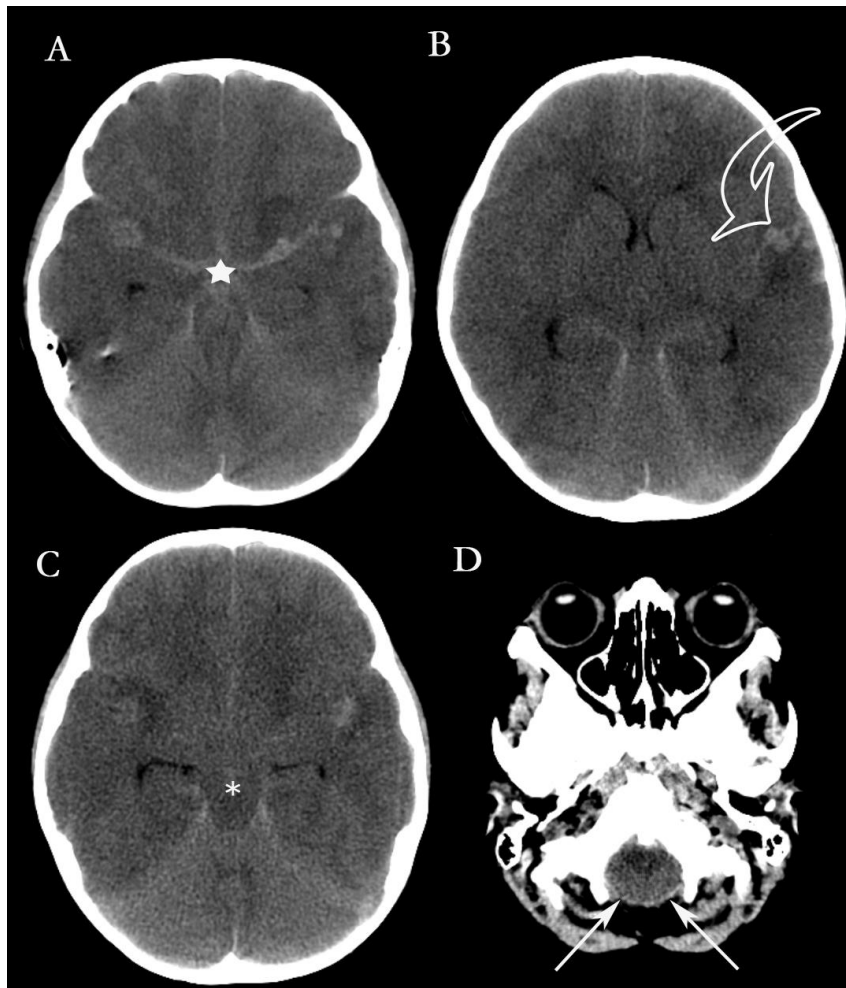


Figure 3. 4 y.o male donor with Balamuthia mandrillaris meningoencephalitis. Nonenhanced CT images prior to death demonstrating diffuse subarachnoid hemorrhage (star)(A) and increased attenuation in the lesion in the left frontal lobe consistent with intraparenchymal hemorrhage (curved arrow) (B). There is effacement of the basal cisterns (asterisk) (C) and herniation of the cerebellar tonsils (arrows) (D).

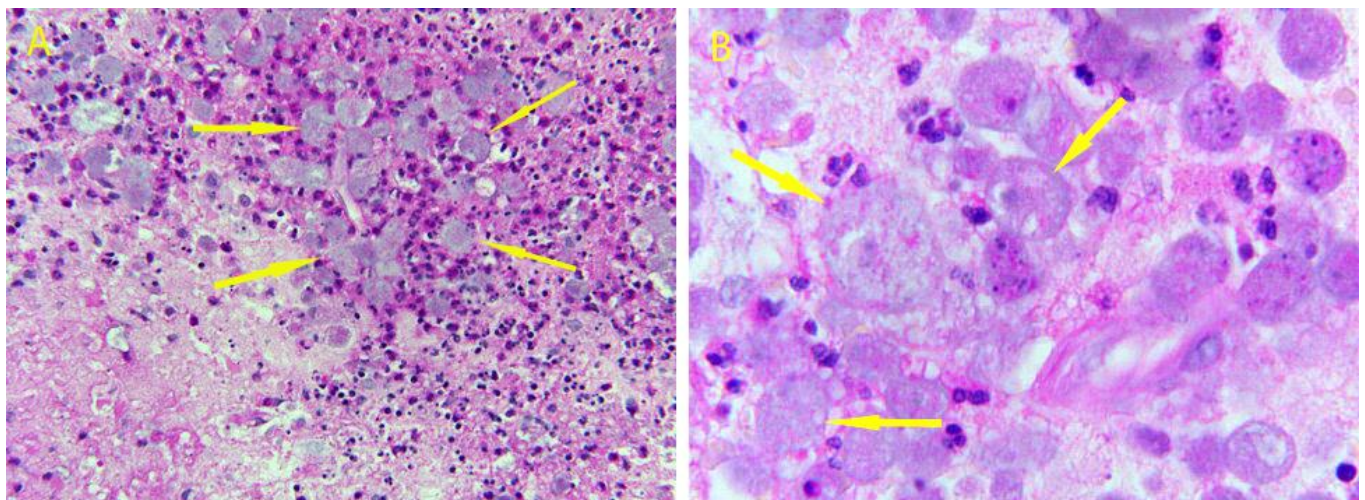


Figure 4. Periodic acid-Schiff-hematoxylin stained pathologic specimen from the 4 y.o. male donor's brain with Balamuthia mandrillaris meningoencephalitis. Low powered (A) and high powered (B) fields, demonstrating numerous trophozoites (arrows) of Balamuthia mandrillaris.

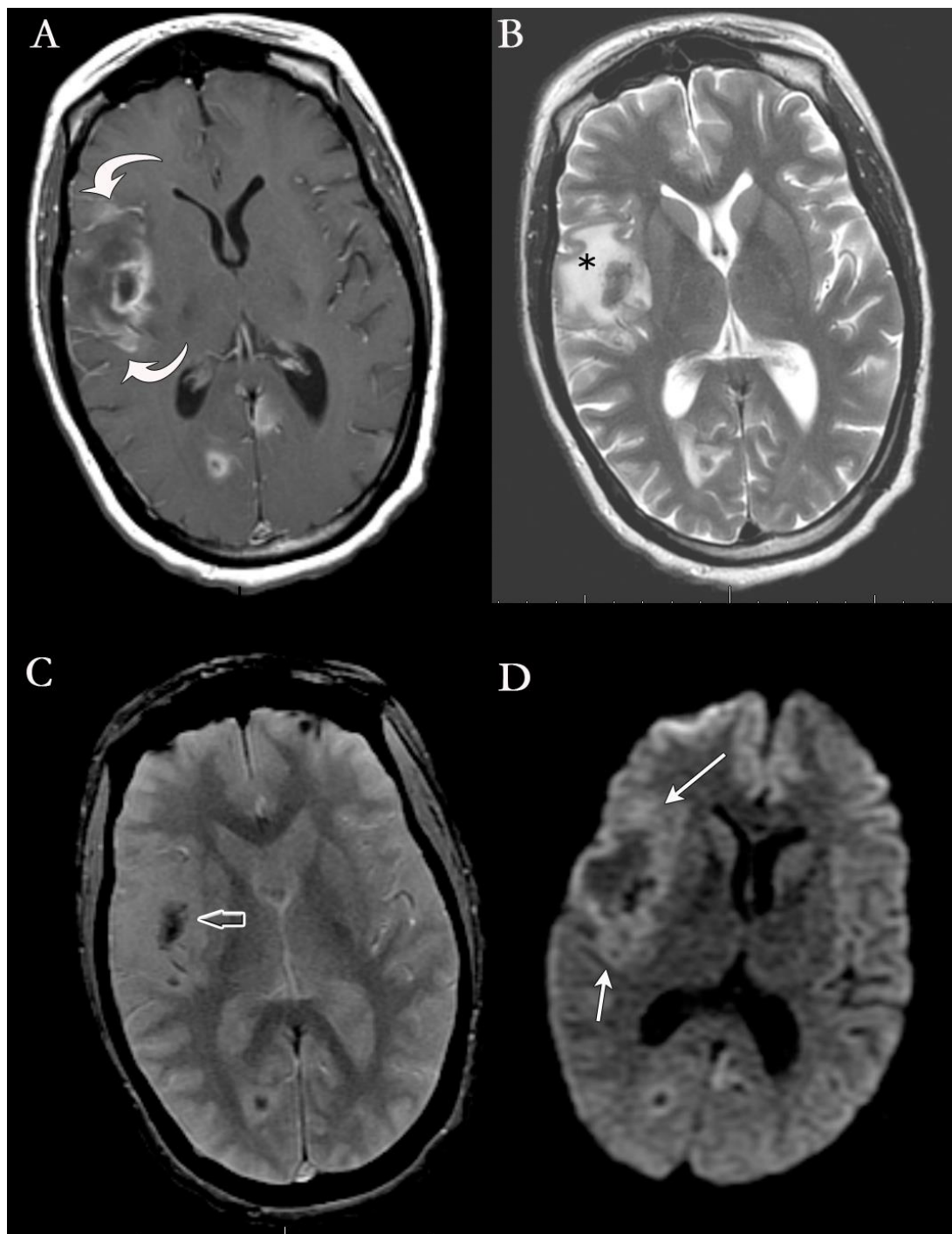


Figure 5. Initial brain MRI of the 31 y.o. female kidney recipient with *Balamuthia mandrillaris* meningoencephalitis. A. T1W+C SE (TR750/TE20 using 10cc IV Optimark) axial image demonstrating multiple bilateral poorly defined ring enhancing lesions throughout the brain parenchyma. Note enhancement of the adjacent leptomeninges in the right frontoparietal lobe (curved arrows). B. Surrounding edema and central low signal are seen on the T2W SE (TR4000/TE130.592) axial images (asterisk). C. Blooming of the central low T2 signal is seen on axial GRE (TR200/TE15) images, suggesting hemorrhage (open arrow). D. Mild restricted diffusion (arrows) is present along the periphery of some of the lesions on Diffusion Weighted Imaging (DWI) (0b and 1000b). All images were obtained on a 1.5T magnet.

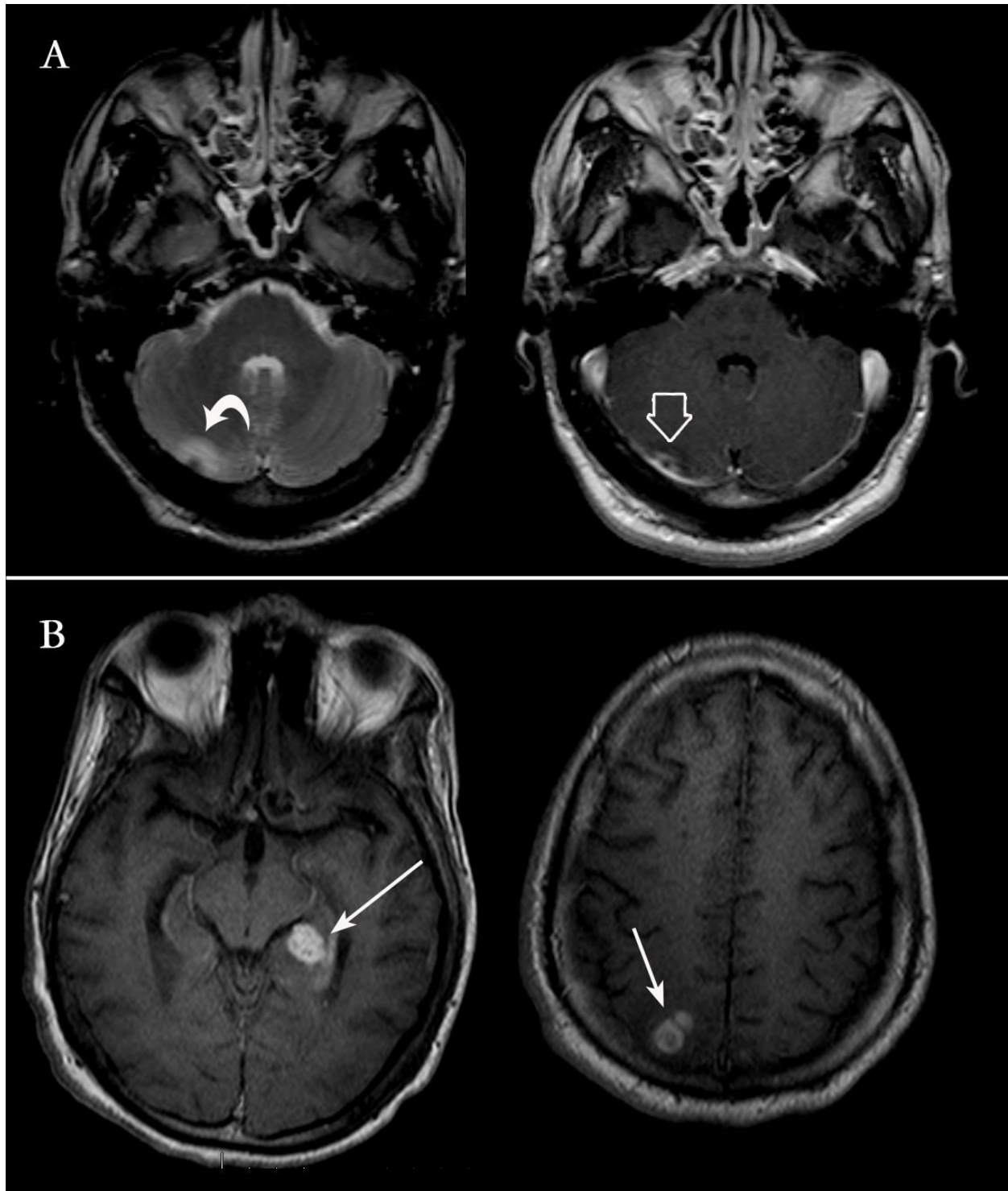


Figure 6. The 2nd kidney recipient, a 27 y.o. male with *Balamuthia mandrillaris* meningoencephalitis. A. Axial T2W SE (TR3740/TE98) and T1W+C SE (TR635/TE17 with 20cc Optimark) images demonstrating a poorly defined ring enhancing lesion in the right cerebellar hemisphere (open arrow) with mild surrounding edema (curved arrow) and enhancement of the adjacent meninges. B. Subsequent axial T1W+C (TR537/TE17 with 15cc Optimark) images of the same patient showing multiple new cerebral parenchymal lesions (arrows). All images were obtained on a 1.5T magnet.

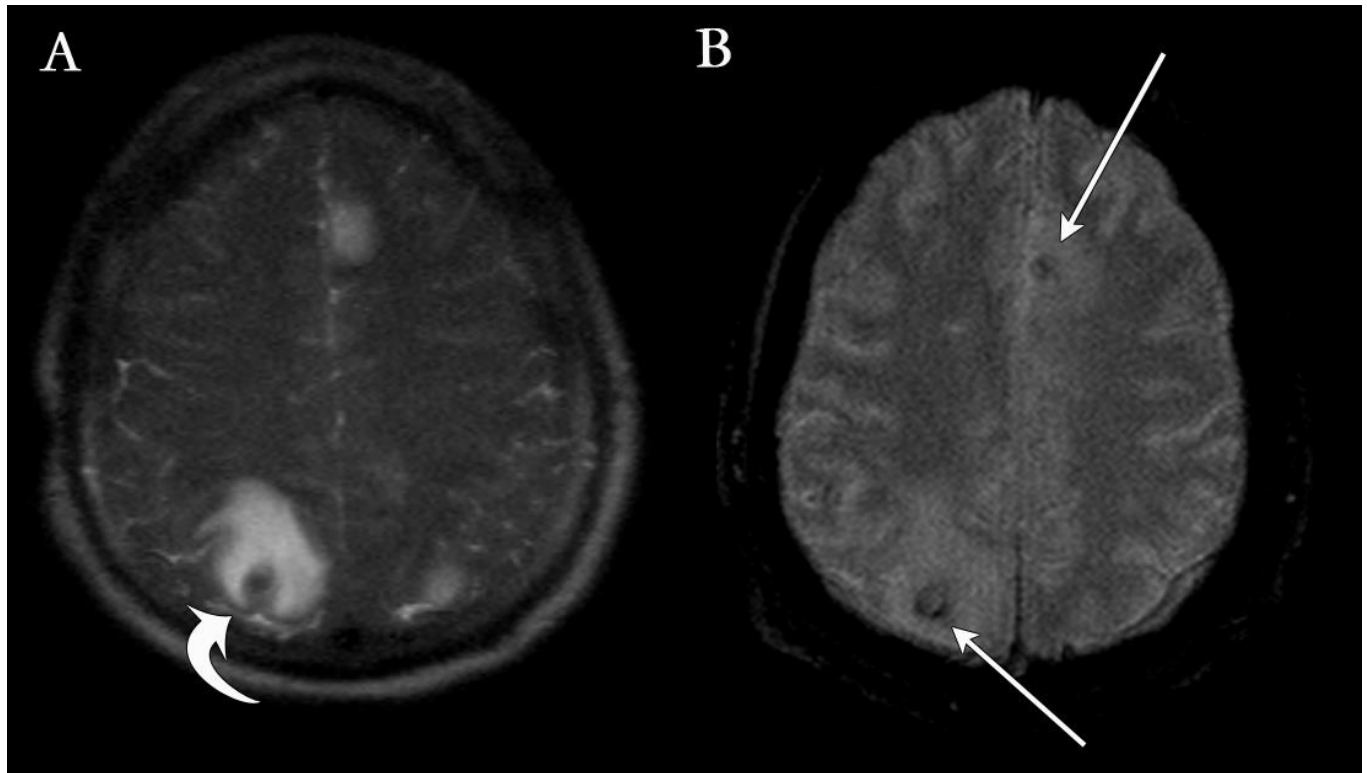


Figure 7. 27 y.o. male kidney recipient with Balamuthia mandrillaris meningoencephalitis. T2W HASTE (TR1500/TE101) axial image (A) demonstrating edema with central low signal (curved arrow) in multiple cerebral lesions with associated blooming (arrows) on the GRE(TR794/TE26) axial image (B) suggesting central hemorrhage. All images were obtained on a 1.5T magnet.

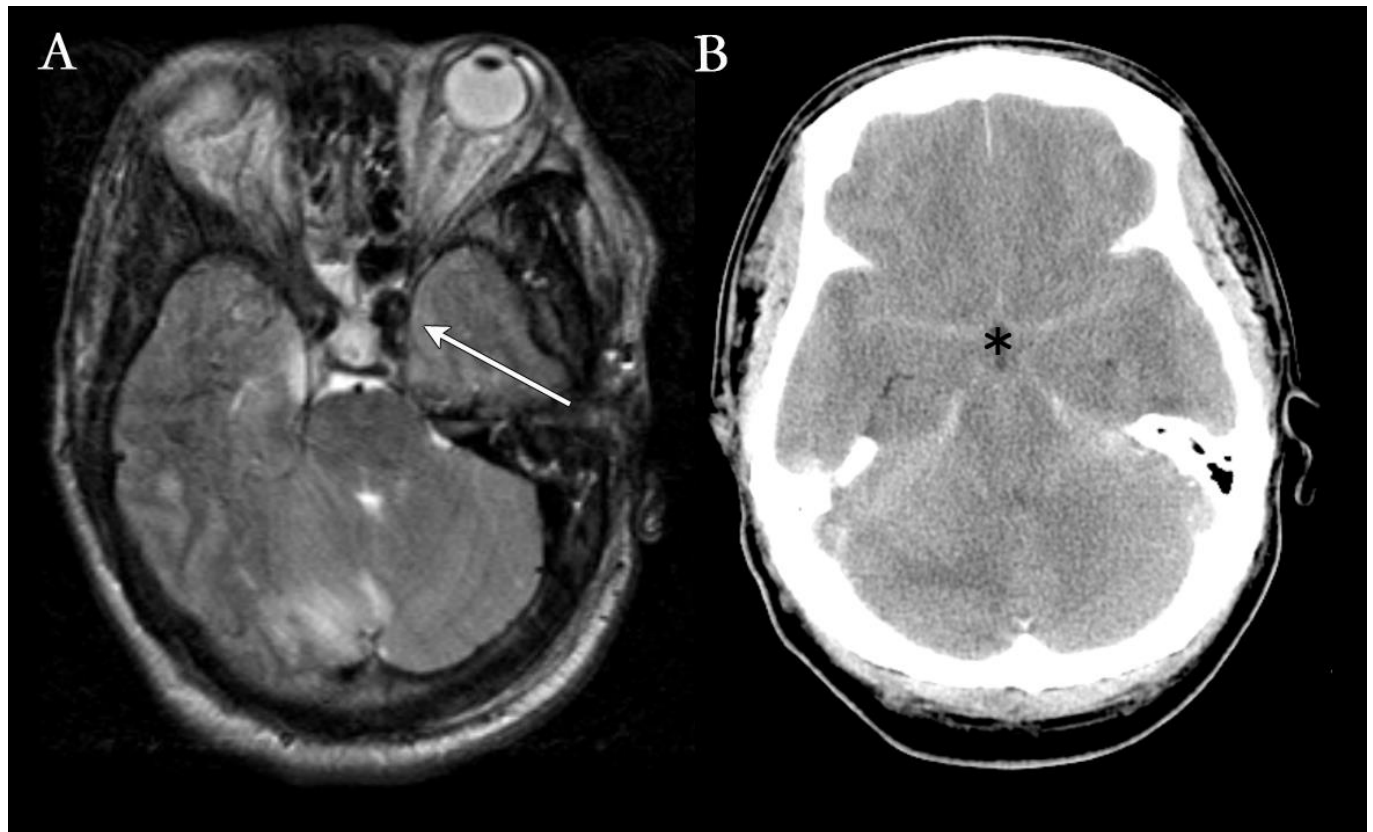


Figure 8. 27 y.o. male kidney recipient with Balamuthia mandrillaris meningoencephalitis. A. T2W SE (TR4210/TE105 on a 1.5T magnet) axial image demonstrating aneurysmal dilatation of the left cavernous/supraclinoid ICA (arrow). B. Nonenhanced axial CT image with subarachnoid hemorrhage within the basal cisterns (asterisk).

Etiology	<i>Balamuthia mandrillaris</i> , a free-living species of amoebae which is found in soil.
Incidence	Rare, with less than 200 cases reported since 1991. There have only been 4 reported cases of <i>B. mandrillaris</i> transmitted through organ transplantation.
Gender Ratio	1:1
Age Predilection	Young children and Elderly
Risk Factors	Immunocompromised status
Treatment	Difficult, requiring a combination of antimicrobials. External ventricular drain placement and intracranial pressure monitoring have been shown to be useful ⁵ .
Prognosis	Poor. Mortality rate is approximately 90%.
Imaging Findings	T1+C MRI demonstrates poorly defined ring-enhancing lesions which are often multiple and commonly associated with adjacent leptomeningeal enhancement. T2W MRI demonstrates parenchymal edema surrounding the lesions. Central low T2 signal within multiple lesions with associated blooming on GRE imaging is suggestive of central hemorrhage. Mild diffusion restriction can be seen along the periphery of some lesions. Intraparenchymal hemorrhage has been demonstrated on noncontrasted CT. Diffuse subarachnoid hemorrhage and mycotic aneurysm formation have been demonstrated. Hydrocephalus has been reported.

Table 1: Summary table for Granulomatous amoebic encephalitis secondary to *Balamuthia mandrillaris* infection.

Differential DX	T1W MRI	T2W MRI	GRE MRI	T1+C MRI	DWI MRI	CT
<i>B. mandrillaris</i> Meningo-encephalitis	Mildly hypointense signal associated with lesions. May see hyperintense signal if there is a large amount of associated hemorrhage.	Moderate degree of edema surrounding lesions. Many lesions may demonstrate central low signal intensity. Hydrocephalus has been reported.	Central blooming artifact common, suggesting central hemorrhage	Poorly defined ring-enhancing lesions, often multiple and variable in size. Enhancement of the adjacent leptomeninges is common. Mycotic aneurysm formation has been demonstrated	Some lesions may demonstrate mild restricted diffusion.	Low density changes associated with parenchymal lesions. May see foci of intraparenchymal hemorrhage with larger lesions. Diffuse subarachnoid hemorrhage can be seen late in clinical course.
Parenchymal Metastases	Variable. Usually iso-hypointense. Can be hyperintense with hemorrhage or melanoma	Variable signal within lesion. Usually a large degree of adjacent edema	Blooming if hemorrhage is present	Almost always avidly enhance. Enhancement pattern is variable	Usually do not demonstrate restricted diffusion unless there is dense cellularity	Lesions are iso-hypodense with surrounding edema. May see associated hemorrhage
Abscess	Usually iso-hypointense centrally. May have hyperintense rim.	Hyperintense centrally with hyperintense edema. Usually with hypointense rim	Blooming artifact is not expected	Avid rim enhancement which varies in thickness and definition depending on chronicity	Central restricted diffusion classically demonstrated	Low density lesion with surrounding edema and mass effect
Toxoplasmosis	Lesions usually hypointense	Hypointense lesions with hyperintense edema	Blooming artifact is not expected	Variable enhancement pattern depending on size of lesion. Usually rim-enhancing with classic "target" sign	May see central restricted diffusion if necrosis is present.	Multiple hypointense lesions with edema

Table 2: Differential diagnosis for *Balamuthia mandrillaris* meningoencephalitis

ABBREVIATIONS

CDC = Centers for Disease Control and Prevention
CSF = Cerebral Spinal Fluid
CT = Computed Tomography
DWI = Diffusion Weighted Imaging
GAE = Granulomatous amoebic encephalitis
GRE = Gradient Echo
MRI = Magnetic Resonance Imaging
PTD = Post Transplant Day
SE = Spin Echo
T1W = T1 Weighted
T2W = T2 Weighted
WBC = White blood Cell Count

KEYWORDS

Balamuthia; Mandrillaris; Parasitic infections; Granulomatous amoebic encephalitis; Meningoencephalitis; Transplant related infections

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