Surgical Neurology International

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: **James I. Ausman,** MD, PhD University of California, Los Angeles, CA, USA

Case Report

Magnetic resonance spectroscopy imaging characteristics of cerebral Blastomycosis

Jay A. Vachhani, William C. Lee, Jeffrey R. Desanto[1], Andrew J. Tsung

Department of Neurosurgery, Illinois Neurological Institute, [1]Department of Radiology, Central Illinois Radiological Associates, University of Illinois, College of Medicine, Peoria, Illinois, 530 NE Glen Oak Avenue, Peoria, IL 61637, USA

E-mail: *Jay A. Vachhani - jay.vachhani@gmail.com; William C. Lee - lee.william.c@gmail.com; Jeffrey R. Desanto - jeffrey_desanto@yahoo.com; Andrew J. Tsung - andrew.j.tsung@ini.org
*Corresponding author

Received: 10 December 13 Accepted: 14 March 14 Published: 28 May 14

This article may be cited as:
Vachhani JA, Lee WC, Desanto JR, Tsung AJ. Magnetic resonance spectroscopy imaging characteristics of cerebral Blastomycosis. Surg Neurol Int 2014;5:80.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2014/5/1/80/133306

Abstract

Background: Blastomycosis is a dimorphic fungus that is endemic to the midwest and southwestern United States. Involvement of the central nervous system (CNS) is thought to only represent 5-10% of cases of disseminated Blastomycosis.

Case Description: A 54-year-old Caucasian female presented to the Neurosurgery service with a 1-day history of progressive right sided hemiparesis. Magnetic resonance imaging (MRI) demonstrated a 2 × 4 cm heterogeneous intracranial mass lesion involving the left motor cortex and extending into the ipsilateral parietal lobe. Single-voxel magnetic resonance spectroscopy (MRS) over the enhancing area demonstrated diminished N-acetyl aspartate (NAA) to creatine ratio (1.10), normal choline to NAA ratio (0.82), normal choline to creatine ratio (0.9), and a diminished myoinositol to creatine ratio (0.39). There appeared to be peaks between 3.6 and 3.8 ppm over the enhancing area that were not present in the contralateral normal brain and thought to represent a "trehalose" peak. Due to worsening symptoms and uncertain preoperative diagnosis, the patient underwent a left fronto-parietal craniotomy for open surgical biopsy with possible resection approximately one month after presentation. Pathological analysis confirmed the diagnosis of Blastomycosis.

Conclusion: We present the second documented case of intracranial Blastomycosis with MRS imaging. There appears to be a characteristic peak between 3.6 and 3.8 ppm that is thought to represent a "trehalose" peak. This peak is rather specific to fungi and can be helpful in differentiating fungal abscesses from pyogenic abscesses and malignant neoplasms.

Key Words: Cerebral Blastomycosis, magnetic resonance spectroscopy, trehalose

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.133306

Quick Response Code:

INTRODUCTION

While quite uncommon, central nervous system (CNS) fungal infections are an important entity to consider when evaluating intracranial mass lesions. Although the majority of lesions occur inimmunocompromised patients, CNS Blastomycosis has been documented in immunocompetent individuals.[1] This dimorphic fungus is endemic to the midwest and southwestern United States. Pulmonary infection is the most common manifestation[18]

and involvement of the CNS is thought to only represent 5-10% of cases of disseminated Blastomycosis.[15] In such rare cases, noninvasive imaging modalities are useful in defining the breadth of the differential diagnosis prior to intervention. We present the second documented case of intracranial Blastomycosis with magnetic resonance spectroscopy (MRS) imaging. A characteristic fungal spectrum containing the trehalose peak was defined, further supporting the specificity of MRS in CNS fungal infections

CASE REPORT

A 54-year-old Caucasian female presented to the neurosurgery service with a 1-day history of progressive right sided hemiparesis with 4/5 strength in both right upper and lower extremities. Past medical history was significant only for hypertension. The social history revealed that the patient resided on a farm during her childhood. There was no evidence of immunocompromise or systemic disease involving lung or other organs. Laboratory investigations were unremarkable. Initial magnetic resonance imaging (MRI) was inconclusive and follow-up imaging was performed at a 1-month interval after a dexamethasone wean with short-term clinical improvement in strength. At one month, and correlating with the steroid wean, there was progression in deficit with increasing weakness similar in degree to that found at presentation. Due to the uncertain diagnosis and worsening clinical symptoms, open surgical biopsy with possible resection was performed.

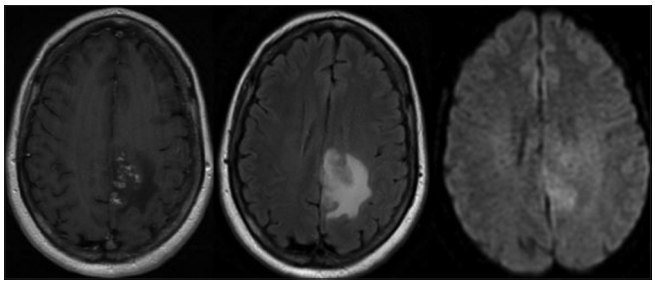

Figure 1: T1 with contrast, FLAIR, and DWI MRI shortly after presentation

Imaging characteristics

MRI performed shortly after presentation [Figure 1] demonstrates a 2 × 4 cm heterogeneous intracranial mass lesion involving the left motor cortex and extending into the ipsilateral parietal lobe. The lesion was hypointense on T1 sequences and had a speckled appearance upon gadolinium administration, hyperintense on T2 sequences with minimal diffusion restriction on diffusion weighted imaging (DWI). Specifically, on T2 imaging there was lack of a defined focal cavity and absence of intracavitary projections with a crenated appearance. Single and multi-voxel MRS was also performed over the area of enhancement as well as the contralateral normal brain. Single-voxel MRS over the enhancing area demonstrated diminished N-acetyl aspartate (NAA) to creatine ratio (1.10), normal choline to NAA ratio (0.82), normal choline to creatine ratio (0.9), and a diminished myoinositol to creatine ratio (0.39). There appeared to be peaks between 3.6 and 3.8 ppm over the enhancing area that were not present in the contralateral normal brain [Figure 2]. Repeat MRI at one month demonstrated worsening edema consistent with worsening of the pathologic process [Figure 3].

Operative and postoperative course

Approximately one month after presentation, the patient underwent a left fronto-parietal craniotomy for open surgical biopsy with possible resection of the lesion using frameless stereotactic guidance, intraoperative 3D-ultrasound, and neurophysiological monitoring with

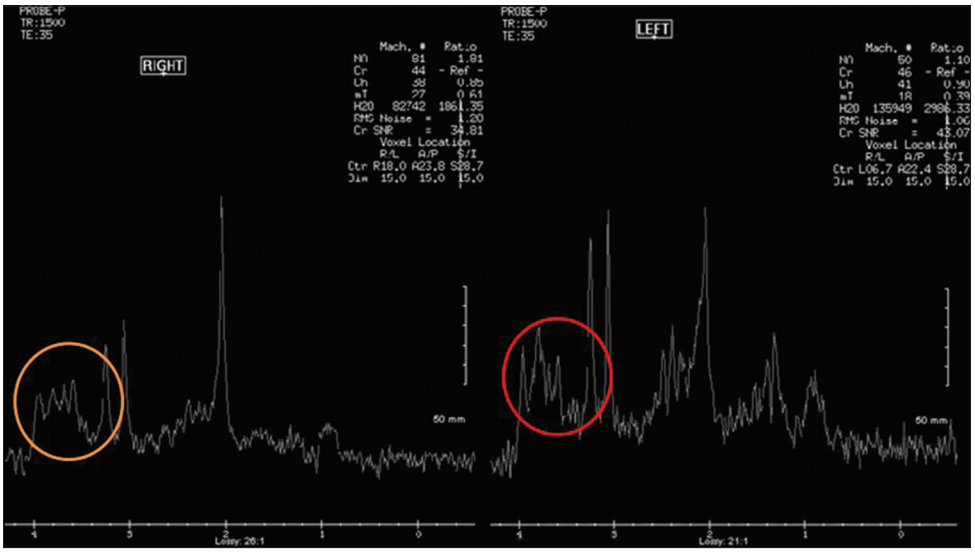

Figure 2: Magnetic Resonance Spectroscopy

cortical/subcortical mapping. The neuropathologist's intraoperative impression of the frozen section was that of high-grade glioma. Therefore, resection was thus continued until subcortical stimulation of motor regions was achieved at three milliamps. Postoperatively no additional deficits were noted. The MRI performed on postoperative day one showed some residual enhancement along the splenium of the corpus callosum [Figure 4]. The patient improved in strength by the time of discharge on postoperative day three. Following pathological confirmation, intravenous liposomal amphotericin B was initiated for 4 weeks, followed by oral itraconazole for 12 months. At last follow-up 1 year postoperation, cerebritis had resolved on MRI [Figure 5] and her neurologic status was normal.

Pathology

Hematoxylin and eosin staining showed chronic granulomatous inflammation with caseating necrosis, multinucleated giant cells, and epithelioid histiocytic cells [Figure 6] Periodic acid-Schiff staining showed broad based budding yeast, compatible with Blastomycosis [Figure 7]. The specimen was sent to the Centers for Disease Control and they confirmed the diagnosis of Blastomycosis.

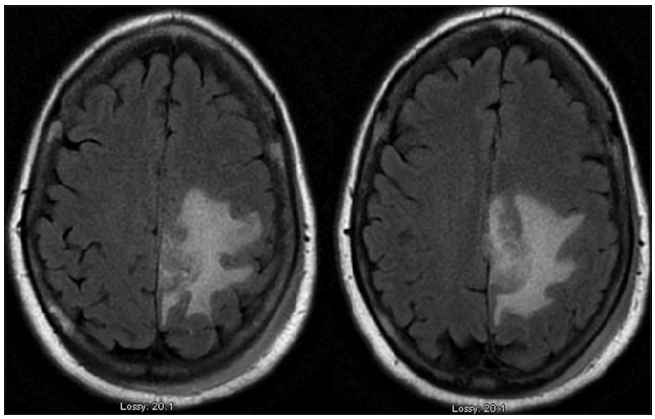

Figure 3: T2 FLAIR MRI one month after presentation

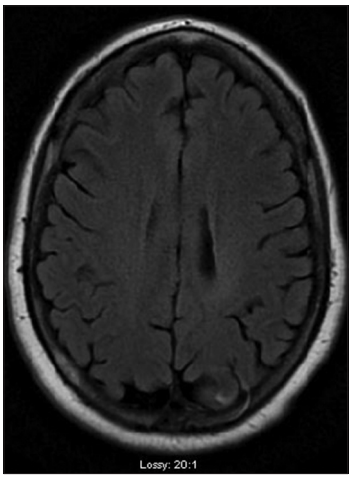

Figure 5: T2 FLAIR MRI one year postoperative

DISCUSSION

Fungal infections of the CNS are extremely rare in the general population. They usually occur in immunocompromised individuals or patients with longstanding diabetes mellitus.[10] Over the past three decades, there has been an increase in the prevalence of invasive fungal infections found on routine autopsy.[4,12] This increase is thought to be attributed to the autoimmune deficiency syndrome epidemic, increasing number of individuals with solid organ and hematopoetic stem cell transplants, and resistance to antifungal agents.[14]

Cryptococcus is the most common fungus to infect the CNS. Although it primarily affects immunocompromised individuals, up to 30% of patients have been reported to have no predisposing condition. CNS infection can be meningeal or parenchymal, with meningeal infections being most pronounced at the base of the brain. Radiographic findings are often minimal, with hydrocephalus being the most common finding.

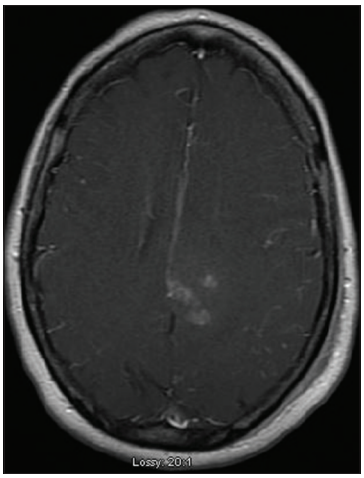

Figure 4: T1 with contrast MRI on postoperative day one

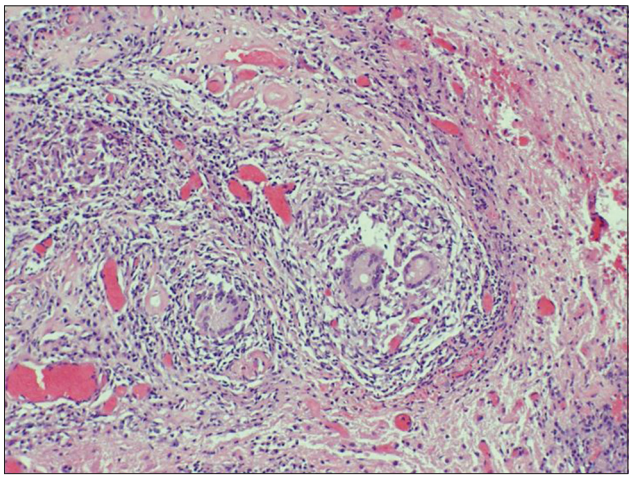

Figure 6: Hematoxylin and eosin stain at ×200 magnification

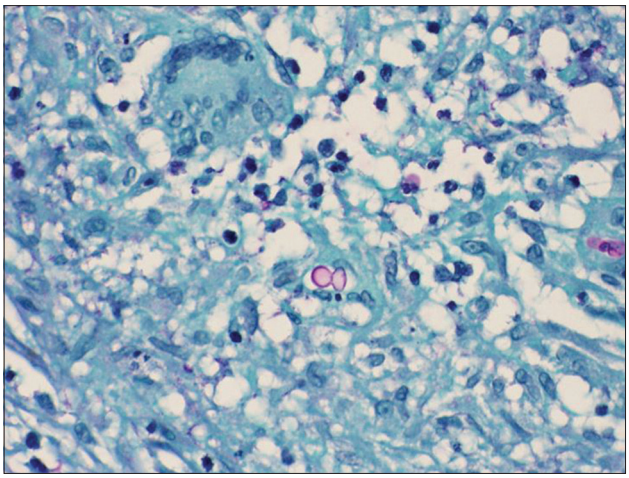

Figure 7: Silver stain at ×400 magnification

Intraparenchymal and intraventricular lesions are uncommon and can present as miliary lesions, which appear dark on T1-weighted imaging and bright on T2-weighted imaging. Enhancement, while often present in immunocompetent hosts, is often absent in immunocompromised hosts due to the lack of immune response and the nonimmunogenic nature of the polysaccharide capsule. MRS imaging shows a marked increase in lactate with a decrease in NAA, choline, and creatine.[8] *Ex vivo* studies in rats have found high concentrations of α,α-trehalose[7] and it is considered diagnostic for cryptococcus.[8]

Aspergillus is the most common organism that has been reported to cause granulomas within the CNS.[3] The pathology of Aspergillus can be classified into three forms; infarction, granulomas, and meningitis. The hyphae can block intracerebral blood flow and cause infarcts.[8] Aspergillus granulomas typically have the appearance of a mass lesion with hypo-to isointense signal on T1-weighted imaging with low signal on T2-weighted images and restricted diffusion on DWI. Usually, there is an increased choline to creatine ratio, decreased NAA peak, and increased lactate peak.[17]

Mucormycosis is a life-threatening fungal infection of the mucoraceal family, with Rizopusoryzaeas the most common. Diabetics comprise at least 70% of cases and infection usually begins in the paranasal sinuses. CNS involvement can occur via direct spread through cribiform plate, retrograde proliferation along blood vessels, or involvement of the orbit with subsequent spread through the superior orbital fissure or optic canal. MRI often shows infarcts related to vascular thrombosis with bony erosion of the sinuses.[8] The MRS profile shows elevated lactate, low NAA, and elevated succinate and acetate. The resonance profile differs from pyogenic abscesses through the absence of the valine, leucine, and isoleucine resonances that are commonly observed in pyogenic abscesses.[15]

Although Blastomycosis has been reported to occur in the CNS, it is far less common than Aspergillus, Mucormycosis, and Candida.[14] The majority of patients' primary site of infection is the lungs. Cutaneous involvement is the most common extrapulmonary site of infection while CNS infection is thought to represent only 5-10% of disseminated cases. Definitive diagnosis requires visualization of the characteristic yeast forms of the fungus in culture as there are no clinical or radiological tests that are diagnostic. Cerebrospinal fluid obtained through a lumbar puncture can help provide the diagnosis. However, the yield has been reported to be quite low and biopsies or ventricular taps are often necessary.[15]

As with all fungal infections, Blastomycosis has a nonspecific appearance on conventional MRI. The lesions usually have increased signal on T2-weighted imaging and enhancement of the leptomeninges and granuloma on T1-weighted postgadolinium imaging.[1,20] Luthra *et al.* report intracavitary projections with a crenated appearance specific to fungal abscess when compared with pyogenic and tubercular lesions. While diffusion restriction is a heterogeneous characteristic, the authors also report restricted diffusion mainly in the intracavitary projections, which may correspond to the fungal hyphae.[13]

Given the absence of a cyst or intracavitary projections on standard MRI, as well as the lack of clinical findings suggesting immunocompromise, MRS was performed prior to any contemplation of surgical intervention given the eloquence of the motor cortex involved by the lesion. We have found the current MRS findings in this case are similar to those in patients with intracranial Aspergillus, Mucormycosis, and Candida.[7,17,19] There was a mildly decreased NAA to creatine ratio (1.10 compared with 1.81 on the contralateral side) and mildly elevated choline to creatine ratio (0.90 compared with 0.85). The choline to NAA and choline to creatine ratios were normal at 0.82 and 0.9, respectively. Gliomas, in contrast, usually present with a markedly elevated choline to NAA and choline to creatine ratios.[5] In a retrospective review of 160 patients with gliomas, Law *et al.* found a mean choline to NAA ratio of 1.96 in low grade gliomas and 3.22 in high grade gliomas. The mean choline to creatine ratio was 1.75 in low grade gliomas and 1.92 in high grade gliomas.[11]

This report does, however, reiterate a theme common to other fungal pathology with a defined peak between 3.6 and 3.8 ppm, but never before defined in Blastomycosis. Corresponding to α, α-trehalose, or simply "trehalose", this biometabolite induced by stress is localized to the cytosol. When exposed to stress, unicellular organisms will synthesize large amounts of trehalose, which help retain cellular integrity by preventing denaturing of proteins. Its bioprotective properties are a result of the existence

of a number of polymorphs in both the crystalline and amorphous state. While controversy exists over the exact bioprotective mechanism of trehalose, it is postulated that it "traps" the biomolecule in a glassy matrix that can transition between different crystalline forms without relaxing its structural integrity. This protects the cell from extremes in temperature and osmolality.[9] While not normally present in humans, it has also been implicated in enhancing the clearance of mutant huntingtin and α-synuclein. This effect is thought to result from reducing levels of mitochondrial complex IV and cytochrome c, independent of the mTOR pathway, suggesting a novel treatment pathway for Huntington's and Alzheimer's disease.[16]

Clinical studies on MRS imaging of cerebral abscesses determined the trehelose peak was present in 5/8 fungal abscesses and absent in all 102 cases of pyogenic and tubercular abscesses.[12] Trehalosepeaks may also be found in MRS imaging of Cryptococcus and Mucormycosis. In his case report on MRS imaging of cerebral Mucormycosis, Siegal described an unidentifiable resonance at 3.8 ppm that may correspond to trehalose.[15] Himmelreich found trehalose peaks in MRS imaging of rat brains inoculated with Cryptococcus. These peaks were not present in normal controls or brains inoculated with Aspergillus or glioma cells.[6] Although the trehalose peak is considered diagnostic for Cryptococcus[8] and specific for fungal infections,[13] further studies are necessary to determine the sensitivity of this peak for other fungal species.

To the authors knowledge, there is only one other published case of intracranial Blastomycosis with MRS data prior to surgery. The patient had a left cerebellar lesion with patchy enhancement and significant vasogenic edema with mass effect upon the brainstem and fourth ventricle. A retromastoid craniotomy was performed and pathological analysis confirmed the diagnosis of Blastomycosis. While their study also showed a MRS profile with a decreased NAA, they also described increased choline, which was not present in the current case. Although not specifically mentioned by the authors, there appears to be a peak between 3.6 and 3.8 ppm that may represent a trehalose peak.[2] While the standard of care for treatment of Blastomycosis is tissue diagnosis via stereotactic biopsy followed by antifungal treatment,[20] the specificity of the trehalose peak for fungus[13] suggests antifungal therapy may be initiated without craniotomy or stereotactic biopsy.

CONCLUSION

We present the second case of cerebral Blastomycosis with MRS imaging. In clinical and imaging circumstances, which lead to ambiguous and wide differential diagnoses, MRS delineation of the trehalose peak is rather specific to fungi and can be helpful in differentiating fungal abscesses from pyogenic abscesses and malignant glial tumors.

ACKNOWLEDGMENTS

The authors thank Dr. Meena Gujrati for providing digital copies of the patient's pathology slides and Mrs. JoAnna Fleckenstein for her assistance with the manuscript.

REFERENCES

1. Bariola JR, Perry P, Pappas PG, Proia, L, Shealey W, Wright PW, *et al*. Blastomycosis of the central nervous system: A multicenter review of diagnosis and treatment in the modern era. Clin Infect Dis 2010;50:797-804.
2. Baruah D, Guleria S, Michel MA, Gill S. Intracranial blastomycosis mimicking high-grade neoplasm on magnetic resonance imagining and spectroscopy. Indian J Neurosurg 2013;2:87-8.
3. Dubey A, Patwardhan RV, Sampth S, Santosh V, Kolluri S, Nanda A. Intracranial fungal granuloma: Analysis of 40 patients and review of the literature. Surg Neurol 2005;63:254-60.
4. Groll AH, Shah PM, Mentzel C, Schneider M, Just-Nuebling G, Huebner K. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. J Infect 1996;33:23-32.
5. Hauck EF, McGinnis M, Nauta HJ. Cerebral phaeohyphomyosis mimics high-grade astrocytoma. J Clin Neurosci 2008;15:1061-6.
6. Himmelreich U, Dzendrowskyj TE, Allen C, Dowd S, Malik R, Shehan BP, *et al*. Cryptococcomas distinguished from gliomas with MR spectroscopy: An experimental rat and cell culture study. Radiology 2001;220:122-8.
7. Hong XY, Chou YC, Lazareff JA. Brain stem candidiasis mimicking cerebellopontine angle tumor. Surg Neurol 2008;70:87-91.
8. Jain KK, Mittal SK, Kumar S, Gupta RK. Imaging features of central nervous system fungal infections. Neurol India 2007;55:241-50.
9. Jain NK, Roy I. Effect of trehalose on protein structure. Protein Sci 2009;18:24-36.
10. Kastrup O, Wanke I, Maschke M. Neuroimaging of Infections. NeuroRx 2005;2:324-32.
11. Law M, Yang S, Wang H, Babb JS, Johnson G, Cha S, *et al*. Glioma grading: Sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopy imaging compared with conventional MR imaging. AJNR Am J Neuroradiol 2003;24:1989-98.
12. Lehrnbecher T, Frank C, Engels K, Kriener S, Groll AH, Schwabe D. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. J Infect 2010;61:259-65.
13. Luthra G, Parihar A, Nath K, Jaiswal S, Prasad KN, Husain N, *et al*. Comparative evaluation of fungal, tubercular, and pyogenic brain abscesses with conventional and diffusion MR imaging and proton MR spectroscopy. AJNR Am J Neuroradiol 2007;28:1332-8.
14. Mathur M, Johnson CE, Sze G. Fungal infections of the central nervous system. Neuroimaging Clin N Am 2012;22:609-32.
15. Saccente M, Woods GL. Clinical and laboratory update on blastomycosis. Clin Microbiol Rev 2010;23:367-81.
16. Sarkar S, Davies JE, Huang Z, Tunnacliffe A, Rubinsztein DC. Trehalose, a Novel mTOR-Independent autophagy enhancer, accelerates the clearance of mutant huntingtin and alpha-synuclein. J Biol Chem 2007;282:5641-52.
17. Siegal JA, Cacayorin ED, Nassif AS, Rizk D, Galambos C, Levy B, *et al*. Cerebral mucormycosis: Proton MR spectroscopy and MR imaging. Magn Reson Imaging 2000;18:915-20.
18. Smith JA, Kauffman CA. Blastomycosis. Proc Am Thorac Soc 2010;**7**:173-80.
19. Turgut M, Ozsunar Y, Oncu S, Akyuz O, Ertugrul MB, Tekin C, *et al*. Invasive fungal granuloma of the brain caused by aspergillus fumigatus: A case report and review of the literature. Surg Neurol 2008;69:169-74.
20. Ward BA, Parent AD, Raila F. Indications for the surgical management of central nervous system blastomycosis. Surg Neurol 1995;43:379-88.