MR Target Sign in Cerebral Aspergillosis

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The Neurohospitalist
2020, Vol. 10(4) 287-290
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DOI: 10.1177/1941874420929191
journals.sagepub.com/home/NHO

Abstract

Magnetic resonance (MR) is an effective imaging modality in the evaluation of infectious brain disease, yet findings are often nonspecific. The presence of a diagnostic feature can facilitate early treatment, particularly where mortality is high. We highlight MR apparent diffusion coefficient/T2-weighted target sign in the diagnosis of cerebral aspergillosis.

Keywords

MR target sign, cerebral aspergillosis, idiopathic CD4 lymphocytopenia

Introduction

The diagnosis of cerebral fungal infection may be problematic considering magnetic resonance (MR) imaging findings are often nonspecific. Appreciation of MR features suggestive of specific neurologic disease can facilitate early diagnosis. We highlight the diagnostic value of MR target sign in the context of a case of cerebral aspergillosis.

Case History

A 71-year-old man with a history of hypertension, chronic pulmonary disease, alcohol use, and longtime smoking history was admitted to an outside hospital with a 1-day history of nonproductive cough, fever, shortness of breath, and malaise. On admission he was alert and oriented and febrile to 100.1 °F. A complete blood count (CBC) and routine chemistries were unremarkable. Chest X-ray showed multilobe right sided pneumonia that was treated with ceftriaxone and azithromycin, yet respiratory difficulties increased requiring intubation. On day 2, a right subclavian triple-lumen catheter was placed. HIV and blood cultures were negative other than one fungal culture positive for yeast for which patient received one dose of micafungin and central line removed. Head computed tomography (CT) and transthoracic echocardiogram were unremarkable. Bronchoscopy revealed purulent secretions. His course was complicated by spiking fevers and increasing respiratory difficulty; and after 2 weeks, the patient was transferred to our hospital with suspected acute respiratory distress syndrome. Chest X-ray showed cavitary lesions in the left lower lobe with worsening pneumonia. Microbiology laboratory results from the outside hospital reported the prior positive blood culture grew *Candida tropicalis*. He was started on Mycamine 100 mg intravenously daily. Repeat fungal cultures were negative. On the third day at our hospital,

fungitell 1,3-β-D-Glucan assay was >500 (N ≤60 pg/mL). Temperature ranged from 101.2 °F to 104.2 °F, with persistent low-grade fever. White blood cell count = 13 600/μL and platelet count = 75 000/μL. Neurologic examination showed patient to be unresponsive while on no sedation, with no response to deep pain and a nonfocal examination. Chest CT showed a low-density mass in left lower lobe and nodular opacities in both lower lobes. Other than anemia routine blood chemistries and serologic testing for toxoplasmosis, cryptococcus, syphilis and Lyme, and *Legionella* were negative as was the urinalysis. Repeat head CT scan was unremarkable. Repeat HIV testing was negative and absolute CD4 count = 74 and 84 cells/mm³ (N = 535-1451 cells/mm³). Review of outside hospital admission CBC showed lymphocyte count of 0.8 (N = 1.5-4.5 thou/UL). Acid fast bacillus smear and culture was negative. Magnetic resonance showed innumerable brain lesions on fluid-attenuation inversion recovery, T2-weighted (T2W) sequence, and diffusion-weighted imaging (DWI) that enhanced on T1-weighted (T1W) imaging with gadolinium. Gradient-echo sequence showed several lesions with areas of magnetic susceptibility, many with a peripheral predilection. Both the DWI/apparent diffusion coefficient (ADC; Figure 1) and T2W (Figure 2) sequences and T1W gadolinium enhanced lesions manifest a ring pattern interpreted as most consistent with metastasis. Cerebrospinal fluid showed 87 nucleated cells (80% neutrophils),

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Figure 1. Magnetic resonance (MR) apparent diffusion coefficient sequence (ADC) showing multiple target lesions with central hyperintense signal (high ADC values), middle hypointense ring (low ADC value), and hyperintense outer rim (increased ADC values) (arrows) (insert).

Figure 2. Magnetic resonance (MR) T2-weighted sequence showing multiple target lesions with central hyperintensity signal, variable middle hypointense ring, and hyperintense outer rim (arrows) (insert).

protein = 113 (N = 15-45 mg/dL), and glucose = 101 (N = 40-70 mg/dL) and routine and fungal cultures were negative. Due to the patient's unstable condition, a planned tissue biopsy was delayed and on the 25th day of his illness he developed bradycardia and asystole. Several rounds of cardiac resuscitation were unsuccessful, and the patient was pronounced dead.

Autopsy showed the cause of death was peritonitis due to intestinal infarct with perforation of the cecum; independent disseminated aspergillus with abscesses of heart, lung, and brain. Microscopic examination of the lung with methenamine silver and immunoperoxidase stain was positive for *Aspergillus* and *Candida pneumonia*. Postmortem culture of blood and lung abscesses grew *Aspergillus fumigatus*. Gross examination of the brain showed numerous lesions in all vascular distributions ranging in size from several millimeters to 2-3 cm. Multiple sections showed septic infarct evolving into abscess with purulent meningitis overlying the infected area.

Figure 3. Section from right frontal brain lesion showing branching septate hyphae of *Aspergillus* (arrow) (methenamine silver stain $\times 40$ objective).

Abundant fungal organisms were present, most apparent at the periphery of the lesion, where there were masses of septate branching hyphae typical of *Aspergillus* with methenamine silver stain (Figure 3). Additional *Aspergillus* abscesses were seen in the medulla and cerebellum. The remainder of the general autopsy showed no other abnormality.

Discussion

Magnetic resonance target sign has been described in association with various neurologic conditions including, toxoplasmosis, central nervous system lymphoma, aspergillosis, tuberculoma, acute necrotizing encephalopathy, and Balo disease.¹⁻⁷ As there are different MR target signs, clarity of definition is essential. The defining characteristics are determined by the MR sequence, enhancement features, and target core signal intensity. These MR findings in combination with patient's immune status, lesion location, and clinical setting can be highly suggestive of select conditions. The MR target sign of cerebral toxoplasmosis is either a T1W gadolinium enhanced lesion² or a T2W lesion.¹ Recent reports of imaging in toxoplasmosis suggest T2W hypointense central core is more specific than the more widely appreciated T1W gadolinium enhanced target lesion.¹ Considering the target sign may fluctuate with treatment, time, and development of hemorrhage or other evolutionary changes, may explain the variable T2W core signal intensity described with toxoplasmosis. The MR sequence and core signal intensity in toxoplasmosis and lymphoma may be similar; however, lesion location, enhancement characteristics, patient immune status, evidence of Epstein Barr virus, and results of a thallium single-photon emission computed tomography (SPECT) scan help discern one from the other.⁴ In cerebral aspergillosis the target sign is ADC and/or T2W defined,³ with a hyperintense central core signal. The target sign seen with both aspergillosis and Balo is characterized by similar MR ADC/T2W changes where

clinical context, immune status, and number of lesions help distinguish the two.^{3,5}

Cerebral aspergillosis results in brain abscess and cerebral infarction due to the angioinvasive nature of fungal organism. Cerebral involvement occurs largely in immunocompromised patients related to immunosuppressive therapy in association with known underlying malignancy, autoimmune disease, or other chronic condition, infectious disease as HIV, acute leukemia, hematopoietic stem cell, or solid organ transplantation. In the absence of an underlying predisposing immunosuppressive risk factor diagnosis is challenging. Admission lymphocytopenia in our patient suggests an asymptomatic immunosuppressive process predisposed to his illness. In the absence of an identifiable cause, with repeated CD4 counts less than 300 cells/mm³ our patient met diagnostic criteria for idiopathic CD4 lymphocytopenia (ICL).⁸ Idiopathic CD4 lymphocytopenia is a rare disease, with most patients diagnosed upon development of opportunistic infections.⁹ Opportunistic infections occur in some 87% of ICL patients and include most commonly cryptococcal infections, mycobacterial infections, candida infections, and varicella zoster virus infections. Aspergillosis, however, was among the least common.⁹ Nervous system involvement by opportunistic infections with ICL is rare and includes nocardia abscess, cryptococcal meningitis and cryptococcoma, progressive multifocal leukoencephalopathy, toxoplasmosis^{9,10} and herpes simplex encephalitis,¹¹ yet we found no report of cerebral aspergillosis with ICL in our review. Of note a positive blood Fungitell result is not specific for candida and may be seen with other invasive fungal pathogens. Our patient showed multiple hypointense lesions on susceptibility-weighted imaging, many of which manifest a peripheral rim distribution. This imaging finding has been previously described with possible etiologies including ferromagnetic fungal deposits, methemoglobin, or presence of free radicals from macrophages.³

Gaviani et al¹² reported imaging features of cerebral aspergillosis that would later be termed MR target-like ADC lesion by Charlot et al¹³ in describing 3 patients with this fungal infection. Despite subsequent reports,^{3,14} the diagnostic significance of MR target ADC lesions continues to be underrecognized. Recently, Marzolf et al described 21 patients with cerebral aspergillosis, 8 with direct spread from paranasal sinus and 13 with hematogenous dissemination.³ Magnetic resonance target ADC lesions were seen in 8 (61.5%) of 13 in the latter group all of whom were immunosuppressed and in 2 of 8 from patients with direct spread, one of whom was immunosuppressed. More recently, MR T2W target lesion has been described with cerebral aspergillosis.¹⁵ Our patient manifest target lesion on both sequences (Figures 1 and 2). It should be noted one may be present without the other^{3,13,14} and the ADC target may be more sensitive and present earlier and more well defined. The pathologic correlate of the MR target sign is appreciated considering the

necrotic center is hyperintense, the middle rim of dense hyphae is hypointense, and the peripheral rim of granular tissue is hyperintense on both ADC and T2W sequences with the imaging signal a result of a combination of ferromagnetic deposits in association with methemoglobin and calcium.^{3,15} Since its initial description 15 years ago,¹² the ADC/T2W target sign in the diagnosis of cerebral aspergillosis especially in the context of immunosuppression remains under recognized. The importance of MR target sign with cerebral aspergillosis is appreciated considering the diagnosis is often problematic and without treatment almost always fatal. We call attention to the diagnostic value of the MR ADC/T2W target sign with cerebral aspergillosis.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

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