

Neurocandidiasis: a case report and consideration of the causes of restricted diffusion

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ABSTRACT

Diffusion weighted magnetic resonance imaging has risen to the forefront of imaging for acute stroke. However, the differential diagnosis of restricted diffusion is wide and includes ischemia, metabolic derangements, infections, and highly-cellular masses. We present a case of central nervous system (CNS) candidiasis presenting radiographically as bilateral punctate areas of restricted magnetic resonance (MR) diffusion in the basal ganglia. This case illustrates the value of carefully considering the causes of restricted diffusion in the brain, notably to be broader than acute stroke and to include invasive fungal infections.

CASE REPORT

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A 37-year-old woman with a history of pre-B-cell acute lymphoblastic leukemia status post two allogeneic stem cell transplants was admitted for salvage chemotherapy in July of 2009. On the day of admission, she had a Hickman catheter placed. One day following admission, she underwent high-dose ara-C and mitoxantrone chemotherapy. On hospital day two, she developed a fever to 101 degrees Fahrenheit and neutropenia. Blood and urine cultures were negative. She was started on cefepime, but continued to spike temperatures daily over the course of the next week. On hospital day eight, she developed progressive mental status changes: she developed increasing somnolence and appeared more withdrawn. She also developed ptosis of her left eye-lid. Blood cultures at this time demonstrated yeast forms seen on gram stain, which later were speciated as *Candida Tropicalis*. She was started on micafungin. Axial T1 with and without contrast, T2-weighted, and diffusion-weighted brain magnetic resonance (MR) images demonstrated multiple punctate foci of restricted diffusion in the basal ganglia bilaterally with no definite contrast enhancement. There was also generalized widening of the ventricles and subarachnoid spaces (Figure 1).

Approximately one month following admission, due to clinical deterioration, follow-up brain MR imaging was obtained. There was new T1 hyperintensity in the basal ganglia suggestive of small foci of recent hemorrhage. Diffusion weighted imaging (DWI) showed marked progression of previously noted abnormalities within the basal ganglia, now more confluent. There were also new additional foci of restricted diffusion scattered within the cerebral hemispheres, notably with involvement of right motor and sensory strip and right insular cortex (Fig. 2).

The patient expired one month and seven days following admission and brain autopsy was performed. The caudate and putamen exhibited distinct areas of reactive gliosis, infarction, and necrosis. High power view of these areas showed neutrophils, necroinflammatory and apoptic debris, and surrounding reactive glial cells most consistent with microabscesses. Methenamine silver stain demonstrated the classic branching pseudohyphae and round yeast forms of *Candida* (Fig. 3). The final pathologic diagnosis explaining the pattern of restricted diffusion seen with brain MRI was Neurocandidiasis.

DISCUSSION

Here we describe a case of CNS involvement of systemic candidiasis in an immunosuppressed patient on catheter-based chemotherapy who presented with progressive mental status change and ptosis. Neuroimaging revealed multiple punctate areas of restricted diffusion bilaterally in the basal ganglia, which then progressed to further restricted diffusion in basal ganglia and cerebral cortex as well as new surrounding T1 hyperintensity consistent with hemorrhage.

True restricted diffusion will appear as areas of hyperintensity on DWI and corresponding areas of hypointensity on the apparent diffusion coefficient (ADC) map. The ADC map is useful for ruling out hyperintensity on DWI from T2-weighting, a phenomenon known as "T2 shine through" [1]. It is important to understand that while DWI has become the gold standard for imaging ischemia in acute stroke, the differential diagnosis of restricted diffusion is broad [2]. The differential diagnosis of restricted diffusion includes ischemia, metabolic derangements (i.e. hypoglycemia and seizures), infections (i.e. HSV and pyogenic infections), and highly-cellular masses (i.e. lymphoma or meningioma).

Pyogenic infections result in restricted diffusion because of the high cellularity and viscosity of pus. Thus, abscess cavities and empyemas are homogeneously hyperintense on DWI with corresponding reduced ADC values [2]. Since both abscesses and necrotic tumors often appear as ring-enhancing lesions with perifocal edema, DWI is the imaging method of choice for differentiating abscesses from necrotic tumors. In contrast to pyogenic infections, necrotic tumors exhibit centrally hypointense or mixed signal on DWI [3].

Fungal infections of the CNS are rare in the general population [3]. They are most frequently seen in patients either with longstanding diabetes or immunocompromised in the setting of AIDS or organ transplantation. Cryptococcal meningoencephalitis is the most common fungal encephalitis. MR imaging of cryptococcal meningoencephalitis shows diffuse meningeal enhancement and ventriculitis. In addition, there are characteristic fungi and mucoid filled dilated perivascular spaces often seen in the basal ganglia, termed "soap bubble lesions". Aspergillus is another opportunistic CNS infection. MRI appearance of cerebral aspergillosis is extremely varied and ranges from edematous to hemorrhagic to solid ring enhancing lesions [3].

Recently, studies have pointed to the utility of diffusion-weighted MR in fungal brain abscesses, specifically for differentiating fungal from bacterial infections. Gaviani and colleagues found that fungal cerebral abscesses have centrally restricted diffusion similar to that of bacterial abscesses. Based on histologic correlation, they proposed that the centrally restricted diffusion most likely reflects proteinaceous fluid and cellular infiltration. This is in contrast to bacterial abscesses, where the restricted diffusion reflects central suppuration [4]. Mueller-Mang and colleagues retrospectively compared diffusion-weighted MR from 9 patients with fungal brain infections and 17 patients with pyogenic brain abscesses. They found that, in contrast to bacterial abscesses, which nearly all

showed homogeneously high signal on DWI, fungal abscesses displayed more DW signal heterogeneity. There was a trend toward higher average ADC values in fungal lesions, which would indicate less average restricted diffusion when compared to bacterial abscesses [5].

Given that the areas of restricted diffusion in our patient initially appeared bilaterally and restricted to the basal ganglia, we should note the differential diagnosis for bilateral abnormalities of the basal ganglia. These include toxic poisoning from carbon monoxide, methanol, and cyanide; metabolic disease such as hypoglycemia, Leigh disease, and Wilson's disease; degenerative diseases such as Creutzfeldt-Jacob Disease, which parenthetically also leads to restricted diffusion in the basal ganglia; neoplasms such as primary CNS lymphoma; and infections such as flavivirus encephalitis and CNS toxoplasmosis. Notably, the reported infectious causes of bilateral basal ganglia abnormalities do not currently include fungal etiologies [6].

Neurocandidiasis usually results from systemic candida infection in immunosuppressed patients or related to intravascular catheter infections. Regarding its incidence, Candida species have become the fourth cause of blood infection in hospitals and studies of the brain of patients who died from systemic candidiasis have concluded that up to 50% had CNS invasion by Candida species [7]. Of the approximately 80 species of Candida, *C. Albicans* is the most frequent species involved in systemic candidiasis and neurocandidiasis [7]. The most frequent pathologic findings in neurocandidiasis are microabscesses, usually found in the gray-white junction, basal ganglia, and cerebellum [8]. Macroabscesses and meningitis also occur, but are less common. The main clinical presentation of neurocandidiasis is diffuse encephalopathy, with diminished consciousness. Focal neurologic findings such as hemiparesis or aphasia are infrequent [7]. Mortality from neurocandidiasis varies between 10 and 30%. In addition, between 18 and 29% of patients have serious sequelae [7].

Neuroimaging for CNS candidiasis is not well defined [7]. The head CT scan in patients with neurocandidiasis is most often normal, as CT has much lower sensitivity for detection of microabscesses and Candida meningitis does not have characteristic CT findings [8]. MR imaging can reveal microabscesses, which are usually seen as small, ring-enhancing lesions with a hemorrhagic component [7].

Here we describe a case of CNS involvement of systemic candidiasis presenting as fungal microabscesses in an immunosuppressed patient on catheter-based chemotherapy. Initial imaging showed multiple punctate areas of restricted diffusion in the basal ganglia bilaterally. This case reports highlights the need for further studies examining the use of DW MR imaging for neurocandidiasis, and for fungal infections of the CNS at large.

TEACHING POINT

The teaching value of this case lies in reevaluating the causes of restricted magnetic resonance diffusion in the brain, notably to be broader than acute stroke. The differential diagnosis of restricted diffusion includes ischemia, metabolic derangements, pyogenic infections, and highly-cellular masses. It should be noted that neurocandidiasis, an invasive fungal infection of the CNS, can present with bilateral restricted diffusion in the basal ganglia.

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FIGURES

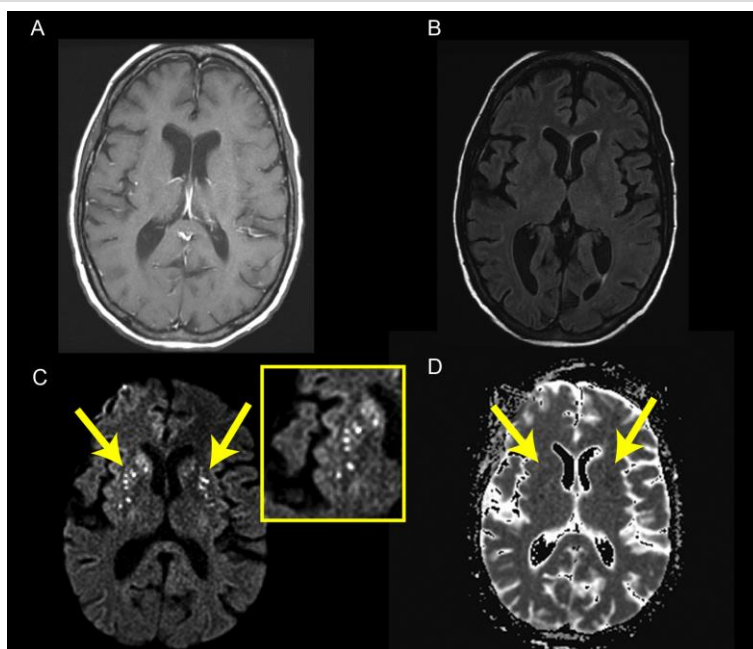


Figure 1: 37 year old woman with Neurocandidiasis. Multiplanar MR imaging of the brain was performed on a Siemens 1.5 Tesla MR before and after the administration of 15 mL intravenous Magnevist. (A) Post-Contrast T1 weighted MRI demonstrates no definite area of abnormal enhancement within the bilateral basal ganglia. There is mild prominence of the lateral ventricles and sulci. (B) Axial FLAIR image through the level of the basal ganglia reveals subtle punctate areas of T2 prolongation within the bilateral globus pallidus. There is no mass effect or midline shift. (C) Axial DWI demonstrates several punctate areas within the bilateral basal ganglia with restricted diffusion (yellow arrowheads). Yellow insert is magnification view of right basal ganglia, which is the region with highest concentration of punctate areas of signal enhancement. (D) Corresponding Axial ADC map confirms that foci of increased DWI signal correspond to areas of restricted diffusion within the bilateral basal ganglia (yellow arrowheads).

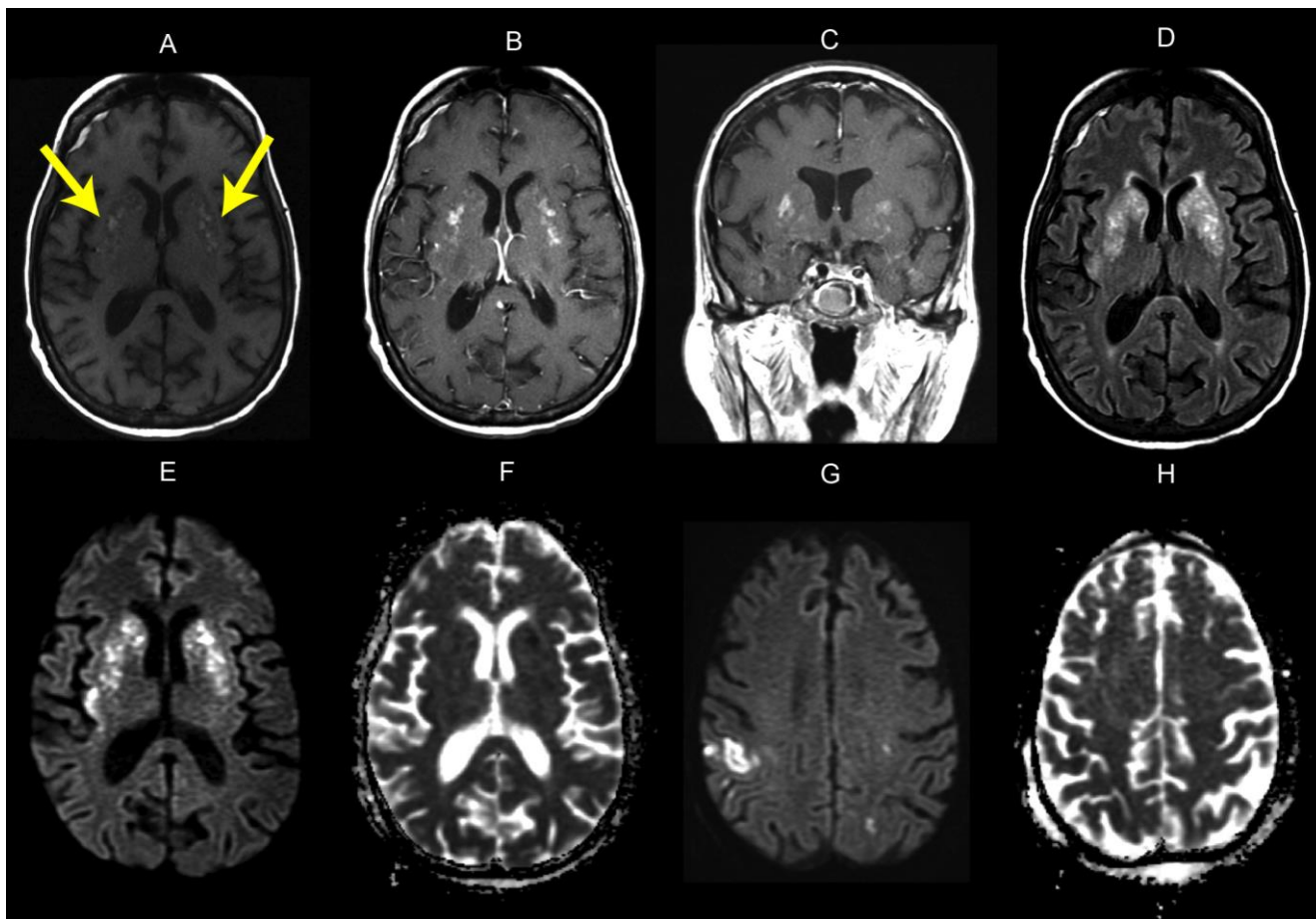


Figure 2: 37 year old woman with Neurocandidiasis. One month follow-up examination was performed for worsening symptoms in the same patient. MR imaging of the brain was performed on a Siemens 1.5 Tesla MR before and after the administration of 20mL intravenous Magnevist. (A) Axial T1 pre-contrast MRI demonstrates punctate hyperintense areas within the bilateral basal ganglia, suggestive of hemorrhage or fungal hyphae (yellow arrowheads). (B) Axial T1 post-contrast image demonstrates striking enhancement within the basal ganglia suggesting a hemorrhagic component to the lesions. (C) Coronal T1 post-contrast again demonstrates enhancement within the bilateral basal ganglia. (D) Axial FLAIR sequence demonstrates interval significantly increased T2 prolongation, which is now more confluent, within the bilateral basal ganglia. (E) Axial DWI shows multiple increasing areas of elevated signal abnormalities within the basal ganglia, which are more confluent compared to prior examination. (F) Corresponding Axial ADC map confirms that the foci of increased DWI signal correspond to areas of restricted diffusion within the bilateral basal ganglia. (G) Axial DWI through the superior parietal and frontal lobes demonstrate new areas of high DWI signal intensity within the right sensory and motor strip. (H) Corresponding ADC map confirms restricted diffusion within the right sensory and motor strip.

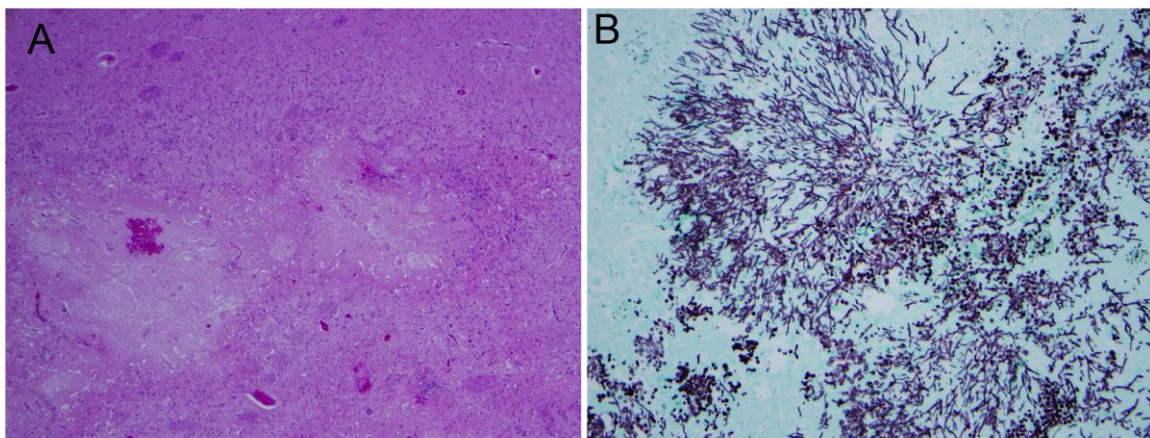


Figure 3: 37 year old woman with Neurocandidiasis. Microscopic pathology from brain autopsy. (A) Low-power Hematoxylin and Eosin stain of basal ganglia (areas of previously noted diffusion restriction) demonstrates reactive gliosis, infarction, and necrosis. (B) Methenamine silver stain of areas of necrosis and acute inflammation highlights fungal forms with typical "spaghetti and meatball" pattern of Candida, with branching pseudohyphal and round yeast forms.

Etiology	Systemic <i>Candida Tropicalis</i> infection in this patient, though most frequent species found in neurocandidiasis is <i>Candida Albicans</i>
Incidence	Unknown, but very rare.
Gender Ratio	Unknown
Age predilection	Unknown
Risk factors	Immunosuppression, previous treatment with antibiotics or corticosteroids, carrier of intravascular catheters, recent abdominal surgery, premature neonate, recent neurosurgery, intravenous drug use
Treatment	Treat underlying immunosuppression; Amphotericin B; Fluconazole
Prognosis	Mortality varies between 10 and 30%, 18 – 29% of patients have serious sequelae [7]
Imaging Findings	Neuroimaging studies of neurocandidiasis. Microabscesses can be observed on MR imaging. This is the first report of candida microabscesses in the basal ganglia

Table 1: Summary table for neurocandidiasis

Diagnosis	CT	MRI T1	MRI T2	Contrast Enhancement Pattern	DWI	ADC Map
Hyperacute ischemic infarction	Isodense evolving to Hypodense	Isointense	Isointense	Non-enhancing	Hyperintense	Hypointense
Glioma	Isodense	Variable	Variable	Heterogeneously enhancing dependent on grade	Variable	Variable
Metastasis	Isodense	Variable	Variable	Variable	Isointense to hyperintense	Isointense to hypointense
Lymphoma	Isodense	Hypointense relative to CSF	Hypointense relative to CSF	Homogenously enhancing	Hyperintense	Hypointense
Epidermoid Cyst	Isodense	Isointense to hyperintense relative to CSF	Isointense to hyperintense relative to CSF	Non-enhancing	Hyperintense	Hypointense
Granuloma	Isodense	Isointense	Hyperintense to brain parenchyma	Homogenously enhancing	Hyperintense	Hypointense
Creutzfeldt-Jakob Disease	Isodense	Isointense	Hyperintense in basal ganglia and cortex	Unknown	Hyperintense in basal ganglia and cortex	
Diffuse Axonal Injury	Isodense; if hemorrhagic punctate hyperdensities	Isointense; if hemorrhagic punctate hyperintensities	Isointense; if hemorrhagic punctate hypointensities	Non-enhancing	Hyperintense	Hypointense
Abscesses (including fungal abscesses)	Isodense	Hyperintense	Isointense to hypointense	Peripheral contrast enhancement	Centrally hyperintense	Centrally hypointense

Table 2: Differential diagnosis table for restricted diffusion

ABBREVIATIONS

ADC = Apparent Diffusion Coefficient
 CSF = Cerebrospinal Fluid
 DWI = Diffusion Weighted Imaging
 CNS = Central Nervous System
 MR = Magnetic Resonance

KEYWORDS

Neurocandidiasis; Central Nervous System Candida; Diffusion Weighted Imaging; Restricted Diffusion; Basal Ganglia

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