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Case Report

# Central nervous system fungal infection in a young male with a history of intravenous drug abuse and hepatitis C

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ABSTRACT

A young male, with a known history of hepatitis C and heroin abuse, was admitted to the emergency department with altered sensorium, left-sided weakness, and no meningeal signs. Initial computed tomography imaging showed hypodensity involving right basal ganglia with mass effect but no hemorrhage. Magnetic resonance imaging revealed multiple nonenhancing small foci of restricted diffusion involving the right basal ganglia, T2 and FLAIR hyperintensity within the right basal ganglia, and internal capsule with mild surrounding edema. The patient was treated for encephalitis and atypical stroke given the history of intravenous drug abuse. Follow-up imaging showed worsening of the brain lesions, with involvement of the contralateral basal ganglia with necrosis and peripheral enhancement. Brain biopsy was ultimately performed and suggested infection with *Aspergillus* species and associated parenchymal infarction. The patient was treated with voriconazole with subsequent significant clinical improvement.



## Introduction

Serious life-threatening infections related to *Aspergillus* are often seen in patients who have undergone bone marrow transplant and chemotherapy, reflecting a lack of cellular immunity [1]. However, patients with other predisposing factors, including drug addiction and hepatic failure, have also been shown to have increased susceptibility to cerebral aspergillosis [2]. Early suspicion and diagnosis of this potentially rapidly fatal infection is essential. With the availability of newer, potentially curable treatments for fungal infections, morbidity and mortality can be reduced. Although the imaging features can have a varied spectrum, certain characteristics can help narrow the differential diagnoses. This article discusses the computed tomography and magnetic resonance imaging (MRI) features of central nervous system (CNS) fungal infection.

## Case report

A 19-year-old man was admitted to the emergency department from an outside hospital with a history of altered mental status. He had been found minimally responsive in his motor home by his father. The patient was known to be hepatitis C positive with a history of intravenous drug abuse (heroin). There was no history of other underlying systemic disease.

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The patient was febrile and intermittently responsive in the emergency department with a Glascow Coma Scale of 10 and was intubated for airway protection. Physical examination demonstrated weakness of left upper and lower limbs, with the strength graded as 2/5 and 3/5, respectively. No meningeal signs were noted. Vitals were stable. Urine was positive for benzodiazepines and opiates. Initial computed tomography imaging showed hypodensity involving right basal ganglia with mass effect but no evidence of hemorrhage (Fig. 1A). MRI revealed scattered small foci of restricted diffusion involving the right basal ganglia as well as T2 and FLAIR hyperintensity within the right basal ganglia and internal capsule with mild surrounding edema (Figs 1B-E). There was no enhancement on post-contrast imaging (Fig. 1F). Susceptibility-weighted images showed subtle, punctate foci of blooming (Fig. 1D). Transthoracic echocardiogram was negative for cardiac valve vegetation. The patient's blood workup revealed increasing leukocytosis (outside hospital,

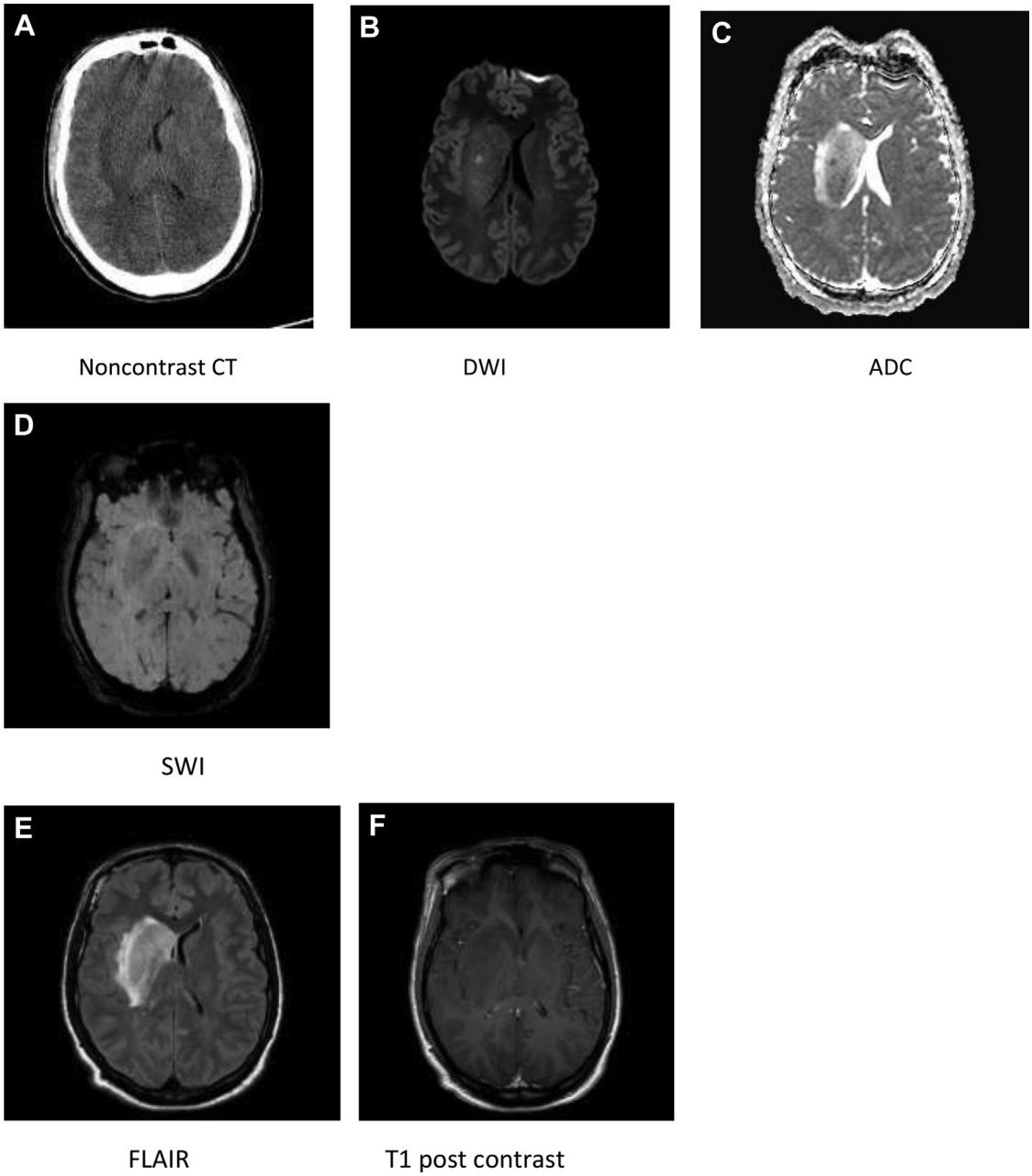


**Fig. 1 – On admission. (A) Noncontrast CT shows hypodensity with mass effect involving right basal ganglia and no evidence of hemorrhage. (B and C) Foci of restricted diffusion with corresponding low intensity on ADC map are seen in the right basal ganglia. (D) Punctate foci of "blooming" seen on susceptibility-weighted imaging involving right putamen and globus pallidus. (E) FLAIR image showing abnormal hyperintensity in the right basal ganglia nuclei with mass effect and effacement of right lateral ventricle. (F) No enhancement is seen on post-gadolinium axial T1-weighted image. CT, computed tomography; ADC, apparent diffusion coefficient; DWI, diffusion weighted imaging; SWI, susceptibility weighted imaging; FLAIR, fluid attenuation inversion recovery.**

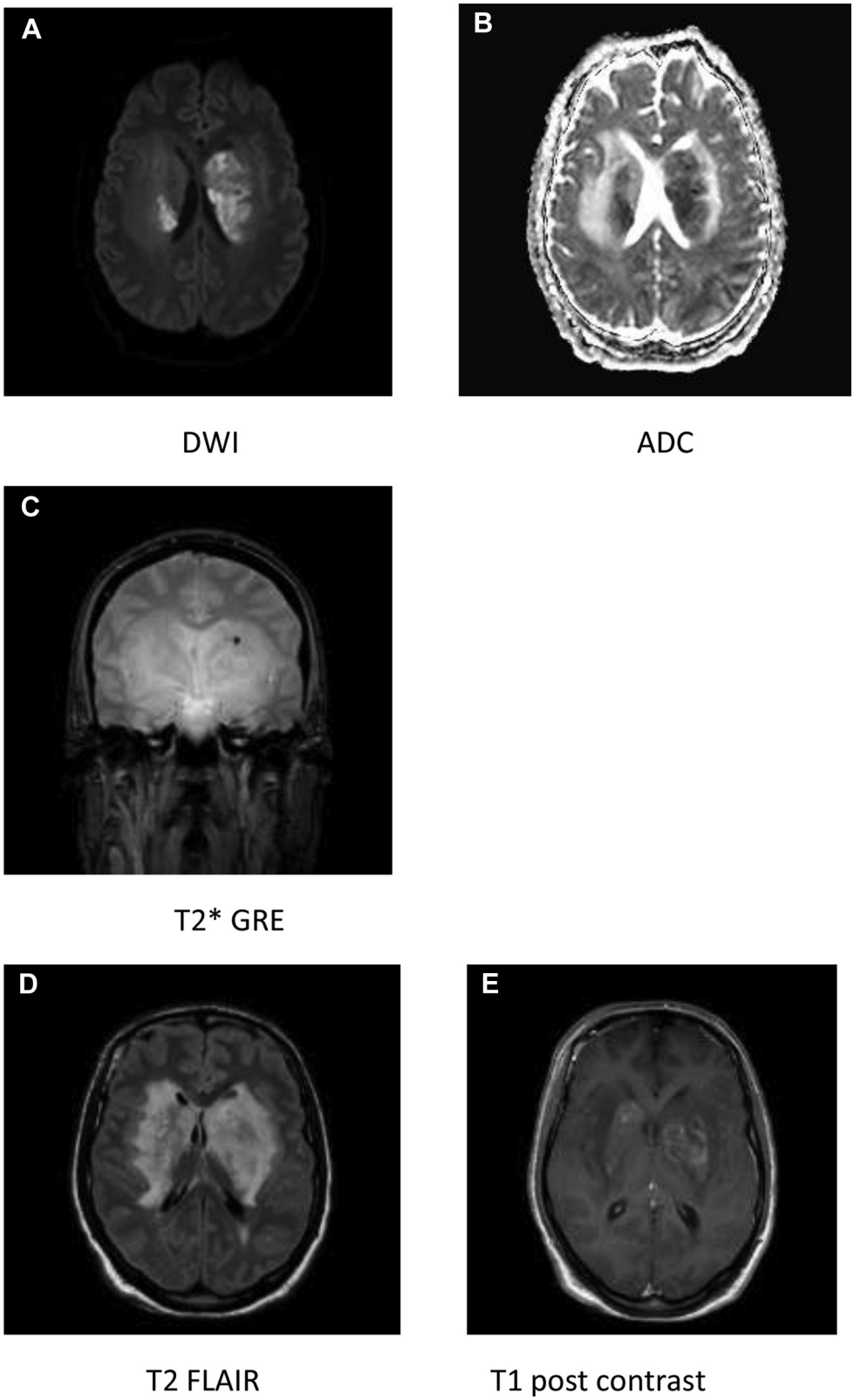


**Fig. 2 – Two weeks after admission. (A and B) Restricted diffusion with corresponding low intensity on ADC map, now involving the left as well as the right basal ganglia. (C) Minimal susceptibility blooming involving left basal ganglia on coronal T2* GRE. (D) There is pronounced FLAIR hyperintensity involving bilateral deep gray matter. (E) Patchy and peripheral contrast enhancement is seen involving both basal ganglia. ADC, apparent diffusion coefficient; DWI, diffusion weighted imaging; FLAIR, fluid attenuation inversion recovery; GRE, gradient recalled echo.**

white blood cell [WBC] = 10.0; on admission, WBC = 14.6). On lumbar puncture, opening pressure was 23 cm $H_2O$ with slightly hazy appearance of cerebrospinal fluid (CSF). CSF analysis showed elevated WBCs (538, 57% polymorphonuclear leukocytes), protein (81 mg/dL), and low glucose (57 mg/dL, serum 121 mg/dL). Gram stain was negative. Initial workup was negative for acid fast bacilli, herpes simplex virus polymerase chain reaction, and fungi.

The patient was started on broad-spectrum IV antibiotics including ceftriaxone, vancomycin, and acyclovir. There was interval clinical improvement with downtrending WBCs and he was extubated although he continued to be febrile. Culture of CSF did not grow any organisms. However, on day 5, the patient fell out of bed and was more difficult to rouse. Basic workup was negative. Repeat lumbar puncture revealed an opening pressure of 30 cm $H_2O$, glucose 30 mg/dL (serum 105 mg/dL), protein 123 mg/dL, WBC 1762 (60% polymorphonuclear leukocytes), and red blood cell 0. Rickettsial studies, multiple viral cultures including John Cunningham virus polymerase chain reaction, quantiferon gold, and protozoal investigations were also negative.

Repeat MRI showed worsening of brain lesions with new involvement of the contralateral basal ganglia (Figs 2A, B, and D). There was new necrosis and peripheral enhancement on post-contrast images (Fig. 2E). As the patient was deteriorating clinically without evident diagnosis, a decision was made to perform brain biopsy for pathologic analysis. Frozen section showed nonnecrotizing granulomatous inflammation containing rare fungal hyphae and associated parenchymal infarction (Figs 3A and B) characterized by scattered multinucleated giant cells, a subset of which exhibited aggregation into granuloma formations. Rare, relatively short segments of fungal septated hyphae were present in the expanded cytoplasm of the multinucleated giant cells. These features suggested infection with *Aspergillus* species, although culture could not isolate the organisms. The patient was treated with voriconazole with subsequent significant clinical improvement.

Despite the lack of definitive culture to confirm the frozen section results, *Aspergillus* was considered to be the most likely organism in this case. The 2 fungal diseases that are pathogenic in the hyphal form are aspergillosis and mucormycosis. In this case, mucormycosis was felt to be less likely, as it almost always extends from a paranasal sinus infection, whereas aspergillosis is more likely to present as disseminated disease with spread to the brain, with abscesses or granulomas [3].

Follow-up MRI a month later showed gliosis and cystic changes in both basal ganglia with significant reduction in size of lesions (Figs 4A-E). The patient was discharged with residual word-finding difficulty and motor weakness.

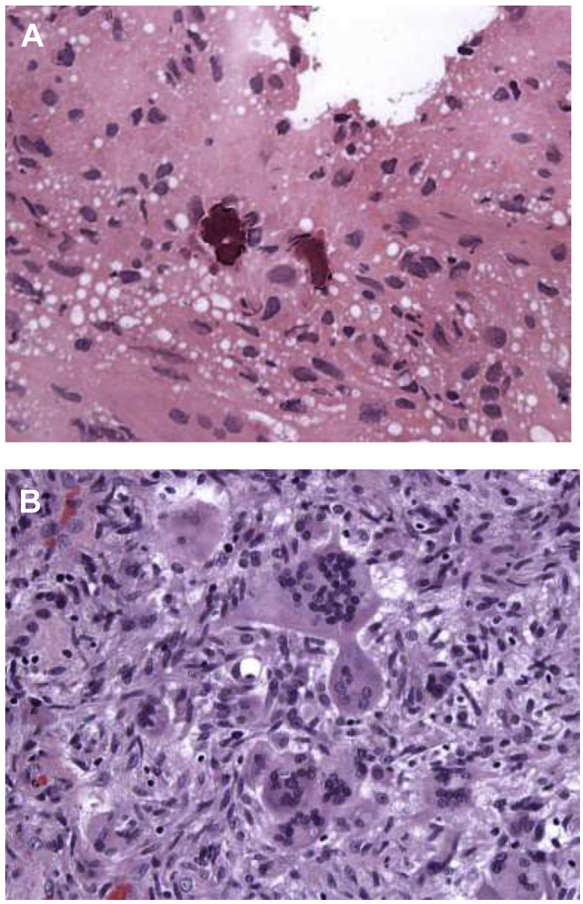


**Fig. 3 – (A) Fragments of hyphae seen on frozen section (H&E 40×). (B) Granuloma with giant cells. Fungal hyphae are not visible on the permanent sections nor on the special stains (H&E 20×).**

## Discussion

Fungal infection of the CNS is predominantly seen in immunosuppressed patients; however, it is important to note that these infections can affect the immunocompetent as well [2]. Although the patient discussed here did have hepatitis C and history of IV drug abuse, he did not have depressed cellular immunity. A literature review by Kim et al. has shown that patients with predisposing factors such as chronic alcoholism, drug addiction, sinusitis, hepatic failure, trauma, and certain occupations are more susceptible to cerebral aspergillosis [2]. Fungal organisms which can invade the CNS include *Cryptococcus neoformans*, *Aspergillus* sp, *Candida* sp., *Coccidioides immitis*, *Histoplasma capsulatum*, *Pseudallescheria boydii*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, and *Zygomycetes* [4]. *Mucor* and *Aspergillus* are the 2 most common angioinvasive fungal infections [5,6].

*Candida* and *Aspergillus* are the most common CNS abscess causing fungal organisms in immunocompromised patients [7]. Earlier studies have shown a yearly rate of 1 to 2 cases of aspergillosis per 100,000 population [8]. An increasing number of solid organ and stem cell transplant recipients and newer immunosuppressive agents have altered the incidence of fungal infections. Prospective surveillance in recent times has shown invasive aspergillosis (43%) to be the most common type of fungal infection among stem cell transplant recipients and second-most common type of fungal infection among solid organ transplant recipients (19%) [9,10].

*Aspergillus* typically enters the respiratory system via inhaled spores and may enter the central nervous system either hematogenously or directly from the paranasal sinuses.

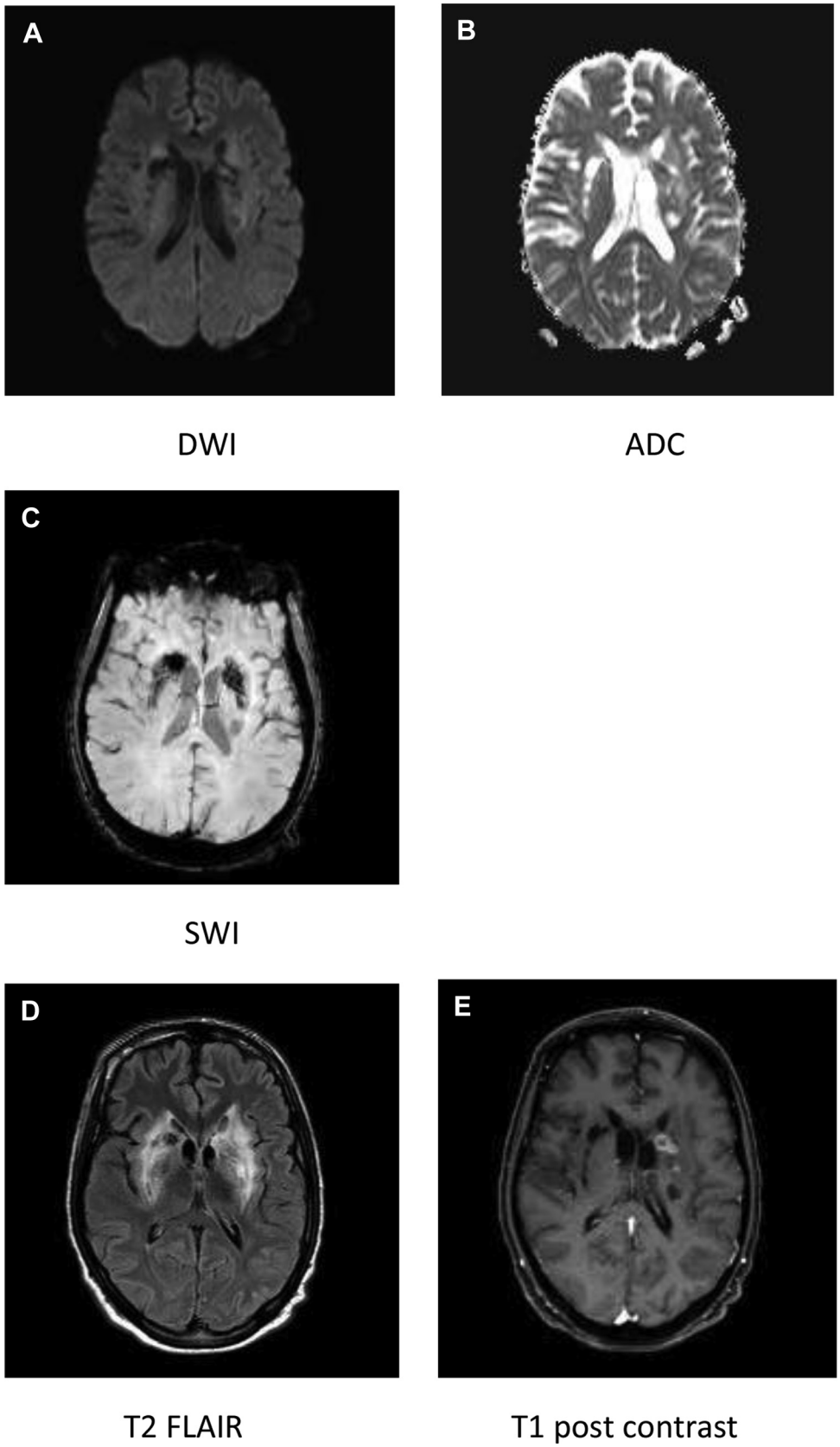


**Fig. 4 – Two months after treatment. (A and B) There has been normalization of restricted diffusion now with some T2 shine through. (C) Increased susceptibility is visualized in both basal ganglia on SWI. (D) Interval regression of FLAIR abnormality. (E) Now with less enhancement. Residual enhancement predominantly involves the head of the left caudate nucleus. ADC, apparent diffusion coefficient; DWI, diffusion weighted imaging; SWI, susceptibility weighted imaging; FLAIR, fluid attenuation inversion recovery.**

Hematogenous dissemination is common in the immunocompromised, whereas immunocompetent patients more often present with extension from the paranasal sinuses [11]. *Aspergillus* can also be directly inoculated by trauma or during surgery. For example, Cho et al. reported a case of intracranial aspergillosis involving the internal auditory canal and inner ear in an immunocompetent patient following mastoidectomy and tympanoplasty for chronic otitis media [12]. Occasionally, *Aspergillus* can be invasive in the immunocompetent [13]. Intracranial aspergillosis can present as meningitis, cerebritis, vasculitis, abscesses, or cerebral infarction. Because of the angioinvasive nature of these organisms, fungi with branched hyphae obstruct the vascular lumen of small arterioles resulting in thrombosis and sterile infarction [14]. Sterile infarcts can become septic by direct invasion of fungi, resulting in abscesses [14,15].

In our case, there was marked T2/FLAIR hyperintensity in the basal ganglia with punctate foci of restricted diffusion, which progressed over time, eventually involving the contralateral basal ganglia. This was felt to most likely represent a combination of infarcts and cerebritis, with possible early abscesses. And indeed, pathologic evaluation of brain lesions associated with proven CNS aspergillosis has revealed the brain lesions show coexistence of infarcts and/or abscesses [11]. In the case of fungal abscess, however, diffusion restriction is similar to that of pyogenic abscess as shown by Gaviani et al. [16]. In our case, there was no centrally diffusion restricting fluid collection.

The distribution of the infarcts in disseminated fungal infection has been commonly reported at the gray-white–matter junction as well as basal ganglia, thalami, corpus callosum, and perforating small artery territories [17]. Some series have found the gray-white junction to be the most common location, whereas others have found most lesions in the lenticulostriate territories, in addition to gray-white junction also being common [11,17]. This discrepancy could be due to the small number of cases studied in all these series. It has been suggested that the affinity for perforating artery distributions may reflect hematogenous spread of *Aspergillus* to the walls of the larger patent arteries, with subsequent compromise of the origins of the perforating arteries [17]. In our case, the initial involvement of the basal ganglia suggests the involvement of lenticulostriate perforators. The involvement of perforating arteries without involvement of the distal major arterial territories stresses the pathophysiologic difference between septic fungal and thromboembolic infarction [11].

Another prominent feature commonly seen in angioinvasive fungal infections is focal microhemorrhages as a result of wall weakening due to the enzyme elastase produced by the fungus, which predisposes to mycotic aneurysms and hemorrhage [18]. T1 hyperintensity, T2 hypointensity, and signal loss on T2* GRE may denote blood products, which can be present in the abscess wall or brain parenchyma. A T2 peripheral hypointense rim often seen in fungal abscess can also be due to densely packed *Aspergillus* hyphae and paramagnetic elements (iron and magnesium) [3,19].

Additional reported imaging features of fungal infection include corpus callosal involvement. Other processes such as gliobastoma multiforme, lymphoma, and multiple sclerosis that typically involve the corpus callosum can often be differentiated, whereas pyogenic infection and thromboembolic infarction do not commonly involve the corpus callosum [17].

Early diagnosis of CNS aspergillosis can be very challenging. Although Yamada et al. report that the most distinct characteristics of their series of cases were multifocal nonenhancing nonhemorrhagic cerebral lesions, with hemorrhage in only approximately 25% patients, this was not how our patient presented [11]. This varied presentation, confounded with the variable enhancement pattern, which may be absent or minimal in immunocompromised, vs more solid enhancement and possible frank abscess in immunocompetent can make identification difficult.

In our patient, there was no enhancement on contrast in the initial scan which progressed into intense, irregular enhancement during the course of the disease. There is commonly a lack of contrast enhancement or surrounding edema in immunosuppressed patients, reflecting impaired immune response. Vasogenic edema and pattern of enhancement can be linked to the immune status of the patient as described by Yuh et al. [20]. Yuh et al. and Enzmann demonstrated that immunocompromised patients with brain abscess who had a normal WBC count showed more vasogenic edema and enhancement compared to patients with a deranged WBC count [20,21]. This can be explained by the fact that WBCs generate an active inflammatory response enabling the immune system to isolate or encapsulate the offending organism. This results in breakdown of the blood-brain barrier which is the basis for contrast enhancement [20]. The wall of the fungal abscess is usually regular and thin. Irregularity of the rim can vary depending on the aggressiveness of the fungus and the host's ability to mount an immune response [22].

Various antifungals have been used in the treatment of CNS aspergillosis including amphotericin B and itraconazole. Schwartz et al. demonstrated that treatment with voriconazole showed complete or partial responses in 28 of 81 patients (35%) with a reported survival in 25 of 81 patients (31%) [23]. A more intensified treatment approach by prolongation of therapy beyond the resolution of all lesions and combination with other antifungals in higher doses was recommended [23].

## Conclusion

Fungal CNS infection has a varied presentation and clinical course depending on the immune status of the patient. Infection is rare in the immunocompetent. Some patients, such as the one discussed here, may not have classic decreased cellular immunity, but rather have likely contributing factors of chronic illness and IV drug abuse. The hallmark of CNS aspergillosis is septic infarcts most commonly involving the gray-white junction, basal ganglia, corpus callosum, and sequela of angioinvasiveness. There should be a high suspicion for fungal infection in immunocompromised patients presenting with new neurologic symptoms. Some have even suggested that in immunocompromised patients presenting with acute infarction, aspergillosis should be

considered, particularly when the infarct involves the basal ganglia or thalami [17]. Early identification of CNS fungal infection is certainly essential given the mortality rate.

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