Review Article

Imaging of CNS Fungal Infections: Review Article

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Fungal infections of the central nervous system (CNS) are usually identified in immunocompromised patients but rare in immunocompetent hosts. The clinical and imaging manifestations are mainly influenced by types of fungal pathogen and immune status of the patients. The CNS fungal infections can develop through hematogenous dissemination from primary site of infection, cerebrospinal fluid seeding, or direct extension from adjacent sources of infection. Fungal infections can result in meningitis, meningoencephalitis, cerebritis, granuloma, or abscess formation, which imaging findings are often non-specific and difficult to distinguish from bacterial or tuberculous infection, non-infectious inflammatory disease, or even intracranial neoplasm. Vascular complications including vasculitis, cerebral infarction, or mycotic aneurysm are commonly present due to angioinvasion of fungal hyphae. In addition, some characteristic imaging features of fungal infections can be identified by computed tomography (CT) or magnetic resonance imaging (MRI), such as intracavitary projections in fungal abscesses and gelatinous pseudocysts in cryptococcosis that could help suggest the diagnosis. Recognizing the imaging findings of common intracranial fungal infections combined with appropriate clinical setting is crucial for allowing early diagnosis and leading to early specific treatment. The present article reviewed common imaging findings of CNS fungal infections and distinct imaging features of specific pathogens.

Keywords: Fungal infection, Brain abscess, Cryptococcosis, Central nervous system (CNS), Computed tomography (CT), Diffusion weighted imaging (DWI), Magnetic resonance imaging (MRI)

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Fungal infections of the central nervous system (CNS) are uncommon and usually secondary to primary fungal infection elsewhere in the body, commonly in the lung via hematogenous spreading or sinonasal region via direct extension. Other routes of spreading are cerebrospinal fluid (CSF) seeding and direct inoculation via penetrating wounds or neurosurgical procedures[1]. CNS fungal infections have been increasingly identified over the last two decades due to increased incidence of immunocompromised patients, improved diagnostic imaging techniques, and more advanced techniques of microbiological investigations. Most of intracranial fungal infections occurred in immunocompromised patients, such as acquired immunodeficiency syndrome (AIDS), receiving chemotherapy or immunosuppressive drugs, post organ transplantation, or poorly controlled diabetes[2,3]. Infection may occur in immunocompetent hosts and those who live in the endemic areas. *Aspergillus*, *Mucor*, *Cryptococcus*, and *Candida* are the most common pathogens[1,4].

The general imaging features of intracranial involvement are often non-specific and depend on types of fungal pathogen, routes of spreading, and immune status of the patients. Additionally, some fungal pathogens have specific imaging features that could help the clinicians get the correct diagnosis and proper management[5]. Early diagnosis of intracranial fungal infections is crucial, leading to early treatment with antifungal therapy resulting in reduction of morbidity and mortality[4].

The fungal pathogens are generally categorized as yeast or hyphae (filamentous fungi) forms. *Cryptococcus* and *Candida* are the most common yeast pathogens that potentially access the microcirculation due to their small size and subsequently seed to subarachnoid space causing leptomeningitis, ischemic brain lesions, granulomas, or abscesses[6,7]. The most common hyphae pathogens are *Aspergillus* and *Mucor* that potentially invade and obstruct the intermediate- and large-sized vessels rather than access to the microcirculations due to their large size resulting in more focal parenchymal diseases, such as cerebritis, abscess, cerebral infarction, and vascular pathology including vasculitis and mycotic aneurysm[7,8].

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Understanding the imaging features of common CNS fungal infections is important and beneficial for disease management. However, the general imaging features are usually non-specific and can mimic other infectious diseases, such as bacterial or tuberculous infections, inflammatory diseases, or even brain tumor. Combination of imaging interpretation and appropriate clinical setting is necessary to refine the correct diagnosis.

Imaging evaluation

Nowadays, computed tomography (CT) is usually used as the first imaging modality for evaluation of CNS infections due to its broad availability with benefits for prompt assessment of specific imaging features and evaluation of associated complications, such as infarction, hemorrhage, brain edema, and hydrocephalus. Contrast enhanced CT should be performed allowing demonstration of leptomeningeal enhancement in meningitis or parenchymal enhancing lesions of cerebral abscesses or granulomas[9].

Magnetic resonance imaging (MRI) is the modality of choice and superior to CT in the detection and characterization of meningitis, cerebritis, ventriculitis, abscess, or vascular complication[7,8]. The MRI pulse sequences in the evaluation of CNS infection include T2 weighted imaging (T2WI), fluid attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), T2-gradient echo sequence (GRE), or susceptibility-weighted imaging (SWI), and contrast-enhanced T1-weighted imaging (T1WI+C)[9,10]. Contrast-enhanced FLAIR imaging is the most sensitive MRI technique in the detection of leptomeningeal enhancement and should be incorporated in the routine contrast-enhanced study of the brain, particularly in the setting of CNS infection[11,12]. Advanced MRI techniques such as MR spectroscopy and MR perfusion may provide some characteristic findings that could suggest the diagnosis or help differentiate fungal infection from bacterial or tuberculous infections and brain tumor[13,14].

In cases of sinonasal or rhinocerebral forms of fungal infection, MRI with dedicated paranasal sinus or base of skull protocols should be performed for better delineation and characterization of the lesions. These protocols should include thin slice fat-saturated T1WI and T2WI in axial, coronal, and sagittal planes. Thin slice post contrast fat-saturated T1WI also should be done in three planes[15,16]. The general imaging features of CNS fungal infections are classified as meningitis, cerebritis, abscess, granuloma, rhinocerebral disease, and vascular complications.

Meningitis

Fungal meningitis is often caused by yeast organisms, such as *Cryptococcus* and *Candida* via hematogenous spreading to meningeal microcirculation leading to meningeal inflammation. In the routine clinical practice, meningitis is a clinical diagnosis and CSF analysis remains the diagnostic gold standard. However, diagnostic imaging of the brain is crucial and can help confirm the clinical diagnosis of meningitis by presence of leptomeningeal enhancement that could differentiate meningitis from mimickers or assess the possible intracranial complications before lumbar puncture[17].

Like bacterial or tuberculous meningitis, fungal infection causes inflammation and increase of protein in the subarachnoid space producing hyperintensity along CSF spaces on FLAIR sequence. Today, contrast-enhanced FLAIR sequence has become the most sensitive imaging technique in the detection of leptomeningeal enhancement due to effect of T1 shortening with no enhancement of normal vessels and thus, may be superior to contrast-enhanced T1WI[11,12].

In contrast to viral or bacterial meningitis that tends to have smooth and linear leptomeningeal enhancement, patterns of leptomeningeal enhancement in fungal meningitis are variable and non-specific. They may be thin or thick, smooth or nodular, localize or diffuse, and may not be differentiated from bacterial or tuberculous infection, and leptomeningeal tumor seeding[17,18] (Figure 1). Leptomeningeal enhancement preferentially involves the basal cisterns and sulci can be seen, referred as basal meningitis that was commonly found in cryptococcal or coccidioidal meningitis and can mimic tuberculous meningitis[19,20]. Secondary communicating hydrocephalus can occur in fungal meningitis due to meningeal adhesion resulting in impaired CSF resorption of arachnoid granulation[17].

Cerebritis

Fungal cerebritis is the focal area of cerebral inflammation due to fungal invasion via hematogenous dissemination, penetrating the Virchow Robin spaces or direct invasion from extracranial sources[21]. Any fungus in both yeast and hyphae forms can cause cerebritis. *Cryptococcus* is the most common pathogen, followed by *Aspergillus* and *Candida*. Fungal cerebritis is the precursor of abscess formation, showing non-specific imaging features that may not differ from bacterial or granulomatous infection[19].

Similar to cerebritis caused by any infectious

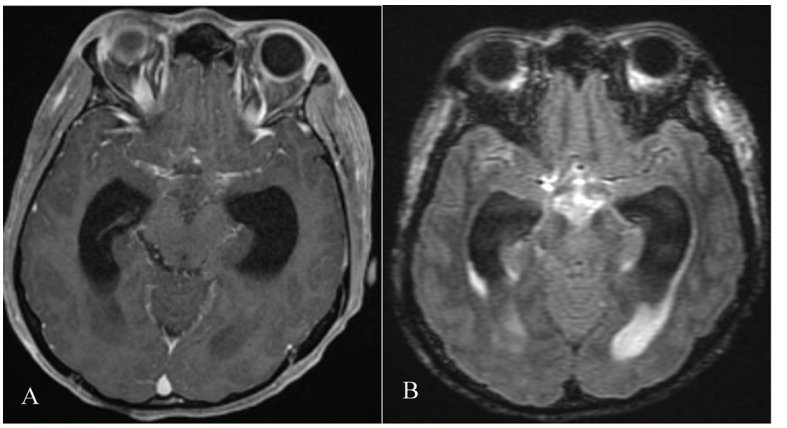

Figure 1. Disseminated aspergillosis with meningitis. (A) Axial T1W FS-Gd shows leptomeningeal enhancement at the suprasellar and perimesencephalic cisterns, indicative of meningitis. (B) Axial FLAIR FS-Gd shows obviously demonstrated leptomeningeal enhancement with dilatation of the temporal horns of lateral ventricles, consistent with hydrocephalus.

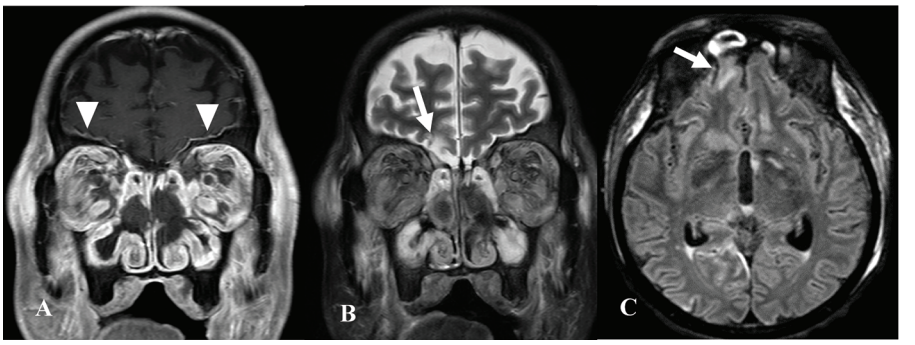

Figure 2. Aspergillus sinusitis with cerebritis. (A) Coronal T1W FS-Gd, (B) Coronal T2W FS, and (C) Axial FLAIR FS show focal non-enhancing hypointense T1W/hyperintense T2W and FLAIR signal at the right inferior frontal lobe (white arrows). Hypointense T2 signal with loss of normal intense mucosal enhancement of the bilateral middle and left inferior nasal turbinates are evident, as referred to "black turbinate" sign due to angioinvasion. Thin dural enhancement along the anterior cranial floor is noted (arrowheads).

organism, fungal cerebritis often appears as ill defined intraparenchymal hypodensity on CT scan representing focal brain edema[22]. Some scattered areas of hyperdensity due to either hemorrhage or deposition of metal ions related to fungal growth are suggestive of fungal cerebritis[21]. On MRI, fungal cerebritis usually appears as ill-defined areas of hypointensity on T1WI, hyperintensity on T2WI and FLAIR sequences with subtle or no contrast enhancement and variable amounts of focal brain swelling (Figure 2). In addition, on T2WI may show scattered areas of hypointensity due to paramagnetic effects of metal ions or hemorrhage. On DWI, these lesions may demonstrate variable areas of restricted diffusion, which can be homogeneous, heterogeneous, or subtle[19,21]. Leptomeningeal enhancement may be accompanied with these parenchymal abnormalities, as referred to meningoencephalitis. Fungal cerebritis typically evolves to fungal abscess due to restriction of infectious process by host's immune response[19]. Cerebritis can be differentiated from early abscess formation through the presence of a thin rim enhancement on postcontrast CT or MRI related to collagen capsule formation of abscess[19,22].

Brain abscess

Similar to pyogenic or tuberculous abscesses, fungal abscesses generally appear as ring enhancing lesions with varying degree of surrounding brain edema[19]. Many studies have found characteristic imaging features of fungal abscesses that may help distinguish fungal from pyogenic or tuberculous abscesses. Fungal abscesses tend to be multiple lesions, located at gray-white matter junction, and involved the basal ganglia, as opposed to pyogenic abscesses, which are more likely to be solitary lesion

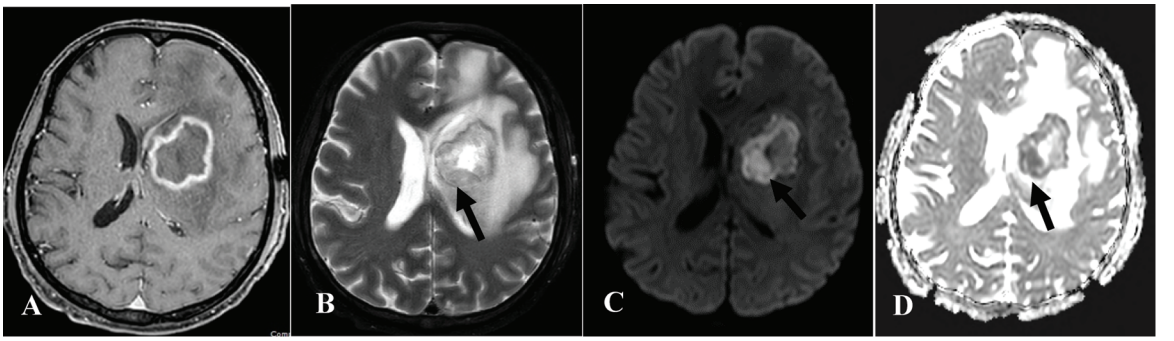

Figure 3. Fungal abscess due to aspergillosis. (A) Axial T1W FS-Gd, (B) Axial T2W FS, (C) Axial DWI, and (D) Axial ADC map show a rim enhancing lesion with mildly lobulated wall at the left basal ganglion and corona radiata with perilesional vasogenic edema. The lesion demonstrates hypointense T2 rim with intracavitary projection along inner wall (arrows), which appears as non-enhancing T1 hypointense and T2 iso- to hypointense signal with restricted diffusion.

and spared the basal ganglia[8,19].

On MRI, fungal abscesses usually demonstrate T1 hypointense and T2 hyperintense center with T2 hypointense rim, similar to bacterial or tuberculous abscesses[7]. The walls of fungal abscesses have been found to have crenated or lobulated margin, as opposed to smooth margin of pyogenic or tubercular abscesses[23]. On SWI, fungal abscesses may demonstrate completely smooth or irregular low signal intensity rim (LSIR), possibly representing paramagnetic substance deposition, such as metal ions or hemorrhage[24,25]. While pyogenic abscesses typically show a characteristic dual rim sign on SWI, this feature has been rarely found in fungal abscesses[23,24]. In addition, fungal abscesses typically demonstrate characteristic intracavitary projections along the inner walls, which appear as non-enhancing T1 iso-to hypointensity and T2 hypointensity with restricted diffusion representing compact fungal hyphae[23] (Figure 3).

On DWI, fungal abscesses usually show inhomogeneous or scattered punctate or peripheral restricted diffusion in the abscess cavity as well as in their walls and intracavitary projections, in contrast to pyogenic abscesses, which typically show homogeneous diffusion restriction in the abscess cavity[23,25,26]. Like bacterial or tuberculous abscesses, uniform wall enhancement is commonly seen on post contrast CT or T1WI. However, fungal abscesses tend to have poor rim enhancement, as referred to weak ring enhancement related to impaired immune response in immunocompromised patients[8].

On MR spectroscopy, fungal abscesses have been reported to contain peaks of amino acid metabolites, such as valine, leucine, and isoleucine at 0.9 parts per million (ppm), acetate (1.9 ppm), succinate (2.4 ppm), lipid (0.9 ppm), lactate (1.3 ppm), and glutamine-glutamate (2.1 ppm) in the central non-enhancing part of the lesions that may be similar to bacterial or tuberculous abscesses but different from the cystic or necrotic brain tumors[13,23,27] (Figure 4). A distinctive feature of fungal abscess on MR spectroscopy is the presence of trehalose that appears as multiple peak signals between 3.6 to 3.8 ppm, attributed to a disaccharide sugar in the fungal wall[13,19]. On MR perfusion, fungal abscesses typically demonstrate no increased perfusion of their walls and intracavitary projections, as opposed to markedly increased perfusion in the enhancing portion of malignant cystic or necrotic brain tumor[14].

Granuloma

Fungal granulomatous lesions are uncommon feature of CNS fungal infections, caused by immune response to hematogenous spreading or direct extension of fungal infection to the brain parenchyma. *Aspergillus* is the most common organism forming granulomas, followed by *Mucor*[28]. While *Cryptococcus* has been found to be the most common organism causing granulomas in HIV-patients, as referred to cryptococcomas[20]. The common locations of fungal granulomas are gray-white matter junction and basal ganglia in cases of disseminated disease, which tend to be multiple and small lesions[28]. Whereas anterior cranial fossa or basal frontal lobes are common locations of granulomas found in rhinocerebral form of invasive fungal disease, which tends to be solitary and large lesion[10]. On CT, fungal granulomas often appear as well-defined round or irregular-shaped hypodense lesions with homogeneous or heterogeneous enhancement and various degrees of perilesional brain edema, which

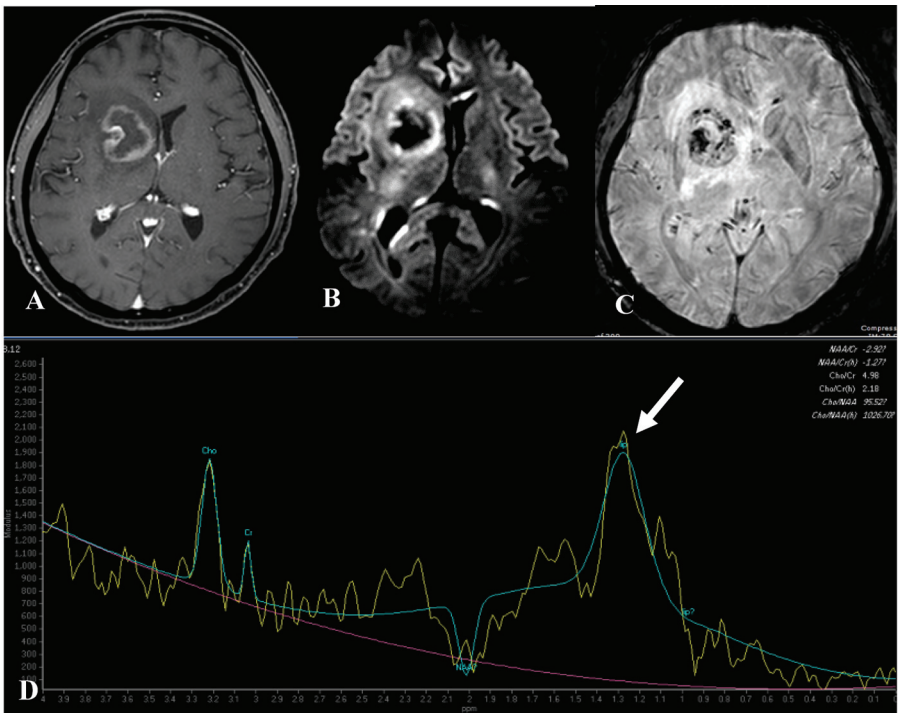

Figure 4. Aspergillus abscess. (A) Axial T1W FS-Gd shows a lobulated rim enhancing lesion at the right basal ganglion. (B) Axial DWI shows restricted diffusion along wall of the lesion. (C) Axial SWI shows multiple linear and punctate foci of susceptibility artifact along wall and within cavity of the lesion, representing paramagnetic substance deposition and/or hemorrhage. (D) Single voxel technique MRS (TE 144 ms) of the lesion demonstrates rising of the choline peak at 3.2 ppm and prominent lipid peak at 1.2 to 1.3 ppm (arrow). No trehalose peak at 3.6 to 3.8 ppm is demonstrated.

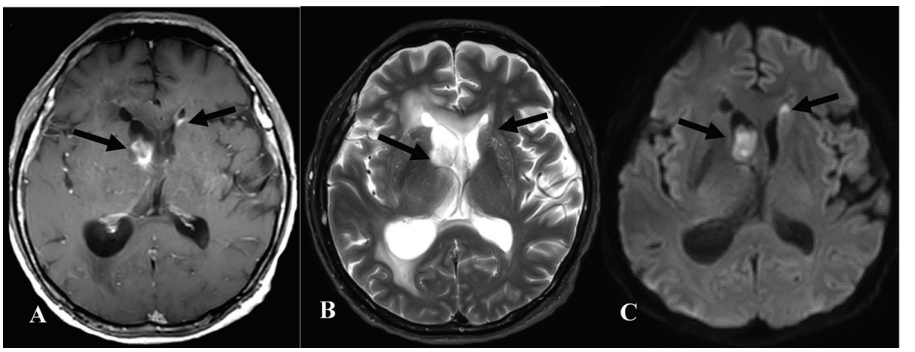

Figure 5. Fungal granulomas due to CNS phaeohypomycosis. (A) Axial T1W-Gd, (B) axial T2W FS, and (C) axial DWI show enhancing nodules in the frontal horn of lateral ventricles, which demonstrate iso-to hyperintense T2 signal with restricted diffusion (arrows).

are non-specific and may not be distinguished from granulomatous diseases, particularly tuberculomas[5]. On MRI, fungal granulomas often demonstrate isointense signal on T1WI and iso-to hypointense on T2WI with variable degrees of diffusion restriction and contrast enhancement[28]. The granulomas may demonstrate faint peripheral or weak ring enhancement, as seen in fungal abscesses reflecting poor host's immune status[8,29] (Figure 5). Proton MR spectroscopy of aspergilloma may show non-specific slightly increased choline with no demonstrable N-acetyl aspartate (NAA). Lactate peak may be present but also non-specific[13].

Rhinocerebral disease

Rhinocerebral disease is referred to brain parenchymal involvement by direct extension of invasive fungal disease from affected paranasal

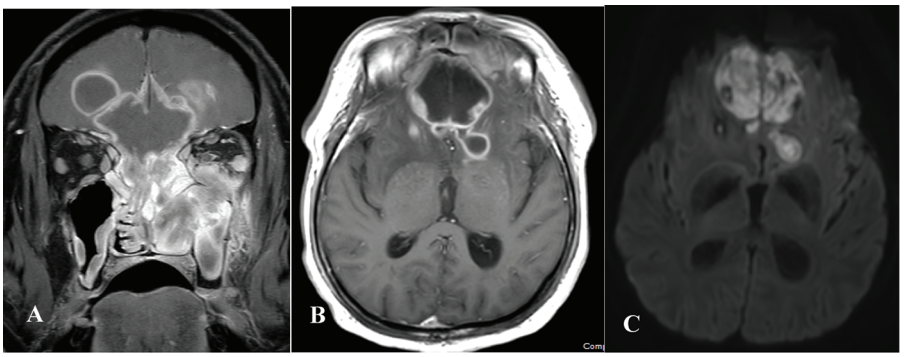

Figure 6. Rhinocerebral aspergillosis with brain abscesses. (A) Coronal T1W FS-Gd and (B) axial T1W-Gd show ill-defined heterogeneous enhancing soft tissue in the bilateral ethmoid and left maxillary sinuses with intracranial extension of infectious process through the cribriform plate and fovea ethmoidalis resulting in rim enhancing lesions of intraparenchymal abscesses at the inferior frontal lobes. (C) Axial DWI shows diffusely restricted diffusion in cavity of the rim enhancing lesions.

sinuses or nasal cavities. *Aspergillus* and *Mucor* are the most common pathogens. Frontal and sphenoid sinuses are most common locations of invasive fungal sinusitis leading to rhinocerebral disease[5,19]. On CT, fungal sinusitis often shows central hyperdense content related to composition of metal ions and calcium in fungal hyphae surrounded by enhancing hypodense thickened mucosa. Presence of frank sinus wall destruction with adjacent fat standing, enhancing soft tissue or mass-liked lesion is highly suggestive of invasive fungal sinusitis[7]. Widening of the neural foramens at the skull base may be evident in cases of perineural spreading along the nerves contiguous from sinus disease[30]. On MRI, fungal sinusitis typically demonstrates marked central hypointensity on T2WI, related to ferromagnetic substances including iron, manganese, and magnesium in the fungal hyphae, as opposed to bacterial sinusitis, which commonly shows central T2 hyperintensity. Heterogeneous or decreased mucosal enhancement of the affected sinuses may be evident[7]. Loss of normal intense mucosal enhancement of the nasal turbinates on MRI in nasal cavity disease has been reported, as referred to "black turbinate" sign due to angioinvasion[31] (Figure 2). Brain parenchymal invasion caused by direct extension from the adjacent sinonasal disease, often appears as an ill-defined area of T1 hypointense and T2 hyperintense signal with variable degrees of restricted diffusion and contrast enhancement. Foci of hyperintensity on T1WI, hypointensity on T2WI or susceptibility artifacts on SWI may be present in the area of brain parenchymal involvement, representing metal ions related to fungal infection or hemorrhage[8,19]. Brain parenchymal abnormalities due to fungal invasion can evolve into cerebritis, meningoencephalitis, or abscess formation[22] (Figure 6).

Vascular complications

The major vascular complications of CNS fungal infections include vasculitis, thrombosis, and mycotic aneurysm[19]. Filamentous fungal organisms, especially *Aspergillus* and *Mucor* have a predilection for angioinvasion affecting the medium and large-sized vessels at the basal brain, skull base, or cavernous sinuses via direct invasion from adjacent sinonasal disease[8,19]. The small-sized vessels including perforating arteries at the basal ganglia and distal branches of intracerebral arteries are commonly involved through hematogenous dissemination of fungal infection. These fungi produce enzyme elastase that destroys elastin in the walls of arteries leading to vascular thrombosis, stenosis, or mycotic aneurysm formation[32]. In addition to lysis of elastin, fungal infection also induces inflammatory reaction in the vessel wall resulting in vasculitis[32,33]. Cerebral ischemia or infarction along the affected vascular territories are commonly present as consequences of arterial thrombosis, stenosis, or vasculitis (Figure 7). Presence of hemorrhage or hemorrhagic transformation within the infarcted areas is commonly evident with cerebral aspergillosis[19,34].

Mycotic aneurysm is a rare complication of CNS fungal infections. *Aspergillus* is the most common organism that preferentially involves the large-sized vessels at the basal brain or skull base[35]. Formation of mycotic aneurysm is possibly the result from direct vessel wall invasion with disruption of elastin, embolic occlusion of vasa vasorum, or immune complex deposition in the vessel wall inducing inflammatory damage[7,19]. Unlike bacterial mycotic aneurysms, which commonly appear as

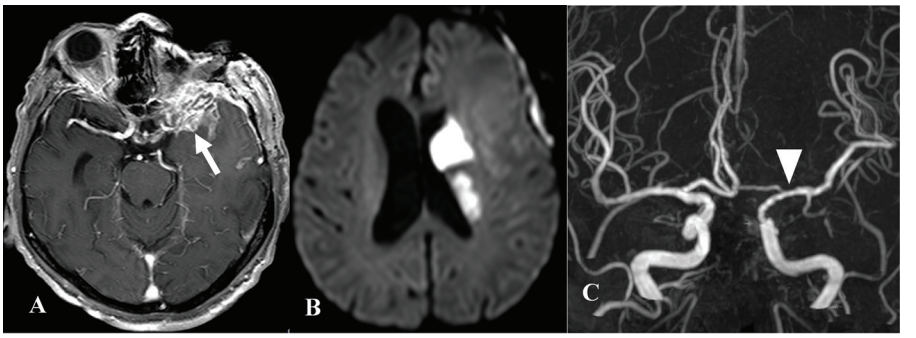

Figure 7. Mucormycosis of the left orbit status post exenteration with vascular invasion. (A) Axial T1W FS-Gd shows ill-defined enhancing soft tissue at the left anterior temporal region extending from the left orbit with involvement of the left middle cerebral artery (white arrow). (B) Axial DWI shows restricted diffusion at the left corona radiata, corresponding with acute left MCA territory infarction. (C) TOF MRA demonstrates segmental irregular narrowing of supraclinoid segment of the left ICA and M1 segment of the left MCA due to angioinvasion (arrowhead).

multiple, small, and spherical lesions locating at distal segments of intracerebral arteries, filamentous fungi preferentially involve long segment of proximal portion of the large intracerebral arteries resulting in fusiform aneurysm[19].

Specific imaging findings of CNS fungal infections

Aspergillosis

Aspergillus species (spp.) is a common opportunistic fungus found in soil, water, plants, and decaying vegetable. *Aspergillus fumigatus* is the most common human pathogen, which has septate hyphae with dichotomous branching, producing numerous spores. Humans are infected by inhalation of *Aspergillus* spores and subsequently spreading into the paranasal sinuses or lungs as the primary sites of infection. Hematogenous dissemination of *Aspergillus* infection from primary infection in the body commonly occurs in the setting of immunosuppression or immunodeficiency[1,33]. CNS aspergillosis is an uncommon condition with increased incidence in immunocompromised patients. The fungal pathogen commonly accesses the brain via hematogenous spreading from the lungs or directly extends from the paranasal sinuses or nasal cavities. The fungus may directly inoculate to the brain in the setting of trauma or contamination of the operative field during a neurosurgical procedure[36].

Angioinvasion is the main pathology in cerebral aspergillosis. The common manifestations of cerebral involvement include cerebritis, infarction, granuloma, abscess, and leptomeningitis. The fungal hyphae typically invade the intracranial vessels, resulting in vascular thrombosis with subsequent cerebral infarction or hemorrhage[8,36]. Disruption of the vessel walls can lead to mycotic aneurysm formation. *Aspergillus* is the most common organism causing fungal mycotic aneurysm[35]. The fungus can also inoculate and spread into the brain parenchyma, resulting in cerebritis, granuloma or abscess formation depending on host's immune status[19].

The imaging features of CNS aspergillosis are commonly non-specific and may depend on immune status of the patients. Variable radiological patterns of cerebral aspergillosis on CT and MRI have been reported including areas of brain edema, foci of hemorrhage, solid enhancing lesions of aspergillomas, ring enhancing lesions of abscess formation, infarction, and mycotic aneurysm[37].

Cerebral infarction in *Aspergillus* infection can be single or multiple areas involving the cortex or white matter along the vascular territories. Infarctions in the deep brain parenchyma, such as basal ganglia and thalamus along perforating artery territories are also common in hematogenous dissemination[19]. Presence of hemorrhage superimposed on infarcted areas is a common feature of CNS aspergillosis due to angioinvasion. This may appear as hyperdensity on CT, hyperintensity on T1WI, hypointensity on T2WI, or susceptibility artifact on T2W GRE or SWI[36].

On MRI, *Aspergillus* granulomas or abscesses typically demonstrate peripheral hypointensity on T2WI or susceptibility foci on T2W GRE or SWI, attributed to fungal hyphae with fungal elements including iron, magnesium, manganese, and hemorrhage with hemosiderin-laden macrophages[8]. *Aspergillus* abscesses usually show inhomogeneous or peripheral restricted diffusion on DWI in the abscess cavity, as opposed to bacterial or tuberculous abscesses, which typically show diffuse

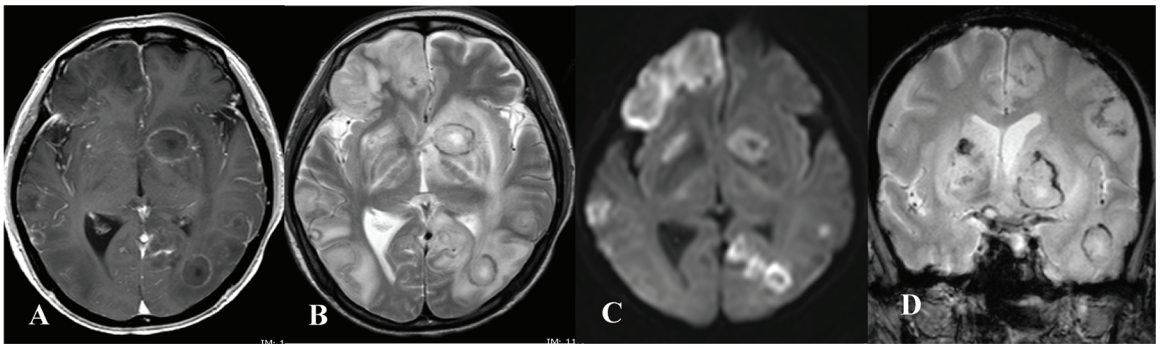

Figure 8. Disseminated aspergillosis with multiple brain abscesses and cerebral infarction. (A) Axial T1W-Gd, (B) Axial T2W, (C) Axial DWI, and (D) Coronal T2 GRE show multiple faint or weak ring enhancing lesions in the left basal ganglion, bilateral temporal, and left occipital lobes, which demonstrate internal heterogeneously restricted diffusion with hypointense T2 and T2 GRE rim, representing paramagnetic substance deposition and/or hemorrhage. Associated perilesional edema and acute infarctions at the right anterior frontal lobe and right putamen are evident.

or homogeneous diffusion restriction[19,23]. Faint peripheral or weak ring enhancement is commonly seen in *Aspergillus* abscesses or granulomas related to poor immune reaction in immunocompromised patients[8] (Figure 8). Presence of a characteristic feature of intracavitary projection is also commonly present in *Aspergillus* abscesses and helpful in establishing the diagnosis[23]. Recognition of these imaging features could help guide or support the diagnosis of cerebral aspergillosis, particularly in immunocompromised hosts or those who have proven systemic *Aspergillus* infection.

Invasive fungal sinusitis is also commonly caused by *Aspergillus* infection. The CT findings of sinusitis in aspergillosis include hyperdense content and more centrally located calcifications in the sinus cavity related to fungal hyphae containing fungal elements, in contrast to more peripherally located calcifications within thickened mucosa in bacterial sinusitis. In most cases of invasive aspergillosis, the sinus wall or adjacent bony structures usually show destruction or sclerotic change[16]. On MRI, *Aspergillus* sinusitis often demonstrate iso-to hypointense signal on T1WI and hypointense signal on T2WI attributed to fungal elements or calcifications, which may simulate normal signal void of air in the sinuses[16]. Dural enhancement adjacent to affected sinuses is commonly present, representing direct extension of invasive fungal infection[5]. Contiguous extension of the sinonasal disease into the orbits, cavernous sinuses, or brain parenchyma commonly occurs and should be concerned in the setting of invasive aspergillosis[16].

Mucormycosis

Mucormycosis is an invasive fungal infection caused by *Mucorales* spp. and commonly occurs in patients with poorly controlled diabetes. Beside diabetes, other predisposing factors include patients with chronic renal failure, anemia, acidosis, cirrhosis, intravenous drug abuse, receiving corticosteroid, and cancer during treatment with chemotherapy[1]. *Rhizopus oryzae* is the most common organism of mucormycosis. The fungal pathogens infect humans via inhalation of the spores. The fungi in *Mucor* have non-septated hyphae with right-angle branching and irregular, non-parallel cell walls, which their spores can be converted into hyphae. Similar to aspergillosis, angioinvasion is the principal pathology in mucormycosis[32,38]. They usually invade the medium and large-sized vessels, leading to vascular thrombosis, cerebral infarction, intracerebral hemorrhage, or pseudoaneurysm formation and subsequently disseminate hematogenously, or directly extend through the involved paranasal sinuses into the brain and orbits[8].

The rhinocerebral mucormycosis is the most common form of infection and caused by inhaled fungal spores infecting the paranasal sinuses or nasal mucosa and then direct extending into the brain or orbits[39]. Cerebral mucormycosis carries a poor prognosis with 70% to 100% mortality rates, even after aggressive surgical debridement combined with administration of antifungal drugs[8]. Similar to *Aspergillus* sinusitis, the infected paranasal sinuses usually show hyperdensity on CT and hypointensity on T2WI of sinus content, related to the presence of paramagnetic fungal elements, calcium or hemorrhage. Extra-sinus extension commonly appears as focal bone erosion with surrounding fat stranding, and ill-defined enhancing soft tissue

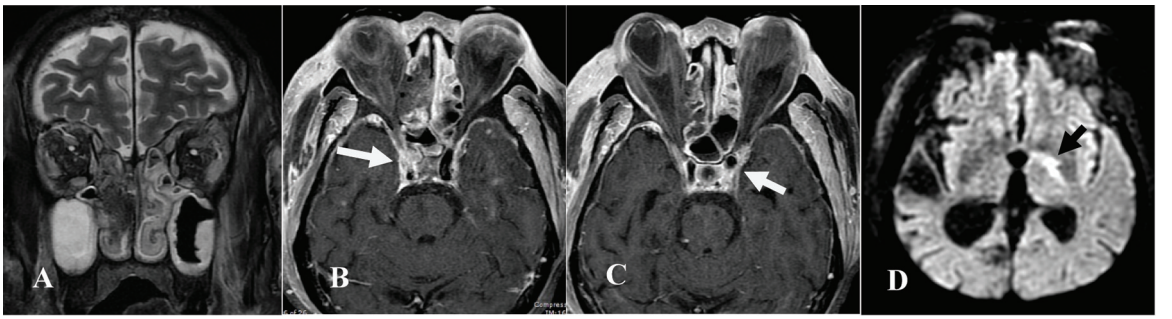

Figure 9. Mucormycosis of the ethmoid sinuses with bilateral orbital cellulitis and cavernous sinuses invasion. (A) Coronal T2W FS shows mucosal thickening in the bilateral ethmoid and maxillary sinuses with hypointense signal of mucous content in the right ethmoid sinus and nasal cavity, representing paramagnetic substance deposition related to fungal sinusitis. (B) and (C) Axial T1W FS-Gd show extension of infectious process into the bilateral orbits causing orbital cellulitis and bilateral cavernous sinuses resulting in cavernous thrombophlebitis, seen as internal enhancing soft tissue with small filling defects (white arrows). Note irregular wall with luminal narrowing of the right cavernous ICA. (D) Axial DWI shows restricted diffusion at posterior limb of the left internal capsule, consistent with acute infarction (black arrow).

directly extended contiguous with the infected sinuses[16]. Direct extension to the orbits commonly demonstrates focal bone erosion of the orbital wall, swelling and displacement of the extraocular muscles, diffuse orbital fat infiltration, preseptal soft tissue swelling, optic nerve involvement, or intraorbital abscess formation[15]. Perineural spreading of infection may occur and has been reported in 70% to 90% of pathological cases but uncommonly depicted on CT or MRI. The nerves locating adjacent to the infected paranasal sinuses or orbits may be involved, which appear as thickening and enhancement of the nerves along their courses, enlargement of the neural foramina, and denervated atrophy of the muscles supplied by the nerves[30]. Brain involvement in rhinocerebral mucormycosis commonly occurs at frontal lobes, particularly at anteroinferior aspect due to direct extension from the frontal and ethmoid sinuses. The common findings of cerebral involvement include vasogenic edema, cerebritis, ischemia or infarction due to vascular thrombosis, intraparenchymal hemorrhage, and frontal lobe abscesses[8,15]. Involvement of the cavernous sinuses is also common and directly extended from infected sphenoid sinuses or orbits. Cavernous sinus thrombophlebitis with thrombosis of the internal carotid artery (ICA) are commonly evident and appear as abnormal filling defect or enhancing soft tissue in the cavernous sinus with loss of normal vascular flow void of the ICA or presence of intraluminal thrombus[15,40] (Figure 9).

Isolated cerebral mucormycosis in the setting of hematogenous dissemination is a rare manifestation and has been found in patients with history of intravenous drug abuse. The common findings include ischemia or infarction, cerebritis, and abscess formation, which typically locate in the deep brain parenchyma, especially at the basal ganglia related to fungal dissemination along the perforating arteries[19].

Cryptococcosis

Cryptococcus neoformans is an encapsulated yeast-like fungus that is the most common fungal organism to affect the CNS and most commonly identified fungal pathogen in CNS infection among the HIV patients. This fungal organism is found in bird feces, particularly in pigeon droppings and some mammal feces[41]. *Cryptococcus* primarily infects the immunocompromised hosts, particularly in patients with AIDS. However, up to 30% of the patients with cryptococcosis have normal immune status or no underlying predisposing conditions[8].

Cryptococcal infection occurs through inhalation of fungal spores, subsequently spreads into the lungs causing asymptomatic pulmonary infection and then disseminates hematogenously to the CNS. The CNS is the common location of cryptococcal infection, owing to absence of anticryptococcal antibody in the CSF and presence of polysaccharide capsule protecting the fungus against host's inflammatory response. Most common clinical manifestation of the patients with CNS cryptococcosis is meningitis or meningoencephalitis. The diagnosis of CNS cryptococcosis can be made by presence of yeast in the CSF by microscopic examination or detection of cryptococcal antigen in the CSF or blood[41].

Cerebral cryptococcosis typically manifests as either meningeal or parenchymal disease.

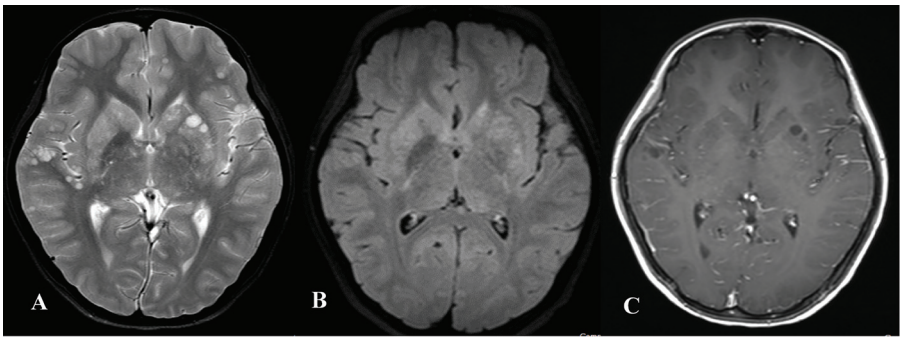

Figure 10. Cryptococcosis in HIV patient. (A) Axial T2W FS and (B) axial FLAIR FS show multiple small hyperintense T2 and FLAIR cystic lesions in the bilateral basal ganglia, left frontal and right temporal lobes, representing gelatinous pseudocysts. (C) Axial T1W-Gd shows no enhancement of these cystic lesions.

Cryptococcal meningitis is the common primary manifestation and predominantly located at the basal brain. Associated communicating hydrocephalus is common. The typical parenchymal lesions are classified as dilated Virchow-Robin (VR) spaces or gelatinous pseudocysts, cryptococcomas, or enhancing cortical nodules. The fungus preferentially extends along the VR spaces and then involves the adjacent brain parenchyma. Basal ganglia is the most commonly affected region[20]. Gelatinous pseudocysts are common brain parenchymal lesions, caused by expansion of the VR spaces filled with abundant mucoid gelatinous material produced by the capsule of *Cryptococcus*[33]. Like gelatinous pseudocysts, cryptococcomas are commonly located at the basal ganglia, caused by fungal invasion of the brain parenchyma in cases of meningitis resulting in chronic granulomas with infiltration of lymphocytes, macrophages, and giant cells. About 4% of patients with cryptococcal meningitis may develop acute infarction in the deep brain parenchyma, predominantly at the basal ganglia and thalami along the territory of lenticulostriate arteries, probably due to direct vascular invasion, secondary vasculitis, or vasospasm[19,42].

The spectrum of imaging findings of CNS cryptococcosis includes leptomeningeal enhancement, dilated perivascular spaces, gelatinous pseudocysts, intraparenchymal or intraventricular cryptococcomas, focal brain edema, and hydrocephalus[5]. Similar to infectious meningitis from other organisms, the imaging pattern of cryptococcal meningitis is non-specific and tends to appear as no or minimal leptomeningeal enhancement. Cryptococcal meningitis, gelatinous pseudocysts and cryptococcomas usually show no or minimal contrast enhancement due to poor inflammatory response in immunocompromised patients and protective effect of polysaccharide capsule of the fungal organism against immune reaction[20]. Dilated perivascular spaces infected by the fungi can coalesce into clusters of gelatinous pseudocysts, giving a "soap bubble" appearance. Gelatinous pseudocysts typically appear as multiple small well-defined, round to ovoid cystic lesions, which show hypodensity on CT, CSF-like signal intensity on both T1WI and T2WI and may not be suppressed high signal on FLAIR images due to effect of mucoid content[19,42]. These pseudocysts may demonstrate restricted diffusion on DWI and usually do not enhance due to poor inflammatory reaction related to impaired immune status of the patients[43]. Presence of clusters of these cystic lesions along the distribution of VR spaces, predominantly at the basal ganglia and thalami is highly suggestive of CNS cryptococcosis (Figure 10).

Cryptococcomas may appear as cystic or solid lesions with variable size, shape, and density on CT. On MRI, these lesions usually demonstrate hypointensity on T1WI, hyperintensity on T2WI, and variable signal on FLAIR[19]. On DWI, cryptococcomas may show centrally restricted diffusion that can mimic pyogenic abscess[44]. The enhancement of these lesions on contrast-enhanced CT or MRI varies from no enhancement to peripheral smooth or irregular nodular enhancement that may simulate cystic or necrotic brain tumor (Figure 11). Numerous scattered cryptococcomas may be evident, resembling miliary disease and similar to disseminated granulomatous infection[20].

CNS cryptococcosis in immunocompetent patients tends to present with cryptococcomas, which are usually large and lobulate. In contrast to setting of impaired immune status, these lesions are likely to show obvious contrast enhancement with variable

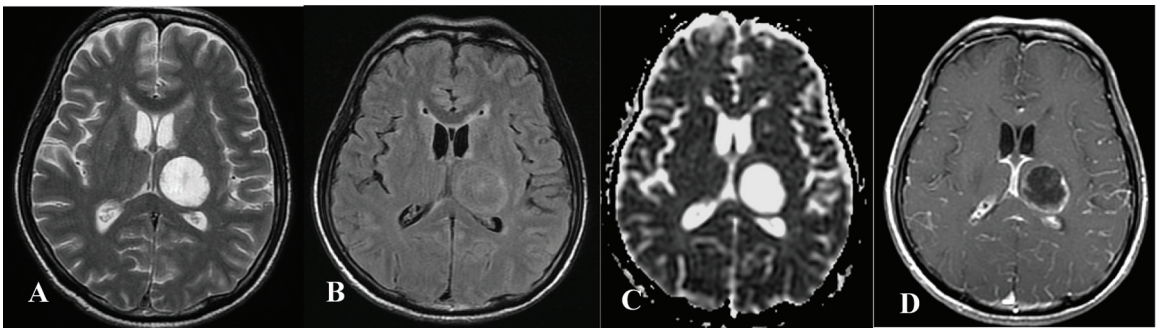

Figure 11. Cryptococcoma in immunocompetent patient. (A) Axial T2W and (B) axial FLAIR show a well-defined round hyperintense T2 and FLAR lesion at the left thalamus without perilesional edema. (C) Axial ADC map shows no restricted diffusion of the lesion. (D) Axial T1W-Gd shows thin irregular rim enhancement of this lesion.

degree of perilesional edema as a result of strong immune reaction in immunocompetent hosts[41,45].

Candidiasis

Candida spp. are small, round to oval-shaped yeasts, found in human body as normal flora of the gastrointestinal tract and mucocutaneous membrane. *Candida albicans* is the most common cause of human candidiasis. Disseminated candidiasis can develop due to disequilibrium between the fungal organism and normal flora in the human body. The incidence of disseminated candidiasis has been increasing due to an expansion of immunocompromised population, especially in HIV patients[33]. Other predisposing factors include treatment with multiple antibiotics, receiving chemotherapy, steroid use, immunosuppression, intravenous total parenteral nutrition, premature infants, on indwelling catheter, and intravenous drug abuse. Cerebral candidiasis almost always results from hematogenous dissemination in the setting of systemic candidiasis and the kidney is the most common primary site of infection. The diagnosis is made by CSF analysis or tissue biopsy[1]. The clinicopathological manifestations of cerebral candidiasis include microabscesses, macroabscesses, leptomeningitis, and vascular complications. Cerebral microabscesses are the most common imaging feature that usually appear as numerous, small (less than 3 mm), poorly demarcated nodular or punctate lesions, commonly located at corticomedullary junction, basal ganglia, or cerebellum with or without surrounding brain edema[5,8].

On CT, cerebral microabscesses often show iso-to hypodensity with nodular or punctate enhancement. On MRI, these lesions are varying in signal intensity on T1WI and T2WI, which may demonstrate hypointensity on T2WI or SWI due to presence of hemorrhage[19]. *Candida* microabscesses commonly demonstrate restricted diffusion on DWI and typical punctate or nodular enhancement. Ring enhancement of the lesions can also be seen[46]. Unlike hyphae fungi, cerebral macroabscesses are uncommonly evident, which can be solitary or multiple and may have imaging characteristics in similar to general fungal abscesses. Like other infectious causes of meningitis, the imaging findings of *Candida* meningitis are not specific and usually accompanied with microabscesses[19]. Associated vascular complications including cerebral infarction and mycotic aneurysm formation can occur due to secondary vasculitis, as opposed to preferential direct vascular invasion found in hyphae fungi. Intraparenchymal or subarachnoid hemorrhage may be evident, particularly in cases with vasculitis or mycotic aneurysm[5,19].

Blastomycosis

Blastomycosis is caused by a dimorphic fungus *Blastomyces dermatitidis* that is endemic to the midwestern and northern United States. Unlike other fungal pathogens, blastomycosis does not have propensity for patients with AIDS or impaired immune status. The fungus appears as a mold form in the environment and converts to yeast form in the human body that can disseminate hematogenously resulting in systemic disease[8]. This infection is acquired through inhalation of fungal spores and then spreading into the lungs, which is the most common primary site of disease. Chronic pneumonia is the main clinical manifestation of blastomycosis. Extrapulmonary disease involving the skin, subcutaneous tissue, bones and joints, prostate gland and CNS is also common. CNS involvement occurs in about 5% to 10% of patients with systemic blastomycosis, resulted

from hematogenous dissemination[47]. However, direct extension of the infection through the infected paranasal sinuses or orbits has been reported. The common manifestations of CNS blastomycosis include meningitis, intraparenchymal mass lesions, intraparenchymal abscess, and subdural or epidural abscess. The imaging features on CT or MRI are non-specific and may be indistinguishable from other fungal lesions. On MRI, the intraparenchymal mass lesions usually present as solitary or multiple T2W hyperintense lesions with strong peripheral enhancement and centrally restricted diffusion[8,47].

Coccidioidomycosis

Coccidioidomycosis is caused by a dimorphic fungus *Coccidioides immitis* that is endemic to the northern Mexico and southwestern United States. It exists in the mycelial form within the soil and becomes infective when the airborne arthrospores are inhaled. The infection usually starts in the lungs through inhalation of fungal spores, and manifests as spectrum of pulmonary disease ranging from self-limited mild respiratory tract infection to pneumonia[19]. CNS involvement is usually due to hematogenous dissemination from primary infection in the lungs[1].

The most common manifestation of CNS coccidioidomycosis is meningitis, which typically shows intense leptomeningeal enhancement at the basal cistern, Sylvian fissures, and interhemispheric cistern. Associated communicating hydrocephalus is commonly seen in 68% to 93% of patients[8,19]. Intraparenchymal lesions including granulomas and abscesses are uncommon in CNS coccidioidomycosis. Cerebral coccidioidal granulomas may appear as single or multiple enhancing nodules, commonly located at the corticomedullary junction and basal ganglia[19,48]. Like other fungal abscesses, coccidioidal abscesses typically show ring enhancement with variable diffusion restriction without specific imaging findings[48]. Vasculitis has been reported in up to 40% of patients with meningitis resulting in cerebral ischemia or infarction predominately at deep brain parenchyma secondary to preferential involvement of the deep perforating arteries[19]. Mycotic aneurysm may occur and can lead to subarachnoid hemorrhage when ruptured.

Histoplasmosis

Histoplasmosis is caused by a dimorphic fungus *Histoplasma capsulatum* that is endemic to midwestern United States, particularly at Mississippi River and Ohio River valleys. Like *B. dermatitidis*, *H. capsulatum* grows as a mold in the environment and converts into yeast form in the lungs through inhalation of fungal spores causing various pulmonary manifestations from mild granulomatous inflammation to pneumonia[8]. Disseminated disease is uncommon in immunocompetent hosts but more common in immunocompromised hosts, particularly in HIV patients. Approximately 5% to 10% of patients with disseminated histoplasmosis develop CNS involvement, whose common sites of infection include meninges, corticomedullary junction and deep brain parenchyma. The common CNS manifestations of cerebral histoplasmosis include meningitis, cerebritis, granuloma, and abscess[19,49].

Imaging findings of CNS histoplasmosis on CT or MRI are often non-specific. Granulomas, known as "histoplasmomas" has been reported in 25% of cases of CNS histoplasmosis, which may occur in corticomedullary junction, basal ganglia, thalamus, brainstem, or cerebellum[19]. On MRI, these lesions tend to be small, round, hypointense on T1WI, variable signal on T2WI and peripheral enhancement with or without perilesional edema. On DWI, histoplasmomas may demonstrate central, multifocal or heterogeneous diffusion restriction[8]. Like other fungal meningitis, diffuse leptomeningeal enhancement may be evident, which is non-specific. Similar to other fungal abscesses, histoplasmosis abscesses usually show hypointense T2W rim secondary to paramagnetic free radicals and peripheral ring enhancement with variable diffusion restriction without distinct imaging findings[8,19].

Conclusion

Fungal infections of the CNS are relatively uncommon and usually identified in immuno-compromised patients. CNS fungal infections can manifest as meningeal or parenchymal diseases secondary to hematogenous dissemination, CSF seeding, or direct extension. The imaging features are often non-specific and influenced by type of fungal pathogens and immune status of the patients. Vascular complications including vasculitis, infarction, or mycotic aneurysm are predominant features of fungal infection due to angioinvasion of hyphae fungi. Some characteristic imaging findings, such as intracavitary projections, weak ring enhancement, and gelatinous pseudocysts could help suggest the diagnosis. Although the general radiological manifestations of CNS fungal infections are relatively non-specific, recognition of characteristic imaging features is

imperative to help suggest the diagnosis and enable early treatment.

What is already known on this topic?

The imaging findings of fungal infections of the CNS are often non-specific. Similar to other infectious organisms, fungal infections can affect the meninges and brain parenchyma resulting in meningitis, meningoencephalitis, cerebritis, granuloma, or abscess formation. However, some characteristic imaging findings, such as intracavitary projections in fungal abscesses and weak ring enhancement in disseminated aspergillosis have been already known that could help suggest the diagnosis in the appropriate clinical setting.

What this study adds?

This review article includes common imaging features of CNS fungal infections and distinct imaging features of specific pathogens that can help refine the diagnosis. Recognizing the characteristic imaging features such as gelatinous pseudocysts in cryptococcosis and multiple cerebral microabscesses in candidiasis is helpful in establish the specific diagnosis. However, the imaging findings may mimic other infectious causes, inflammatory disease, or even brain tumor. Advanced MRI techniques including MR spectroscopy and MR perfusion may aid in differentiating fungal infection from the mimickers. Therefore, combination of conventional imaging and advanced MRI techniques could help narrow the differential diagnosis or get to the specific diagnosis in the appropriate clinical setting.

Conflicts of interest

The authors declare no conflict of interest.

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