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REVIEW ARTICLE

MRI of CNS Fungal Infections: Review of Aspergillosis to Histoplasmosis and Everything in Between

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Abstract Fungal infections of the central nervous system (CNS) represent a wide spectrum of diseases with some common magnetic resonance imaging (MRI) features. Risk factors include immunocompromise of any cause and living in endemic areas. CNS infection occurs through hematogenous spread, cerebrospinal fluid seeding, or direct extension. MRI features include heterogeneous or ring reduced diffusion and weak ring enhancement. Angioinvasive aspergillosis is characterized by multifocal hemorrhagic lesions with reduced diffusion. Cryptococcosis results in gelatinous pseudocyst formation in the basal ganglia. Mucormycosis is characterized by frontal lobe lesions with markedly reduced diffusion. Candidiasis is usually manifest by numerous microabscesses of less than 3 mm occurring at the corticomedullary junction, basal ganglia, or cerebellum. Coccidioidomycosis often results in meningitis with contrast enhancement of the basal cisterns. Blastomycosis and histoplasmosis are rare infections with parenchymal abscesses or meningitis. Recognizing the imaging features of CNS infections allows for early, aggressive treatment of these otherwise rapidly fatal infections.

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Introduction

Fungal central nervous system (CNS) infections are relatively rare and occur almost exclusively in immunocompromised hosts [1]. Aspergillosis, cryptococcosis, mucormycosis, and candidiasis are among the most common ones [2, 3]. Intracranial fungal infections occur through hematogenous spread, infection of cerebrospinal fluid (CSF), or direct extension from sinonasal disease, each route with typical imaging features. Additionally, each organism has typical imaging features that help refine the differential diagnosis, and in some cases, allow specific diagnosis.

Potentially curative treatments for fungal infection include administration of amphotericin B, voriconazole, or other newer agents at high enough doses to cross the blood–brain barrier, correction of any underlying predisposing conditions where possible, and surgical debridement [4–6]. Understanding the imaging appearance of CNS fungal infections is imperative because early diagnosis facilitates early treatment of these otherwise rapidly fatal infections [7]. In this article, we review the magnetic resonance imaging (MRI) appearance of fungal CNS infections.

Clinical Risk Factors

Immunocompromise is the main risk factor for development of CNS fungal infection, and as such, highly virulent fungal infection should be suspected in any immunocompromised patient with neurologic symptoms and signs, especially when acute in onset [1].

Often the immunocompromise is treatment related. Chemotherapy can cause profound neutropenia and immunocompromise. Immunosuppressive therapy in post-transplant patients is also a common cause of immunocompromise. Corticosteroid treatment in patients with autoimmune diseases like inflammatory bowel disease, rheumatoid arthritis, or multiple sclerosis is a commonly overlooked cause of immunosuppression. Other times, reduced immunity is related to intrinsic or extrinsic illness, such as in patients with primary immunodeficiency, lymphoma/leukemia, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), or diabetes. Because immunocompromise may not be a prominent feature of the clinical presentation prompting imaging and may be omitted from the referral indication, evidence of immunocompromise should be specifically sought in any patient with new intracranial lesions that may be infectious.

Aside from immunocompromise, the other major risk factor for specific fungal infections is living in endemic areas. In the USA, the Southwest, Midwest, and Northeast are associated with coccidioidomycosis, blastomycosis, and histoplasmosis, respectively.

Routes of Infection

Fungal infection of the brain occurs most commonly through hematogenous spread, CSF seeding, or direct extension (Fig. 1).

All virulent fungi can hematogenously seed the CNS [7]. Early on, hematogenous spread produces radiologically invisible cerebritis with lack of abscess formation, mostly adjacent to blood vessels, followed by frank abscess formation with reduced diffusion being common. In the disseminated type of infection, mycotic vasculopathy/vasculitis-mediated septic infarction occurs predominately at the gray–white junction (Fig. 1a) or perforating arterial locations with subtle enhancement and heterogeneous reduced diffusion. This anatomic distribution is different from other infarcts, cerebritis, or abscess [8]. Consequently, while the differential diagnosis of single or multiple brain lesions in an immunocompromised patient must include fungal infection along with bacterial infection, septic emboli, multiple infarcts, metastatic disease, and lymphoma, fungal infection can be specifically suggested when lesions occur at the gray–white junction and perforating arterial zones.

Infectious seeding of the CSF is less common and typically occurs with *Cryptococcus* (Fig. 1b) or *Aspergillus*. These infections produce variable imaging appearances: enhancing or non-enhancing lesions of the meninges, choroid plexus, or ependyma, hydrocephalus, and/or white matter edema.

Direct intracranial extension from the sinuses occurs with *Zygomycetes*/*Phycomycetes* or *Aspergillus* infection, producing characteristic lesions at the inferior frontal lobes adjacent to the posterior sinuses (Fig. 1c), usually with enhancement and reduced diffusion.

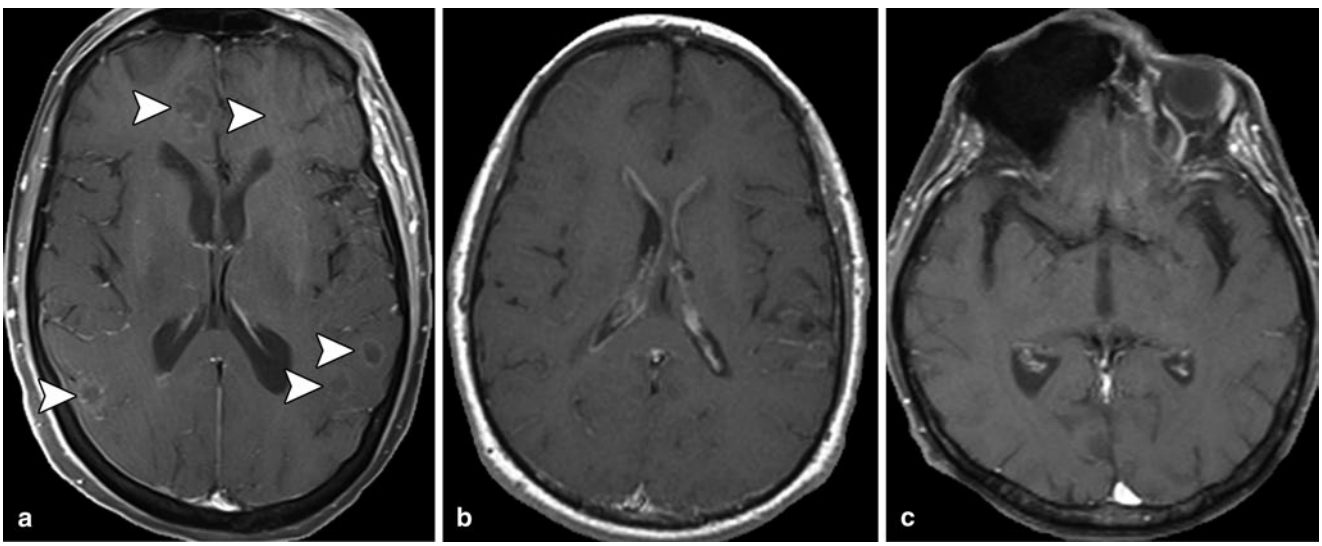

Fig. 1 Fungal CNS infection may occur via hematogenous spread, CSF seeding, or direct extension. **a** Axial T1 post-gadolinium image shows typical lesions of multifocal angioinvasive aspergillosis at the gray–white junction (*arrowheads*). **b** Axial T1 post-gadolinium image shows typical cryptococcal meningitis with ventricular wall enhancement and subtle frontal and occipital leptomeningeal enhancement. **c** Axial T1 post-gadolinium image shows mucormycosis with intracranial extension and enhancement at the inferior frontal lobe following a sinus infection

General MRI Features: Heterogenous or Ring Reduced Diffusion and Weak Ring Enhancement

The high viscosity and cellularity of fungal pus leads to reduced diffusion and is often the earliest diagnostic imaging clue to fungal infection, even preceding enhancement (Fig. 2). The reduced diffusion pattern is frequently heterogeneous (Fig. 3a) but may also be ring-like and peripheral, mirroring the post-gadolinium enhancement pattern in larger lesions (Fig. 3b). In smaller lesions, reduced diffusion

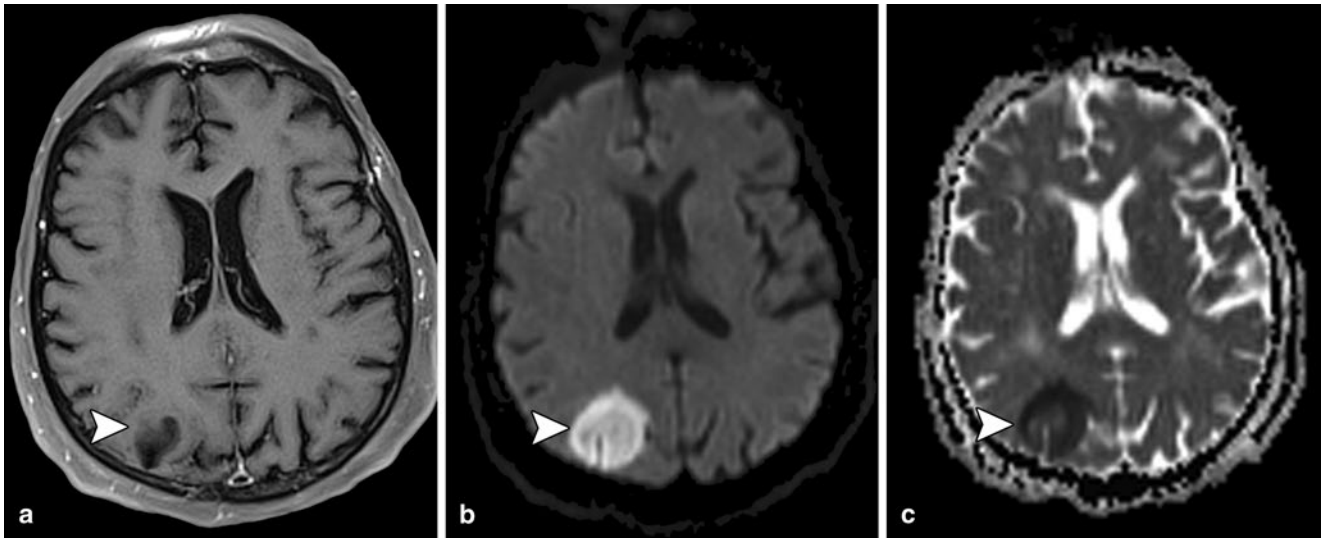

Fig. 2 Reduced diffusion is often the first imaging finding in fungal infection, even preceding enhancement. **a** Axial T1 post-gadolinium, **b** DWI (b = 1000 s/mm²), and **c** apparent diffusion coefficient (ADC)-map (calculated from b values of 0 and 1000 s/mm²) demonstrate minimal enhancement but obvious reduced diffusion (*arrowhead*). The patient was a 69-year-old man with acute myeloid leukemia who developed pneumonia following chemotherapy. He subsequently developed altered mental status, and MRI was obtained. He died a day later. Post-mortem evaluation confirmed disseminated aspergillosis

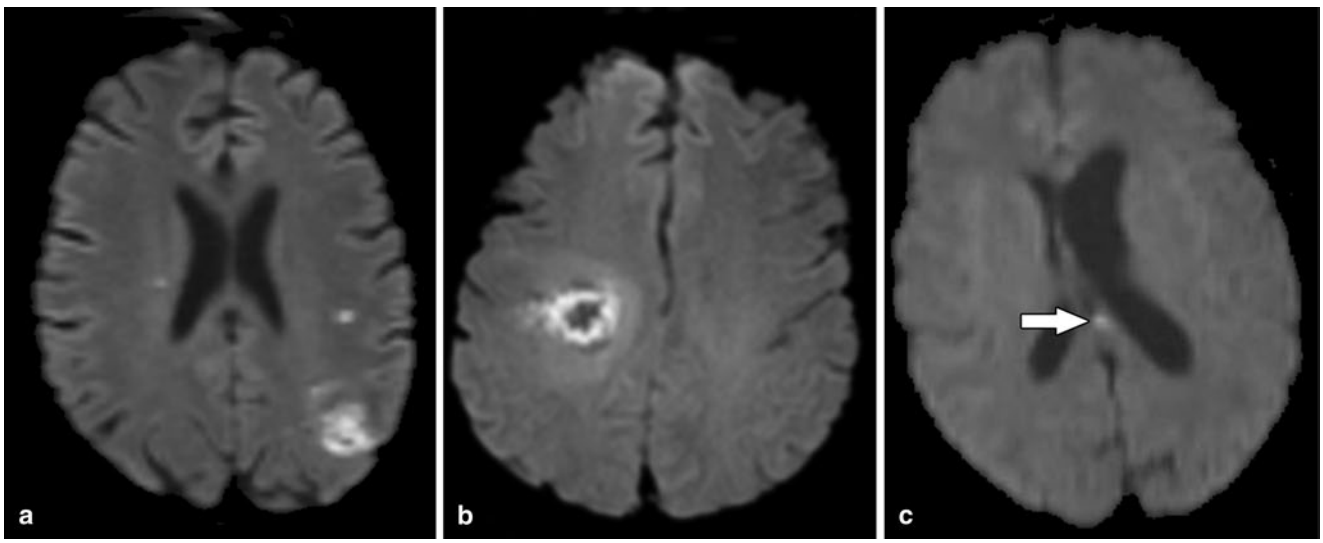

Fig. 3 Patterns of reduced diffusion in fungal infection may be heterogeneous, ring-like, or punctate. **a** Axial DWI sequence shows heterogeneous diffusion restriction in the lesion at the left posterior parietal lobe. The patient was a 37-year-old woman who was intoxicated and fell, with normal head computed tomography (CT) on admission. She was treated with glucocorticoid therapy for acute alcoholic hepatitis and developed mental status changes on hospital day 11. **b** Axial DWI sequence shows ring-like reduced diffusion in the posterior right frontal lobe. The patient was a 61-year-old man with a history of neck cancer and on dexamethasone for radiation edema who presented with a 2-week history of left-sided arm, leg, and facial weakness. He was without fevers and was started on high-dose corticosteroids. The patient died 2 days later, and autopsy confirmed angioinvasive aspergillosis. **c** Axial DWI sequence shows punctate reduced diffusion at the splenium of the corpus callosum. Note the asymmetric dilation of the left lateral ventricle indicating ventriculitis. The patient was a 50-year-old woman with acute lymphoblastic leukemia who developed leukocytopenia after chemotherapy and subsequently developed aspergillosis

may be punctate (Fig. 3c). In contrast, bacterial abscesses tend to have a more homogeneous, highly restricting center. Diffusion-weighted imaging (DWI) has important limitations because it cannot reliably differentiate (1) fungal from pyogenic abscess, (2) early cerebritis with edema from late cerebritis with necrosis, or (3) focal infection from small infarct lesions as sequelae of cerebral thromboembolism [9].

In contrast to their often striking reduced diffusion, fungal lesions often demonstrate only a thin rim of peripheral "weak ring" enhancement (Fig. 4a). Pathologic correlation shows marked absence of inflammatory response, which may explain this weak ring appearance (Fig. 4b, c). In our case series, in contrast to weak or absent enhancement in most patients, one patient with recent initiation of short-term steroid treatment and likely little immunocompromise showed relatively robust enhancement more typical of bacterial infections (Fig. 4a) with brisk inflammatory response at the microscopic level (Fig. 4b), supporting the idea that an intact immune system leads to relatively robust enhancement, while the lack of a host response and inflammation may lead to weaker enhancement [10]. In some cases, enhancement may be absent altogether despite large, aggressive lesions (Fig. 2).

Differential Diagnostic MRI Features of Non-fungal Entities

Many entities can have a similar appearance to fungal infection. Table 1 summarizes major differential diagnostic features that may suggest non-fungal entities.

Review of Specific Infections

Aspergillosis

Aspergillus is a saprophytic opportunistic fungus found in soil and on plants. It is a mold on decaying organic material [11]. It has septate (cross-walled) branching hyphae that show dichotomous (i.e., "Y" shaped) branching, and irregular, non-parallel cell walls (Fig. 4b, c). It produces numerous spores. It is not dimorphic. Infections are usually caused by *Aspergillus fumigatus*.

Risk factors include immunosuppression of any form, although fungal infection in HIV patients is somewhat uncommon because of relative sparing of polymorphonuclear cell function [9]. Patient presentation is variable, but can include altered mental status (AMS), weakness, and seizures. Fevers may or may not be present [12–14]. Mortality rates were near 100% regardless of therapy in the past but have greatly improved with early aggressive antifungal therapy and surgical resection [2, 3, 9, 13, 15–21]. Voriconazole and amphotericin B are first-line agents, while caspofungin is second line.

Hematogenous spread from the lungs is common [22], but less than half of patients have documented co-existing lung lesions [23].

Aspergillus has a characteristic intermediate to low peripheral T2 signal intensity with central hyperintensity in a target-like pattern (Fig. 5b), likely reflecting increased iron related to peripheral fungal elements, hemorrhage, and possibly due to ferromagnetic elements related to fungal metabolism, including calcium and manganese [10, 24–26].

Aspergillus species are angioinvasive [22]. They produce the enzyme elastase and digest the internal elastic lamina of arteries (all sizes), leading to focal microhemorrhage [27]. Digested, weakened walls also allow mycotic aneurysm formation and subarachnoid hemorrhage, which are common in aspergillosis; their presence should prompt institution of antifungal therapy in immunocompromised patient populations when the clinical picture suggests infection. Fungal elements can also fill vessels, leading to occlusive thrombosis, embolism, and infarction with hemorrhagic transformation (Fig. 5). Likely owing to a predilection for perforating arteries, aspergillosis commonly involves the basal ganglia, thalamus, and corpus callosum. Aspergillus elements at these sites block the origins of small perforating arteries and cause sterile infarction [8]. Because infarction of the corpus callosum is not typically seen in thromboembolic infarction or pyogenic infection, when present, it suggests aspergillosis (Fig. 3c) [8], though this finding is present in a minority of cases [28]. Breakdown of brain tissue at sites of infarction leads to direct fungal extension into surrounding brain [9, 14, 16, 22, 29, 30]. Thus, aspergillus vasculopathy/vasculitis-mediated septic infarction often leads to hemorrhage and rapid extension of infection into the surrounding tissues with associated cerebritis and abscess formation.

The high viscosity and cellularity of *Aspergillus* pus can lead to reduced diffusion, although infarcted tissue and cerebritis can also contribute to reduced diffusion seen in aspergillosis. Often the lesion center is hypointense on DWI surrounded by hyperintense tissue on DWI with low ADC values, giving a typical ring pattern of reduced diffusion (Fig. 3b). Weak ring or no enhancement is most common [8], and this is an important diagnostic clue [30]. When present, ring enhancement can correlate with capsule formation from chronic inflammation and production of granulation tissue on pathologic examination [7].

Meningitis and ventriculitis are also common though often radiographically occult and only seen with pathologic examination on autopsy [8]. Ependymal enhancement is distinctly uncharacteristic, and often the only clue to meningitis/ventriculitis is hydrocephalus or ventricular asymmetry (Fig. 3c) [8].

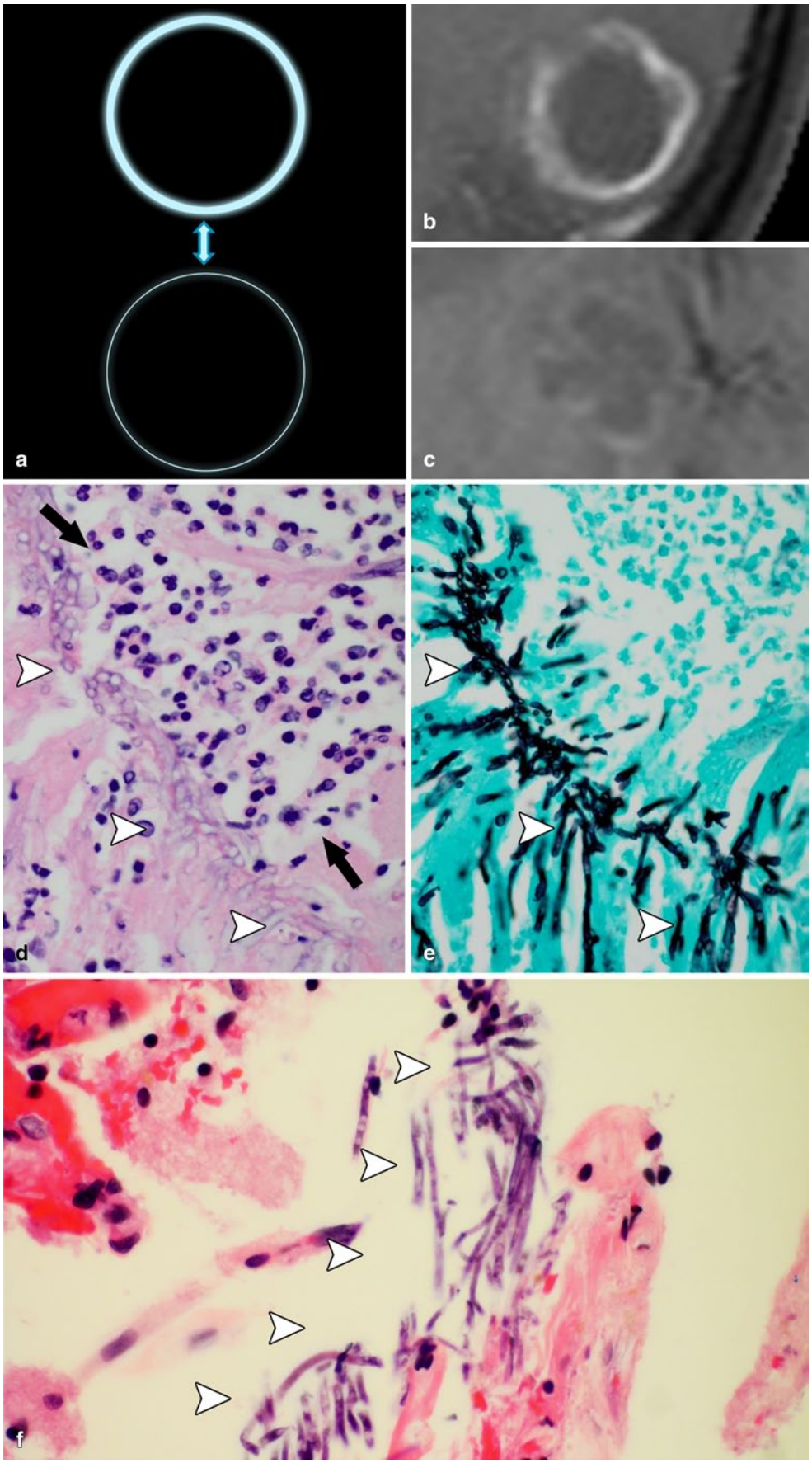

Fig. 4 "Weak ring" enhancement in fungal infection may be explained by the relative lack of inflammatory response. **a** Illustration showing typical thick ring of bacterial (*top*) and weak ring of fungal enhancement (*bottom*). **b** Post-contrast T1 image shows thick ring enhancement more typical of bacterial abscess in a relatively healthy patient with presumably relatively preserved immune function who developed aspergillosis while on corticosteroid taper for acute alcoholic hepatitis, compared with **c** typical weak ring enhancement in a patient with leukemia who developed aspergillosis while receiving corticosteroids. The microscopic findings mirror these findings, with photomicrographs **d** [original magnification 400×; Periodic acid–Schiff (PAS) stain] and **e** [original magnification 400 ×; Grocott's methenamine silver (GMS) stain] from the patient shown in Fig. 4b showing brisk polymorphonuclear and giant cell aggregation (between arrows) adjacent to fungal elements with septate branching hyphae (arrow heads), in contrast to **f** (original magnification, 400×; PAS stain) from the patient shown in Fig. 4c with fungal elements (arrowheads) but lacking any associated inflammatory response

Table 1 Common entities that have a similar appearance to fungal infection and their differential diagnostic features

Major differential diagnosis	Differential diagnostic features
Brain metastasis	Thicker ring enhancement. Usually no reduced diffusion in the necrotic center
Infarction	Gyral enhancement or no enhancement. Distribution conforms to a vascular territory
Bacterial abscess	Thicker ring enhancement. Reduced diffusion in the necrotic center
Toxoplasmosis	Thicker ring enhancement. Usually no reduced diffusion in the necrotic center
Demyelinating lesion	Incomplete ring enhancement. Usually no reduced diffusion or leading-edge reduced diffusion
Enlarged perivascular space	No enhancement, characteristic distribution

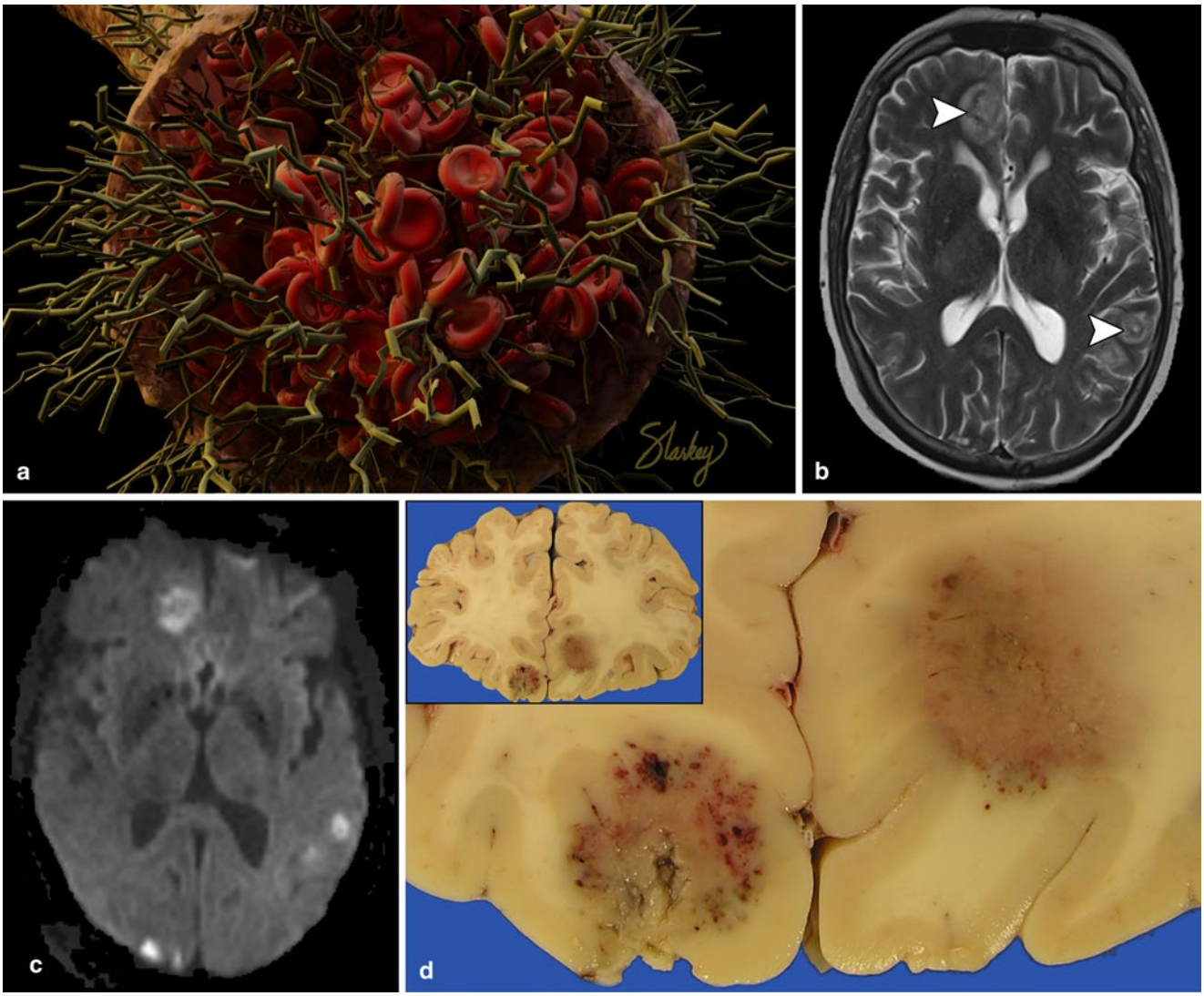

Fig. 5 *Aspergillus* species are often angioinvasive, multiplying within blood vessels and producing artery-destroying elastases with resultant microhemorrhage and infection of adjacent brain parenchyma. Fungal elements also clog vessels and cause downstream sterile infarction. **a** Illustration shows angioinvasive nature of *Aspergillus* with fungal elements in the vessel lumen and hypha invading through the vessel wall. **b** Axial T2 sequence shows characteristic peripheral low intensity (*arrowheads*), which may be due to hemorrhage and increased iron due to fungal elements and hemorrhage. **c** Axial diffusion-weighted sequences show magnetic susceptibility artifact indicating microhemorrhage and reduced diffusion indicating infarction in lesions at the gray–white junction. **d** Gross pathologic examination shows corresponding lesion with peripheral hemorrhage and central necrosis. (Post-contrast image shown in Fig. 1a.) The patient was a 56-year-old woman with acute myelogenous leukemia who developed widely disseminated multiorgan aspergillosis while receiving corticosteroids status after allogeneic grafting. She died soon after

Aspergillosis also affects the sinuses and is the most common cause of fungal sinus infection. Like the peripheral low T2 hyperintensity of intracranial lesions, fungal sinusitis has a characteristic low T2 hyperintensity, but diffuse rather than peripheral [10, 24–26]. Intracranial extension (invasive sinus aspergillosis) is often not visible or subtle

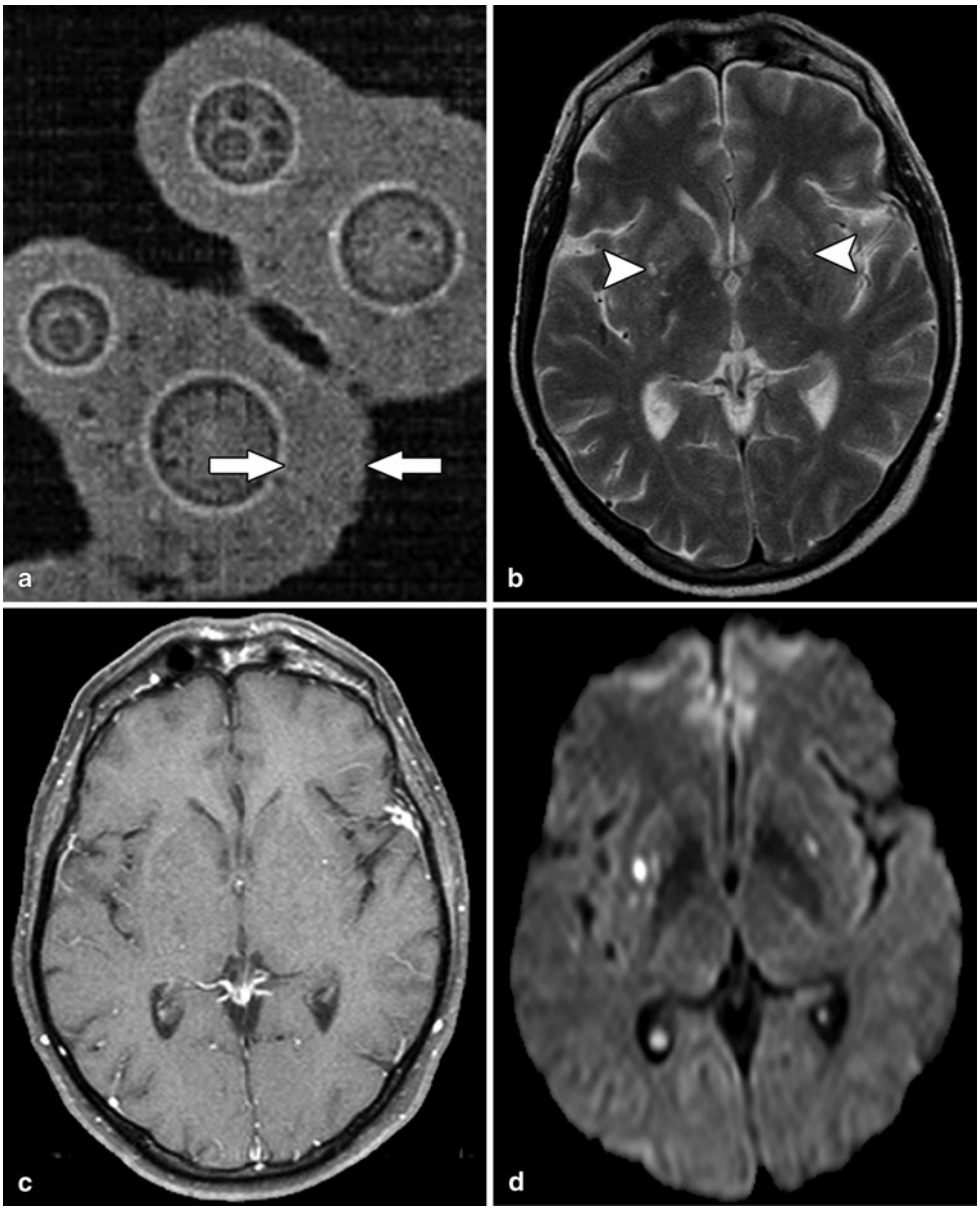

Fig. 6 *Cryptococcus* CNS infection leads to meningitis or cryptococcoma formation. **a** Transmission electron micrograph shows hydrated thick capsule (*white arrows*) of *Cryptococcus* organisms (adapted with permission from Hurst et al. [29]). The forms stain positive with mucicarmin, indicating they have a mucopolysaccharide (mucin) capsule (not shown). **b** Axial T2 sequence shows hyperintense punctate lesions within the ganglia (*arrowheads*) with fluid-attenuated inversion recovery (FLAIR) nonsuppression (not shown). **c** Axial T1 post-gadolinium sequence shows no enhancement, typical of cryptococcal infection. **d** Axial DWI shows reduced diffusion within the basal ganglia. The patient was a 40-year-old HIV-positive man with a CD4 count of 22 and viral load of 1.3 million. Serum was positive for cryptococcal antigen. The patient died several months after the scan

on MRI in the early stages [3, 13, 19, 31, 32]. When present, intracranial granuloma formation affords poor antifungal penetration because of dense fibrosis [27].

Cryptococcosis

Cryptococcus neoformans is an encapsulated, yeast-like fungus that is found in animal droppings, notably from pigeons and other birds, but also some mammals [11]. Outside of an animal host, *C. neoformans* forms sexual spores or yeast cells that become dehydrated and weakly encapsulated. The capsule is composed of a high-molecular-weight polysaccharide that, when rehydrated within a host, thickens and gives rise to its macroscopic gelatinous features (Fig. 6) [33].

The strongest risk factor for infection is T-cell dysfunction, namely HIV. However, up to a third of patients have no identifiable pre-existing illness [34]. Patients typically present with AMS, headache, lethargy, or seizures. While untreated infection is always fatal, with treatment, mortality is relatively low compared with other fungal infections, limited to 15–30 % with modern antifungal therapies [33].

The *C. neoformans* spores in the dehydrated state are small enough to be inhaled and cause an asymptomatic lung infection followed by meningitis. The CNS is thought to be a preferred site of infection because anticryptococcal antibodies are absent there [35].

The brain regions most commonly affected are the basal ganglia and meninges [27, 36]. While meningitis is more common overall, in the basal ganglia, localized pockets of

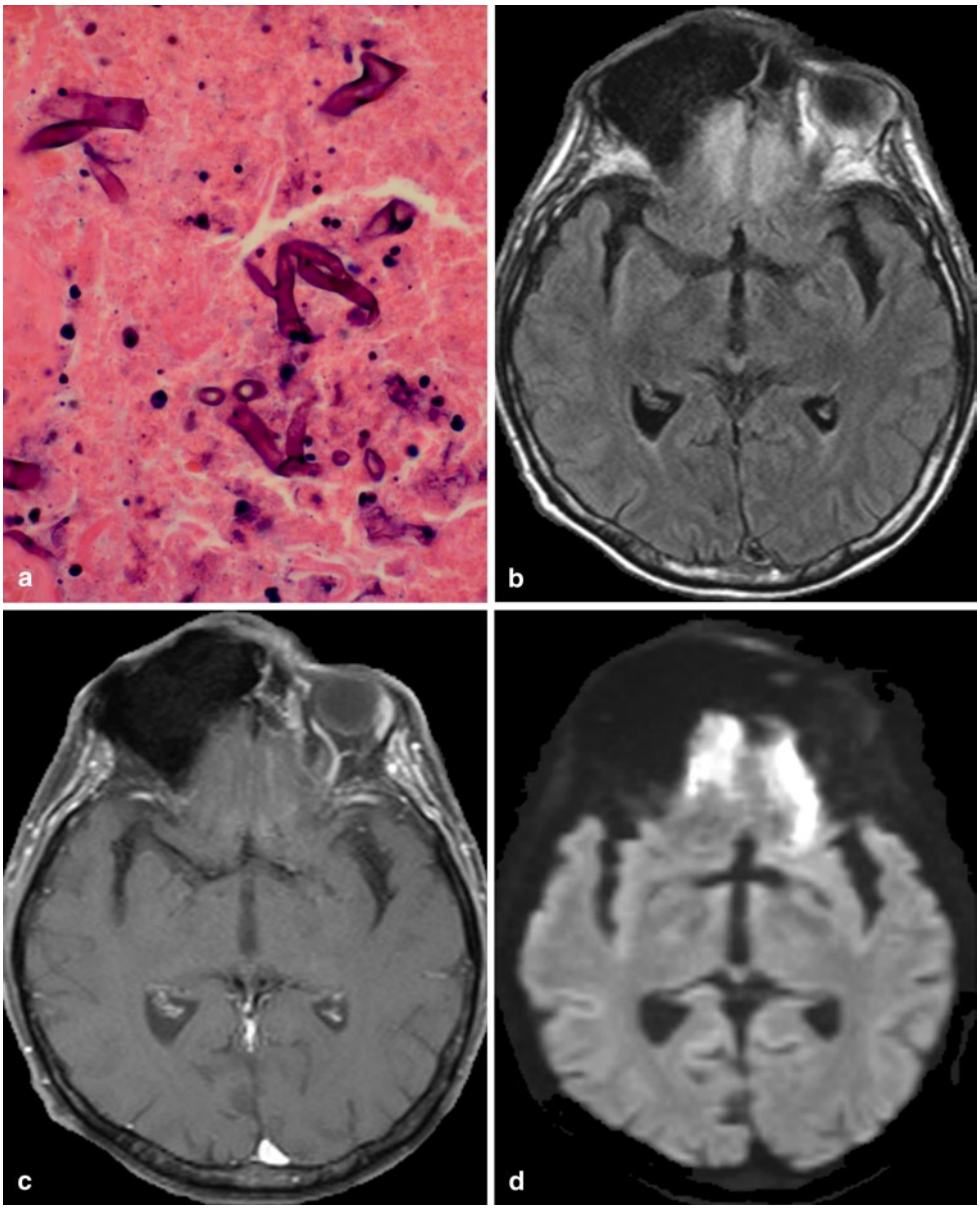

Fig. 7 Typical gyrus rectus involvement in mucormycosis. **a** Photomicrographs (original magnification, 400×; PAS stain) show fungal forms with broad, pleomorphic hyphae that branch at right angles in a background of necrotic brain tissue and occasional red cells. No abscess wall is apparent. **b** Axial FLAIR imaging in the same patient shows areas of hyperintensity within the bilateral gyrus recti. **c** Axial T1 post-gadolinium sequence shows minimal enhancement, while **d** axial DWI shows markedly reduced diffusion. Patient is a 47-year-old man with a history of diabetes mellitus type I who developed diabetic ketoacidosis (DKA). He originally presented with fevers, headaches, and cranial nerve (CN) III palsy with right facial swelling. He was diagnosed with maxillary and ethmoid sinus infection that did not respond well to therapy or aggressive surgical measures. The patient died 14 days after imaging was obtained

organisms up to several millimeters in size may develop with a pathognomonic appearance of gelatinous pseudocyst formation, known as a cryptococcoma [36, 37]. Gelatinous pseudocysts are T1 hypointense. T2 imaging shows a hypointense ring surrounding a hyperintense center (Fig. 6b). The outer hypointense ring likely represents methemoglobin blood products in the capsule wall or activated macrophages producing free radicals and paramagnetic susceptibility artifact [38]. The pseudocyst center often lacks enhancement owing to its avascular nature (Fig. 6c) and may or may not cause reduced diffusion (Fig. 6d). A large pseudocyst may convert into a frank abscess with enhancement and reduced diffusion.

Mucormycosis

Mucormycosis is caused by molds belonging to the *Mucor*, *Rhizopus*, and *Absidia* genera [39]. These ubiquitous pathogens infect humans through spore inhalation. Within tissue, they grow as non-septate molds and have right-angle branching and irregular, non-parallel cell walls (Fig. 7a) [3, 40]. Like *Aspergillus*, they are monomorphic.

Risk factors for mucormycosis include diabetes, acidosis, steroid use, hematologic malignancy, solid organ transplantation, neutropenia, and renal failure [40, 41]. Rhino-orbital-cerebral mucormycosis develops when inhaled spores infect the paranasal sinuses and extend into the orbits, optic nerves, oral cavity, and cranium. With CNS involvement, mortality rates are greater than 70% [40, 41], but early initiation of

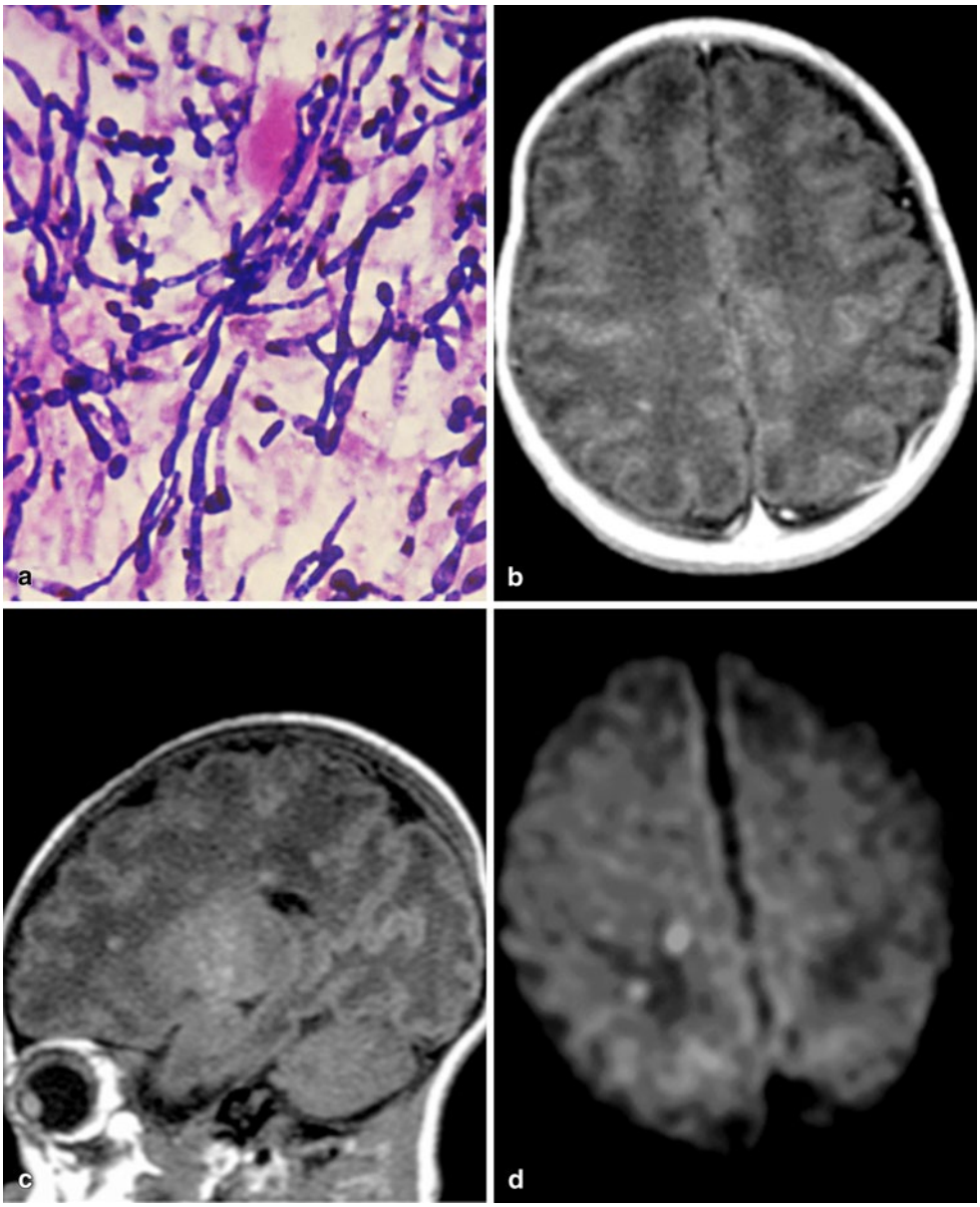

Fig. 8 Cerebral candidiasis usually appears as microabscesses measuring less than 3 mm. **a** Photomicrograph (original magnification, 600×; PAS stain) shows rounded bodies with some pseudohyphae typical of *Candida* species (courtesy of Centers for Disease Control (CDC)/Sherry Brinkman). **b**, **c** Axial and sagittal T1 post-gadolinium sequences show punctate subcortical foci of enhancement. **d** Axial DWI shows reduced diffusion of multiple lesions, including several not seen on contrast-enhanced sequence. The patient was a 6-year-old boy with meconium ileus who developed lethargy

antifungal agents combined with aggressive surgical resection can improve outcomes [6].

CNS infection almost always involves the frontal lobes (Fig. 7b–d); any lesion of the frontal lobes in an immunocompromised patient, especially in an inferior location, should raise suspicion of mucormycosis (along with aspergillosis). Although lesions may be bilateral, unilateral lesions are also seen. As with aspergillosis, blood vessels become infected with a tendency to cause infarction [27]. Bony erosion is also common.

Lesions have a variable appearance on T2-weighted imaging and can be hypo- to hyperintense (Fig. 8b) [42]. Contrast enhancement of the involved sinuses and orbits is common (Fig. 8c). DWI often shows markedly reduced diffusion (Fig. 7d) [43–46].

Candidiasis

Candida species are small, round to oval, thin-walled, yeast-like fungi that lack a sexual cycle and reproduce by budding or fusion (Fig. 8a) [47]. Pseudohyphae predominate, but occasionally true hyphae are also seen. While candidal infections are most commonly caused by the albicans species overall, roughly half of infections are caused by other species including *Candida glabrata* and *Candida parasilosis* [48].

Risk factors for candidiasis include treatment for bacterial sepsis, intravenous hyperalimentation, HIV infection with low CD4 count (<135/mm^3), immunosuppression, hematologic malignancy, and prematurity [48, 49]. The clinical presentation is variable but generally includes lethargy and AMS with insidious onset. Infection of the CNS is almost

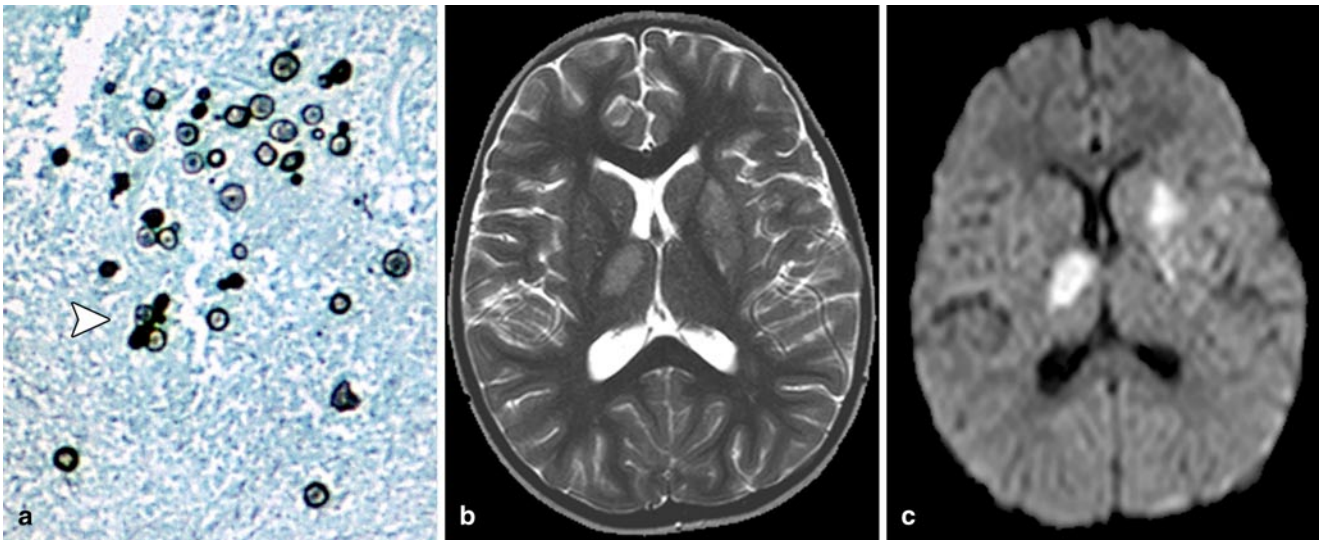

Fig. 9 *Coccidioides* CNS infections are rare and generally occur only in endemic regions of the southwestern USA. **a** Photomicrograph (original magnification, 400×; GMS stain) shows rounded spherules of *Coccidioides immitis* (*arrowhead*) (courtesy of CDC/Martin D. Hicklin). **b** Axial T2-weighted sequence shows hyperintensity in the right globus pallidus and left putamen with mild narrowing of the left lateral ventricle. **c** Axial DWI shows reduced diffusion in a similar distribution. Contrast-enhanced imaging was not performed. The patient was a 4-year-old girl with a history of recurrent rashes who had a sudden onset of acute neurologic deficits following 3 days of nausea, vomiting, and dehydration with persistent headaches and "fuzzy" vision. The patient developed low-grade fevers. CSF fungal cultures grew *Coccidioides immitis*. The patient was living in the midwestern USA and had no history of travel to endemic areas. She was later diagnosed with hyper-IgE-related immunodeficiency. She developed frank ventriculitis requiring shunt placement and did well with antifungal therapy

always caused by hematogenous spread with disseminated systemic infection. Mortality rates for cerebral candidiasis are unknown but likely high given the high mortality rates for candidal sepsis in general [48, 49, 50].

While frank abscess formation and meningitis do occur [51], numerous microabscesses of less than 3 mm occurring at the corticomedullary junction, basal ganglia, or cerebellum are most common, often with enhancement (Fig. 8b, c) and less often with associated hemorrhage or infarction [52]. The lesions are T1 hypointense and T2 variable. Reduced diffusion is also variable but may be more prominent than enhancement (Fig. 8d). Diagnosis is usually not a dilemma because the patient will usually develop the microabscesses in the setting of known candidal fungemia.

Coccidioidomycosis

Coccidioides immitis is a fungus found in the soil and endemic to the southwestern USA and northern Mexico. It produces spores (Fig. 9a) and is dimorphic [53].

Because the *C. immitis* is geographically limited to the southwest USA, the strongest risk factor is living in an endemic area. Pulmonary infection is common, while CNS involvement is distinctly uncommon, and only a few cases of CNS infection are reported in the literature [54–56]. Patients usually present with headaches, lethargy, and fevers. CNS involvement is usually secondary to hematogenous dissemination from the lungs.

The meninges is the most common site of infection [53], but parenchymal infection is also seen (Fig. 9b, c). Approximately 4–5% of symptomatic patients may develop disseminated disease with high morbidity and mortality, with dissemination more common in immunocompromised patients [53].

Contrast enhancement of the basal cisterns is typical in coccidioidomycosis meningitis [54]. DWI with peripheral lesion restriction has been reported [55].

Blastomycosis

Blastomycosis is caused by the dimorphic fungus *Blastomyces dermatitidis*. It exists as a mold in the environment and a yeast at body temperatures (Fig. 10a) [57].

Infections are usually sporadic. The only recognized risk factor is living in endemic areas of the midwestern USA, classically near the states surrounding the Ohio or Mississippi river [57]. Presentation is non-specific with headache, AMS, fever, vision changes, and seizures. The lungs are affected most often following introduction of spores by inhalation. However, the organism can infect the skin, genitourinary system, and CNS, and isolated CNS infection can be seen in patients with diabetes or immunosuppression [58].

The few available case reports suggest that leptomeningeal enhancement and enhancing mass lesions are com-

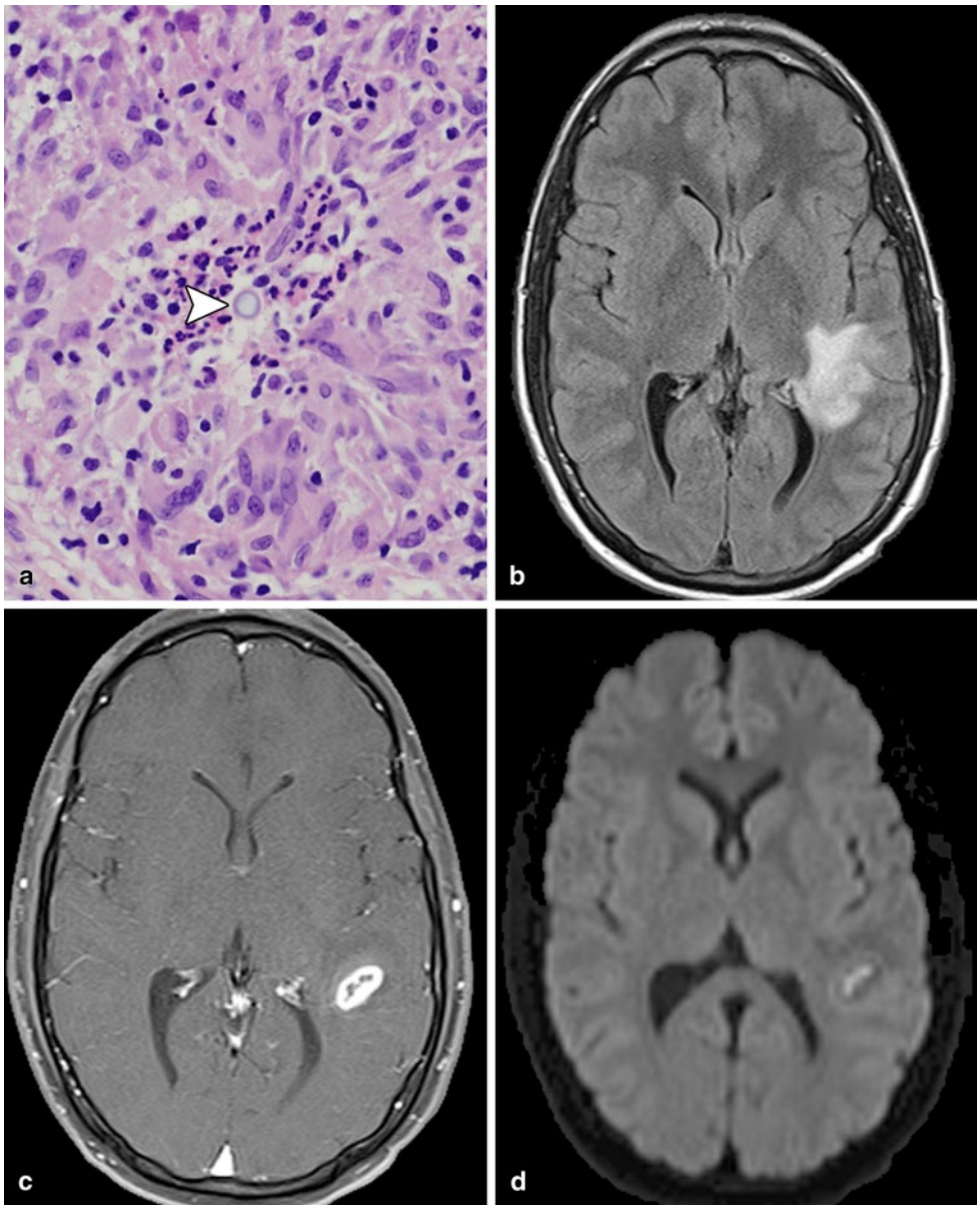

Fig. 10 *Blastomyces* CNS infections are rare and generally only occur in endemic regions of the midwest USA. **a** Photomicrograph (original magnification, 600×; PAS stain) shows granulomatous inflammation with central neutrophils surrounding a single fungal form in the center of the image to form a granuloma. **b** Axial FLAIR sequence shows hyperintensity within the left temporal lobe. The lesion exerts minimal mass effect on the posterior horn of the left lateral ventricle. **c** Axial T1 post-gadolinium sequence shows thick ring enhancement. The patient was a 17-year-old boy living in the midwestern USA with a history of extensive pulmonary blastomycosis 2 years prior and who was in his usual state of health when he developed acute-onset neurological symptoms followed by seizure. He had no known immunodeficiency. **d** Axial DWI shows mild central reduced diffusion

mon (Fig. 10b) [58, 59]. Reduced diffusion may be central (Fig. 10c).

Histoplasmosis

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. Like *Blastomycoses*, *Histoplasma* exists as a mold in the environment and yeast at body temperatures (Fig. 11a) [57].

As with *Blastomycoses*, *Histoplasma* infections are usually sporadic, and the only consistent risk factor is living in endemic areas of the midwestern USA. Patients with AIDS are prone to developing disseminated histoplasmosis [57], with 5–10% of cases progressing to CNS involvement. Patients may present with confusion, lethargy, weakness, and fevers [60].

Lesions, also known as "histoplasmomas," tend to be small (<2 cm) and round with peripheral ring enhancement (Fig. 11b) [60–63]. Lesions can be singular but are more often multifocal (cerebral histoplasmosis) and may occur in subcortical gray matter structures, the gray–white junction, the cerebellum, the brain stem, or the spinal cord. The lesions are T1 hypointense and T2 variable. Reduced diffusion may show various signals depending on the presence of inflammatory cells and the type of necrosis (e.g., coagulative or liquefactive; Fig. 11c). Diffuse meningitis has also been described [64].

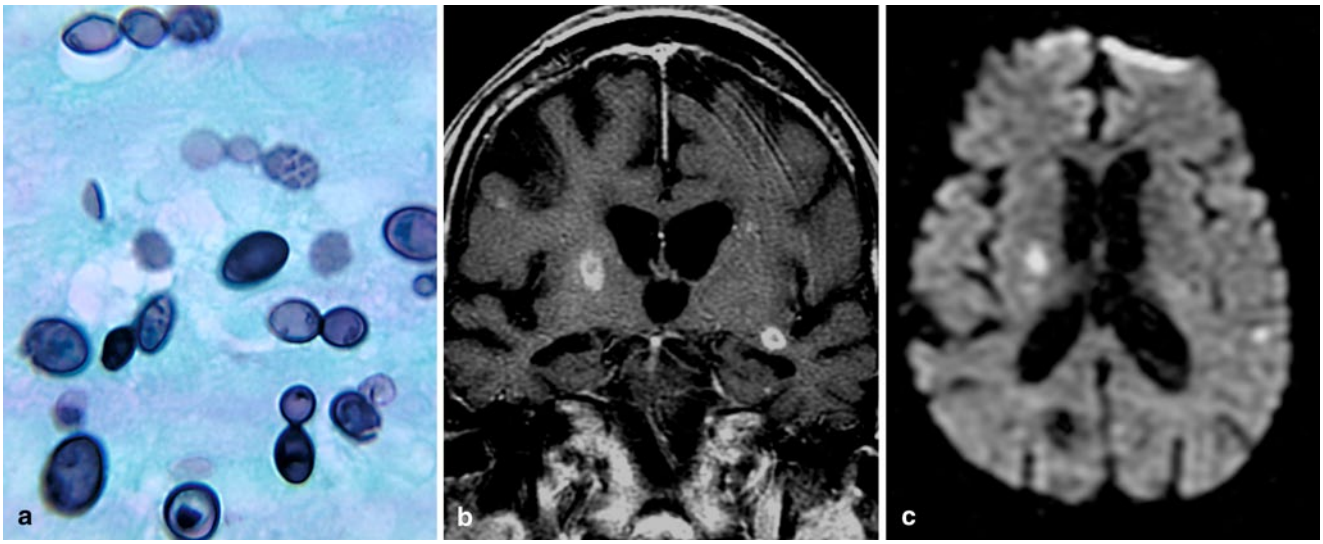

Fig. 11 Cerebral histoplasmosis with multifocal rounded ring-enhancing lesions. **a** Photomicrograph (original magnification, 600×; MAS stain) shows budding yeast forms of *Histoplasma capsulatum* (courtesy of CDC/Martin L. Ajello). **b** Post-contrast T1 image shows basal ganglia and left parietal ring-enhancing lesions. **c** DWI shows punctate central restriction. The patient was an 80-year-old man with diabetes and alcoholism who presented with subacute cough, fever, and mental status changes. Chest CT revealed a 2-cm cavitary lung lesion (not shown)

Conclusions

Fungal CNS infections are relatively rare infections that occur almost exclusively in immunocompromised patients. MRI findings such as weak ring enhancement and reduced diffusion can help suggest the diagnosis, with additional features like lesion distribution sometimes enabling specific diagnosis. Recognition of characteristic imaging findings is imperative to enable early treatment of these otherwise rapidly fatal infections.

Conflict of Interest The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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