American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2023; 24: e939241
DOI: 10.12659/AJCR.939241

Received: 2022.12.14
Accepted: 2023.01.23
Available online: 2023.02.09
Published: 2023.02.23

Nodulisporium Fungal Brain Abscess In Early Post-Renal Transplant: A Rare, Unexpected, Mysterious Pathogen

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Financial support: None declared
Conflict of interest: None declared

Patient: Male, 34-year-old
Final Diagnosis: *Nodulisporium* brain abscess
Symptoms: Fatigue • headache
Clinical Procedure: CT brain • MRI brain
Specialty: Infectious Diseases • Nephrology

Objective: Rare disease

Background: Central nervous system fungal infections are rarely encountered in current medicine, with fungal abscesses even less commonly seen. Clinical entities and their development largely depend on the interplay between the host's immune system and fungal virulence factors. Due to the large size of fungal organisms, they are prevented from entering the meningeal circulation. Hence, they cause focal diseases like cerebritis, abscesses, vasculitis of larger vessels, vascular occlusion, cerebral infarcts, and aneurysms.

Case Report: A 34-year-old male patient of Indian descent diagnosed with stage 5 chronic kidney disease, bilaterally small kidneys, and hypertension underwent cadaveric renal transplantation and subsequent immunosuppression. Three months later, he returned with complaints of high-grade fever with chills and rigor, along with massive headaches. Plain brain computed tomography showed an intra-axial heterogeneously hypodense area with a hyperdense rim in the right temporal lobe. MRI revealed a well-defined enhancing lesion with irregular crenated margins and satellite lesions. Abscess wall biopsy showed fragments of hyaline septate filamentous fungal hyphae. Craniotomy with excision and drainage of the abscess was done and sent for histopathological examination along with culture. The results showed the growth of *Nodulisporium* fungus. The patient was then managed on amphotericin B and voriconazole for completion of treatment.

Conclusions: This is the first case reported of a *Nodulisporium* species fungal abscess developing in the brain after cadaveric kidney transplantation. Urgent evaluation via imaging and biopsy is crucial in determining the exact causal organism of brain abscesses, which can lead to better patient outcomes.

Keywords: Brain Abscess • Kidney Transplantation • Meningitis, Fungal

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/939241

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Background

Organ transplantation has always been a standard therapeutic intervention in patients with end-stage organ failure. Renal transplants are widely carried out around the globe with high success rates. A major challenge faced by medical practitioners is overcoming post-transplant infections, which tend to occur due to the highly immunosuppressed state of the patient. Various regimens consisting of various drug combinations are accepted as standard practice. Infections developing in such patients tend to have a high overall mortality rate.

Fungi are ubiquitous organisms that tend to drastically alter the post-transplant patient status [1]. Overall mortality due to invasive fungal infections (IFIs) in solid-organ transplant recipients varies and depends on individual patient profiles. The risk of such infections following renal transplant is related to the dosage of immunosuppressive agents, environmental factors, and post-transplant duration. Most fungal infections occur in the first 6 months after transplant due to the use of numerous immunosuppressors. *Candida* spp. and *Cryptococcus* spp. are the yeasts most frequently isolated, while the most frequent filamentous fungi (molds) isolated are *Aspergillus* spp. [2]

Brain-specific fungal infections are rarely seen, and when they do occur, the larger morphology of fungal organisms precludes their entry into the meningeal microcirculation. This results in a more focal disease when fungi are seen in the central nervous system (CNS), leading to cerebritis, abscess formation, or involvement of larger vessels resulting in vasculitis, vascular occlusion, cerebral infarctions, or mycotic aneurysms.

The CNS may be invaded by some pathogenic fungi that show neurotropism and ability to invade to establish an infection. The etiological agent described in our case is *Nodulisporium* species. To date, only 1 case of invasive *Nodulisporium* has been previously reported as an agent of CNS infection in humans, ours being the second. Cox et al reported the first allergic fungal sinusitis case, with a persistent *Nodulisporium* species isolated from mucus in 1994, but did not mention any signs of fungal tissue invasion [3].

Case Report

A 34-year-old male patient with comorbid hypertension was diagnosed with stage 5 chronic kidney disease. He had bilaterally small kidneys on imaging. A cadaveric renal transplantation was carried out, and he was subsequently put under anti-thymocyte globulin (ATG) and triple immunosuppression therapy consisting of low-dose cyclosporine, azathioprine, and prednisone. Three months after the transplant, he returned and presented with complaints of a high-grade fever associated with chills and rigor and a holocranial headache for the previous 2 days. There was no history of nausea/vomiting, blurring of vision, seizures, bowel/bladder dysfunction, or behavioral changes. Physical examination was otherwise unremarkable. No overt signs of meningeal irritation and no focal neurological deficits were seen in the patient. Fundoscopic examination also revealed no papilledema. All his vital signs were stable. Initial radiological tests, including chest X-ray and echocardiography, were normal. A routine blood and biochemistry panel consisting of elements including basic liver and kidney function tests showed no abnormal values.

A plain computed tomography (CT) scan of the brain was conducted, which showed an intra-axial heterogeneously hypodense area with a hyperdense rim in the right temporal lobe measuring around 3×2×2 cm with surrounding perilesional edema. A mass effect was noted in the form of effacement of adjacent sulci and compression of bilateral third and lateral ventricles. MRI (plain and contrast) revealed a well-defined enhancing lesion with irregular crenated margins in the right temporal lobe, along with satellite lesions showing blooming foci and a mass effect. This was associated with ventriculitis and meningitis. Magnetic resonance spectroscopy showed a lipid lactate peak with N-acetyl aspartate (NAA) level reduction (**Figures 1, 2**).

A decision was made to biopsy the lesion, and microscopy of the abscess wall showed areas of necrotic cell debris, granulation tissue, lymphoplasmacytic infiltrate, and fragments of hyaline septate filamentous fungal hyphae that were periodic acid-Schiff (PAS) and Gomori's methenamine silver (GMS) positive. Also present in the biopsy sample were foreign body giant cells, congested blood vessels, reactive gliosis, and hemorrhage.

A right temporal craniotomy with excision and drainage of the abscess was carried out, and the specimen was sent for histopathological examination along with culture (**Figures 3, 4**). This was suggestive of a fungal brain abscess. Mycological culture of the abscess fluid showed growth of *Nodulisporium* species. The patient was then managed on amphotericin B and voriconazole. He showed significant symptomatic improvement with no further complications and was subsequently discharged. The patient was subsequently kept on followup with strict monitoring of any new symptoms, along with kidney status monitoring. There were no further complications.

Discussion

A brain abscess is a focal suppurative process of variable size that develops within the brain parenchyma and is surrounded by an inflammatory exudate. In the immunocompetent host, brain abscesses are usually bacterial. They consist of a central

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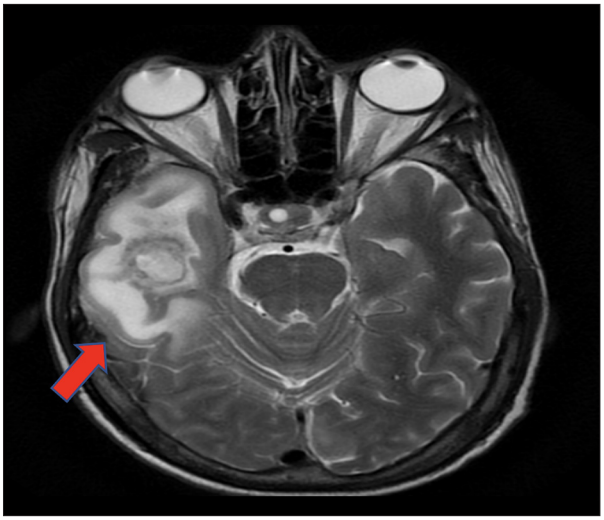

Figure 1. Brain MRI scan report. The red arrow points to a right-sided temporal lobe lesion (abscess). MRI – magnetic resonance imaging.

Figure 2. Brain CT scan report. The yellow arrow points to a right temporal lobe lesion. CT – computed tomography.

area of necrotic debris and leukocytes with a fibroblastic capsule surrounded by cerebritis and perivascular infiltrates. In the immunocompromised host, however, fungal brain abscesses predominate and usually originate via hematogenous spread from a primary invasion site. Under a microscope, the picture resembles arteritis with vessel thrombosis and obliteration leading to ischemic/hemorrhagic infarct [4].

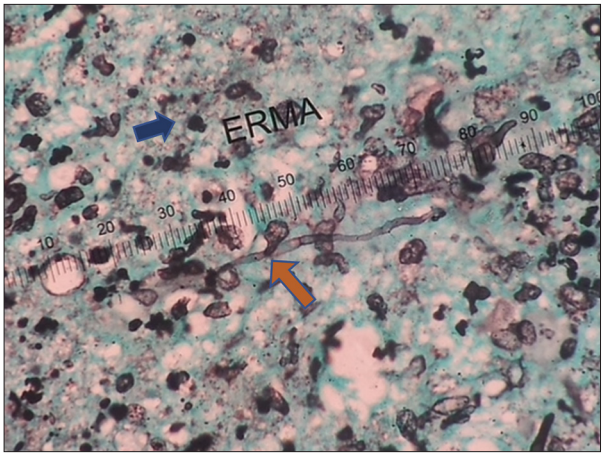

Figure 3. Histopathology slide with GMS staining. The orange arrow points to the hyaline septate filamentous fungus. The blue arrow points to foreign body giant cells in the background with granulation tissue and necrotic cell debris. GMS – Gomori's methenamine silver.

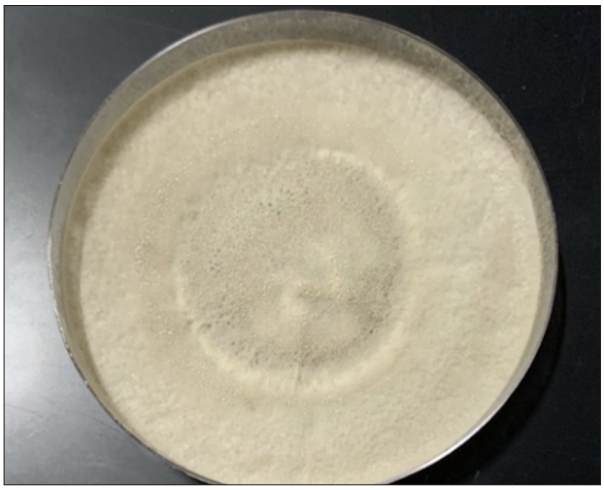

Figure 4. *Nodulisporium* species grown on Sabouraud dextrose agar after 7 days incubation at 28°C.

A CT scan usually reveals multiple low-density, non-enhancing lesions most frequently located in the CNS regions of the basal ganglia and cerebral hemispheres. In our case, the lesion was restricted to the right temporal lobe with surrounding tissue changes like edema and vasculitis. The criterion standard for reliable diagnosis is a biopsy with histopathological and tissue analysis. Due to the high virulence of fungal CNS-targeting organisms, complete and successful treatment remains a challenge. The tendency to occlude blood vessels, leading to difficulty delivering antifungal agents to infected brain tissue, adds to morbidity and the risk of mortality. Established CNS fungal abscesses are therefore considered a surgical emergency and end up being fatal in most cases. In those who survive, there may be a high risk of neurological sequelae [5].

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Host and environmental factors are critically essential determinants in the epidemiology of fungal infections following transplantation. The highest risk is in small bowel (11.6%) and lung (8.6%) transplants, followed by liver (4.7%), heart (4.0%), pancreas (3.4%), and kidney (1.3%) transplants [6]. Drug-induced immunosuppression given post-kidney transplantation is a well-known risk factor for fungal infections.

Nodulisporium species comprise a small proportion of the fungal biota. This genus is most closely related to *Geniculosporium*, *Hansfordia*, and *Calcarisporium*. It is a dematiaceous fungus not usually known to cause human disease or infections. A case report published in 1994 by Cox et al [7] revealed this organism to be the causal agent of allergic fungal rhinosinusitis in a young woman. From the many subdivisions of organisms that affect the CNS, the following 2 are caused by dematiaceous species:

1. Rhinocerebral phaeohyphomycosis- typically a secondary infection from airborne conidia that germinates in body sinuses to eventually land and grow into the brain (cerebral involvement is usually secondary in nature)
2. Cerebral phaeohyphomycosis- typically a primary infection by fungus located exclusively inside the brain parenchyma, with the first symptoms being related to cerebral dysfunction.

Lungs are the most common primary site of infection in cases of fungal spread to the brain via blood route transportation [8]. Principal pathogens causing these infections are *Aspergillus* and *Candida* species, but the isolation of endemic fungi and other opportunistic molds is not unusual [9].

Patients who have undergone kidney transplantation under immunosuppression must be kept under close followup and be advised to return immediately at signs of any symptoms like fevers, headaches, or seizures. If an abscess is suspected on imaging, surgery plays a crucial role in obtaining tissue for histopathology and culture. Based on laboratory reports, appropriate therapeutic treatment may be started that targets the causative organism. Therapy should be continued until complete radiographic resolution occurs or there is evidence of halted progression on repeat MRI scans spanning a significant time period.

Interesting to note is the fact that the treatment of a fungal brain abscess tends to differ from that of a bacterial brain abscess. Surgical excision, which is usually performed for a bacterial abscess, may prove less effective for fungi since fungal hyphae are known to penetrate and extend beyond the fibrous capsule, making surgical resection complicated [10].

In our case, the *Nodulisporium* brain abscess was the only significant post-renal transplant pathology seen. There was no evidence of sinusitis or any underlying CNS disease before the infection establishment and no lesion outside the CNS that could have served as a potential primary source. The entry portal of infection and mode of invasion into the CNS has yet to be determined with certainty.

Conclusions

Nodulisporium fungal brain abscess is an extremely rare complication following kidney transplantation. Fever and altered mental status are the most common clinical findings in such CNS infection cases. Our case is only the second *Nodulisporium* fungal brain abscess to be reported in the literature, and the first to be reported to occur within 3 months after kidney transplantation. The role of biopsy and histopathological examination culture has been emphasized, to lead to a definitive diagnosis that can indicate targeted treatment.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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