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CNS Aspergilloma with associated mucormycosis presenting in a patient with AML: A case report and review of current literature

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Abstract

Introduction

Aspergillus species are ubiquitous fungi in the environment and are readily acquired through inhalation. Immunocompromised individuals are at particularly high risk of progressing to invasive fungal infections following inhalation. It can present with deep-seated invasive infections in immunocompromised hosts such as those with HIV/AIDS and acute leukemias.

We describe here a case of CNS Aspergilloma and phycomycosis resembling Mucor presenting as homonymous hemianopsia due to an occipital mass in a patient with a history of Acute Myelogenous Leukemia (AML).

Case presentation

Our patient is a 64-year-old white male with a past medical history of acute myeloid leukemia (AML), currently in remission who presented from his ophthalmologist with left sided visual disturbances and facial numbness. He was found to have retinal hemorrhages and left sided hemianopia. An MRI brain showed an enhancing right occipital mass measuring 2.5x2.1x1.8cm with surrounding vasogenic edema. The initial differential diagnosis was broad, ranging from infectious, benign to malignant causes. Of note, he had a history of invasive pulmonary aspergillosis during his induction phase of chemotherapy for AML which was promptly treated. This time, he was empirically started on liposomal amphotericin B while awaiting results of the biopsy. Biopsy showed extensive angio-invasive fungal organisms. Some appeared as septate hyphae with 45 angle branching, with features of aspergillosis, while other hyphae were non-septate with 90 angle branching, demonstrating features of phycomycosis such as Mucorales. The mass was completely removed during surgery and the patient was continued on Amphotericin B which was later shifted to Isavuconazole due to renal failure. Post treatment MRI of the brain and aspergillus antigen were negative for residual disease.

Discussion

CNS aspergilloma is a rare form of invasive aspergillosis associated with high morbidity and mortality that can be difficult to diagnose and treat. The gold standard for diagnosis remains to be histopathology as most forms of imaging poorly differentiate between CNS aspergilloma and alternative infections or neoplasms.

Conclusion

The combination of aspergillosis and mucormycosis in the same fungal element is exceedingly rare with only one other case published. This case shows that both diseases can be treated with surgical excision and Isavuconazole treatment.

Introduction

Aspergillus species are ubiquitous fungi in the environment and are readily acquired through inhalation. It is well known that immunocompromised individuals are at high risk of developing invasive Aspergillus infections. The population most at risk are those being treated for hematological malignancies and those receiving either solid organ or bone marrow transplantation **[1]** (5-13 % in HSCT recipients and 10-20 % in patients receiving high-intensity chemotherapy for leukemia.) **[2]** However, immunocompetent individuals require a high inoculation dose and rarely develop invasive disease. Invasive aspergillosis (IA) usually presents as pulmonary invasive aspergillosis (0.4-3.1 % of all autopsies performed, it is one of the most common diagnostic errors revealed at autopsy) **[3]**, invasive aspergillus sinusitis (5-10 % of cases of invasive aspergillosis) or

disseminated Invasive aspergillosis. (Average incidence on autopsy is around 0.19 %) **[1,4]** Less commonly, CNS aspergillus infection is identified. (Seen in 10-20 % of all cases of invasive aspergillosis) **[5]**

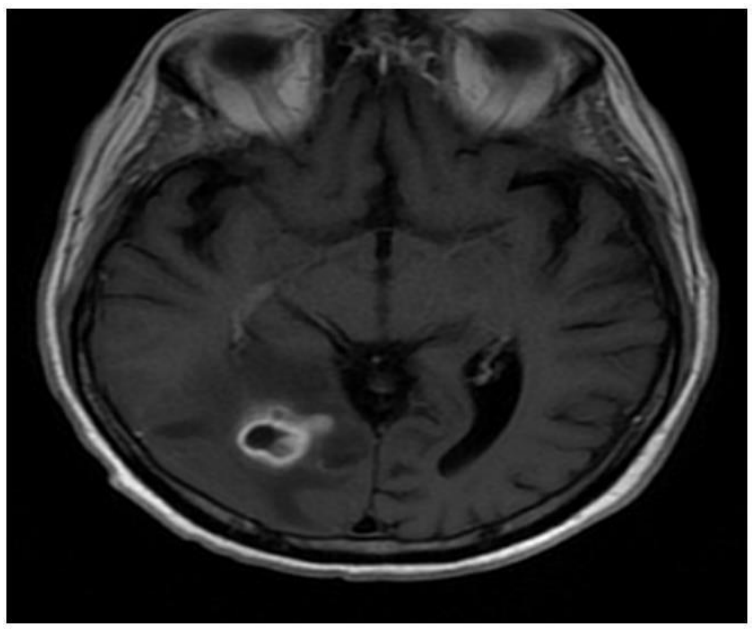
Phycomycosis is tissue invasion of molds and fungi and can be divided into the following types of infection: pythiosis, zygomycosis, and lagenidiosis. Zygomycosis infection can be further subdivided into those caused by the family of organisms Entomophtlorales and Mucorales, which include Mucor, Rhizopus and Rhizomucor. Mucorales organisms commonly lead to Mucormycosis in susceptible patients. Zygomycosis typically involves the skin, sinuses, and gastrointestinal tract, however, can have deep-seated invasive infections in patients with immunocompromised conditions such as HIV/AIDS and acute leukemias.

We describe here a case of CNS aspergilloma and phycomycosis resembling Mucor presenting as homonymous hemianopsia due to an occipital mass in a patient with a history of Acute Myelogenous Leukemia (AML). Pathology of this mass shows a mixed fungal ball with elements of Aspergillosis and Phycomycosis. We discuss this patient's rare presentation, diagnosis, management, and perform a literature review to describe the incidence of CNS Aspergilloma in immunocompromised and immunocompetent patients.

Case Presentation

Our patient is a 64-year-old white male with a past medical history (PMH) of acute myeloid leukemia (AML) who presented to his ophthalmologist with left-sided peripheral visual field defects and subjective numbness on the left side of his face. He was found to have retinal hemorrhages and left-sided hemianopia upon further evaluation. In consideration of the patient's oncological history, a magnetic resonance imaging (MRI) of his brain was obtained: this showed an enhancing right occipital mass measuring 2.5x2.1x1.8cm with surrounding vasogenic edema, effacement of the atrium, and the occipital horn of the right lateral ventricle with likely central necrosis **(Figure 1).** The patient was then promptly admitted to the hospital for further workup and evaluation. The initial differential diagnosis was broad, ranging from infectious to malignant causes (i.e., bacterial abscess, fungal ball, toxoplasmosis, cysticercosis, primary CNS lymphoma, and unknown primary with CNS metastasis).

Figure 1: This depicts a coronal view of the MRI brain showing the occipital mass.



His past medical history was significant for acute myeloid leukemia diagnosed in early 2020 with increased blast forms on peripheral smear. He was urgently started on induction therapy with cytarabine and daunorubicin. During his induction, he developed neutropenic fever with associated signs of hypoxia and dyspnea. Computerized tomography (CT) of the chest was done at that time, patchy ground-glass opacities with focal consolidations of both lungs. He was initially treated for gram negative pneumonia; however, this was changed to Micafungin after a positive aspergillus galactomannan antigen resulted (1.007). He completed 14 days of Micafungin then switched to 4 weeks of Voriconazole. Due to his fevers, as part of the workup, he had a CT scan of his brain showing normal brain tissue with thickening of his sinuses. Otorhinolaryngology was consulted and evaluated for mucor infection, however, sinoscopy was done which showed no fungal elements. He subsequently underwent two cycles of High dose ara-cytarabine (HiDAC) consolidation without recurrence.

On admission for his vision loss, he had no other focal neurological deficits other than numbness on the left side of his face and left-sided peripheral vision. On examination, he had no focal neurological deficits except for the loss of the left-sided visual field. No sensory, motor, or other cranial nerve deficits were noted. Neurosurgery evaluated the patient for possible biopsy / resection of his brain mass, and he was started on intravenous dexamethasone to prevent worsening of the

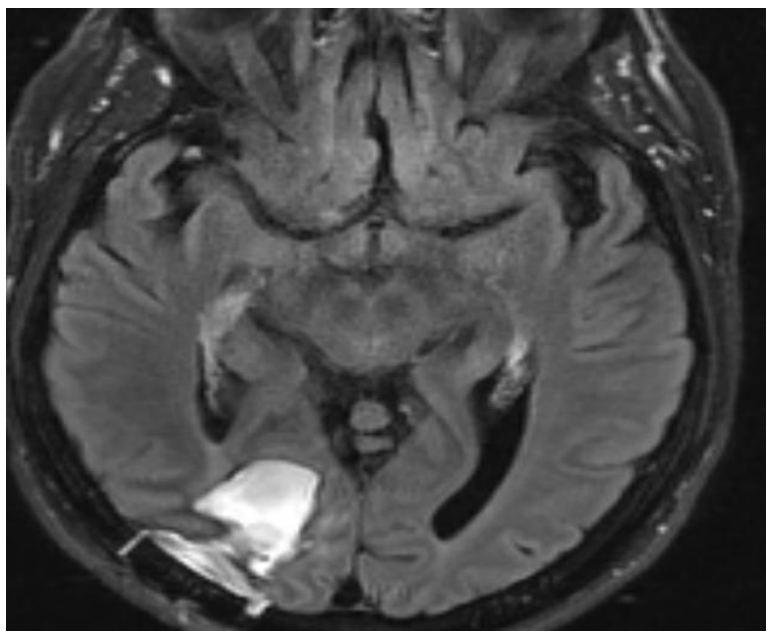
vasogenic edema. Following evaluation by neurosurgery, dexamethasone was held to prevent complicating the biopsy results if the mass was, in fact, a lymphoma.

Initial labs were significant for a leukocyte count of 21.61k/uL, Hb of 12.3g/dL, mean corpuscular volume of 98fL, Absolute neutrophil count of 18.6k/uL, and differential with 84 % granulocytes, 8 % lymphocytes, 4 % monocytes, 2 % bands, and occasional teardrop cells. Blood bacterial and fungal cultures showed no growth. Procalcitonin was negative. Fungi tell assay for 1,3-beta-di-glucan (BDG) was negative. CMV IgM was negative, and IgG was positive.

A lumbar puncture was performed while the patient was awaiting a biopsy and spinal fluid was sent for studies. It was clear and colorless with 1 WBC/mm^3 and 202 RBC/mm^3, Glucose of 64 mg/dL, protein of 54 mg/dL. CSF studies were inconsistent with an infectious process. Microbiology studies obtained on CSF were negative for cryptococcal antigen, JC virus PCR, Toxoplasma gonidii PCR, Mycobacterium tuberculosis PCR, Histoplasma antigen, Coccidioides antibody, and Aspergillus antibody testing. CSF India Ink stain, gram stain, aerobic culture, anaerobic culture, and fungal culture were negative. Following the collection of CSF, the patient was started on liposomal amphotericin B for empiric coverage of fungal infections.

The patient underwent right stealth-guided craniotomy with open biopsy of the cranial mass after three days of hospital admission. Intraoperative findings indicated that the mass was a discrete, firm nodule and, therefore, it was dissected and removed completely in a piecemeal fashion **(Figure 2).** Frozen section analysis of the mass was concerning for a fungal infection. Biopsy and cultures were sent. The postoperative course was complicated by seizure activity (well controlled with antiseizure medications), post-surgical hypoxia requiring intubation for an additional day in the intensive care unit. The patient recovered well post-extubation.

Figure 2: Post-operative coronal view of MRI brain showing complete resection of the mass.



Histopathology revealed extensive angio-invasive fungal organisms with significant surrounding acute and chronic inflammatory changes. Some organisms appeared as septate hyphae with 45-degree branching, with occasional fruiting bodies and features of aspergillosis, while other hyphae were non-septate with 90-degree branching, demonstrating features of phycomycosis such as Mucorales **(Figures 3)**. Frozen section and intraoperative cytology preparations, including touch prep and squash prep, were reviewed to confirm the diagnosis. Grocott's methenamine silver (GMS) and periodic acid-Schiff (PAS) histochemical stains for fungal organisms were performed **(Figures 4,5,6).** Results supported the diagnosis of CNS aspergilloma.

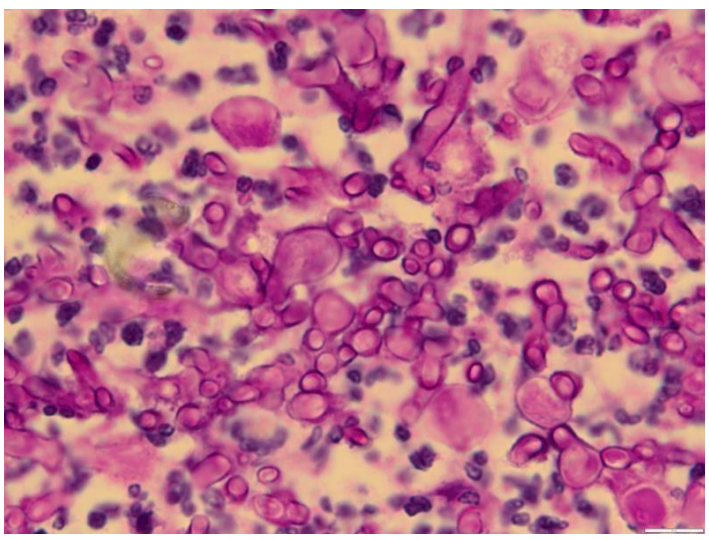
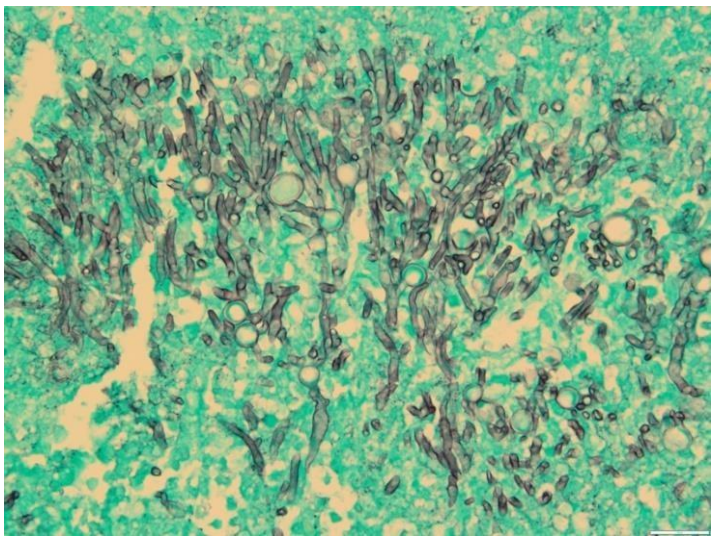


Figure 3: Histopathology with PAS stain showing fungal elements.



Figures 4: Histopathology with GMS stain showing fungal elements.

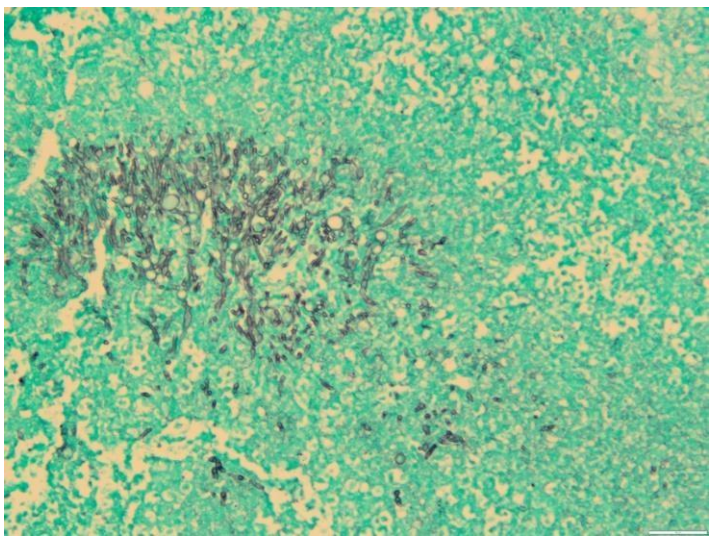


Figure 5: Histopathology with GMS stain showing fungal elements.

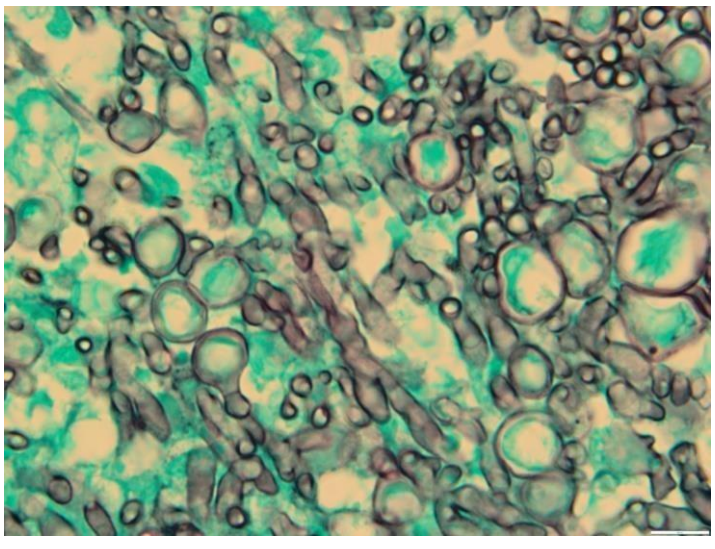


Figure 6: Histopathology with GMS stain showing fungal elements.

The patient was continued on Liposomal Amphotericin post-operatively with close monitoring of renal and liver functions. The case was discussed with Infectious Diseases about continuing amphotericin B as opposed to switching to Isavuconazonium for the duration of treatment, however, it was decided to continue Ampho for six weeks from the day of surgery. The patient was discharged with plans to follow up with the Oncology clinic and receive intravenous antibiotics at a local hospital. Two weeks after initiating antibiotics, he was admitted for renal failure requiring emergent dialysis. At that time, due to his renal failure, he was switched to Isavuconazonium to complete 4 more weeks of therapy. Post-treatment MRI of the brain and aspergillus antigen were negative for residual disease. However, he later had a relapse of his acute myelogenous leukemia and required readmission for induction treatment with Venetoclax and Decitabine. He eventually developed progressive respiratory failure concerning Pneumocystis jirovecii pneumonia or acute respiratory distress syndrome and eventually succumbed to his disease.

Discussion

The incidence of CNS aspergilloma in this patient is atypical because the patient was not immunosuppressed at the time of presentation. As much as 90 % of invasive aspergillosis is said to arise in patients with active hematological cancer or peripheral stem cell transplant recipients **[6]**. It is considerably rarer to encounter invasive aspergillosis, such as CNS aspergilloma within the occipital lobe, in an immunocompetent patient. Additionally, the presence of aspergillus alongside

presumed phycomycosis is a unique distinction to this patient's presentation that is rare and noteworthy.

In the immunocompetent patient, aspergillomas are anticipated to be found as a mass lesion with a thick, irregular wall, thereby indicating an active immunologic defense mechanism by the host.**[7,8]** This wall surrounding the granuloma with fibrosis results in little meningeal involvement and, therefore, rare CSF positive aspergillus cultures with likely negative pan fungal PCR of the CSF.**[9]** In regards to imaging, MRI typically demonstrates a hypo-to-iso-intense mass on T1 weighted images and a hypointense mass with bright, homogenous enhancement on T2 weighted images. **[10]** Additionally, on CT, the collection of paramagnetic materials, such as iron, manganese, and magnesium, within fungal hyphae produce scattered regions of hyperdensity. **[11]** Consistent though this description of aspergilloma on imaging may be, it can be difficult to differentiate from other differential diagnoses, such as intracranial neoplasms and inflammatory responses. Imaging via positron emission tomography (PET) may be used to differentiate neoplastic from non-neoplastic lesions, with neoplastic lesions having increased 18-fluorodeoxyglucose (FDG) uptake.**[12]** However, the gold standard of diagnosis for aspergilloma is histopathology, often obtained via image-guided stereotactic biopsy **[13-15]**. Once diagnosed, medical treatment with voriconazole (preferred due to high CNS penetration) and surgical resection are considered best practices. **[14,16,17]** However, amphotericin B and itraconazole are considered reasonable medical alternatives when voriconazole is contraindicated or unavailable. **[18]** Even with prompt medical treatment and surgical resection of the aspergilloma, clinical outcomes are generally poor, with mortality ranging from 40-80 % in immunocompetent hosts.**[19]**

CNS aspergillosis can also commonly present as multiple infarctions or hemorrhages secondary to angio-invasion by the fungus in immunosuppressed patients.**[13]** This may be due to an inability of the immune system to mount the appropriate immune response to the fungus, as would be required for granuloma formation. Additionally, in immunocompromised patients, infection is often disseminated and more likely to reach the CNS via hematologic spread **[20-23]**. Therefore, in an immunosuppressed patient with a history suggestive of pulmonary aspergillosis who presents with focal brain lesions, CNS aspergillosis should be high on the differential. Once the diagnosis is confirmed, prompt treatment of CNS aspergillosis in the immunosuppressed patient is critical. Immediate efforts to reverse the immunocompromised state, if possible, will be necessary to achieve the resolution of the infection. For example, growth factors may be used to quicken the recovery from neutropenia and granulocyte transfusions may sustain circulating neutrophils until the neutropenia is resolved. **[16]** Voriconazole, if tolerated, and surgical resection remain the preferred treatment method for CNS infection with Aspergillus species regardless of a patient's immunologic status. **[14,16,17]**

Regarding the case reported above, the patient's history of invasive pulmonary aspergillosis, which presented during the consolidation phase of his chemotherapy, along with a history of maxillary sinusitis, are likely important predisposing factors toward his development of CNS aspergilloma. It has been documented that individuals with a history of acute leukemia, hematopoietic stem cell transplants, and chronic sinusitis are at an increased risk for developing invasive aspergillosis during their lifetime.**[1]** Once a patient develops invasive aspergillosis, it is then possible for the fungi to enter the CNS through the direct spread, as is the case for those with aspergillus sinusitis, or hematologic spread, commonly from the lungs.**[18]** The patient identified in this case report previously experienced invasive aspergillosis in the form of pulmonary aspergillosis. That the aspergilloma arose within the occipital lobe indicates hematologic spread as the most likely route of infection. This conclusion is supported by histopathology demonstrating angio-invasion by the fungus. Although previous reports indicate angio-invasion is more common within immunocompromised patients, the aspergilloma's gross pathology, as a discrete, firm nodule indicates that this patient's immune system mounted an appropriate immunologic response, effectively walling off the infection from the remainder of neural tissue. This patient demonstrates that the hematologic spread of aspergillosis is not impossible for immunocompetent patients. Prompt treatment remains the foundation for achievin good clinical outcomes. The use of liposomal amphotericin B prior to and following surgical resection of the mass has resulted in good outcomes **[24]**

Isavuconazole, the prodrug being isavuconazonium has gained widespread interest in the treatment of invasive fungal species, particularly involving CNS disease. As amphotericin B administration puts patients at risk for acute renal failure, hyperkalemia, hyponatremia, and hypomagnesemia, isavuconazole has become a more favorable option in many aggressive fungal species. Isavuconazole is an intravenous antifungal that is highly water-soluble and not requires a beta-cyclodextrin to help with solubility, as cyclodextrin is known to cause nephrotoxicity. It is 98 % protein bound and has a high volume of distribution including brain penetration. In rat animal models, mean plasma concentrations were similar to brain concentrations after a single dose of 25mg/kg of isavuconazole. In a phase three double-blind study of 527 patients between 2007 and 2008 and From March 2011 to December 2013, voriconazole was compared to isavuconazole in patients with allogeneic stem cell transplantation or active malignancy (SECURE trial). **[25]**

Mortality rates were similar between both isavuconazole and voriconazole at 19 % and 20 %, respectively. Patients receiving isavuconazole had fewer liver derangements as compared to voriconazole. The current guidelines for invasive aspergillosis in patients with hematological malignancies include the addition of isavuconazole with voriconazole.

In, the VITAL trial, patients with mucormycosis were treated with Isavuconazole and compared to patients who were treated with amphotericin B **[26]**. Thirty-seven patients received Isavuconazole for a median of 84 days. Day-42 all-cause mortality in 33 % (seven out of 21) was similar to amphotericin – B treated matched controls at 39 % (13 out of 33). Due to this Isavunazole was approved for the treatment of mucormycosis.

In a study was done by Schwartz et al., patients with CNS invasive fungal diseases (IFD) were evaluated from data from the VITAL and SECURE trial. **[27]** Of the 36 patients with CNS disease, 47.2 % had hematological malignancies. Mucorales, Aspergillosis, Cryptococcus species accounted for 30.6 %, 22.2 %, and 13.9 % of infections. Overall survival rate was 80 % at day 42, 69 % at day 84, and a complete or partial treatment response seen in 58 % of patients. The use of Isavuconazole in our patient showed favorable outcomes with complete resolution and no recurrence. Hence through this case, we propose to highlight that a high index of suspicion is required to identify invasive CNS aspergillosis in immunocompetent patients. Any remote history of Aspergillosis in the past as well as a history of immunosuppression also appears to play a crucial role in the pathogenesis of the disease. Early histopathological diagnosis with a biopsy and prompt antifungal therapy is critical in reducing mortality associated with this disease process.

Conclusion

CNS aspergilloma is a rare form of invasive aspergillosis associated with high morbidity that can be difficult to diagnose and difficult to treat. The gold standard for diagnosis remains to be histopathology as most forms of imaging poorly differentiate between CNS aspergilloma and alternative infections or neoplasms. Once the diagnosis is established, however, it is critical to start prompt treatment with antifungal agents and perform surgical resection of the lesion. Close follow-up and adherence to medications are essential for a good clinical outcome. For those that can't tolerate voriconazole due to hepatotoxicity or liver disease, and in those with risk factors for nephrotoxicity, isavuconazole is a non-inferior treatment option. The combination of aspergillosis and mucormycosis in the same fungal element is exceedingly rare with only one other case published. This case shows that both diseases can be treated with surgical excision and Isavuconazole treatment.

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