Locally Invasive Central Nervous System Aspergillosis Presenting as Subacute Vision Loss

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ABSTRACT

Introduction: *Aspergillus* is a ubiquitous environmental fungus that has the potential to cause a wide array of clinical illnesses, from an allergic response to invasive disseminated disease – particularly in those with immune dysfunction or underlying disease.

Case Presentation: An 83-year-old immunocompromised man presented to the emergency department with fever and subacute vision loss over 3 to 4 months after multiple prior emergency department and outpatient ophthalmology visits. After a complicated course, locally invasive central nervous system aspergillosis was diagnosed. Although the patient eventually recovered, he experienced permanent vision loss.

Discussion: This case demonstrates the importance of aggressive workup in immunosuppressed patients with onset of any concerning ocular or other symptoms. A multidisciplinary approach is necessary for optimal patient outcomes.

Conclusions: Aspergillosis has the potential to cause devastating disease and long-term consequences in immunocompromised patients. Clinicians should be alerted to the importance of early detection and intervention for this population.

INTRODUCTION

Aspergillus is a widely prevalent environmental fungus with the potential to cause an array of clinical presentations in humans, from an allergic response to invasive disseminated disease.[1] While exposure to the fungus is widespread, most people do not develop any signs or symptoms and acquire no antibody- or cell-mediated immunity.[1] However, for hosts with immune dysfunction, traumatic injury, or underlying lung disease, *Aspergillus* species have the ability to cause devastating and severe consequences.[1,2] Underlying conditions that serve as risk factors for invasive aspergillosis include severe and prolonged neutropenia, receipt of high-dose glucocorticoids, and other drugs that lead to chronically impaired cellular responses.[2-5]

Central nervous system (CNS) aspergillosis is an invasive form with high mortality that may occur through either hematogenous spread from disseminated infection or by direct extension from a locally invasive infection.[4,6] Hematogenous dissemination most frequently originates from an invasive lung infection in an immunocompromised host or those with underlying lung conditions. On the other hand, locally invasive CNS aspergillosis most commonly spreads from the paranasal sinuses in either an immunocompromised host or following cranial trauma or neurosurgery.[6,7] The clinical presentation of CNS aspergillosis is nonspecific and heterogeneous as patients may present with headache, focal neurological deficits, altered mental status, or vasculitis depending on the extent of intracranial involvement.[4-6] The most notable risk factor is persistent and significant neutropenia. In a literature review of 235 patients with CNS aspergillosis, the predisposing factors to infection included corticosteroid use (22.6%), malignancy (19.1%), and diabetes (14%).[4] Furthermore, of those with a malignancy, 75% had a hematologic malignancy.[4]

Here we present a case of CNS aspergillosis resulting in permanent vision loss in an immunocompromised patient with lymphoma-associated amyloidosis.

CASE PRESENTATION

An 83-year-old man presented to an outside emergency department (ED) with worsening vision loss in his left eye and a subjective fever. His medical history was significant for low-grade B-cell

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lymphoma with plasmocytic differentiation and associated organ-limited amyloidosis post splenectomy and partial pancreatectomy (6 years prior to presentation), bortezomib course (6 years prior to presentation) with long-term dexamethasone and pomalidomide use, diabetes secondary to pancreatectomy, and prior right eye blindness from an unrelated injury. He reported worsening of vision loss for 3 to 4 months with recent escalation to complete darkness in the left eye in the 24 hours prior to presentation. He also reported 3 ground-level falls in the prior 48 hours, which he attributed to the visual disturbances.

Moreover, the patient had been seen in the ophthalmology clinic 4 months prior to this presentation for drainage and discomfort of his right blind eye with minor discomfort in the left eye and was diagnosed with bacterial conjunctivitis. Superficial keratectomy was completed to remove the calcific densities in the right eye, and tobramycin drops were prescribed for the suspected bacterial conjunctivitis. At a follow-up appointment 1 month later, he continued to report right eye pain and headaches while noting new floaters in his left eye. An additional keratectomy was performed to further remove calcifications of the right eye. Another month later, he continued to have significant pain in the right eye and was then noted to have numbness on the right side of his nose and face. Finally, 1 additional month later, he was found to have cranial nerve 3, 4, 5, and 6 palsies, and a neurologic follow-up was recommended by ophthalmology. Within 1 week of his last ophthalmology appointment, he presented to an outside ED for complete darkness in the left eye as described above.

Upon presentation to the ED, the patient was febrile to 38.89 °C with elevated erythrocyte sedimentation rate (ESR) to 120 mm/hr and a white blood cell count (WBC) of 11 500. Magnetic resonance angiography (MRA) of the head and neck obtained in the ED demonstrated a right anterior temporal lobe abscess with associated diffuse paranasal sinus thickening and a right mastoid effusion (see Figure 1). The patient was admitted to an outside hospital for observation and underwent a lumbar puncture with cerebrospinal fluid (CSF) demonstrating >100 000 red blood cell count (RBC), 95 000 WBC, 250 mg/dL protein, and 61 mg/ml glucose consistent with a bacterial versus fungal infection. He was started empirically on vancomycin, cefepime, and metronidazole. Blood and CSF cultures were obtained, and a CSF meningitis/encephalitis panel was negative. Magnetic resonance imaging (MRI) of the brain with contrast and magnetic resonance venography (MRV) showed invasive right sphenoid sinusitis with right orbital apex and cavernous sinus involvement and a right temporal abscess. He was then transferred for admission to our hospital, a quaternary academic care center.

Upon arrival to our hospital, the patient was in no acute distress, with a mild headache and complete immobility of the right eye, which was atypical for him. He was only able to appreciate light and shadows from his left eye. On initial examination, his right eye appeared clouded with no erythema or purulent drainage, and the nasopharynx had minimal edema with no areas of necrosis. He had right eye ptosis and ophthalmoplegia, as well as loss of vision in the left eye as demonstrated by his inability to visualize finger count. He also had right-sided facial numbness in a V1 and V2 distribution, with pain to palpation along the right mandible. His labs at that time showed leukocytosis with WBC of 15 700 and thrombocytosis with a platelet count of 562 000. Neurosurgery; ear, nose, and throat (ENT); and infectious disease (ID) were consulted. The patient was transitioned to linezolid, cefepime, metronidazole, and amphotericin B. ENT performed biopsies of the right palate as well as the middle and inferior turbinates. Computed tomography (CT) sinus stealth indicated additional mucosal disease in the right maxillary sinus most consistent with invasive fungal disease (see Figure 2). The decision was made to continue the current antimicrobial regimen and monitor for improvement of symptoms and imaging findings.

On hospital day 4, preliminary culture results from the right nasal cavity indicated gram-positive rods and yeast with 1 colony of pan-sensitive *Staphylococcus lugdunensis*, and the patient was narrowed from cefepime to ceftriaxone. On hospital day 6, linezolid was discontinued since he was clinically stable. Biopsy results showed no evidence of fungal organism or neoplastic growth. On hospital day 9, he spiked a temperature up to 37.83 °C and still had no return of vision despite antimicrobial treatment. ID recommended repeat biopsy and MRI brain. ENT determined

Figure 1. Axial T2-weighted Magnetic Resonance Angiography of Head With Contrast Taken Two Days Prior to Admission

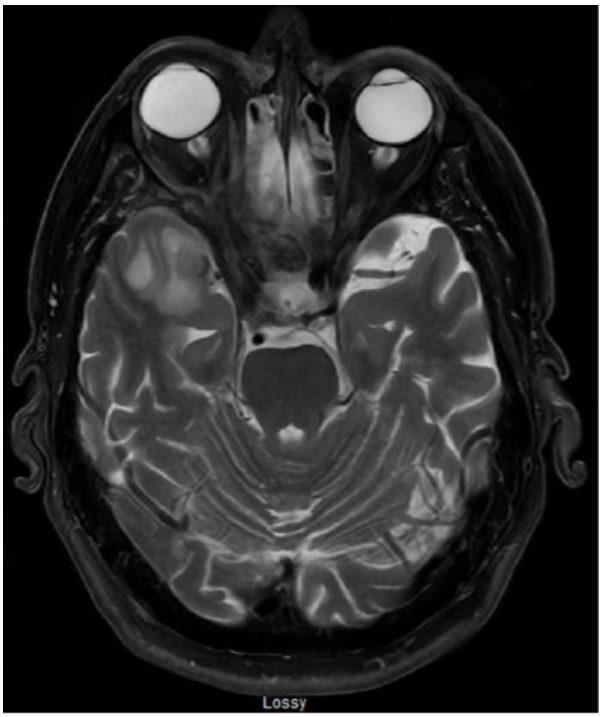

Image Shows Diffuse Paranasal Sinus Thickening and Right Mastoid Effusion.

Figure 2. Axial Computed Tomography Sinus Stealth Marker Without Contrast Taken on Day 2 of Admission

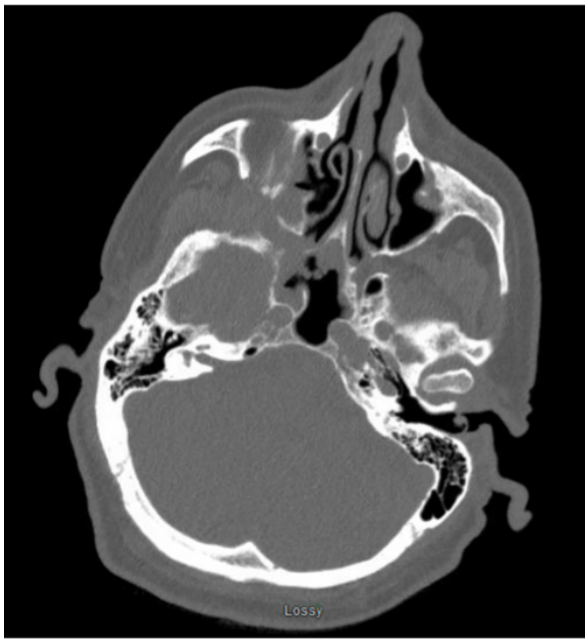

Image shows aggressive-appearing soft tissue in the right sphenoid and posterior ethmoid sinuses with progressive destruction of bone and infiltration of the soft tissues of the right orbital apex, central skull base, and right cavernous sinus.

Figure 3. Coronal T1-weighted Magnetic Resonance Imaging of Head with Contrast on Day 10 of Admission

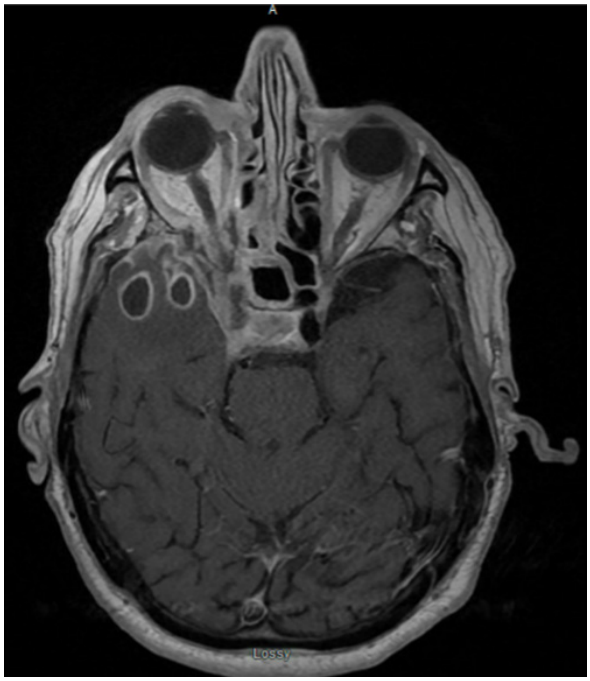

Image shows small cerebral abscesses in the right temporal pole with slightly increased surrounding vasogenic edema and similar invasive sinus disease involving the right orbital apex, cavernous sinus, pterygopalatine fossa, and retroantral fat suggestive of fungal etiology.

that there was no safe area for biopsy and recommended moving forward with craniotomy. MRI brain indicated worsening of vasogenic edema and an acute lacunar infarct in the right corona radiata most consistent with small vessel etiology but also potentially related to the ongoing temporal abscesses and fungal infection (see Figure 3). Craniotomy was performed for abscess resection on hospital day 13 and purulence was noted intraoperatively. Then, on hospital day 16, intraoperative cultures grew 1 colony of *Aspergillus* species. Amphotericin B, metronidazole, and ceftriaxone were discontinued, and the patient was then transitioned to oral voriconazole. He recovered and was discharged with oral voriconazole for an additional 6 months of treatment. Nevertheless, his vision loss was permanent at discharge.

DISCUSSION

Here we report a case of locally invasive CNS aspergillosis in an immunocompromised patient with a history of low-grade B-cell lymphoma and organ-limited immunoglobulin light chain (AL) amyloidosis who presented with subacute vision loss. Aspergillosis is known to be associated with immunosuppression, particularly in those with hematologic malignancies as well as diabetes. Therefore, this diagnosis should be suspected in immunocompromised patients who present with orbital pain or vision deficits. Although voriconazole treatment was effective in clearing the infection, the patient's vision loss could have been prevented if infection was identified and appropriate treatment was initiated earlier.

Moreover, AL amyloidosis is a potential complication of any plasma cell dyscrasia that produces monoclonal immunoglobulin light chains, and treatment involves various immunosuppressive therapies and steroids.[8] The patient in our case had a history of long-term dexamethasone use, had undergone 2 rounds of chemotherapeutic treatment, and had undergone previous splenectomy. However, this combination of therapies for amyloidosis further increased his risk of serious fungal infection.[9]

With such significant risk factors, it is vital to identify early warning signs and ensure thorough workup is completed in similar immunosuppressed patients. Our patient had presented to the ED and outpatient ophthalmology on multiple occasions for a potential eye infection in the 4 months leading up to admission. Warning signs for immunosuppressed patients should include ongoing, increasing, and new alarming symptoms. Our patient had recurring visits and, at each visit, presented with new symptoms, including extension to additional eye, headaches, floaters, and progressive numbness. Identifying these presentations in patients at risk and ensuring full workup could better detect infections prior to invasive spread in the future.

Nonetheless, laboratory tests to detect aspergillosis are lacking. CSF examination is not always helpful in the diagnosis of neuroaspergillosis, but it can aid in ruling out other opportunistic infections. CSF culture is rarely positive, and a galactomannan (GM) assay may be a useful predictor of invasive aspergillosis.[10] A study by

Chong et al reported a 93.8% positive predictive value of CSF GM in patients with cerebral aspergillosis.[10] In addition, CSF polymerase chain reaction (PCR) is another emerging tool for diagnosis of cerebral aspergillosis. A study by Imbert et al showed 75% sensitivity for CSF PCR.[11] With specificity of 98.3% reported in the same study, CSF PCR can be an alternative tool that may abate the need for tissue biopsy. In addition, tissue biopsy is not always readily available. As seen in the case presented, the first biopsy was inconclusive, and on the second attempt, the team was unable to achieve adequate tissue for biopsy prior to craniotomy. Therefore, both CSF GM and CSF PCR could be interesting diagnostics tools in the event of nonavailability of tissue biopsy and negative cultures.

Invasive aspergillosis carries a high mortality rate despite treatment.[4] In the past, amphotericin B therapy was the treatment of choice for CNS aspergillosis; however, this drug produced negligible effects.[4] Recently, voriconazole has been reported to be more effective than amphotericin B, and response rates of about 35% have been achieved with voriconazole for patients with CNS aspergillosis.[3] Of note, there is extensive variability with voriconazole due to its nonlinear pharmacokinetics, requiring therapeutic drug monitoring to achieve adequate blood trough and prevent breakthrough disease.[5] To achieve optimal outcomes, a combined medical and neurosurgical treatment should be considered in all patients with this disease as it has been shown to improve survival rates.[4] The duration of antifungal therapy is not well defined, and current recommendations are to continue treatment based on clinical and radiological improvement.[5] Also, antifungal prophylaxis has been recommended in certain high-risk groups such as transplant patients; however, future research is necessary to determine if preemptive prophylaxis has a role during immunosuppression in neurosarcoidosis or amyloidosis.[12] Moreover, the role of combination therapy in neuro-aspergillosis is an area of ongoing research and has yet to be fully elucidated. Although randomized studies are lacking, limited data from a few case reports have suggested a promising role for a combination of voriconazole with caspofungin.[13]

This case underscores the challenges associated with disseminated CNS aspergillosis in immunocompromised patients—particularly those with hematologic malignancies and long-term glucocorticoid use. The intricate interplay between immunosuppression, underlying medical conditions, and opportunistic infections like aspergillosis necessitates a multidisciplinary approach for optimal management.

Despite the effectiveness of voriconazole in treating aspergillosis, the irreversible vision loss in our patient demonstrates the critical importance of early detection and intervention. Vigilant infectious disease monitoring in immunocompromised individuals, coupled with advancements in diagnostic tools such as CSF galactomannan and CSF PCR, potentially could enhance the timeliness and accuracy of diagnosis.

As we continue to unravel the intricacies of CNS aspergillosis, future research should focus on refining combination therapies, exploring prophylactic measures during immunosuppression in conditions such as neurosarcoidosis or amyloidosis, and improving laboratory tests for early detection.

CONCLUSIONS

We present a case of CNS aspergillosis in an immunocompromised patient resulting in permanent vision loss bilaterally for this patient. This case highlights the importance of infectious disease monitoring in immunosuppressed patients, aggressive workup upon onset of any concerning signs and symptoms, and the need for a multidisciplinary approach involving infectious disease, ENT, ophthalmology, and neurology in a complex scenario to achieve the best outcomes. Collaborative efforts across medical disciplines and ongoing research endeavors will be instrumental in improving outcomes for patients facing disseminated CNS aspergillosis. The lessons learned from this case contribute to the growing body of knowledge in the field, emphasizing the continuous pursuit of advancements that can positively impact patient outcomes.

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