Intracranial Aspergillus Infection Associated with an Amyloid Tumor and Lymphoma

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ABSTRACT

Intracranial aspergillus infection is an uncommon finding. The importance of a high index of clinical suspicion, coupled with an early diagnosis, can potentially be lifesaving. We illustrate the case in a patient who developed right-sided visual disturbance and facial paresthesia, where radiological diagnosis was meningioma but histopathology revealed an amyloid tumor with synchronous aspergillus infection and lymphoma at the same site. This diagnosis should always be considered, especially in immunodeficient patients, using a combination of neurological and thoracic imaging and histopathology of a resected specimen.

KEYWORDS: Intracranial aspergillosis, lymphoma, skull base, amyloid, meningioma

Morbidity and mortality caused by invasive aspergillus infections are increasing due to the higher number of patients with malignancies treated with intensive immunosuppressive therapy regimens, as well as their improved survival from formerly fatal bacterial infections, and the rising number of patients undergoing allogeneic hematopoietic stem cell or organ transplantation.¹ Intracranial aspergilloma is, however, a rare disease. Among its varied presentations, a solitary intracranial mass is very uncommon. A preoperative diagnosis of it is very difficult, but a perioperative squash smear/frozen section can identify the

pathology.² The synchronous development of aspergillus infection and lymphoma on the same location has never been reported in the literature, along with very few cases of radiological misdiagnosis of meningioma.

CASE REPORT

A 59-year-old fit and well veterinary doctor presented with an insidious, very mild proptosis of the right eye. Photographs suggest the proptosis

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became noticeable 18 months before presentation. Despite the vision being initially on the whole unaffected, apart from slight blurring on prolonged exercise, the eye had become more uncomfortable, particularly on pressure and especially when sleeping. During the preceding 12 months, he also had occasional headaches around the right temple and strange sensation around the eye in the ophthalmic and maxillary territories of the trigeminal nerve. Neurological examination did not reveal any obvious sensory or motor deficit. Blood results on presentation were unremarkable, including normal inflammatory markers along with urea and electrolytes. There were no features indicating immunodeficient status in the patient.

Magnetic resonance imaging (MRI) scan of his head revealed a layer of dural enhancement that extended widely within the cranial cavity, which was thought to be a sphenoid wing meningioma (Fig. 1A–C). There was no involvement of the paranasal sinuses. The patient began to lose his sight in the right eye, and although no great mass lesion was identified behind the eye, he proceeded to a frontozygomatic craniotomy, a procedure performed with the combined expertise of maxillofacial and neurosurgical specialists. At surgery, the bone of the skull base was softened and there was an extensive sugarcoating of a tumorlike lesion over much of the dura. Histological assessment revealed extensive amyloid deposition filling bone marrow spaces (“amyloid tumor”) with focal collections of fungi, which had branching septate hyphae (Fig. 2). In addition, there were scattered collections of CD20-positive, small lymphoid cells (Fig. 3), which had the immunophenotype of a low-grade B-cell lymphoma with aberrant CD5 expression and lambda light-chain production.

Due to the nature of the patient’s work, he admitted to being constantly exposed to aspergillus. The patient was subsequently commenced on treatment with voriconazole.

Further investigation failed to identify any further foci of either lymphoma or aspergillus infections. Postoperatively, the patient underwent radiotherapy for his lymphoma; chemotherapy was

contemplated but not required. He also developed a persistent nasal discharge, with presumption that it could be a cerebrospinal fluid leak, but this settled conservatively.

Ultimately he made a very good recovery with improving visual acuity on that eye.

DISCUSSION

The pathogenesis of intracranial aspergillus is largely comprehended in terms of the route of pathogen dissemination into the brain. The main source of infection is from the inhalation of spores, making lungs the primary site of infection, with subsequent hematogenous disseminated spread. Direct extension can also occur from the paranasal sinuses and orbits. Although particularly uncommon in patients with no known immunodeficiencies, it is still a diagnosis not obvious in those where such immunocompromise is present. Varied presentations can include altered consciousness, focal neurological deficits, and seizures.³ Features on imaging are often nonconclusive, and hence cannot be relied on alone for an accurate diagnosis, and are made even more difficult without an accurate account of clinical history and physical examination.

Invasive aspergillus has a significantly high mortality rate of 30 to 95%, and treatment is mainly comprised of oral antifungal drugs like voriconazole, amphotericin B, itraconazole, and caspofungin.⁴ The gold standard of systemic antifungal treatment is voriconazole, which has been proven to be significantly superior to conventional amphotericin B and has led to profound improvement of survival rates in patients with cerebral aspergillosis.⁴

Our patient was known to be exposed to fungal aspergillus as a direct consequence of his occupation as a veterinary doctor. This, combined with the histological diagnosis of non-Hodgkin’s lymphoma, can be assumed to have put him at a much higher risk for invasive infection as well as causing the formation of an amyloid tumor as a consequence of immunoglobulin production. The

Figure 1 (A) Axial T2-weighted magnetic resonance imaging (MRI) through the level of the midorbits and cavernous sinus. The right globe is proptosed and shows thickening of the extraocular muscles and distortion of the retro-orbital fat. There is signal alteration within the right cavernous sinus, Meckel's cave, and sphenoid wing, which also involves the superior orbital fissure. (B) Axial T1-weighted MRI at the same level as A. The changes demonstrated on the T2 study are more apparent with more convincing orbital and skull base involvement. There is also a plaque of soft tissue lining the posterior aspect of the petrous ridge. (C) Axial T1-weighted MRI after gadolinium. This shows diffuse meningeal enhancement within the middle cranial fossa extending along the lateral margin of the cavernous sinus and posterior margin of the petrous ridge and clivus. There is relative underenhancement of the cavernous sinus on the right with soft tissue surrounding the cavernous internal carotid artery and passing anteriorly into orbit via the superior orbital fissure.

Figure 2 Section showing collection of fungi that have septate hyphae (periodic acid-Schiff stain, magnification $\times 400$).

slow and unassuming course of his illness also made it difficult to ascertain his immune status.

Cerebral invasive aspergillosis can manifest in single or multiple lesions. On computed tomography, the lesions generally have low attenuation and may or may not be accompanied by areas of hemorrhage. The lesions often appear as a mass lesion producing hypo- to isointense signals on T1-weighted, extremely low signals (hypointense) on T2-weighted images, with bright homogenous

Figure 3 Infiltrate of small lymphoid cells, which have the immunophenotype of a low-grade B-cell lymphoma (hematoxylin and eosin, magnification $\times 400$).

enhancement on postgadolinium T1-weighted imaging, but the imaging findings vary widely.⁵ Ring enhancement can occur if abscesses form, but this is uncommon because lesions rarely become “walled off” in severely immunocompromised patients. In our patient, MRI showed a likely sphenoid wing meningioma; this diagnosis (of meningioma) has been confused for intracranial aspergillus in other cases published in literature, on imaging alone.^{6,7}

The synchronous presence of lymphoma and aspergillus infection has never been reported in the literature. The only reported case of simultaneous presence of aspergillus infection was with meningotheiomatous meningioma.⁷

One of the main reasons for the high level of morbidity and mortality associated with this condition is the delay in diagnosis. The similar MRI findings of meningioma and aspergillosis make preoperative diagnosis difficult. However, aspergillosis should be included in the differential diagnosis when a skull base meningioma-like lesion is identified in immunocompromised patients and in diabetic patients with or without paranasal sinus involvement. Biopsy results are often not available for a few days, and without a high index of suspicion, antifungals are not routinely prescribed until the biopsy result is known. It is not unheard of, therefore, for patients to deteriorate rapidly even with aggressive surgical management.

CONCLUSION

Immunodeficient patients presenting with unusual neuroimaging appearances of doubtful etiology should prompt a high index of suspicion for the possibility of having acquired invasive fungal infection, as well as the more recognized diagnosis of tuberculosis. Early aggressive treatment with sensitive antifungal agents has been shown to improve survival in this group of patients. As the diagnosis is much less common in immunocompetent patients, when diagnosed it would be

considered appropriate to investigate for the presence of other contributing disease states.

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