CASE REPORT

Aspergillosis of the Cranial Base

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Abstract—*Aspergillus* is an ubiquitous organism seldom pathogenic in normal hosts. *Aspergillus* osteomyelitis of the spine occurs rarely in immunocompromised patients as a result of hematogenous spread from distant foci. We present a case of *Aspergillus* osteomyelitis in the region of the jugular foramen in a previously healthy male with no antecedent event. He presented with dysphagia, hypophonia, and weight loss of several months duration. Diagnosis was delayed due to nonspecific results of various imaging tests. We review the clinical course of fungal osteomyelitis, including appearance on magnetic resonance imaging and computed tomography, culture characteristics, and gross appearance. Current treatment consists of surgical debridement and antifungal medications such as amphotericin B and itraconazole, and the efficacy of these are discussed. (*Skull Base Surgery*, 4(3):159–163, 1994)

CASE REPORT

A 65-year-old male of Italian descent presented with a 1-week history of hoarseness, dysphagia, left otalgia, and decreased hearing. He complained of right fronto-occipital headaches of 1 month's duration. He had been well until 4 months prior when he had an abscessed left maxillary molar extracted with a subsequent maxillary sinus infection. He had taken multiple courses of antibiotics and was currently on cephalexin. He reported a 20-lb weight loss over this time, which he associated with reduced ability to eat because of oral pain. His past medical history included vocal cord polypectomy 12 years prior to admission, from which he recovered well, a 20-pack-a-year smoking habit that he had ended 6 months previously, and daily moderate alcohol intake.

On examination he was edentulous, with a fibrous epulis and a lichenoid white lesion on the right buccal mucosa. On the right side he had an absent gag reflex, paralysis of the right vocal cord in a paramedian position with the left cord compensating, sternomastoid muscle wasting, and weaker shoulder shrugging. There was an

old perforation in the right tympanic membrane which was retracted, and the right cervical lymph nodes were palpable.

Audiometry revealed a sensorineural hearing loss on the right side.

Skull radiographs, computed tomography of the head, skeletal survey, cerebral angiograms, and chest radiographs were within normal limits. Gallium bone scan showed increased uptake in the right petrous bone. Repeated lumbar punctures did not reveal organisms.

He was admitted to hospital and started on oral dexamethasone. His blood sugar became erratic and was controlled with insulin. He had an episode of aspiration pneumonia treated with penicillin and tobramycin. With worsening clinical status computed tomography of the head was repeated, revealing bony erosion near the right jugular foramen (Fig. 1). Magnetic resonance imaging showed a pancake-shaped lesion close to the right jugular foramen thought to be representative of thickened meninges (Fig. 2).

One month after admission he underwent a posterior fossa craniotomy and dural biopsy. Histology revealed fungal hyphae, necrosis, and chronic inflammatory cell infiltrate (Fig. 3). Cultures grew *Aspergillus*.

Figure 1. Coronal computed tomogram showing bony erosion adjacent to right jugular foramen (arrow).

The patient was started on amphotericin B following his operation but became febrile 1 week later with purulent drainage from his craniotomy incision. He gradually succumbed to multi-system organ failure and died 5 weeks following his operation.

Autopsy results included a fungal *Aspergillus* abscess in the right petrous bone (Figs. 4 and 5) with micro-

scopic foci in the right kidney and left adrenal, acute bilateral bronchopneumonia (*Klebsiella*), micronodular cirrhosis with necrotic foci, splenic congestion, ascites, and widespread mild atherosclerosis.

INTRODUCTION

Of the 350 species of *Aspergillus*, *A. fumigatus* is most frequently associated with human disease.¹⁻³ Inhaled fungal spores are commensals in the respiratory tract and external auditory canal.^{1,4-6} *Aspergillus* is the fungus most likely to be associated with sinusitis, most commonly in the maxillary sinus,^{5,7} which may be of dental origin.⁶ Overall the lung is the most frequent site of infection.^{6,8} Forms of the disease include allergic bronchopulmonary aspergillosis, aspergilloma (a "fungus ball" forming in a preexisting cavity), and disseminated aspergillosis.^{6,9,10} All forms can be invasive in immunosuppressed patients.²

Factors associated with invasion include steroids (iatrogenic or endogenous), ethanol abuse, drug abuse, chemotherapy, broad spectrum antibiotics, neutropenia, leukemia, transplant or other surgery, trauma, liver failure, tuberculosis, lupus, and diabetes mellitus.^{3,6,11-13} Bone or central nervous system (CNS) involvement occurs through hematogenous or contiguous spread.^{4,14} Contiguous spread from sinuses^{5,8,15-20} or external ear²¹⁻²³ occurs when hyphae invade bone^{5,7,19} and can result in intracranial aspergillosis. A lung focus can spread to the spine,^{3,9,14,24} or CNS infection can occur following neurosurgery.^{8,11} Most CNS aspergillosis is associated with osteomyelitis^{17,21,22,25,26} which has been reported in ver-

Figure 2. Unenhanced parasagittal magnetic resonance image showing pancake lesion adjacent to right jugular foramen (arrow). This may represent thickened dura.

Figure 3. Methenamine silver stained section from biopsy specimen of petrous bone. Confluent septate branching hyphae are characteristic of *Aspergillus*.

tebrae, wrist, and sternum^{14,24,27-36} as well as maxilla and skull base.^{6,7,17,19,21-23,26,37,38} Patients present with focal neurologic findings, headache, malaise, and nuchal rigidity^{5,14,15,18,21,38} or spinal cord compression.^{14,39}

DIAGNOSIS

Diagnosis of aspergillosis depends on clinical and radiological evidence of infection, isolation and identification of *Aspergillus* at this site, and histological evidence of tissue invasion by a fungus with the same morphological characteristics as the cultured agent.¹³ Problems in diagnosis occur because the specimen can become contaminated with airborne spores, or the site may be colonized with noninvasive *Aspergillus* species.^{13,29}

Aspergillus grows on any media (Sabouraud's is opti-

mal⁸), forming characteristic conidiophores.^{13,40} Blood cultures in disseminated disease are usually negative,^{8,13} as are cerebrospinal fluid cultures in CNS infection.^{4,14} Cerebrospinal fluid may show increased protein and a pleocytosis.^{2,14}

Biopsy specimens stained with hematoxylin and eosin, periodic acid-Schiff, or methenamine silver reveal acute-angle branching septate hyphae and larger numbers of conidia characteristic of the species.^{8,14,15,34,40} Fluorescein labelled antibodies and antigen detection in sera by enzyme-linked immunosorbent assay or radioimmunoassay are not routinely available but may be useful to detect early disease.^{13,14}

Pathology includes granulomata, mycotic aneurysms, and thrombosis.^{2,8} Necrosis and acute inflammatory infiltrates surround areas of granulomatous reaction.² Hyphae invade vessel walls causing necrosis and polymorpho-

Figure 4. View of cranial base from above after removal of brain. *Previous surgical site; small arrow, jugular foramen; large arrow, *Aspergillus* abscess.

Figure 5. Autopsy specimen of right petrous temporal bone revealing *Aspergillus* osteomyelitis with multiple abscesses (arrow).

nuclear cell infiltrates which allow weakening of the vessel wall.^{2,12,38} These mycotic aneurysms burst, resulting in hemorrhagic infarction.^{1,12,16} Intraluminal hyphae can serve as a nidus for thrombosis.^{1,38,41}

The immune response to the spores and conidia is via macrophages, while polymorphonuclear cells kill mycelia.^{13,26} Steroids are thought to inhibit intracellular killing by macrophages, allowing intracellular germination.^{9,10}

Radiographs of fungal osteomyelitis show ill defined bony lucencies.^{5,19,25,42} Gallium and technetium scans are positive.²⁶ Computed tomography may show cerebral edema or involved sinuses with opacification, or a dense mass with hyperdense foci related to calcium sulfate deposits in necrotic areas of an aspergilloma.^{16,43} Magnetic resonance imaging shows intermediate signal areas surrounded by high signal intensity edema in the brain.⁴¹ Fungal sinusitis is low intensity on T1, and very low on T2, related to the high level of iron, magnesium, and manganese in the fungus.¹⁶

TREATMENT

Mainstays of therapy for aspergillosis include antifungals and debridement.^{13,37} Amphotericin B is currently the drug of choice, despite its systemic toxicity, and is titrated against response.^{13,35,37,42} Some authors recommend adding rifampin or 5-fluorocytosine.^{5,8,9,18,23} Newer antifungals include miconazole,¹⁵ fluconazole,¹³ and itraconazole,^{13,44,45} which have fewer side effects but whose efficacy versus *Aspergillus* is still being debated.¹³ Liposomal amphotericin B and gamma interferon are future possibilities.¹³ Debridement to remove necrotic debris is important because drugs penetrate abscesses poorly.¹⁸ Hyperbaric therapy has been suggested but has not gained wide acceptance.¹⁸

Prevention of aspergillosis in immunocompromised patients has gained some attention with studies of amphotericin B nasal spray or itraconazole used prophylactically to prevent colonization in those at high risk.¹³

Prognosis for cranial and CNS aspergillosis is poor. Most reported cases are fatal unless the patient was initially healthy and diagnosed early.^{8,9}

DISCUSSION OF THE CASE

This patient had several subclinical risk factors for invasive fungal disease. His alcohol intake was sufficient to have possibly caused micronodular liver cirrhosis. His remote medical history included a perforated tympanic membrane on the side of the fungal abscess which may have been associated at some point with otitis externa allowing ingress of organisms into the middle ear and subsequently the mastoid sinus. He had an abscessed maxillary molar extracted 4 months before his cranial symptoms, which was complicated by a maxillary sinus infection (although on the opposite side of the fungal abscess). He was treated with multiple courses of broad spectrum antibiotics with little relief.

In hospital, administration of oral dexamethasone instigated hyperglycemia requiring insulin therapy, suggesting that the patient may have had subclinical glucose intolerance of longer duration.

At admission, examination revealed sensorineural hearing loss, loss of gag reflex, vocal cord paralysis, and weakness of sternomastoid and trapezius muscles, all on the right side only. This suggests involvement of cranial nerves (CNs) 8 to 11. This is somewhat unusual for jugular foramen syndromes, since CN 8 is not usually involved. Loss of CNs 9 to 11 with sparing of CN 12 localizes the lesion to the jugular foramen and is known as Vernet's syndrome.⁴⁶ Usual causes are tumours or aneurysms.⁴⁶

CONCLUSION

Aspergillosis of the cranial base is an unusual clinical entity, usually occurring in cases with known associated factors such as immunosuppression and maxillary sinusitis. We present a case with no obvious instigating factors which underlines the need for clinical suspicion and early diagnosis of fungal infections.

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