

Central Nervous System Aspergillosis: A Case Report and Literature Review

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A *aspergillus* is a common fungus that lives in soil and decaying vegetation¹ and is ubiquitous throughout the world. The incidence of invasive central nervous system (CNS) aspergillosis has increased in recent years, most often in immunocompromised patients. However, invasive CNS aspergillosis remains difficult to diagnose and treat. Early diagnosis appears to be the key in the small number of successfully treated cases. This article presents a case of disseminated aspergillosis with significant CNS invasion in an immunocompetent patient. Patient population, signs and symptoms, clinical course, and diagnosis are reviewed.

CASE PRESENTATION

A 26-year-old man with asthma and severe dyspnea presents to the emergency department by ambulance. In the ambulance, he is given albuterol treatment, sedated, and intubated. He requires vecuronium bromide and pancuronium infusions for severe agitation during intubation.

History

The patient's medical history is significant for 4 years of asthma treated with bronchodilators. He takes epinephrine and albuterol aerosols on a regular basis. The patient had two previous asthma exacerbations requiring steroid treatment but no intubation. In addition, the patient had been exhibiting symptoms of an upper respiratory tract infection 1 week prior to presentation.

Physical and Laboratory Evaluations and Hospital Admission

The patient's physical examination is significant only for diffuse wheezing in all lung fields. Mechanical ventilation is instituted, and chest radiography reveals an infiltrate in the middle lobe of the right lung.

The patient is admitted to the hospital and treated with cefuroxime (1 g), erythromycin (500 mg), aminophylline (0.5 mg/kg/hr), and methylprednisolone (250 mg). After admission, the patient is persistently febrile and his leukocyte count increases to 59,700/mm³ 10 days postadmission, after which it remains above 20,000/mm³.

The initial diagnostic work-up is completed within 10 days of admission. The patient's echocardiogram is normal. Serial sputum cultures grow *Candida albicans*, multiple cultures of *Enterobacter aerogenes*, and *Aspergillus* species, which is presumed in this case to be a contaminant. Multiple blood, urine, and stool cultures are negative. Mycoplasma antibody, acid-fast bacilli, sputum influenza A and B, and urine *Legionella* cultures are all negative. Serum HIV-1 and HIV-2 tests are negative. Pleural fluid cultures are all negative.

One week after admission. One week following admission, the patient is placed on a variety of antibiotics, including cefuroxime, erythromycin, ciprofloxacin, fluconazole, imipenem, metronidazole, and ceftriaxone. Despite antibiotic therapy, the patient's fever persists. Abdominal and pelvic computed tomography (CT) scans are inconclusive; lung perfusion scan, abdominal ultrasound, and sinus films are normal. Serial radiography of the patient's chest demonstrates the persistent infiltrate in the middle lobe of the right lung.

Two weeks after admission. Two weeks after hospital admission, the patient undergoes tracheotomy and is

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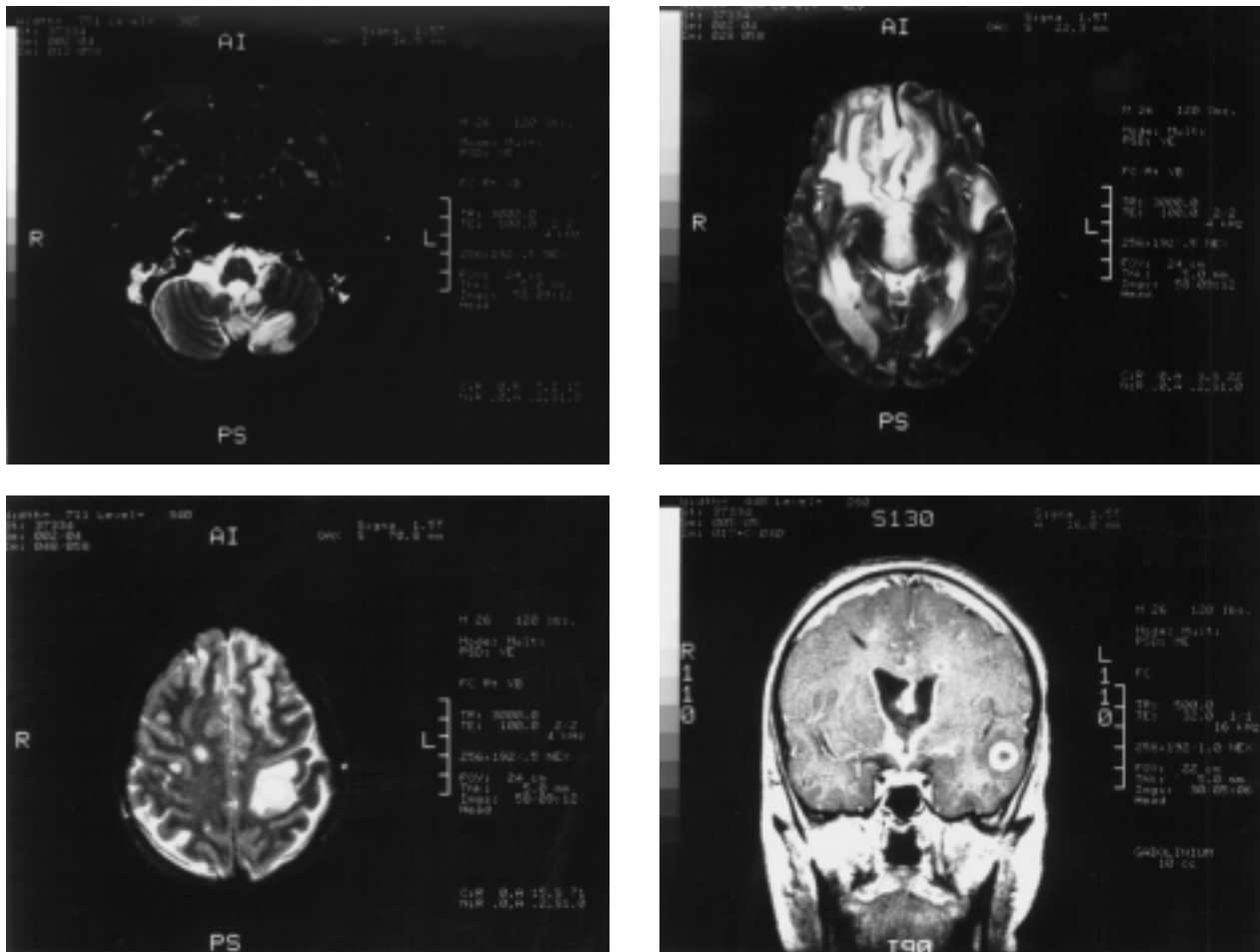


Figure 1. Gadolinium-enhanced magnetic resonance imaging of the patient's brain demonstrates multiple ring-enhancing foci located in the left frontal, parietal, and temporal lobes, in the left cerebellar hemisphere, and diffusely in the periventricular white matter.

placed on methylprednisolone taper for more than 3 weeks. Following taper of the vecuronium bromide and pancuronium drips, the patient is slow to respond to the treatment. Quadriplegia and global areflexia set in; the patient is able to demonstrate eyebrow movements but no movement of any other facial muscles or the tongue. An electroencephalograph demonstrates a normal awake pattern with no abnormal focus. Electromyograph (EMG) and nerve conduction velocity (NCV) exhibit diffuse denervation and evidence of axonal loss.

Three weeks after admission. Three weeks postadmission, serial chest radiography reveals that the infiltrate in the middle lobe of the lung has progressed to multiple basilar infiltrates. A sinus CT scan is normal; but a CT scan of the patient's head demonstrates a 5.5- by 3.1-cm ring-enhancing lesion with surrounding edema in the right frontal lobe and a 1.5-cm ring-enhancing lesion in the left parietal lobe. The posterior cranial fossa is nor-

mal. Stereotactic brain biopsy of the right frontal lesion yields a dark purple fluid. Gram stain of the fluid reveals multiple neutrophils but no organisms. Frozen sections of the brain biopsy show necrotic brain and inflammatory cells, but no organisms.

Hospital Transfer and Additional Evaluation

Four weeks after admission, the patient remains unresponsive and is transferred to a neuroscience critical care unit for further management. On transfer, the patient is in a coma. His pupils are bilaterally reactive to light with mild anisocoria. Bilateral corneal reflexes, oculocephalic reflexes, and gag reflex are intact. Flaccid quadriplegia, global areflexia, and equivocal, bilateral plantar flexion responses are present. Significant laboratory findings include a serum leukocyte count of 7300/mm³ with 43% band forms. Serum chemistries are within normal limits. Electrocardiography is normal.

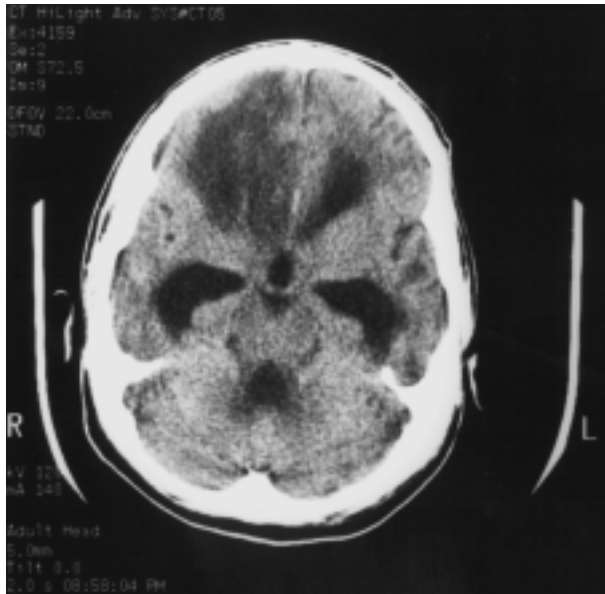


Figure 2. Computed tomography scan demonstrates right frontal lobe edema and massive communicating hydrocephalus 5 weeks after symptom onset.

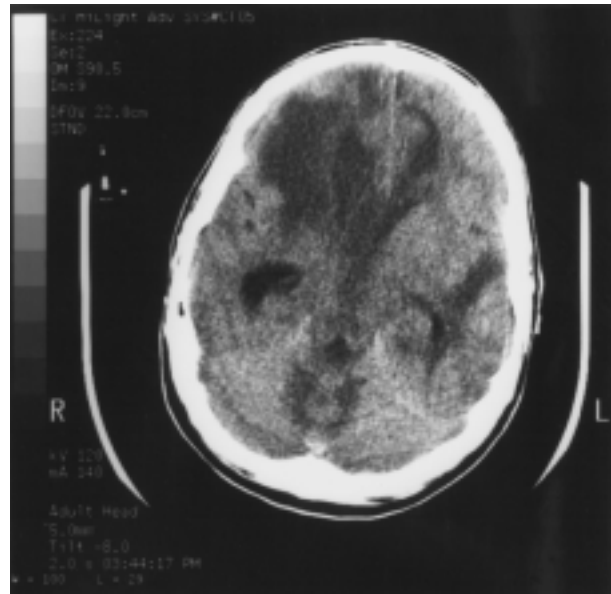


Figure 3. Computed tomography scan demonstrates the right frontal lobe following external drainage of cerebrospinal fluid via an intraventricular catheter. The trapped right temporal horn is evident.

Chest radiography no longer demonstrates signs of infiltrates or effusion. Head CT scan shows an increase in the size of the lateral cerebral ventricles compared with head scan results obtained 3 days earlier at the first hospital; results are consistent with moderate hydrocephalus with no evidence of herniation. Blood, urine, and stool cultures are negative on admission, but sputum culture grows *Enterobacter aerogenes*.

An intraventricular catheter is placed in the left frontal cerebrum. The patient's initial intracranial pressure (ICP) is 29 mm Hg. Laboratory evaluation of the patient's cerebrospinal fluid (CSF) includes the following values: leukocytes, 12/mm³ with 58% segmented neutrophils; erythrocytes, 7/mm³; glucose, 72 mg/dL; and protein, 20 mg/dL. Gram stain of the patient's CSF shows moderate neutrophils and no organisms. Gadolinium-enhanced magnetic resonance imaging (MRI) of the patient's brain demonstrates multiple ring-enhancing foci located in the left frontal, parietal, and temporal lobes; the left cerebellar hemisphere; and diffusely in the periventricular white matter (Figure 1). Repeat CT scan of the patient's brain reveals a 5-cm ring-enhancing mass in the right frontal region and several masses posterior to the fourth cerebral ventricle; evidence of communicating hydrocephalus is also present (Figure 2). MRI of the cervical spine is unremarkable. Repeat CSF analysis by lumbar puncture demonstrates the following values: leukocytes, 1300/mm³ with 98%

segmented neutrophils; no erythrocytes; glucose, 40 mg/dL; and protein, 110 mg/dL. The CSF is negative for cytology and bacteria. Multiple samples of CSF are taken from the intraventricular catheter and repeat cultures remain negative. The preliminary pathology report from the stereotactic biopsy demonstrates fungal elements in the brain tissue. The patient is immediately placed on intravenous amphotericin B.

A few hours after initiation of amphotericin B therapy and placement of the intraventricular catheter, the patient can open his eyes on command. His mental status continues to improve; he is consistently able to follow commands, but remains quadriplegic. Repeat EMG and NCV demonstrate normal sensory responses except for reduced motor amplitudes and mildly reduced nerve conduction velocities consistent with acute axonal motor neuropathy. Final results of brain biopsy demonstrate growth of *Aspergillus fumigatus*. Parathyroid, cortisol, thyroid, and follicle-stimulating hormone serum levels are normal.

Outcome

Three days after intraventricular catheter placement, the catheter stops draining and the patient's mental status deteriorates. An emergent CT scan of the head demonstrates a decompressed left lateral cerebral ventricle and enlargement of the right lateral cerebral ventricle (Figure 3). A second intraventricular catheter is

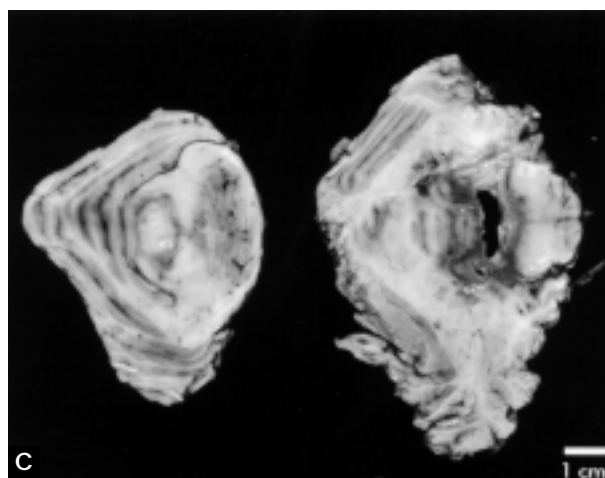
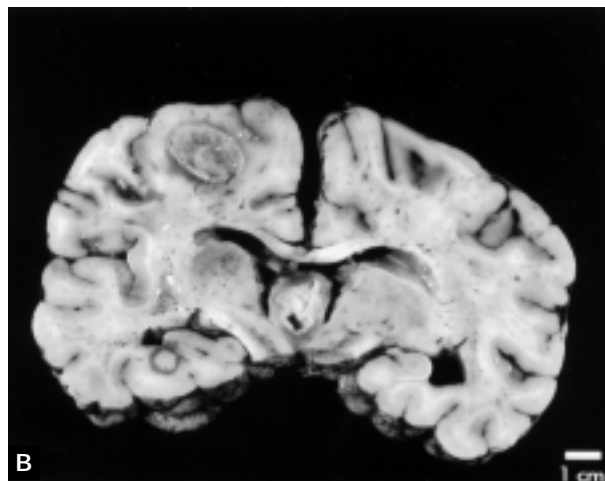
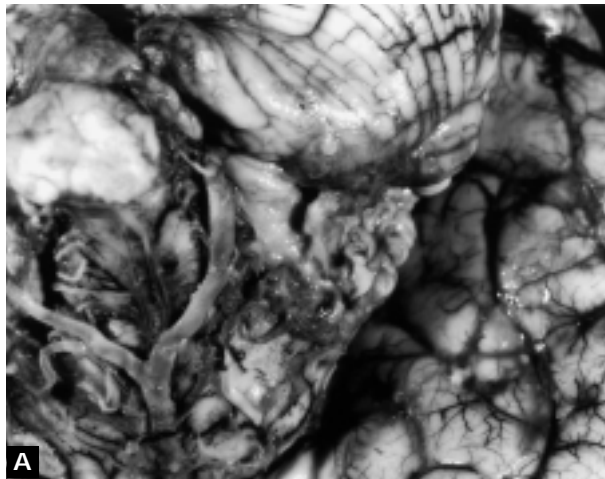


Figure 4. Autopsy examination of the patient's brain demonstrates A) abscess at the base of the brain, B) multiple abscesses in the cerebrum, and C) abscess in the periaqueductal region of the brainstem.

placed in the right lateral cerebrum and the patient is able to follow commands again. MRI of the brain demonstrates an 8- by 3-cm ring-enhancing collection of fluid in the right frontal lobe with rim enhancement extending into the third ventricle; MRI also reveals subependymal enhancement of the third, fourth, and a large portion of the lateral ventricles, as well as an increase in the size and number of lesions throughout the brain parenchyma including the posterior fossa.

Intrathecal amphotericin B and 5-flucytosine (5-FC) are added to the treatment regimen. A CT scan of the head shows worsening edema with obliteration of the brain stem cisterns. Ten days after hospital transfer, the patient is no longer able to follow commands, although brain stem reflexes remain intact. The patient demonstrates increased ICP and responds transiently to mannitol infusion, therapeutic hypernatremia, furosemide, and hyperventilation. On day 12 of transfer, the patient develops intractable intracranial hypertension. On day 13 of transfer, the patient is certified brain dead.

Autopsy Results

Autopsy reveals widely disseminated *Aspergillus* infection involving the brain, meninges, cauda equina, lungs, and thyroid. Multiple gray and white matter target lesions with central cavitation are present throughout the brain (Figure 4). Bilateral uncal herniation is present with associated parenchymal necrosis. The lower lobes of the lungs bilaterally demonstrate multiple hemorrhagic parenchymal lesions, the largest lesion revealing a 3-cm central cavity.

Histologic examination reveals fungal organisms morphologically consistent with the *Aspergillus* species growing in the brain (Figure 5), meninges, lungs, and thyroid. The thyroid reveals multiple fungal abscesses. The lungs demonstrate a necrotizing, granulomatous infectious process with prominent giant cell reaction and multiple fungal microabscesses. The bronchi reveal smooth muscle and mucin-secreting cell hypertrophy, mucous plugging with thickened basement membranes, and peribronchial and intrabronchial inflammation consistent with long-term asthma. The brain reveals diffuse, multiple cystic abscesses with surrounding reactive gliosis and giant cells. *Aspergillus* has diffusely invaded the subarachnoid space and extends down the spinal cord. Plastic sections of the right sural nerve are normal. Frozen sections of the quadriceps muscle show evidence of acute insult, manifested by degenerated and regenerated fibers and necrotic and atrophic fibers, consistent with myopathy or acute neuropathy.

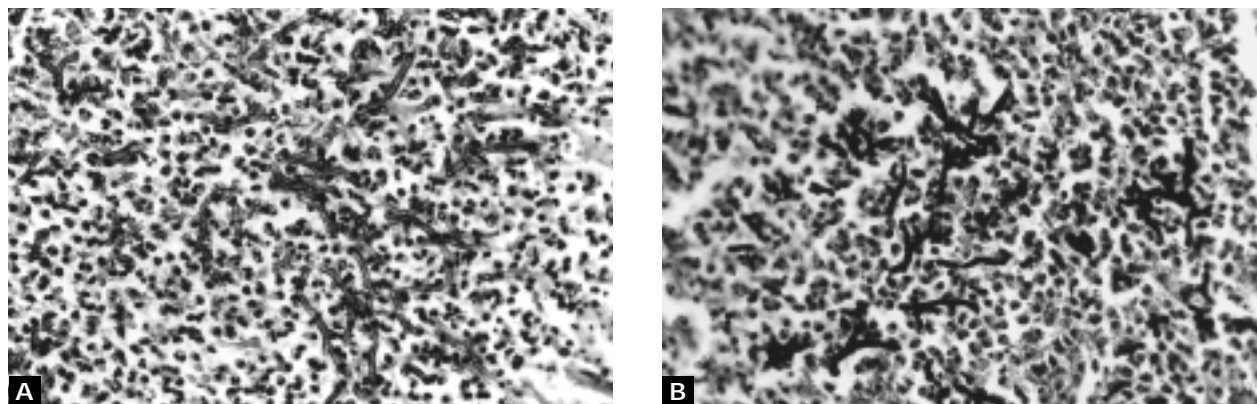


Figure 5. Histologic examination at autopsy reveals *Aspergillus* in the abscess cavity of the frontal lobe. A) Hematoxylin and eosin stain, X 100. B) Silver stain, X 100.

DISCUSSION

Pathogenesis

As noted previously, *Aspergillus* is an ubiquitous fungus that lives in soil and decaying vegetation.¹ There are more than 350 species of *Aspergillus*; however, only a few species are pathogenic in humans.² The most common pathogenic species is *Aspergillus fumigatus*,³ but *A. flavus*, *A. niger*, *A. nidulans*, *A. restrictus*, and *A. ochraceus* have also been reported to cause disease in humans. These pathogenic species produce spores or conidia approximately 2 to 3 μm , and 90% of these spores are retained in the alveoli when inhaled. Inhalation into the lung is the most common portal of entry, although entry through the skin and by ingestion into the gastrointestinal tract has been reported.² In infected tissue, species of *Aspergillus* appear as branching septate hyphae 3 to 4 μm in length. *A. fumigatus* can be distinguished by its rather long, uniform hyphae when compared with the short, irregular hyphae of other *Aspergillus* species.

Inhalation of *Aspergillus* into normal, healthy lungs does not typically cause disease, although a large exposure may result in a self-limited pneumonitis that resolves spontaneously within weeks.¹ In a patient with preexisting lung disease, such as a cyst, inhalation of *Aspergillus* spores can lead to colonization of the cyst resulting in a fungal ball or an aspergilloma. Direct tissue invasion does not occur. Asthma patients are at risk for allergic bronchopulmonary aspergillosis, which is characterized by eosinophilia, IgE antibody to *Aspergillus*, and variable pulmonary infiltrates. There is no evidence of eosinophilia in the patient presented in this case study; however, the patient did have asthma, which may be a risk factor for aspergillosis.

If colonization of the lungs does occur, the *Aspergillus* infection can become invasive and spread through a

hematogenous route.^{1, 3, 4} *Aspergillus* species may also infect the sinuses in otherwise healthy patients.⁵⁻⁹ Although direct invasion of the brain does not usually occur, direct invasion from a middle ear infection has been reported.¹⁰ At least one case of CNS aspergillosis in an intravenous drug user has been reported. In this case, no pulmonary focus was found; direct inoculation of the pathogen was the most likely portal of infection.¹¹ Isolated cases of CNS aspergillosis following direct inoculation during neurosurgery have also been reported.^{9,12} Very rarely, aspergillosis is confined to the CNS and no route of infection can be identified.^{13,14}

Patient Population

Immunocompromised patients are at the greatest risk for invasive aspergillosis.^{3,15} Recently, the incidence of invasive aspergillosis has increased in patients who have undergone organ transplantation or who have cancer or AIDS.^{3,5,12,15} The most common underlying diseases that predispose patients to invasive aspergillosis include acute leukemia, lymphoma, and aplastic anemia. Transplant recipients are at an increased risk for invasive aspergillosis secondary to immunosuppressive therapy; the rate of infection in these patients noted in one review was 9%.³ Although classical immunocompromised patients are the most susceptible to disseminated aspergillosis, CNS aspergillosis has also been reported in patients with such predisposing conditions as diabetes,¹⁰ heroin abuse,¹¹ bullous pemphigus on steroids and immunosuppressants,¹² and alcoholism.¹³ Patients with increased concentrations of steroids from either endogenous (eg, Cushing's disease) or exogenous sources^{9,15,16} are also at risk for invasive aspergillosis. One explanation for the association between aspergillosis and increased steroid concentration is the ability of steroids to depress cell-mediated

immunity.¹⁶ The patient in this case study was given high doses of methylprednisolone for an extended period of time as treatment for asthma exacerbation. The patient's steroid therapy may have been the predisposing factor for CNS aspergillosis because no other predisposing condition, including HIV infection or endocrine disorder, was evident.

In the majority of cases reviewed, patients were taking a variety of antibiotics for presumed bacterial infection for an extended period of time before *Aspergillus* was identified.^{7,9,12,15,17} The patient in this case study was given multiple broad-spectrum antibiotics empirically for fever of an undetermined etiology. Prolonged antibiotic use suppresses normal flora and can contribute to the pathogenicity of an otherwise infrequent organism such as *Aspergillus*.

Pathophysiology

Aspergillus can cause a wide spectrum of disease in the CNS. *Aspergillus* has a predilection for blood vessels and is capable of invading the vessel walls, which can lead to the formation of a thrombus, hemorrhage, or, more rarely, mycotic aneurysm. Hemorrhagic infarcts are the most common pathologic finding on autopsy.^{3,9,15} Formation of cerebral abscess is the next most frequent manifestation of CNS aspergillosis. Cerebral abscesses, which are often multiple,^{3,6,15} are associated with cerebral edema and have a predilection for the cortical gray-white junction.⁹ In comparison with the cerebrum, the cerebellum and brainstem are less commonly affected.³ CNS aspergillosis rarely causes focal meningitis^{3,15} or ventriculitis.^{9,11} However, meningitis has been shown to be a more common pathologic finding in patients who are drug abusers.¹¹ Infrequently, *Aspergillus* may cause the development of a granuloma.⁷

The components of several pathological features may be present within the same patient. For example, cerebral infarction and meningitis involving the spinal cord have been described in a patient with AIDS.¹⁸ In the patient in this case study, multiple cerebral abscesses, ventriculitis, meningitis, and multiple areas of hemorrhagic necrosis were present on postmortem examination. Thus, the ventriculitis most likely resulted from the rupture of an abscess into the lateral ventricle, as was seen on MRI. However, development of acute obstructive or communicating hydrocephalus could also have caused clinical deterioration in this patient.

Signs and Symptoms

Clinical presentation of CNS aspergillosis is variable. Alteration of mental status with or without focal neurologic deficits is the most common presentation. Hem-

orrhagic infarction secondary to *Aspergillus* invasion and subsequent rupture of cerebral blood vessels or cerebral abscess formation^{8,15} produces focal neurologic deficits.³ Specific focal signs are dependent on the location of the lesion. CNS aspergillosis in the form of focal meningitis presents with symptoms such as a focal headache.^{3,15} Mycotic aneurysm may rupture causing symptoms of a subarachnoid hemorrhage.⁵ In one reported case, ventriculitis presented with seizure.¹¹ Headache is rarely the presenting symptom of CNS aspergillosis¹⁵ but has been the first presenting symptom in cases with a varied pathology.^{7,8,19} Patients taking immunosuppressive therapy have an increased incidence of encephalopathy even without additional fungal infection. This factor may explain the increased incidence of change in mental status as the presenting factor in patients taking immunosuppressive therapy.³

In the patient in this case, the clinical presentation of CNS aspergillosis was complicated by long-term sedation and a peripheral neuropathy of an undetermined etiology. The patient's iatrogenic paralysis and neuropathy made the central focal motor deficit assessment difficult to ascertain. The patient had no overt seizure activity and electroencephalogram was normal; however, the patient was prophylactically treated with phenytoin, which has been shown to control seizures in patients with CNS aspergillosis.^{4,6}

Clinical Course

CNS aspergillosis takes either an acute or chronic course depending on the immune status of the patient and the mechanism of spread of disease. In the chronic, slowly progressive form of CNS aspergillosis, fulminant disease has been reported to occur several months to years after the initial signs of infection.^{6,8,17} Extension from the sinuses into the brain is usually seen in cases of profound neutropenia; in this setting, the course is fulminant and not indolent. Patients who are drug abusers are more prone to a prolonged disease course, even though the focus of inoculation seems to be hematogenous rather than direct fungal invasion.³ Severely immunocompromised patients are more likely to have the acute onset of severe symptoms and a rapid, downhill course of disease.^{7,8}

The clinical course of a patient with CNS aspergillosis depends on the underlying pathology, as does the initial presentation. Focal deficits secondary to cerebral abscess are most often followed by progressive deterioration of mental status as the abscess increases in size and causes increased edema and ICP. *Aspergillus* abscess is also associated with seizure activity in many

cases.^{3-6,13,19,20} Symptoms of bronchopneumonia are often present at some point during the disease course, often preceding CNS symptoms. However, the symptoms of bronchopneumonia are usually retrospectively recognized as signs of CNS aspergillosis.⁹ In this case study, it was difficult to determine whether the patient's upper respiratory infection symptoms experienced prior to the asthma exacerbation were *Aspergillus* bronchopneumonia. However, chest radiography did reveal a middle lobe infiltrate in the patient's right lung on hospital admission. Fever is also a common symptom of CNS aspergillosis, especially in patients with acute disease.^{7,11} The presence of fever is variable in patients taking steroid therapy because the fever may be masked.^{9,16} For example, the patient in this case study exhibited no fever while taking dexamethasone.

Diagnosis

Unfortunately, the diagnosis of invasive aspergillosis is extremely difficult, as demonstrated by the large proportion of cases that are diagnosed postmortem. Walsh et al¹⁵ reviewed 16 patients with the autopsy diagnosis of CNS aspergillosis and found that no cases were clinically diagnosed. Clinical presentation varies so greatly that the index of suspicion must be high to even entertain the diagnosis of *Aspergillus* infection. Chest radiography often reveals an infiltrate suggestive of pneumonia or granulomatous disease at some point in the disease course.^{9,15,20} Neuroradiologic findings may also be variable. Cerebral abscess can be recognized most often as discrete, ring-enhancing lesions, although variability in the degree of ring enhancement has been reported.^{6,9} Infected blood vessels and ventricles can be recognized as enhancement on MRI, but again ring enhancement varies and the extent of disease may be underestimated on CT or MRI.^{6,15}

Diagnosis of CNS aspergillosis from laboratory examination remains difficult as well. Sputum cultures may reveal *Aspergillus* if pneumonia is present, but *Aspergillus* is not always revealed. In contrast, just a single positive sputum isolation in a neutropenic patient with pneumonia can suggest the diagnosis of invasive aspergillosis.¹ Blood and CSF cultures are invariably negative for *Aspergillus* but have been reported positive in a few cases.^{11,12,17} Patients with involvement of the ventricles or meninges are more likely to have positive CSF cultures. However, a positive culture from CSF can take up to 1 month; therefore, the culture's positive results may be revealed late in the disease process.¹⁷ Antibody to *Aspergillus* antigens is demonstrated in the serum of many colonized patients, but antibody levels are often low and not readily detectable. If detectable,

this finding should be considered significant especially when accompanied by clinical suspicion.² Biopsy of the involved region is almost always necessary for diagnosis. Tissue histology is diagnostic of invasive fungal disease, but culture is needed for speciation.¹

CSF findings are variable and nonspecific. Leukocyte pleocytosis is generally evident, but both mononuclear^{15,17} and polymorphonuclear cells¹⁸ have been reported as the predominate cell type. Erythrocytes may be present.¹⁵ Generally, protein levels are mildly elevated and glucose levels are normal to decreased.^{8,17} In this case study, the patient had a marked polymorphonuclear cell pleocytosis. The patient's glucose level was normal and protein content was only slightly elevated.

Treatment

CNS aspergillosis has been successfully treated in only a few cases. Only one case has been reported in which amphotericin B as single agent therapy was used successfully.⁹ The remainder of the successful cases utilized a combination of surgery and medical treatment. Stereotactic drainage and amphotericin B have been used successfully in patients with a single abscess.^{4,6} In other patients, craniotomy and cranial resection in combination with amphotericin B with²⁰ or without^{13,19} 5-FC have been successful. In one reported case, successful treatment was achieved through combined craniotomy and resection and conventional amphotericin B followed by liposomal amphotericin B and long-term itraconazole.²¹

Amphotericin B. Amphotericin B is the antifungal drug of choice for treatment of aspergillosis^{1,4} and can be delivered either intravenously or intrathecally. CSF penetration of the drug is poor, therefore intrathecal administration may be more useful in CNS aspergillosis. Potential side effects of amphotericin B are numerous and may include severe febrile reactions to the initial dose. A 0.1 mg/kg test dose followed by an increase to the maintenance dose is recommended. The optimal maintenance dose as well as the total dose required for treatment of invasive aspergillosis remains debatable.^{4,20,22} A total dose of 2.3 g was used successfully in an adult patient following stereotactic drainage,⁴ whereas only 500 mg and 450 mg were used following craniotomy and resection in a 12-year-old patient²⁰ and 38-year-old patient,¹³ respectively. Given the small number of cases, it is difficult to determine whether the type of surgery had a significant effect on the difference of necessary drug dose. High dosages and extended duration of amphotericin B therapy are associated with increasing frequency of such side effects as anemia, hypokalemia, azotemia, hypomagnesemia, and phlebitis.

The use of liposomal amphotericin B allows delivery of higher doses of the drug without the associated toxic side effects. The high doses that are attainable with liposomal amphotericin B may help to achieve higher drug concentrations in the brain, but clinical reports of this effect are few.

Amphotericin B has been most commonly used in combination with 5-FC, but amphotericin B has also been used in combination with rifampin.^{10,22} In vitro studies have demonstrated that amphotericin B and 5-FC have a synergistic effect against *A. fumigatus*, but in vivo studies have produced conflicting results although clinical data is limited. Amphotericin B in combination with rifampin is even less well-described, although the combination therapy has been reported to be successful against CNS aspergillosis in at least one case.²²

SUMMARY

CNS aspergillosis in immunocompetent patients remains uncommon. This case study exemplifies the importance of a high index of suspicion for CNS aspergillosis in an immunocompetent patient who presents with persistent fevers, evidence of pneumonia, and the suspicion of CNS disorder. Unfortunately, the patient in this case study is the rule rather than the exception in terms of the difficulty of diagnosing CNS aspergillosis. However, the small number of successfully treated cases of CNS aspergillosis give hope that aggressive therapy can provide a cure to what is more often thought of as a fatal disease. **HP**

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