Invasive aspergillosis extensively involving the brain and multiple organs in a bone marrow transplant patient

D Feng, R Heffner, J Wright

Citation
D Feng, R Heffner, J Wright. Invasive aspergillosis extensively involving the brain and multiple organs in a bone marrow transplant patient. The Internet Journal of Pathology. 2007 Volume 7 Number 2.

Abstract
We report here a 16-year-old Caucasian male with an 8 years history of acute lymphoblastic leukemia who died of an acute invasive systemic aspergillosis 163 days after allergenic bone marrow transplantation. One week prior to death, he had drowsiness, lethargy, and fever. Both CT scan and MRI of the head demonstrated multiple ring enhancing lesions consistent with intracerebral abscesses. Autopsy showed extensive brain involvement of aspergillosis in the frontal cortex, occipital cortex, hippocampus, basal ganglia, medulla, ponds, and cerebellum. Aspergillosis also presented in multiple organs including heart, lungs, liver, kidney, thyroid gland, and lymph nodes.

INTRODUCTION
Invasive aspergillosis is a serious opportunistic disease among immunocompromised and immunosuppressed patients (1,2,3). Aspergillus spp. is the most common fungus in intracerebral granuloma or abscess. Invasion of the CNS occurs either by direct extension from an area anatomically adjacent to the brain or by the hematogenous route. Brain abscesses are frequent in disseminated invasive aspergillosis (1). Bone marrow transplant patients, particularly allogenic transplant with graft versus host disease, treated with large doses of steroids represent a major risk of CNS aspergillosis. Prolonged severe neutropenia and high-dose corticosteroids are the major predisposing factors in cancer and solid organ-transplant patients. However, the disease may occur even in an apparently immunocompetent host. The incidence of the invasive aspergillosis is dramatically increased in susceptible individuals (1,2,3).

CASE REPORT
The patient was a 16 year-old white male with a history of acute lymphoblastic leukemia (ALL), which was diagnosed 8 years back. He was then treated with extensive chemotherapy, but his ALL was relapsed twice. Therefore, he received allogenic bone marrow transplantation. His graft versus host disease (largely limited to the skin) was well controlled with high dose of immunosuppression medication including high doses of steroids. Two weeks prior to death, he was very weak and presented to the hospital on wheelchair for a checkup. His parents informed that he had fallen on the floor on several occasions at home. On the same day he was admitted to the hospital for severe myopathy, and depression.

On admission, his vital signs were stable, and lab tests showed a white blood cell count of 17,000, hemoglobin 7, platelets 24,000, BUN 23, creatinine 0.6, glucose 278, alkaline phosphatase 134, total bilirubin 1.7, aspartate aminotransferase (AST) 45, alanine aminotransferase (ALT) 147, and lactate dehydrogenase (LDH) 1826. He had steroid-related diabetes, and appeared emotionally depressed associated with his disease and steroids. He had had pancytopenia for a few weeks. During his admission, he was treated with physical therapy for his myopathy, and was given multiple prophylactic antibiotics including amoxicillin, acyclovir, pentamisine, and caspofungin. He was also blood transfusion and growth factor (G-CSF) dependant. Five days after admission, the patient was noted to have change in mental status including drowsiness and lethargy. He complained of fatigue and weakness. Three days later, the patient became febrile and his blood culture revealed Staphylococcal Aureus infection from the central venous line, sensitive to oxacillin. He was treated with vancomycin and ceftazidime. Laboratory tests showed AST 2015, ALT 1900, alkaline phosphatase 255 and LDH 8100. Meantime, CT scan with and without contrast and MRI of the head, both demonstrated multiple ring enhancing lesions consistent with abscesses secondary to septic embolism.

Another three days later, the patient developed tonic-clonic
seizures, which lasted about one half hour despite antiepileptic therapy. Chest–portable diagnostic imaging reported a possible pulmonary nodule. Bilateral ventriculostomy with burr holes to place the tip of catheters in the ventricles was performed to reduce the increased ICP. The patient was treated with Amphotericin B liposome 420 mg IV daily. CT scan of his head demonstrated progression of the multiple hypodensity suggesting abscesses and increase in ventricular size due to hematoma, compared to the prior study each day. Brain biopsy was performed through the burr hole. The patient expired 2 weeks after admission. The presence of aspergillus infection was identified in the brain biopsy material one day after death. Complete autopsy was performed.

AUTOPSY FINDINGS
The patient presented a typical appearance of Cushing’s syndrome including moon face, truncal obesity, buffalo hump, hirsutism, multiple abdominal purple striae. He had bruises over his external body surface, and petechial hemorrhages on skin of his lower extremities. There was straw-colored fluid in the bilateral pleural cavities (right side 100 ml and left 220 ml), pericardial (120 ml) and peritoneal cavities (320 ml).

On gross examination, the brain was diffusely edematous and enlarged with flattened gyri and sulci. Multiple foci of recent hemorrhagic infarct and nodules, varying in size from 1 to 3 cm in diameter, were present in the frontal and occipital cortex, hippocampus, basal ganglia, medulla, ponds and cerebellum. Two foci showed recent hemorrhages draining into bilateral ventricles, which were enlarged and asymmetric (Figure 1). Bilateral pulmonary lobes showed multiple white to yellow, irregularly shaped demarcated, firm nodules varying in size with central necrosis. There were also similar nodules present in the heart, liver, spleen, left and right kidneys, thyroid, cecum, and lymph nodes.

Microscopically, numerous thin septate Aspergillus hyphae with 45 degree branching were identified in every portion of the brain on random sections. Vascular invasion by Aspergillus associated with extensive thrombosis, hemorrhage, infarct and edema were seen in bilateral cerebral hemispheres. Aspergillus was present in virtually every organ microscopically, including heart, lungs, liver, kidneys, thyroid gland, and lymph nodes on random sections. Aspergillus invading vessels with associated extensive thrombosis, hemorrhage and infarct were present in lungs (Figure 2), spleen, and kidneys. Bilateral lungs also showed necrotizing pneumonia, and edema. The liver exhibited diffuse necrosis and hemorrhage often adjacent to portal triads. There were cytopathic effects consistent with viral hepatitis. In the thyroid gland, multiple aspergillus fungal balls were noted spreading into adjacent follicles.

Figure 1
Figure 1: Photograph showing multiple foci of Aspergillus invasion in the cerebrum with recent hemorrhage into bilateral ventricles.
DISCUSSION

Aspergillosis is a serious infectious complication in immunocompromised patients. Other commonly affected patients include those with neutropenia from hematologic malignancy or chemotherapy, those with AIDS, and those on chronic corticosteroids (1-3). Life-threatening invasive aspergillosis is dramatically increasing, and commonly occurs in immunocompromised or immunosuppressed patients via inhalation of fungal spores (mold conidia) causing pulmonary infection (4). Clues to pulmonary infection are development of pleuritic chest pain and elevation of serum LDH (5). Aspergillus spp. is the most common fungus in intracerebral granuloma or abscess. Brain abscesses are frequent in disseminated invasive aspergillosis (1). Argani et al reported that most fully immunocompromised patients have few pulmonary symptoms initially but the progression rate is rapid. The earliest symptoms are a dry cough and low-grade fever (2). Vascular invasion by Aspergillus may cause hemorrhagic and ischemic necrosis, infarction, and potential dissemination to other sites in susceptible patients (so-called “angioinvasive infection”) (5). Disseminated aspergillosis may involve virtually every organ in the body if a wide search is performed. For early diagnosis and then early treatment, imaging studies are important tools. Chest radiography and CT can help in diagnosing primary pulmonary infection. Radiologic features include multiple, irregularly shaped pulmonary nodules surrounded by ground glass halos due to hemorrhage. More advanced disease is associated with cavitory lesions (50% of nodules cavitate within 2 weeks). Thoracic CT scans are more sensitive for detecting pulmonary infiltrates compatible with aspergillosis than are chest radiographs. CT scanning or MRI may also help to reveal fungal abscesses in the brain. Infarction or hemorrhage is the early radiologic presentation due to the angioinvasive nature of the infection (6,7). Recently, detection of Aspergillus flavus-specific DNA in brain biopsy and serum specimens has been used to diagnose a case of cerebral aspergillosis (8).

Systemic mycoses affecting severely immunocompromised patients often have acute or subacute presentations with rapidly progressive pneumonia, fungemia, and manifestations of extrapulmonary dissemination. Disseminated aspergillosis is associated with a mortality rate of greater than 90% (10). Treatment of invasive aspergillosis including early high doses of amphotericin B may be life-saving (9).

ACKNOWLEDGEMENTS

Authors wish to thank Dr. G. Brink for review of the manuscript.

References


Author Information

Dian Feng, MD
Department of Pathology and Anatomic sciences, Buffalo General Hospital

Reid Heffner, MD
Department of Pathology and Anatomic sciences, Buffalo General Hospital

John Wright, MD
Department of Pathology and Anatomic sciences, Buffalo General Hospital