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Aspergillus flavus epidural abscess and osteomyelitis in a diabetic patient

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A 63-year-old man had a history of diabetes mellitus for more than 10 years and took oral hypoglycemic agents regularly. He visited Taipei Veterans General Hospital with the complaint of progressive weakness in all 4 limbs and neck pain for 6 months. Computed tomography of the cervical spine revealed increased soft tissue density in the epidural space from C_2 to C_5 with cord compression. Surgical decompression was done and *Aspergillus flavus* was isolated from the inflammatory tissue. He was initially treated with oral itraconazole 200 mg 3 times per day for 4 days and then twice daily. Later, the treatment regimen was shifted to intravenous amphotericin B 25 mg/d. He died of intraventricular hemorrhage and complicated fungal meningoencephalitis 2 weeks postlaminectomy. This case reminds us that a prolonged history of back pain accompanied with peripheral neuropathy in diabetic patients should raise the suspicion of *Aspergillus* epidural abscess. Prompt aggressive diagnostic testing and management is needed to improve the likelihood of a good outcome of these patients.

Key words: *Aspergillus flavus*, diabetes mellitus, epidural abscess, osteomyelitis

Aspergillus species are ubiquitous saprophytic fungi. They are frequently found in water, soil, decaying vegetation, straw, air, grains, hay, mattresses, damp cellars, dusty spaces, potted plants, and ground black pepper [1-3]. Exposure to *Aspergillus* is universal and the major cause of invasive aspergillosis [1]. At least 250 species have been identified, a few of which are pathogenic for humans. Invasive aspergillosis is extremely rare in the absence of immunosuppression [1-3]. Epidural abscess as the initial manifestation of invasive aspergillosis is uncommon [4-7]. We report the case of a diabetic patient with epidural abscess and osteomyelitis caused by *Aspergillus flavus*.

Case Report

A 63-year-old man, carrier of hepatitis B and with a 10-year history of diabetes mellitus which was controlled with oral hypoglycemic agents, suffered from posterior neck pain and numbness of 4 limbs for 6 months prior to visiting a regional hospital for evaluation, where chest roentgenogram revealed a mass lesion in the right lung field and magnetic resonance imaging (MRI) of the brain disclosed cerebellar infarction. Biopsy of the pulmonary lesion was recommended, but the patient refused and so was followed up at the outpatient department without any medical intervention. Follow-up chest roentgenogram 3 months later did not show any space-occupying lesion in the lung. However, the posterior neck pain and progressive 4-limb weakness were aggravated and he could not walk at all. He was referred to Taipei Veterans General Hospital for further management.

On admission, the patient's body temperature was 37.6°C, blood pressure 140/90 mm Hg, pulse rate 92/min, and respiratory rate 20/min. Physical examination showed mild tenderness over the posterior neck without stiffness. Neurologic examination disclosed increased deep tendon reflex and decreased muscle power of all 4 extremities. Plantar reflex was positive. Decreased sensation below the neck was also found. Chest roentgenogram did not show any mass lesion. Mild widening of the retropharyngeal space was found on neck roentgenogram.

The white blood cell count was 8500 /mm^3 (normal range, 4800-10 800 /mm^3) with 68% neutrophils and 23% lymphocytes (normal range, 40%-74% and 19%-48%, respectively). Elevated alkaline phosphatase (183 U/L; normal range, 10-100 U/L) and γ-glutamyltransferase (286 U/L; normal range, 8-61 U/L) were found. Erythrocyte sedimentation rate was 70 mm/h (normal range, <20 mm/h). Abdominal sonogram disclosed chronic liver disease. The other laboratory data were unremarkable, including cerebrospinal fluid

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(CSF) study. Magnetic resonance imaging of the neck showed a prevertebral soft tissue lesion at levels of C_2 to C_5 with spinal cord compression, suggesting an infectious process (Fig. 1). A neurosurgeon was consulted and decompressive laminectomy with open biopsy and drainage of the abscess was performed. The specimen of pus was cultivated in blood agar and stained with lactophenol cotton blue which revealed *Aspergillus* (Fig. 2). *A. flavus* was isolated from the pus culture. The pathologic reports of the biopsy specimens of bone disclosed chronic inflammation with necrosis and osteomyelitis and Gomori methenamine silver stain of the biopsy specimens showed fungal invasion of the bony element (Fig. 3).

He was treated with oral itraconazole 200 mg 3 times per day for 4 days, then shifted to 200 mg twice daily. Three days later, owing to poor clinical response, intravenous amphotericin B deoxycholate in the dose 25 mg/d was used. After 1-week duration of conventional amphotericin B treatment, sudden onset of conscious change was found. Computed tomography of the brain disclosed intraventricular hemorrhage (Fig 4). Repeat CSF study showed pleocytosis and low glucose level. The culture of CSF grew *Aspergillus* spp. Chest roentgenogram did not show any active inflammatory process. He died of intraventricular

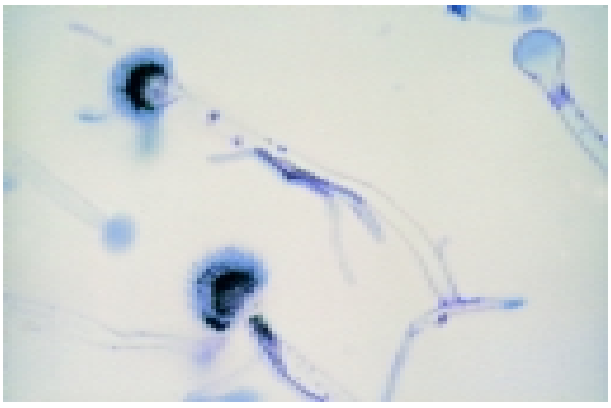

Fig. 2. Lactophenol cotton blue stain of epidural abscess reveals *Aspergillus* spp. (400x).

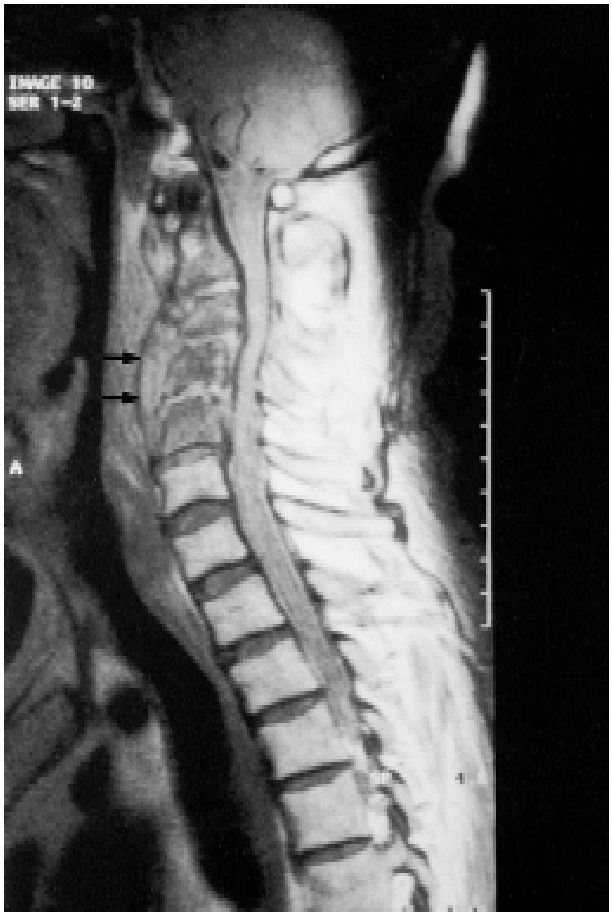

Fig. 1. Sagittal MRI (T1-weighted) of the cervical spine shows a prevertebral soft tissue mass and destructive process in vertebral bodies with cord compression at the levels of C_2 to C_5 (arrows).

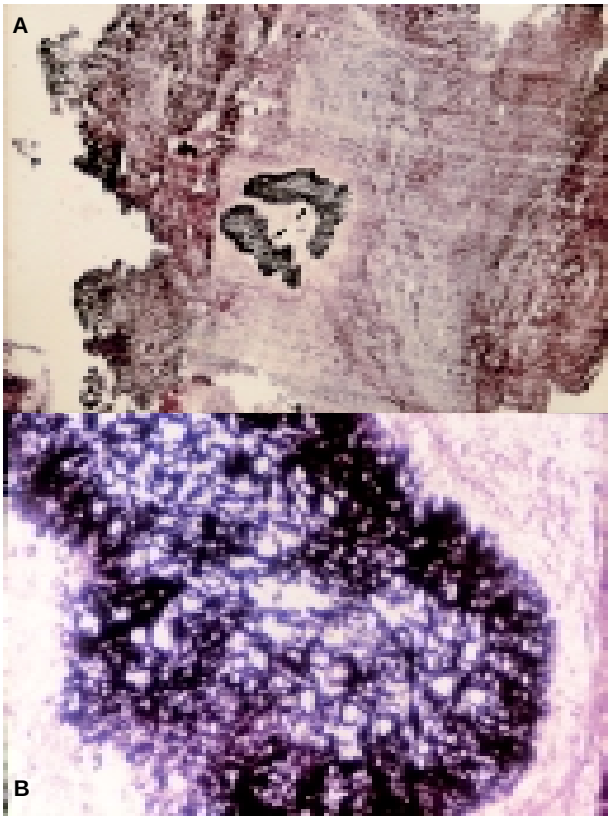

Fig. 3. Gomori methenamine silver stain of the biopsy specimens of bone shows dark-septated and distorted hyphae. **(A)** 40x (arrows); **(B)** 400x.

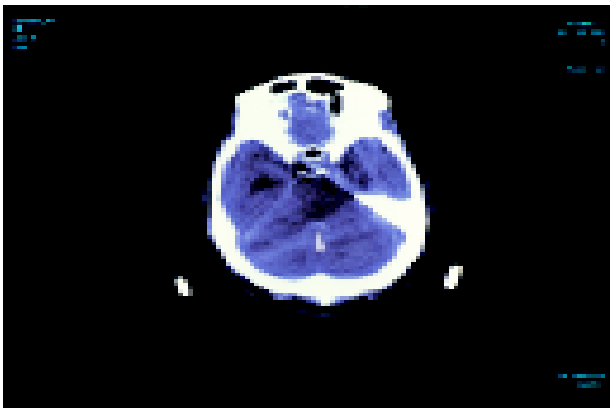

Fig. 4. Brain CT showing a high-density lesion in the 4th ventricle (arrowhead).

hemorrhage and complicated fungal meningoencephalitis 2-weeks postlaminectomy.

Discussion

The most common species of *Aspergillus* causing invasive disease is *Aspergillus fumigatus* [1-8]. Less commonly, infection due to *A. flavus*, *A. niger*, *A. terreus*, and *A. nidulans* have been described [2,3]. The portal of entry is usually by inhalation through the respiratory tract. Other pathways have also been described, such as gastrointestinal tract or direct inoculation through the skin. There are several risk factors for invasive aspergillosis, including granulocytopenia, high-dose corticosteroid or cytotoxic drug therapy, and bone marrow or organ transplantation [1, 3-10]. Other conditions associated with invasive aspergillosis include acquired immunodeficiency syndrome, liver cirrhosis, alcoholism, leukocyte dysfunction, chronic granulomatous disease, prolonged use of broad-spectrum antibiotics, and use of prosthetic material [3,4,6,8,11-13]. In patients with predisposition to invasive aspergillosis, the most common presentation is pulmonary disease [1-3,5]. The extrapulmonary sites commonly involved by aspergillosis are the brain, heart, kidney, and gastrointestinal tract [3]. The majority of *Aspergillus* spinal epidural abscesses arise from contiguous infection in vertebral bone [5,8,14]. Hematogenous dissemination occurs almost exclusively in patients with depressed immune function. Disseminated disease may result from pulmonary, gastrointestinal, external auditory canal, skin, or other foci [4]. Tissue invasion is enhanced by underlying debilitating disease; antimicrobial, corticosteroid, or cytotoxic therapy, and breakdown of local barriers [5].

Pulmonary alveolar macrophages form the first line of defense against *Aspergillus* conidia, which prevent germination and kill conidia. Once germination occurs, polymorphonuclear leukocytes are the most important ones in killing hyphae, with some contribution from monocytes [1,8]. Oxidative killing by phagocytes is necessary for recovering from invasive aspergillosis [2]. Impaired neutrophil oxidative burst and phagocytic function in diabetic patients may predispose them to aspergillosis [15]. In addition to accelerating the growth of *Aspergillus*, corticosteroid also impairs macrophage killing of *Aspergillus* spores and neutrophil and mononuclear cell killing of *Aspergillus* hyphae [2,10, 11]. Alcohol may interfere with polymorphonuclear cell function and contribute to invasive infection [11]. In this patient, the only notable risk factor was a history of diabetes mellitus, and there was no history of use of steroid or alcoholism.

In previous reports the time from the onset of symptoms to the definite diagnosis ranged from 5 to 7 months [4,5,7]. The symptoms and signs are nonspecific. In this patient, symptoms persisted for more than 6 months before definite diagnosis.

Ordinary laboratory examinations are of little help in the diagnosis of invasive aspergillosis. *Aspergillus* spp. may present as commensals, most commonly in the respiratory tract. Some species can be isolated from the oropharynx and gastrointestinal tract of normal hosts. In patients at risk of invasive aspergillosis, positive sputum cultures are highly significant [1]. Computed tomography of the chest may reveal a "halo sign" initially and, later, the "crescent sign" [14]. Magnetic resonance imaging offers the most reliable means of examination and monitoring of *Aspergillus* epidural abscess [7]. Lumbar and thoracic spines are usually involved [3-8,13], while cervical spine involvement, as in this patient, is less usual [3]. Cultures of blood, sputum, bone marrow, and gastrointestinal tract specimens are rarely positive and laboratory contamination is a well-recognized problem. Analysis of CSF is usually not diagnostic [4,11,14,16]. The most reliable method of diagnosis is biopsy with histologic examination and culture [4,7,8,14,16], which discloses acute-angle branching, septated nonpigmented hyphae measuring 2 to 4 μm in width. In this patient, the definite diagnosis was made from histologic examination and culture of biopsy specimens. Cultures of CSF and blood were negative.

Invasive aspergillosis is highly lethal in immunocompromised patients. Intravenous therapy is mandatory. Amphotericin B should be given at maximum tolerated doses. Lipid formulations of amphotericin are used for patients who have impaired renal function or who develop nephrotoxicity during

treatment. Oral itraconazole is an alternative for patients who can take oral regimens. Voriconazole is a novel triazole that can be used as a therapeutic agent. For adults, the dose of oral itraconazole should be 200 mg 3 times per day for 4 days, followed by 200 mg twice daily. The recommended dose of conventional amphotericin B is in the range 0.8 to 1 mg/kg/d; and 1 to 1.25 mg/kg/d is appropriate for neutropenic patients [17]. The optimal duration of treatment is unknown. The duration of therapy should be prolonged until resolution of underlying predispositions [14]. The response and outcome of these patients to therapy is largely dependent on host factors, including neurologic condition at presentation, underlying medical diseases, and early diagnosis and treatment [17].

In conclusion, *Aspergillus* epidural abscess is an uncommon presentation of invasive aspergillosis. Many risk factors and conditions have been described for the development of invasive disease, but there are few reports in diabetic patients. Witzig *et al* [18] suggested that *Aspergillus* epidural abscess may be due to impaired neutrophil function caused by hyperglycemia. It should be included in the differential diagnosis of chronic back pain combined with peripheral neuropathy in diabetic patients. A high index of suspicion is necessary for early diagnosis and treatment, which are essential to good outcome.

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