CASE REPORT

Invasive Pulmonary Aspergillosis with Cerebral Abscess in a Patient with Idiopathic Thrombocytopenic Purpura

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Invasive aspergillosis is a devastating infection in immunocompromised hosts. The lung is the most common site of primary infection, and the central nervous system is the most common secondary site of invasive disease. Invasive aspergillosis in autoimmunopathies treated with corticosteroids has rarely been reported in the literature. Herein, we report the case of a 48-year-old female patient with idiopathic thrombocytopenic purpura complicated with fatal invasive pulmonary and cerebral aspergillosis. She had been given 1,016 g intravenous amphotericin B empirically for lung infection during a previous admission. At presentation, she had fever, cough, and shortness of breath for 4 weeks. Chest radiography revealed a huge cavity over the left upper lung field. Bronchoscopic biopsy and culture showed *Aspergillus* species. She was initially treated with intravenous amphotericin B (0.9 mg/kg/day), and intravenous hydrocortisone for her idiopathic thrombocytopenic purpura. However, deterioration of consciousness occurred 12 days after hospitalization. Computed tomography of the brain showed ring-like cystic mass lesions in the right side basal ganglion. Stereotactic aspiration of the brain revealed *Aspergillus* species. Her condition exacerbated despite combination treatment with high-dose amphotericin B (1.2 mg/kg/day) and itraconazole (400 mg/day). She died 24 days after admission. This case suggests that treatment with corticosteroids and premature discontinuation of antifungal drugs bear the risk of fatal cerebral involvement in patients with invasive pulmonary aspergillosis. [*J Chin Med Assoc* 2006;69(6):278–281]

Key Words: brain abscess, idiopathic thrombocytopenic purpura, invasive pulmonary aspergillosis

Introduction

In the immunosuppressed host, pulmonary *Aspergillus* infection is invasive in nature, potentially gaining access to the systemic circulation and disseminating throughout the body.[1] The brain is a common secondary end organ of involvement.[2–4] Brain aspergillosis has an estimated crude mortality rate between 90% and 99%.[5,6] Central nervous system aspergillosis in patients with idiopathic thrombocytopenic purpura treated with corticosteroids and immunosuppressive agents has rarely been reported in the English literature.[2,3] In this report, we present a patient with idiopathic thrombocytopenic purpura who, during the course of treatment with oral prednisolone and azathioprine, developed invasive pulmonary aspergillosis and brain abscess.

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E-mail: hctsai1011@yahoo.com.tw • Received: September 30, 2005 • Accepted: February 6, 2006

Case Report

A 48-year-old woman presented to a local hospital with fever, cough, and shortness of breath for 2 weeks. A diagnosis of invasive pulmonary aspergillosis was made by bronchoscopic culture and biopsy. The patient was transferred to our hospital because of poor response to treatment with amphotericin B (1.2 mg/kg/day). She had a history of psoriasis for 20 years, treated intermittently with UV light, and cervical carcinoma, for which she had undergone anterior total hysterectomy and bilateral salpingo-oophorectomy 8 years previously.

Seven months before this admission, she experienced bruising and ecchymoses over her extremities. A diagnosis of idiopathic thrombocytopenic purpura was made by bone marrow biopsy. She was treated with 30 mg prednisolone and azathioprine 50 mg daily. Four months before hospitalization, she was admitted to our hospital with cough, headache, fever and chills for days. Her white blood cell count was 0.33×10^9/L, hemoglobin was 8.8 g/L, and platelet count was 10×10^9/L. She was given broad-spectrum antibiotics empirically for neutropenic fever. Although her leukopenia resolved 12 days after admission, her fever persisted and she was given intravenous hydrocortisone 200 mg every 8 hours for treatment of idiopathic thrombocytopenic purpura. High-resolution computed tomography of the chest (HRCT) performed 17 days after admission showed bilateral pleural effusion and diffuse ground-glass pattern with multiple tiny nodules over both lung fields. The patient was then given intravenous amphotericin B and trimethoprim/sulfamethoxazole for empirical treatment of fungal or *Pneumocystis jiroveci* pneumonia. Her fever subsided and clinical improvement was shown after treatment with 1,016 mg amphotericin B. No maintenance antifungal drug was given. Fifty-three days after hospitalization, she was discharged and followed-up at the outpatient department with trimethoprim/sulfamethoxazole (160/800 mg) and prednisolone 80 mg/day.

At this presentation, she was febrile and appeared to be acutely ill, although she was alert. Her blood pressure was 105/65 mmHg, pulse rate was 105/min, and respiratory rate was 20/min. Physical examination showed diminished breathing sounds over the left upper lung field. Laboratory results showed a white blood cell count of 8.83×10^9/L with granulocyte 77%, band 19%, lymphocyte 1% and monocyte 2%. Her platelet count was 142×10^9/L, and plasma glucose was 443 mg/dL. A chest radiograph showed a thick-walled cystic lesion in the left upper lung field (Figure 1). Three days after hospitalization, she developed respiratory failure, requiring mechanical ventilation. Intravenous hydrocortisone 100 mg every 8 hours and amphotericin B (0.9 mg/kg/day) were administered. Five days after admission, sputum culture grew *Aspergillus*. Consciousness deteriorated 12 days after admission and brain computed tomography (CT) disclosed ring-like cystic lesions in the right side basal ganglion with compression of the right side frontal horn of the lateral ventricle (Figure 2). Stereotactic brain aspiration showed aspergillosis (Figure 3). She was then given combination antifungal therapy with amphotericin B (1.2 mg/kg/day) and itraconazole (400 mg/day) due to poor response to amphotericin B alone. She died of hospital-acquired pneumonia 24 days after hospitalization. Autopsy was not performed.

Discussion

Invasive aspergillosis is a devastating infection that usually affects patients with prolonged neutropenia,[7] or neutrophil dysfunction,[8] cytotoxic chemotherapy, long-term corticosteroid therapy, bone marrow[9,10] or organ transplant,[11] or congenital or acquired immu-

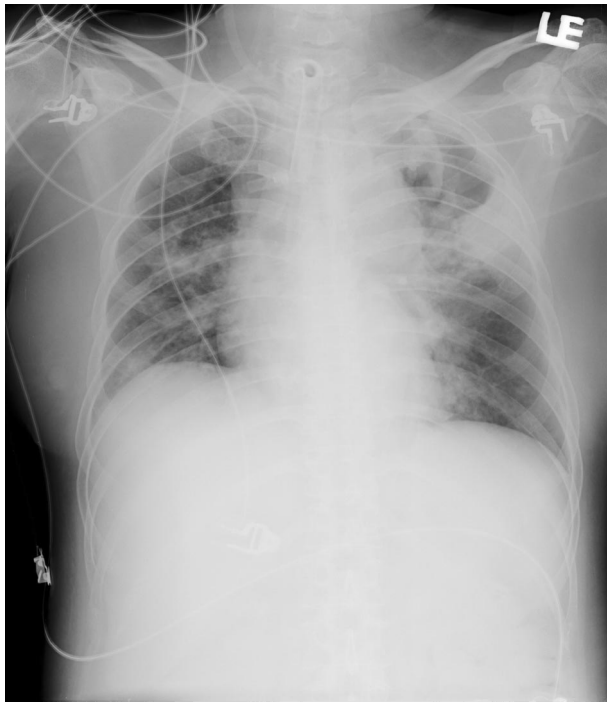

Figure 1. Chest radiography shows a thick-walled cystic lesion in the left upper lung fields.

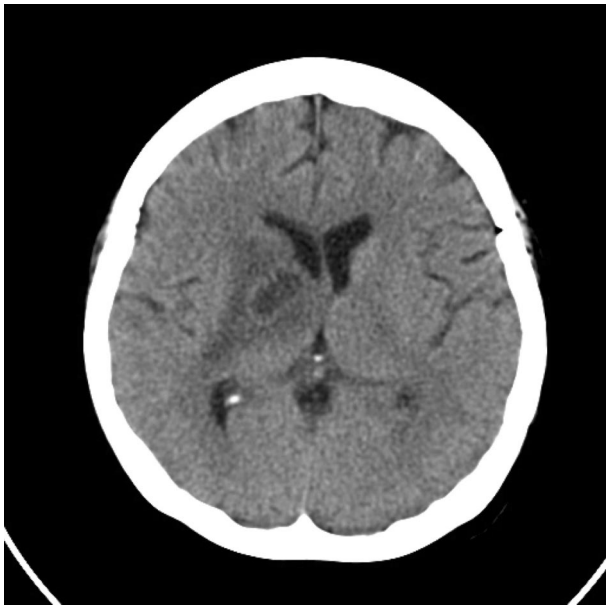

Figure 2. Brain computed tomography shows right side basal ganglion ring-like cystic lesions with compression of the right side frontal horn of the lateral ventricle.

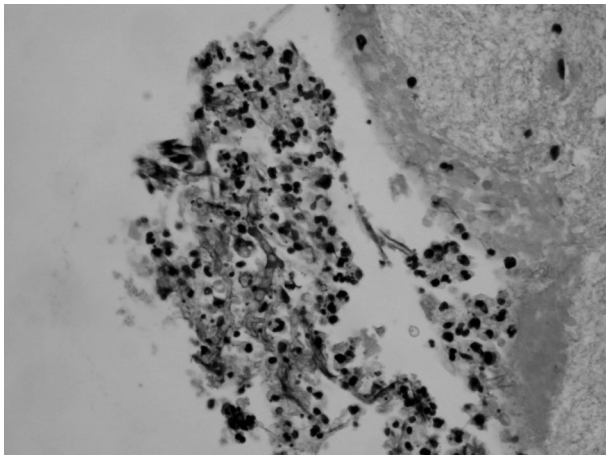

Figure 3. Photomicrograph showing branching septate hyphae within the area of inflammation (hematoxylin & eosin stain; original magnification ×200).

nodeficiency.[12] Definite diagnosis requires both histopathologic evidence of acute-angle branching, septate, nonpigmented hyphae measuring 2–4 μ in width, and culture yielding *Aspergillus* species from specimens obtained by biopsy or aspiration from the involved organs. The septated hyphae of *Aspergillus* can be detected by Gomori methenamine silver and periodic acid-Schiff stains. *Aspergillus* hyphae are difficult to distinguish from those of *Fusarium* species, *Pseudallescheria boydii*, agents of phaeohyphomycosis, and some other molds.

The lung is the most common site of primary infection, and the central nervous system is the most common secondary site of invasive disease,[2–4] as in our patient. Brain aspergillosis has an estimated crude mortality rate between 90% and 99% in large-scale studies.[5,6] Cerebral aspergillosis often involves the basal ganglion, thalami, corpus callosum, and areas supplied by the perforating artery territories, and may cause occlusion of the intracranial vessels, resulting in cerebral infarction.[13]

Our patient had atypical findings on HRCT of the chest at the initial admission. Typical chest CT findings were multiple nodules, the halo sign, which is an early radiologic sign that appears as a zone of low attenuation due to hemorrhage surrounding the pulmonary nodule,[14] and the air crescent sign, which is a crescent-shaped lucency in the region of the original nodule secondary to necrosis.[15] The air crescent sign usually correlates with recovery from neutropenia and is a relatively late sign.[16]

There has been increasing interest in *Aspergillus* antigen detection from serum and bronchoalveolar samples. Some studies suggest that antigenemia may be detected before the presence of clinical features of invasive pulmonary aspergillosis. A sandwich enzyme-linked immunosorbent assay technique that utilizes monoclonal antibodies to galactomannan (i.e. the cell wall glycoprotein that binds lectin) has been developed to detect the *Aspergillus* antigen in serum, urine, and bronchoalveolar lavage fluid, and has a reported sensitivity and specificity > 90%.[17] Serum *Aspergillus* antigen was not measured in our patient.

The optimal duration of therapy is unknown and dependent on the extent of invasive aspergillosis, the response to therapy, and the patient's underlying disease or immune status. A reasonable course of treatment would be to continue therapy for microfoci of infection after clinical and radiographic abnormalities are resolved, cultures (if they can be readily obtained) are negative, and reversible underlying predispositions have abated. Duration of therapy should be guided by clinical response rather than any arbitrary total dose.[18] Antifungal treatment was discontinued in our patient after radiographic resolution and a total of 1,016 mg amphotericin B, despite continued corticosteroid treatment. She developed cerebral aspergillosis 2.5 months after discharge from hospital. Relapse of invasive pulmonary aspergillosis and secondary cerebral involvement in our patient could have been avoided if she had received a serum *Aspergillus* antigen test, and been kept on antifungal therapy after discharge with tapering of corticosteroid therapy as soon as possible.

We used combination antifungal therapy with amphotericin B (1.2 mg/kg/day) and itraconazole (400 mg/day) due to cerebral involvement and poor response to amphotericin B alone. Combination therapy using amphotericin B with azoles, flucytosine or rifampin has advantages *in vitro* and in animal models, although antagonism has also been shown.[19] This approach has limited success in case reports, but the role and efficacy of such combinations have not been established for invasive aspergillosis.[19] Recently, a multicenter, randomized, unblinded trial compared voriconazole and amphotericin B for the primary therapy of invasive aspergillosis in an intent-to-treat study of 277 patients, 10 of whom had cerebral aspergillosis. The superiority of voriconazole was proven in terms of response rate, survival rate and safety at week 12 of treatment.[20] Voriconazole also has a favorable pharmacokinetic profile, with good blood–brain barrier penetration and a mean cerebrospinal fluid concentration/plasma concentration ratio ranging from 0.22 to 1.0.[21] Voriconazole levels were above the minimal fungicidal concentration for *Aspergillus* species in most cerebrospinal fluid specimens tested in 1 study.[22] Voriconazole was unavailable in our hospital at the time our patient was treated.

In conclusion, immunosuppressed patients with central nervous system aspergillosis have a poor prognosis, and most immunosuppressed patients with secondary cerebral abscess die quickly. Our patient might have avoided relapse with pulmonary and cerebral aspergillosis if definite diagnosis had been established early by a serum galactomannan antigen test, prolonged therapy with suppressive antifungals had been given, and reduction or discontinuation of immunosuppressive therapy with corticosteroids had been initiated. This case suggests that treatment with corticosteroids and immunosuppressive drugs bears the risk of fatal invasive pulmonary aspergillosis and central nervous system involvement in patients with idiopathic thrombocytopenic purpura.

References

1. DeLone DR, Goldstein RA, Petermann G, Salamat MS, Miles JM, Knechtle SJ, Brown WD. Disseminated aspergillosis involving the brain: distribution and imaging characteristics. *AJNR Am J Neuroradiol* 1999;20:1597–604.
2. Apostolidis J, Tsandekidi M, Kousiafes D, Pagoni M, Mitsouli C, Karmiris T, Bakiri M, et al. Short-course corticosteroid-induced pulmonary and apparent cerebral aspergillosis in a patient with idiopathic thrombocytopenic purpura. *Blood* 2001; 98:2875–7.
3. Buchheidt D, Hummel M, Diehl S, Hehlmann R. Fatal cerebral involvement in systemic aspergillosis: a rare complication of steroid-treated autoimmune bicytopenia. *Eur J Haematol* 2004; 72:375–6.
4. Lastours V, Lefort A, Zappa M, Dufour V, Belmatoug N, Fantin B. Two cases of cerebral aspergillosis successfully treated with voriconazole. *Eur J Clin Microbiol Infect Dis* 2003;22: 297–9.
5. Denning DW. Therapeutic outcome in invasive aspergillosis. *Clin Infect Dis* 1996;23:608–15.
6. Darras-Joly C, Veber B, Bedos JP, Gachot B, Regnier B, Wolff M. Nosocomial cerebral aspergillosis: a report of 3 cases. *Scand J Infect Dis* 1996;28:317–9.
7. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. *Ann Intern Med* 1984;100:345–51.
8. Cohen MS, Isturiz RE, Malech HL, Root RK, Wilfert CM, Gutman L, Buckley RH. Fungal infections in chronic granulomatous disease: the importance of the phagocyte in defense against fungi. *Am J Med* 1981;71:59–66.
9. Morrison VA, Haaeke RJ, Weisdorf DJ. The spectrum of non-*Candida* fungal infections following bone marrow transplantation. *Medicine (Baltimore)* 1993;72:78–89.
10. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* 1997;175:1459–66.
11. Hibberd PL, Rubin RH. Clinical aspects of fungal infection in organ transplant recipients. *Clin Infect Dis* 1994;19:33–40.
12. Denning DW, Follansbee SE, Scolaro M, Norris S, Edelstein H, Stevens DA. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *N Engl J Med* 1991;324:654–62.
13. Guermazi A, Gluckman E, Tabti B, Miaux Y. Invasive central nervous system aspergillosis in bone marrow transplantation recipients: an overview. *Eur Radiol* 2003;13:377–88.
14. Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: the contribution of CT to early diagnosis and aggressive management. *Chest* 1987;92:95–9.
15. Curtis AM, Smith GJ, Ravin CE. Air crescent sign of invasive aspergillosis. *Radiology* 1979;133:17–21.
16. Gefter WB, Albelda SM, Talbot GH, Gerson SL, Cassileth PA, Miller WT. Invasive pulmonary aspergillosis and acute leukemia: limitations in the diagnostic utility of the air crescent sign. *Radiology* 1985;157:605–10.
17. Rogers TR, Haynes KA, Barnes RA. Value of antigen detection in predicting invasive pulmonary aspergillosis. *Lancet* 1990; 336:1210–3.
18. Stevens DA, Kan VL, Judson MA, Morrison VA, Dummer S, Denning DW, Bennett JE, et al. Practice guidelines for diseases caused by *Aspergillus. Clin Infect Dis* 2000;30:696–709.
19. Johnson MD, MacDougall C, Ostrosky-Zeichner L, Perfect JR, Rex JH. Combination antifungal therapy. *Antimicrob Agents Chemother* 2004;48:693–715.
20. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;347:408–15.
21. Lutsar I, Roffey S, Troke P. Voriconazole concentrations in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. *Clin Infect Dis* 2003;37:728–32.
22. Schwartz S, Milatovic D, Thiel E. Successful treatment of cerebral aspergillosis with a novel triazole (voriconazole) in a patient with acute leukaemia. *Br J Haematol* 1997;97:663–5.