



UNUSUAL INVASIVE BRONCHIAL ASPERGILLOSIS IN A PATIENT WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Invasive tracheobronchial aspergillosis is an uncommon form of *Aspergillus* lung infection observed in immunocompromized patients. A 43-year-old patient diagnosed with acute lymphoblastic leukemia presented prolonged fever and hemoptysis during remission induction chemotherapy. The bronchoscopic examination showed pale mucosa with multiple raised white-colored nodules of 3 to 5 millimeters in diameter in all the bronchi. Hyphae of *Aspergillus* sp were observed in the biopsy of one of the nodules and in the examination of

the bronchoalveolar lavage. Despite amphotericin B therapy, the patient developed bilateral necrotizing pneumonia and multiple abscesses in the brain and in the thyroid gland, and died. From a review of the literature in the Medline® database, four similar cases (two in AIDS patients, one in lymphoma and the remaining case in an acute myeloid leukemia patient) have been reported.

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Key words: *Aspergillus*, tracheobronchial involvement, leukemia

A *Aspergillus* sp and *Candida* sp are the fungal organisms responsible for most of the systemic fungal infections in immunocompromized patients. The lung is the organ most frequently involved in invasive aspergillosis, usually in the form of necrotizing pneumonia. Tracheobronchial invasive aspergillosis is a relatively new disease that affects severely immunocompromized patients, patients with AIDS and heart-lung and lung transplant recipients.^{1,2} The first clinical sign of airway involvement is often wheezing.^{3,4} A bronchoscopic examination with biopsy is the main diagnostic tool. Several clinical-histological varieties of invasive tracheobronchial aspergillosis have been described based on the finding of ulcers, pseudomembranes or diffuse inflammation.⁵ The treatment of choice is amphotericin B.¹

We report one case of invasive tracheobronchial aspergillosis in a patient suffering from acute lymphoblastic leukemia (ALL) with unusual involvement of the lower respiratory airways.

Case report

A 43-year-old man was admitted to our hospital for petechiae and ecchymosis which had begun the previous week. The physical examination was otherwise normal. At the time of admission the hemoglobin level was 105 g/L, the platelet count was

$16 \times 10^9/L$ and the white blood cell (WBC) count was $4.5 \times 10^9/L$ with 38 percent neutrophils, 10 percent lymphocytes and 52 percent lymphoid blast cells. Biochemical serum values were normal, except for LDH 616 IU/L (normal: up to 270 IU/L). The chest x-ray film was normal. A bone marrow aspirate showed complete infiltration by lymphoblasts and morphologic and immunophenotypic studies yielded the diagnosis of a common subtype ALL.⁶ The cytogenetic study was normal. Chemotherapy with vincristine, daunorubicin, prednisone and asparaginase was started, in addition to intrathecal prophylactic chemotherapy with methotrexate, cytarabine and hydrocortisone, and prophylactic antibiotics (ciprofloxacin, 200 mg/12h, po, and fluconazole 100 mg/12h, p.o.).

On day 20 of treatment, the patient presented fever, dyspnea and pleuritic chest pain. Body temperature was 39°C and wheezing was detected upon respiratory auscultation. The WBC count was $3.23 \times 10^9/L$ with 50 percent neutrophils, 45 percent lymphocytes and 5 percent monocytes. Both chest x-ray film and urine analysis were normal and arterial oxygen blood pressure (breathing *en plein air*) was 80 mmHg. Cultures were performed and empiric intravenous antibiotic therapy with cef-tazidime (2 g/8h, iv) and amikacin (1.5 g/day, iv) was initiated. Vancomycin (1 g/12h, iv) and erythromycin (1 g/6h, iv) were added after 24 hours

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Figure 1. Bronchoscopic examination. Two white-colored nodules of 3-5 mm in diameter on the anterior wall of the bronchus intermedius and on the division between the middle lobe and the right inferior bronchus. An exofitic white mass in the posterior wall of the bronchus intermedius is also present.

because of the persistence of fever. Three days later the patient presented hemoptysis. The platelet count was $47 \times 10^9/L$, with a normal level in the remaining coagulation study. A chest x-ray showed alveolar infiltrates in the lower lobes of both lungs; arterial oxygen blood pressure (room air) was 53 mmHg. Amphotericin B (1 mg/kg/day, iv) was added. The bronchoscopic examination showed pale mucosa with multiple raised white-colored nodules of 3 to 5 millimeters in diameter in both main and some lobar bronchi associated with inflammatory stenosis (Figure 1). No lesions were observed in the trachea or the larynx. Hyphae with the typical morphology of *Aspergillus sp.* were isolated from the bronchoalveolar lavage. The bronchial aspirate and the biopsy of one of the nodules also showed infiltration by *Aspergillus sp.*

Despite amphotericin B therapy, five days later the patient lost consciousness. A CT scan of the brain revealed multiple hypodense lesions in both cerebral hemispheres that showed no enhancement after the addition of intravenous contrast. The patient died 4 days later due to massive hemoptysis. The autopsy showed pulmonary hemorrhage, bilateral bronchopneumonia and multiple abscesses in the brain and in the thyroid gland with presence of *Aspergillus sp.*

Discussion

Aspergillus sp. infections are the primary cause of death from invasive mycoses in immunocompromized patients. Invasive pulmonary aspergillosis constitutes about 90% of the clinical forms, but infection is possible in any other site of the body as well.¹ About 7-20% of pulmonary infections by *Aspergillus sp* simultaneously manifest tracheobronchial involvement.^{2,7} Most of the cases are observed in immunocompromized patients such as patients undergoing organ transplantation or those

with solid tumors, leukemias or AIDS.^{2,8} Respiratory symptoms are non-specific, although the presence of wheezing has been reported as a sign of suspected tracheobronchial involvement by *Aspergillus* in neutropenic patients with persistent fever during antibiotic therapy, even before any radiologic abnormality is found,^{3,4} as occurred in our patient.

Several different clinical-pathological forms of *Aspergillus* pulmonary infection can be observed with flexible bronchoscopy: tracheobronchitis, ulcerative tracheobronchitis, pseudomembranous tracheobronchitis and obstructive bronchial aspergillosis.⁵ Our case presented an atypical involvement of the airways with multiple raised white-colored nodules in the bronchi with no ulceration of the surrounding mucosa. Ping-Hung *et al.* have recently described similar lesions in the trachea of a patient with peripheral T-cell lymphoma;¹ according to Medline® research (1982-1996), tracheobronchial involvement resembling that of our patient has been reported in two cases with AIDS² and in one with acute myeloblastic leukemia.⁹

The treatment of choice in most cases of *Aspergillus* tracheobronchitis is amphotericin B, although some patients have shown a response when amphotericin B was substituted by itraconazol.^{1,2,8} Nevertheless, the mortality is high, and death is usually due to either airway obstruction^{2,10} or pulmonary invasion and systemic dissemination, as occurred in our case.

In conclusion, invasive tracheobronchial aspergillosis, although uncommon, is a form of *Aspergillus* respiratory infection that has to be taken into account in immunosuppressed patients with fever and wheezing even before the presence of any radiologic finding.

References

1. Ping-Hung K, Li-Na L, Pan-Chyr Y, Yao-Chan C, Kwen-Tay L. *Aspergillus* laryngotracheobronchitis presenting as stridor in a patient with peripheral T cell lymphoma. *Thorax* 1996; 51:869-70.
2. Kemper CA, Hostetler JS, Follansbee SE, et al. Ulcerative and plaque-like tracheobronchitis due to infection with *Aspergillus* in patients with AIDS. *Clin Infect Dis* 1993; 17:344-52.
3. Tait RC, O'Driscoll BR, Denning DW. Unilateral wheeze caused by pseudomembranous *Aspergillus* tracheobronchitis in the immunocompromised patient. *Thorax* 1993; 48:1285-7.
4. Sridhar M, Jeffers M, Brankin E, Soukop M, Banham S. Wheeze in a heart transplant patient with lymphoma. *Postgrad Med J* 1995; 71:375-7.
5. Denning DW. Unusual manifestations of aspergillosis. *Thorax* 1995; 50:812-3.
6. Second MIC Cooperative Study Group. Morphologic, immunologic and cytogenetic (MIC) working classification of the acute leukemias. *Br J Haematol* 1988; 68:487-94.
7. Germaud P, Morin O. Aspergillose et hemopathies malignes. *Pathol Biol* 1994; 42:656-60.
8. Kramer MR, Denning DW, Marshall SE, et al. Ulcerative tracheobronchitis after lung transplantation. A new form of invasive aspergillosis. *Am Rev Respir Dis* 1991; 144:552-6.
9. Sabuni Y, Tashiro T, Ishii T, et al. A case of tracheobronchial aspergillosis complicated with acute myeloblastic leukemia [English abstract]. *Kansenshogaku Zasshi* 1992; 66:1120-4.
10. Putnam JB Jr, Dignani C, Mehra RC, Anaisse EJ, Morice RC, Libshitz HI. Acute airway obstruction and necrotizing tracheobronchitis from invasive mycosis. *Chest* 1994; 106:1265-7.