

Pseudomembranous Tracheobronchitis Caused by *Aspergillus* in a Patient after Peripheral Blood Stem Cell Transplantation

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Abstract

Introduction: We report a case of pseudomembranous tracheobronchitis caused by *Aspergillus fumigatus* 2 years after matched unrelated stem cell transplant. **Clinical Picture:** The patient presented with dyspnoea and obstructive airway disease coinciding with the onset of chronic graft-versus-host disease (GVHD). Following treatment with higher immunosuppressive therapy for presumptive diagnosis of bronchiolitis obliterans, he subsequently developed recurrent spontaneous pneumomediastinum and progressive respiratory failure. **Treatment and Outcome:** Tracheobronchial biopsy and culture of bronchoalveolar lavage (BAL) fluid revealed *Aspergillus tracheobronchitis*. Despite mechanical ventilation and antifungal therapy, he succumbed to progressive respiratory failure. **Conclusions and Clinical Implications:** *Aspergillus tracheobronchitis* should be suspected in heavily immunosuppressed stem cell transplant recipients presenting with recurrent pneumomediastinum and progressive respiratory failure.

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Introduction

Pseudomembranous tracheobronchitis caused by *Aspergillus* is a rare and lethal variant of invasive aspergillosis. It has been reported in a few series of immunocompromised patients.¹⁻³ The clinical presentation is acute, with wheezing, dyspnoea, cough, progressive respiratory failure and rapid death. We report a patient who initially presented with dyspnoea, obstructive airway disease and intermittent attacks of acute diarrhoea one year after allogeneic peripheral blood stem cell transplantation. He subsequently developed recurrent spontaneous pneumomediastinum and rapidly progressive respiratory failure and was found to have pseudomembranous tracheobronchitis due to *Aspergillus* infection.

Case Report

A 20-year-old Chinese man was admitted with complaints of diarrhoea and progressive exertional dyspnoea.

He was diagnosed to have acute myeloid leukaemia 2 years earlier. After achieving remission with 2 cycles of chemotherapy with idarubicin and cytosine arabinoside,

he received allogeneic granulocyte colony stimulating factor (G-CSF) mobilised peripheral blood stem cell transplantation from a HLA-matched unrelated donor. The conditioning regime consisted of cyclo-phosphamide 120 mg/kg and total body irradiation with 1200 cGy in 6 fractions over 3 days. Short courses of methotrexate, cyclosporin and prednisolone were used as prophylaxis against graft-versus-host disease (GVHD). Post-transplant recovery was uneventful with granulocyte counts more than 500/mm³ and self-sustaining platelet counts achieved on day 14 and day 20 onwards, respectively.

Cyclosporin and prednisolone were reduced gradually at outpatient follow-up with prednisolone discontinued in the fifth month post-transplant as he remained well and showed good haematopoietic recovery. However, he started having erythema of skin, diarrhoea, xerostoma and dry eyes 1 year post-transplant. This was treated as for extensive chronic GVHD with re-initiation of corticosteroid and higher doses of cyclosporin. There was adequate control with partial relief of bowel symptoms.

Six months later, he began to have exertional dyspnoea

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associated with slight productive cough. There was no fever. Repeated chest X-ray and microbiological studies of the sputum were negative. A pulmonary function test showed severe airway obstruction: FEV₁ decreased to 1.64 L (which was 37.2% of the predicted value) from 4.44 L before transplantation. Air trapping was suggested by an increased residual volume of 7.41 L (313% of predicted) and by an increased ratio of residual volume to total lung capacity. Carbon monoxide diffusing capacity (DLCO) was normal. A high resolution computed tomography (CT) thorax revealed hyperinflated lung and bilateral perihilar bronchial wall thickening. There was no evidence of pulmonary infiltrate or fibrosis. The presumptive diagnosis of obstructive lung disease secondary to post-transplantation bronchiolitis obliterans was made. The prednisolone dose was increased to between 20 to 30 mg per day and azathioprine was added. He continued to receive prophylactic therapy against fungus and *Pneumocystis carinii* with itraconazole tablet 200 mg once daily and cotrimoxazole (trimethoprim 80 mg/sulfamethoxazole 400 mg) 1 tablet twice daily, respectively.

Three months later, he was admitted for spontaneous pneumomediastinum and subcutaneous emphysema without clear precipitating causes. This was associated with fever, productive cough and diarrhoea. White blood cell count was $8.4 \times 10^9/L$ with neutrophil count of 56%. Blood and sputum cultures were all negative. *Clostridium jejuni* was isolated from the stool. The symptoms responded to empirical antibacterial therapy. A repeat chest X-ray done 2 weeks later showed resolution of the pneumomediastinum. He was also given a short course of oral ganciclovir for cytomegalovirus antigenemia which resolved subsequently.

He was admitted a month later with another episode of acute diarrhoea, dry cough, progressive exertional dyspnoea and low-grade temperature. Clinical examination of the respiratory system revealed slightly diminished breath sounds and bilateral expiratory rhonchi. Chest X-ray showed increased bronchial markings. He was managed as for uncontrolled GVHD of the gut and lungs with higher dose of immunosuppressants, with concomitant empirical antibacterial therapy for possible infective gastroenteritis and respiratory tract infections. Serial chest X-ray done upon admission showed progressively increased bronchial marking, pneumomediastinum and subcutaneous emphysema. On day 7 of hospitalisation, he developed acute respiratory distress. He was intubated and supported with mechanical ventilation. A repeat chest X-ray showed pneumomediastinum and subcutaneous emphysema. There was no pneumothorax. Arterial blood gas findings on 100% oxygen prior to the intubation were: PO₂ 112 mmHg, PCO₂ 70 mmHg, pH 7.2.

Bronchoscopy disclosed pseudomembranous plaque lesion in the entire tracheobronchial tree, which could not be removed with suctioning. Tracheobronchial biopsy revealed *Aspergillus* organism with 45° branching and septated hyphae (Fig. 1). Culture from the bronchoalveolar lavage (BAL) confirmed the presence of *Aspergillus fumigatus*. Stains and culture for bacteria, pneumocytis, mycobacteria and viruses including cytomegalovirus were all negative.

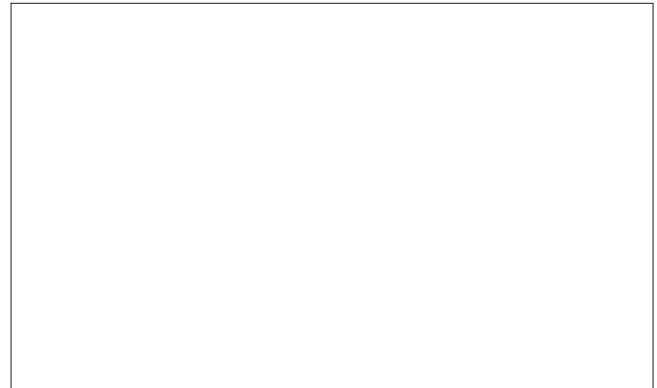


Fig. 1. Photomicrograph of *Aspergillus* organisms demonstrating 45° branching and septated hyphae taken from the bronchial biopsy specimen (GMS stain, original magnification $\times 400$).

The patient was started on amphotericin B at the dose of about 1 mg/kg and itraconazole solution 5 mg/kg twice daily. He continued to have rapidly deteriorating clinical course over the next 5 days with progressive obstructive respiratory failure. This was further complicated by hepatic and renal insufficiency. The arterial blood gas showed a high pCO₂ of between 100 to 160 mmHg and pH of 6.9 to 7.1 on the day before his demise.

Despite mechanical ventilation, 4 days of amphotericin B 1 mg/kg and broad spectrum antibiotics, the patient died of progressive respiratory insufficiency on day 15 of hospitalisation.

Discussion

Aspergillus infection constitutes a major problem after allogenic bone marrow transplantation. The incidence has varied between 3% and 11% in recent series.⁴⁻⁶ The infection primarily affects the lung. Pseudomembranous tracheobronchitis, a rare and lethal variant of invasive aspergillosis, has been reported in a few series of patients with lymphoma, AIDS, post bone marrow transplant, broad spectrum antibiotic and steroid therapy.¹⁻³ Massive subcutaneous and mediastinal emphysema as a presentation of pseudomembranous tracheobronchitis has only been reported once previously.¹ All patients presented with fever, dyspnoea, cough, wheezing and died between 1 to 6 weeks of presentation.

Spontaneous pneumomediastinum in allogeneic bone marrow transplant patients has been reported in 8 cases.⁷⁻⁹ Bronchiolitis obliterans complicating GVHD, pneumonitis with pneumothoraces related to the conditioning regime and cytomegalovirus infections have been implicated.

The spontaneous pneumomediastinum in this patient could have been precipitated by either bronchiolitis obliterans or airway obstruction due to pseudomembranous tracheobronchitis. Our patient had other evidence of extensive chronic GVHD 1 year post-transplant as manifested by skin rash, diarrhoea, xerostoma and dry eyes. In addition, allogeneic peripheral blood stem cell transplantation as in this patient, is associated with a higher risk of chronic GVHD.¹⁰ This patient's symptoms may have been a clinical manifestation of bronchiolitis obliterans. The development of pseudomembranous tracheobronchitis in our patient may have been facilitated by several factors:

- 1) chronic GVHD,
- 2) prolonged immunosuppressive therapy, and
- 3) broad-spectrum antibiotic therapy.

It has also been found that *Aspergillus* infections may occur late after bone marrow transplant. They are associated with GVHD and its treatment and are often fatal.¹⁰ This use of higher doses of immunosuppressive agents to control his chronic GVHD and the use of broad-spectrum antibiotics could have predisposed him to invasive aspergillosis.

Some clinical aspects in this case deserve special emphasis:

First, the diagnosis of pseudomembranous tracheobronchitis, as in any other fungal infection, remains a major problem for clinicians. Physicians should bear this rapidly-evolving entity in mind when they encounter immunosuppressed patients presenting with progressive respiratory failure, fever, cough and wheezing.

Second, both pseudomembranous tracheobronchitis and bronchiolitis obliterans should be suspected in bone marrow transplant recipients presenting with pneumomediastinum without other clear precipitating causes. This is especially so if they show evidence of GVHD, signs of obstructive respiratory disease and respiratory failure. Chest radiographs are usually non-specific or diagnostic. Bronchoscopy should be performed early to establish diagnosis as the management of the 2

entities are entirely different. However, should pseudomembranous tracheobronchitis be diagnosed, it is uncertain if early treatment for this fatal disease will improve outcome.

Third, the use of itraconazole 200 mg once daily as antifungal prophylaxis in this patient does not seem to have protected him against *Aspergillus* infection. The unpredictable bioavailability of itraconazole, the presence of GVHD of gut which may have compromised its absorption and the uncertain efficacy of itraconazole for prophylaxis against invasive pulmonary aspergillosis may account for this failure.

REFERENCES

1. Pervez N K, Kleinerman J, Kattan M, Freed J A, Harris M B, Rosen M J, et al. Pseudomembranous necrotising bronchial aspergillosis. *Am Rev Respir Dis* 1985; 131:961-3.
2. Hines D W, Haber M H, Yaremko L, Britton C, McIlwain R W, Harris A A. Pseudomembranous tracheobronchitis caused by *Aspergillus*. *Am Rev Respir Dis* 1991; 6:1408-11.
3. Lortholary O, Meyohas M, Dupont B, Cadranet J, Salmon-Ceron D, Peyramond D, et al. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: report of 33 cases. *Am J Med* 1993; 95:177-87.
4. McWhinney P H M, Kibbler C C, Hamon M D, Smith O P, Gandhi L, Berger L A, et al. Progress in the diagnosis and management of aspergillosis in bone marrow transplantation: a 13 years' experience. *Clin Infect Dis* 1993; 17:397-404.
5. Morrison V A, Haake R J, Weisdorf D J. Non-candida fungal infections after bone marrow transplantation: risk factors and outcome. *Am J Med* 1994; 96:497-503.
6. Jantunen E, Ruutu P, Niskanen L, Volin L, Parkkali T, Koukila Kahkola P, et al. Incidence and risk factors for invasive fungal infections in allogeneic bone marrow transplant recipients. *Bone Marrow Transplant* 1997; 19:801-8.
7. Hill G, Helenglass G, Powles R, Perren T, Selby P. Mediastinal emphysema in marrow transplant recipients. *Bone Marrow Transplant* 1987; 2:315-20.
8. Galanis E, Litzow M R, Tefferi A, Scott J P. Spontaneous pneumomediastinum in a patient with bronchiolitis obliterans after bone marrow transplantation. *Bone Marrow Transplant* 1997; 20:695-6.
9. Toren A, Or R, Breuer R, Nagler A. Bronchiolitis obliterans presenting as subcutaneous emphysema and pneumomediastinum: a case report. *Med Oncol* 1996; 13:195-7.
10. Storek J, Gooley T, Siadak M, Bensinger W I, Maloney D O, Chauncey T R, et al. Allogeneic peripheral blood stem cell transplantation may be associated with a high risk of chronic graft-versus-host disease. *Blood* 1997; 90:4705-9.