INTERNAL MEDICINE

□ CASE REPORT □

Fulminant Laryngeal-tracheobronchial-pulmonary Aspergillosis: A Rare and Fatal Complication in Allogeneic Hematopoietic Stem Cell Transplantation Recipients

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Abstract

A 23-year-old man who had previously undergone allogeneic hematopoietic stem cell transplantation (allo-HSCT) for severe aplastic anemia was diagnosed with invasive laryngeal-tracheobronchial-pulmonary aspergillosis after presenting with a persistent dry cough at six months post-transplantation based on the findings of laryngoscopy and fiberoptic bronchoscopy. A fiberoptic bronchoscope was used to remove the obstructive material from the patient's airway and posaconazole plus caspofungin were administered to successfully to treat the patient. Our report suggests that laryngoscopy and fiberoptic bronchoscopy should be considered as alternative approaches to the diagnosis and treatment of allo-HSCT recipients with persistent respiratory symptoms when invasive laryngeal aspergillosis and invasive tracheobronchial aspergillosis are suspected.

Key words: aspergillosis, larynx, tracheobronchial, HSCT

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Introduction

Invasive fungal disease (IFD) remains a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT) (1); aspergillosis is the most common IFD infection among HSCT recipients (2, 3). The most common form of disease due to *Aspergillus* species in immunocompromised patients is invasive pulmonary aspergillosis (IPA), which mainly involves the lung parenchyma (4), the development of invasive tracheobronchial aspergillosis (ITBA) and invasive laryngeal aspergillosis is rare; however, the development of fulminant ITBA is associated with a serious prognosis (5, 6). While there are a few reports on ITBA in immunocompromised or immunocompetent hosts (7, 8), laryngeal aspergillosis is extremely rare (9). Unfortunately, there is limited experience in the treatment of ITBA and laryngeal aspergillosis in allo-HSCT patients.

We herein report a case of invasive laryngeal-tracheobronchial-pulmonary aspergillosis in a Chinese allo-HSCT patient who was successfully treated and a review of the literature on serious complications after HSCT.

Case Report

A 23-year-old man with a history of severe aplastic anemia (SAA) underwent bone marrow transplantation from his HLA-haploidentical mother in January 2014. The conditioning regimens consisted of busulphan cyclophosphamide and antithymocyte globulin (BUCY+ATG) (10). Cyclosporine A (CsA) and short-term methotrexate (MTX) plus mycophenolate mofetil (MMF) were used as prophylaxis against graft-versus-host disease (GVHD) (11). Standard measures were adopted for the prevention of infectious complications, which included fluconazole for antifungal prophylaxis and acyclovir to prevent herpes-related infections. A hemogram revealed the reconstruction of granulocytes (ANC>0.5×10^9/L) on day +12 post-transplantation. The patient developed

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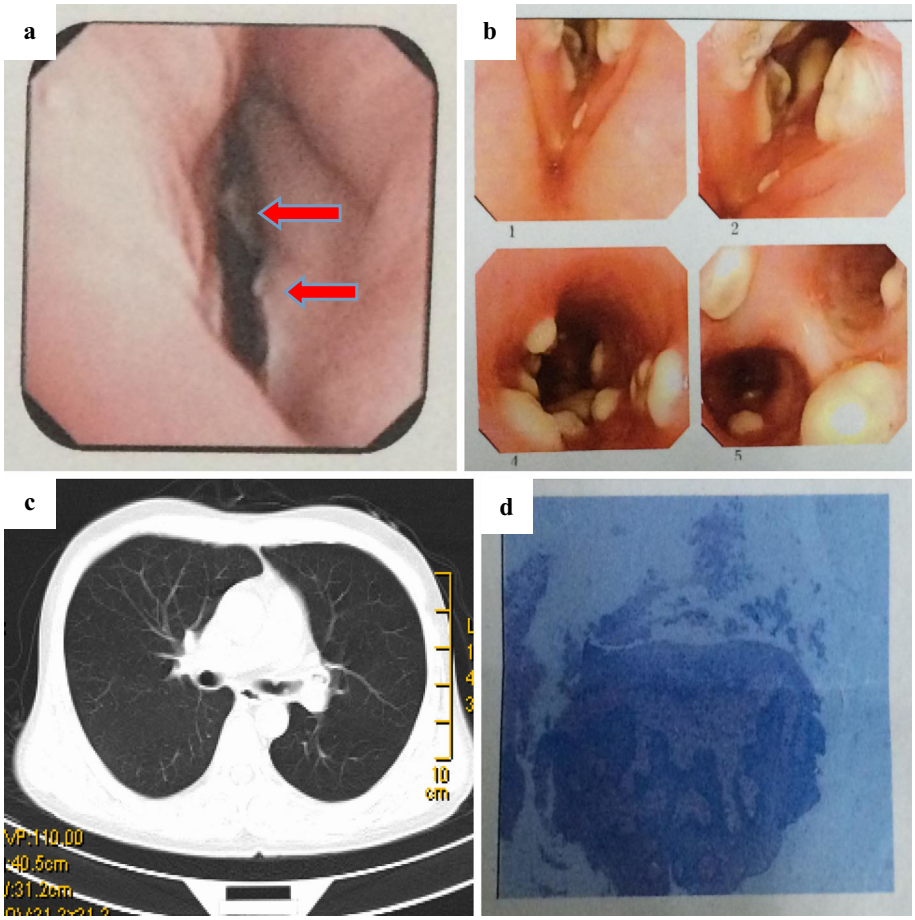

Figure 1. **(a) Laryngoscopy revealed that the patient's throat was full of swollen ulcers with white plaque (marked by arrows). (b) Fiberoptic bronchoscopy demonstrated some irregular, nodular materials with white moss, which completely obstructed the bronchial wall. (c) Chest computed tomography (CT) revealed no specific findings. (d) A histopathological examination of the biopsy specimen revealed *Aspergillus* spp.**

grade II acute GVHD of the skin on day +42 post-transplantation. This was treated by treatment with a standard-dose of methyl-prednisolone, which achieved a complete response (CR). The patient's chronic GVHD (cGVHD) of the skin gradually progressed from day +100 post-transplantation and he was treated with prednisolone and CsA. On day 120 post-transplantation, he complained of a cough and antibiotics were administered. A blood analysis revealed the following: WBC, 2.34×10^9/L; ANC, 1.72×10^9/L; hemoglobin, 85 g/L; and platelets, 72×10^9/L. Although both a chest computed tomography (CT) scan and tests for pathogens via routine culturing, including blood tests for Beta-D glucan (G-test) and Galactomannan (GM-test) were all negative, the patient's cough did not respond to antibiotics and we empirically initiated treatment with voriconazole (6 mg/kg/12h for the first day, followed by 4 mg/kg/12h). Liver toxicity occurred during voriconazole treatment, thus the anti-fungal regimen was changed to micafungin (100 mg/d). However, the persistent cough did not improve and hoarseness developed after two weeks of treatment - ulcers were then observed in the throat by laryngoscopy (Fig. 1a). The patient developed severe dyspnea in the following week when anti-infection and topical treatments were applied. Fiberoptic bronchoscopy revealed an irregular, nodular material with white moss, which nearly obstructed the bronchus; however, chest CT imaging was negative (Fig. 1b and c). The histopathological examination of biopsy specimens revealed an *Aspergillus* species (Fig. 1d). The patient was diagnosed with pseudomembranous *Aspergillus* tracheobronchitis type ITBA based on the results of bronchoscopy and a pathological examination (12). The antibiotic and micafungin treatments were ceased and liposomal amphotericin B (liposomal AmB) was administered daily at a target dose of 3 mg/kg. The patient's serum creatinine level rose from 60.4 μmol/L to 168 μmol/L during the first 7 days of liposomal AmB treatment. Due to progressive renal dysfunction, the anti-fungal regimen was switched to a combination of posaconazole (400 mg/12 h) and caspofungin [50 mg, daily (70 mg for the first dose)]. The combination therapy continued for 2 weeks, until the previous nodules in the throat completely disappeared under bronchoscopy (Fig. 2a); however, a repeat chest CT scan showed progression (Fig. 2b). The symptom of dyspnea gradually progressed, thus fiberoptic bronchoscopy was performed to remove the obstructive

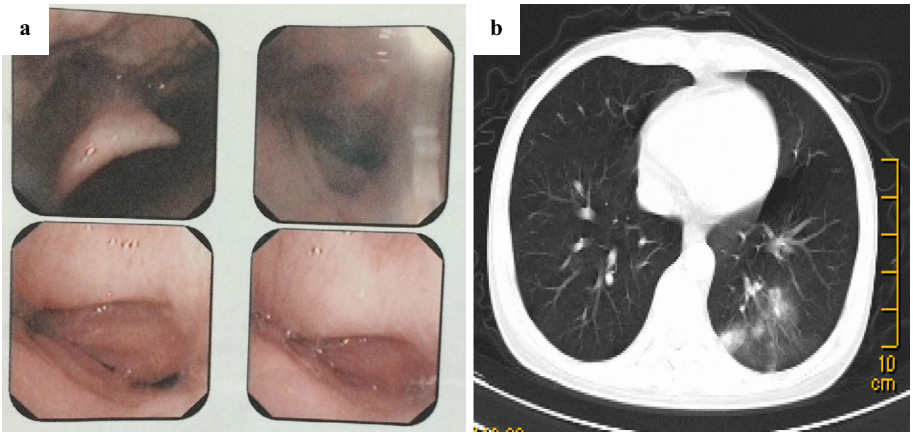

Figure 2. **(a) The previous ulcers and nodules in the throat completely disappeared under bronchoscopy after the a combination anti-fungal therapy was administered for 2 weeks. (b) A repeat chest CT scan showed nonsegmental consolidation in the left lower lobe with the disappearance of the laryngeal lesions.**

material from the patient's airways once a week for two weeks. All of the symptoms were relieved and the final chest CT scan showed negative results before the discontinuation of anti-fungal therapy, and all of the tests were negative for *Aspergillus*. Posaconazole was administered as a secondary prophylactic treatment and the patient was discharged from hospital. The patient is still being followed and remains free of any recurrence of invasive fungal infection.

Discussion

The latest multicenter study of the Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) showed that the rate of invasive fungal infections (IFIs) among patients undergoing HSCT was lower than that in earlier studies (13). However, recent epidemiological studies in China have shown that the incidence of IFDs is increasing due to the increase in hematopoietic malignancies as well as the wide development of allo-HSCTs (14, 15). The incidence of IFDs after haploidentical stem cell transplantation is significantly higher than that after HLA-matched sibling transplantation (2); *Aspergillus* is the most common pathogenic species of IFD in Chinese patients undergoing allo-HSCT (3). Patients with aGVHD and cGVHD, and elderly patients were reported to be at higher risk for fungal infections (16). ITBA and invasive laryngeal aspergillosis are rare clinical forms of IFD in which the *Aspergillus* infection is mainly limited to the tracheobronchial tree and larynx, and the incidence and the risk factors for these diseases are not fully defined in HSCT (17, 18). Machida et al. (19) presented the case of a patient with ITBA after allo-HSCT together with a review of the literature. The prognosis of ITBA is significantly worse than that in organ transplant recipients due to the administration of immunosuppressive therapy and delayed immune reconstruction in HSCT patients. We would therefore like to add our recent experience, which shows that the larynx is an *Aspergillus*-susceptible organ in allo-HSCTs recipients. Recently, we have successfully treated 3 cases of ITBA and/or invasive laryngeal aspergillosis in HSCT recipients, including the present case. Generally speaking, ITBA and invasive laryngeal aspergillosis should not be ignored as serious and potentially fatal complications after allo-HSCT.

Because of the low yield of cultures, the Food and Drug Administration (FDA) has approved the *Aspergillus* galactomannan and β-D-glucan assays as diagnostic tests for *Aspergillus* (20, 21). However, the tests are not useful for the early diagnosis of ITBA or invasive laryngeal aspergillosis, as their nonspecific clinical presentation and the sensitivity of the current tests are incompletely accurate (22). Persistent cough, dyspnea, hoarseness and fever were the most frequent symptoms observed in the pooled series of immunocompromised patients with ITBA and invasive laryngeal aspergillosis (17, 18). In the clinical setting, chest CT scan is still the first imaging modality to be applied in the initial diagnosis of ITBA. However, it is noteworthy that as the course of the infection progresses, radiologic abnormalities appear and that specific radiographic findings are not present in the early stages in these patients (23). According to the bronchoscopic appearance, there are two classifications of isolated ITBA that have been generally accepted (12, 24). Thus, numerous studies seem to confirm the point of view that these forms represent a progressive evolution of the disease, which ranges from mild to widespread bronchitis and are thus of educational rather than clinical value (25). The pseudomembranous and obstructive forms are most frequently observed in ITBA patients; the pseudomembranous type is usually found in severely immunocompromised hosts after HSCT (26). However, the manifestations of ITBA and invasive laryngeal aspergillosis under fiberoptic bronchoscopy and laryngoscopy, respectively, in HSCT patients have not been fully understood. The current patient was diagnosed with an *Aspergillus* infection by laryngoscopy and fi-

beroptic bronchoscopy in a timely manner because he presented with a persistent cough at six months after transplantation. The rapid diagnosis and treatment of these complications improves survival after transplantation (27). Hence, we conclude that because the radiological signs are negative in the early disease period (when ITBA and/or invasive laryngeal aspergillosis were suspected), fiberoptic bronchoscopy and laryngoscopy should be employed as first-line investigations to obtain biopsy specimens and determine the etiology as soon as possible, and that thrombocytopenia or coagulopathy should be considered prior to obtaining a final diagnosis (28-30). In the present case, bronchoscopy revealed the presence of a large amount of obstructive material. Furthermore, the strong anti-fungal treatment did not improve the patient's dyspnea. The aggressive removal of the obstructive material (localized bronchial aspergillosis) using a fiberoptic bronchoscope was the key to the survival of this patient. Thus far, there is no consensus on the bronchoscopic or laryngoscopic management of allo-HSCT recipients and bronchoscopic removal has only been mentioned in a series of case reports (31, 32). The present case suggests that fiberoptic bronchoscopy should be considered as an alternative treatment option in patients with airway aspergillosis.

Voriconazole is the primary choice of medication for the treatment of *Aspergillus* (33, 34); however, we were forced to discontinue voriconazole treatment due to liver dysfunction. Micafungin has demonstrated *in vitro* and *in vivo* activity against *Aspergillus* spp. (33, 35); however, the obvious development of the obstructive material was observed in the airway under bronchoscopy during micafungin treatment in the present patient; which suggests that that *Aspergillus* may develop during micafungin therapy (36). Renal dysfunction is frequently observed in patients receiving liposomal AmB (37), which might have limited the use of this agent in the present patient. Several investigators have noted further improvements in the outcome based on *in vitro* and animal studies that have demonstrated the synergistic or additive effects of the combination of triazole or amphotericin B with echinocandin (38, 39). Combination antifungals should be considered for the treatment of invasive *Aspergillus* in the salvage setting (40). However, whether combination therapy is better than monotherapy remains to be determined (41). The present patient was treated successfully with a combination of posaconazole and caspofungin, demonstrating that the protocol is a feasible choice and that it should be considered as a salvage therapy (42).

In summary, ITBA and laryngeal aspergillosis should be considered as serious and potentially fatal complications after HSCT. Moreover, when ITBA and/or invasive laryngeal aspergillosis are suspected fiberoptic bronchoscopy and laryngoscopy should be performed as first-line investigations, as they allow for biopsy specimens to be rapidly obtained and for the etiology to be determined. Furthermore, fiberoptic bronchoscopy should be considered as an alternative treatment option in patients with airway aspergillosis. Finally, the results of the present case suggest that the combination of posaconazole and caspofungin is a feasible treatment choice and that it should be considered as a salvage therapy.

The authors state that they have no Conflict of Interest (COI).

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