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CENTRAL AIRWAYS OBSTRUCTION DUE TO *ASPERGILLUS FUMIGATUS* FOLLOWING LUNG TRANSPLANTATION

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Abstract

Background—*Aspergillus* fumigatus may affect immunocompromised lung transplant patients in many ways.

Method—We report a new pulmonary manifestation of *Aspergillus fumigatus* in a case series of three patients who underwent bilateral lung transplantation.

Results—All three subjects developed rapid drops in pulmonary function and were found to have large central airways obstruction with thick plugs of mucus, heavily laden with *Aspergillus* species.

Conclusion—All three patients presented with atypical features of *Aspergillus* infection but all responded to treatments with either steroids, antifungals, or both.

Introduction

Infections with *Aspergillus* species are common following lung transplantation. *Aspergillus fumigatus* is a ubiquitous fungus found in water, soil, aerosols, and decaying organic matter,[123] and its distribution facilitates nosocomial transmission in the hospital unit as a result of contamination of air or potable water.[4] Clinical manifestations of *Aspergillus fumigatus* in immunocompromised hosts include invasive aspergillosis, allergic bronchopulmonary aspergillosis (ABPA) with asthma, chronic necrotizing aspergillosis, and aspergillomas.[156] Following lung transplantation, *Aspergillus* infections of the airways have been reported, particularly in CF patients. In addition, there have been two reported cases of ABPA developing after lung transplant for cystic fibrosis, one of which appeared as a recurrence of a previously acquired *Aspergillus* infection[78]. We document a new

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manifestation of *Aspergillus* infection following lung transplantation in a case series of three patients with central airways obstruction due to *Aspergillus* that responded to treatment with steroid or antifungals.

Patient #1

A 59-year-old Caucasian male with a history of chronic obstructive pulmonary disease and bronchiectasis received a bilateral lung transplant. The patient had good recovery of pulmonary function after transplant. Bronchoscopy performed one and a half months after the transplant revealed patent airways with normal mucosa, mild purulent secretions, no signs of rejection, and no evidence of organisms. At this time, post-operative medications included cyclosporine, prednisone, mycophenolate, valacyclovir, trimethoprim-sulfamethoxazole, and esomeprazole.

Four months post-operative, the patient began experiencing several episodes of bronchitis with a drop in FEV1. Although his chest radiograph was unremarkable, bronchoscopy revealed significant plugging of his segmental and subsegmental airways with thick green secretions, which had to be removed using a snare. Microscopic examination of the plugs revealed *Aspergillus* species. Over the next two weeks, his dyspnea increased, especially when trying to expectorate the exceptionally viscous greenish sputum. A repeat bronchoscopy revealed patent airways but more heavy thick green plugs were removed with a snare. Therapy with itraconazole and 40 mg of prednisone was initiated. Over the next several months, these symptoms resolved and the FEV1 subsequently improved (Figure 1a).

Patient # 2

A 54-year-old Caucasian woman underwent bilateral lung transplantation for advanced emphysema. Two years after the transplant, the patient began complaining of generalized malaise and experienced a decline in pulmonary function. She was afebrile with a non-productive cough, rhinorrhea, and wheezing. She was treated empirically with levofloxacin. The patient developed three focal ill-defined opacities with irregular margins in the right lung on CT scan. Bronchoscopy revealed mucus plugs occluding the bronchus intermedius with friable mucosa; *Aspergillus* was cultured. Although she still experienced several episodes of productive cough after the bronchoscopy, she appeared clinically improved and spirometric values had returned to baseline with no antifungal therapy. Six months later the patient again had a cough productive of yellow-green mucus with a decline in her FEV1 (Figure 1b). Bronchoscopy revealed a thick yellow plug in the right mainstem bronchus and fungal elements consistent with *Aspergillus* (Figure 2). She was treated with itraconazole and predinisone and had rapid improvement.

Patient #3

A 51-year-old African-American female with a history of idiopathic bronchiectasis underwent bilateral lung transplantation. The post-operative course was complicated with several infections as well as the development of cerebral post-transplant lymphoproliferative disorder (PTLD). Four years post-transplant, she developed chest congestion, wheezing, shortness of breath, a non-productive cough and declining PFTs. Bronchoscopy

demonstrated persistent secretions and marked stenosis of the medial and superior aspect of left anastomosis secondary to an adherent polypoid mass-like plug, shown to be *Aspergillus fumigatus*. Itraconazole was begun and spirometry improved, approaching baseline values (FVC=2.30 liters; FEV_1=2.07 liters). With resurgence of her PTLD five years post-transplant and over a year after the infection, rituximab treatment was instituted. Coincident with the induction of monoclonal antibody therapy was the reappearance of respiratory symptoms (rhinorrhea, diffuse wheeze, persistent sniffling, shortness of breath, dark yellow sputum) with a severe obstructive pattern. FVC and FEV_1 had decreased by 1.20 liters and 0.55 liters, respectively, with a drop in the FEV/FEV_1 ratio of 53% (Figure 1c). Complete occlusion of the left anastomosis secondary to fungal infiltrates was shown by bronchoscopy. Cultures grew *Aspergillus fumigatus* which was treated with itraconazole and an increase in corticosteroids. PFTs improved again with therapy.

Discussion

We report three cases of atypical manifestations of *Aspergillus* infection occurring after bilateral lung transplant. The primary manifestation of infection in these patients was obstruction of the central bronchi. All three exhibited obstructive patterns on their pulmonary function tests and subsequently had mucus plugs recovered which grew *Aspergillus*. Patients demonstrated productive coughs and lacked a progression to invasive disease. Symptoms were often intermediate between the more well-established conditions caused by this organism. Many manifestations of the infection have been noted in the literature to be outside the established classifications of the disease.[5910111213141516171819202122232425][34–38] In the lung transplant population, though, this is the first report of the major presenting symptoms being infectious obstructive mucus plugging.

Colonization of the airways is very common in the post-lung transplant population with an incidence of 29% in the first year[26] and overall incidences between 20 and 50%[127]; yet colonization is asymptomatic.[28] In our patients, the signs and symptoms were sufficiently different from either ABPA or bronchitis to preclude exact categorization, although certain aspects of the presentation of the diseases appeared similar to ABPA. It is also possible that there was a coexistence of more than one form of Aspergillus syndromes that accounted for the presentations. Roentgenographic changes characteristic of ABPA such as consolidation, segmental or lobar atelectasis, and shadows from mucous impaction were notably absent in patient 1 and 3. However, the chest radiograph of patient #2 disclosed numerous, ill-defined pulmonary nodules. Although tracheobronchitis with severe inflammation has been observed to progress to airway obstruction, it is usually presaged by symptoms of bronchopneumonia.[29] Additionally, tracheobronchitis and anastomotic infections most often occur within 3 months after transplantation whereas disease in our patients occurred up to four years later.[30]

Immunosuppression of this population may in part account for the varying presentations. For example, *Aspergillus* infections in lung transplant recipients were accompanied by fever in only 15% of the patients in one report.[30] Similarly, among our patients, only patient #3 had fevers. Radiographic features are also commonly lacking. Nodular infiltrates, as occurred in

patient #2, occur in 27 to 30% of patients.[31] Perhaps our patients' immunocompromised state predisposed them to persistent colonization and infection by the organism rather than more transient manifestations. It appears that the process developed without a clear association to immunosuppression reduction. Although immunosuppressive regimens were reduced gradually over time, the patient's time to presentation varied from 4 months to 4 years after transplantation so patient #1 who presented after 4 months had no sizable immunosuppression diminution. In addition, no institutional factors such as construction or renovation could be identified as a risk factor. Although we cannot specifically classify the manifestations ABPA or an infection, evidence appears to point to an ABPA-like picture, mostly responsive to steroids, perhaps made worse by impaired mucociliary clearance or partially masked by immunosuppression.

In all three of our patients, medications were given to combat the two targets in ABPA therapy, namely corticosteroids to attenuate the immunologic response and the inflammatory reaction and intraconazole to decrease the fungal antigen load.[6, 32, 33] One patient was treated with prednisone alone and two with itraconazole. All responded with resolution of their symptoms and negative fungal cytology. Resolution of *Aspergillus* infection was obtained with the combined use of corticosteroids plus itraconazole, the preferred treatment for most patients with ABPA.[32]

One limitation of this case series is that application of a rigorous definition of ABPA was not employed as the patients' presentations were sufficiently distinct from this clinical phenomenon. None of the patients had cutaneous sensitivity to *Aspergillus* or levels of immunoglobulins or antibodies tested. Thus, none of the patients could be evaluated for the full complement of diagnostic criteria necessary for ABPA. In addition, all of these patients presented prior to the routine use of voriconazole therapy. Thus, we do not know the relative utility of voriconazole in treatment of this new syndrome. Furthermore, our program does not employ routine anti-fungal prophylaxis in our patients; thus the effect of prophylaxis on the syndrome could not be evaluated. However, all of our patients presented beyond the window for routine prophylaxis employed by most programs. Finally, this is a case series, and should be interpreted as such; we have no evidence that therapy with itraconazole and prednisone is superior to any other therapy. We are merely describing a syndrome and the empiric therapies our clinicians chose.

In conclusion, we report a case series of a new manifestation of *Aspergillus* infection in lung transplant recipients. All of our subjects presented with a rapid drop in FEV1, with evidence of large, fibrinous *Aspergillus*-laden mucus plugging that responded to increased doses of corticosteroids and itraconazole. To our knowledge, this is the first description of central airways obstruction due to *Aspergillus fumigatus* in lung transplant recipients.

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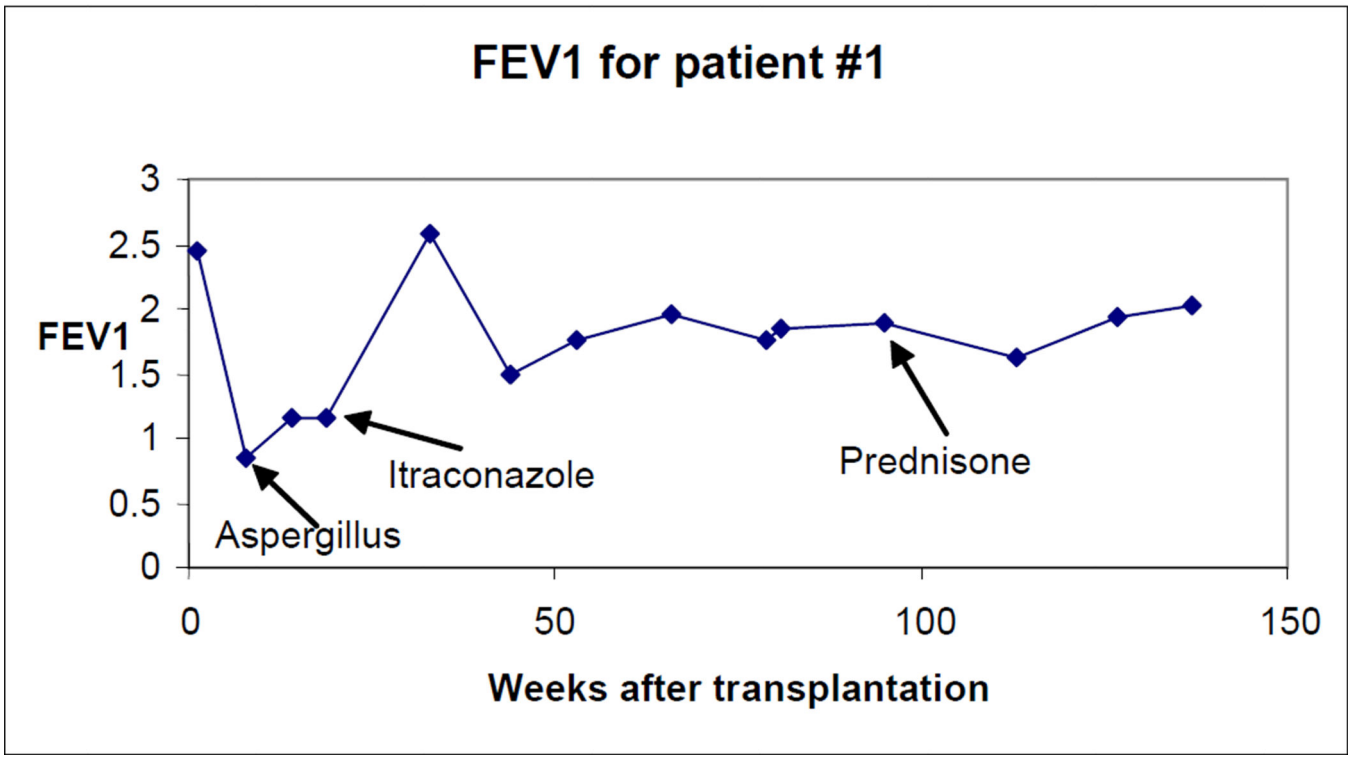
References

1. Soubani A, Chandrasekar P. The clinical spectrum of pulmonary aspergillosis. Chest. 2002; 121:1988–1989. [PubMed: 12065367]
2. Kradin R, Mark E. Case 32-1998: An 83-year-old woman with long-standing asthma and rapidly progressing pneumonia. New England Journal of Medicine. 1998; 339:1228–1236. [PubMed: 9786749]
3. Lai K. A cluster of invasive aspergillosis in a bone marrow transplant unit related to construction and the utility of air sampling. American Journal of Infection Control. 2001; 29:333–337. [PubMed: 11584261]
4. Fishman J, Rubin R. Infection in organ-transplant recipients. New England Journal of Medicine. 1998; 338:1741–1751. [PubMed: 9624195]
5. Chalumeau M, Adamsbaum C, Raymond J, Iniguez J, Gendrel D. Mediastinal aspergilloma ten years after thoracic surgery. The Pediatric Infectious Disease Journal. 2000; 19:662. [PubMed: 10917230]
6. Vlahakis N, Aksamit T. Diagnosis and treatment of allergic bronchopulmonary aspergillosis. Mayo Clinic Proceedings. 2001; 76:930–938. [PubMed: 11560305]
7. Fitzsimons E, Ars R, Patterson R. Recurrence of allergic bronchopulmonary aspergillosis in the posttransplant lungs of a cystic fibrosis patient. Chest. 1997; 112:281–282. [PubMed: 9228393]
8. Casey P, Garrett J, Eaton T. Allergic bronchopulmonary aspergillosis in a lung transplant patient successfully treated with nebulized amphotericin. Journal of Heart and Lung Transplant. 2002; 21:1237–1241.
9. Ulusakarya A. Aspergilloma. New England Journal of Medicine. 2002; 346:256. [PubMed: 11807150]
10. Chambers J, Blauth C, Bucknell C, Eykyn S. Aspergilloma as a complication of pacemaker implantation. New England Journal of Medicine. 2002; 346:428. [PubMed: 11832531]
11. Ricaute K, Greenberger P, Fullerton D. Allergic bronchopulmonary aspergillosis with multiple Streptococcus pneumoniae lung abscesses: an unusual initial case presentation. Journal of Allergy and Clinical Immunology. 1999; 104:238–241. [PubMed: 10400868]
12. Barker J, Weisdorf D, Wagner J. Creation of a double chimera after the transplantation of umbilical-cord blood from two partially matched unrelated donors. New England Journal of Medicine. 2001; 344:1870–1871. [PubMed: 11407361]
13. Warris A, Bjørneklett A, Gausted P. Invasive pulmonary aspergillosis associated with infliximab therapy. New England Journal of Medicine. 2001; 344:1099–1110. [PubMed: 11291675]
14. White D, Mark E. Case 10-2001: A 53-year-old woman with arthritis and pulmonary nodules. New England Journal of Medicine. 2001; 344:997–1004. [PubMed: 11274627]
15. Ledesma D, Pearce W. Septic (Aspergillus) embolus. New England Journal of Medicine. 2000; 342:1015. [PubMed: 10749963]
16. Gori F, Nesi G, Pedemonte E. Aspergillus fungus balls on mitral valve. New England Journal of Medicine. 2001; 344:310–311. [PubMed: 11191669]
17. Aversa F, Tabilio A, Velardi A, et al. Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched. New England Journal of Medicine. 1998; 339:1186–1193. [PubMed: 9780338]
18. Rochester C, Kradin R. Case 39-2000: A 47-year-old woman with multilobar pulmonary consolidation. New England Journal of Medicine. 2000; 343:1876–1884. [PubMed: 11117981]
19. Hummel M, Schuler S, Hempel S, Rees W, Hetzer R. Obstructive bronchial aspergillosis after heart transplant. Mycoses. 1993; 36:425–428. [PubMed: 7935576]
20. Ko J, Kim D, Shepard J. Pulmonary aspergillosis in an immunocompetent patient. Journal of Thoracic Imaging. 2002; 17:70–73. [PubMed: 11828215]
21. Máiz L, Cuevas M, Quirce S, Pacheco A, Escobar G. Allergic bronchopulmonary aspergillosis with low serum IgE levels in a child with cystic fibrosis. Journal of Allergy and Clinical Immunology. 1997; 100:341–342. [PubMed: 9314346]

22. Kradin R, Mark E. Case 18-2002: A 48-year-old man with a cough and bloody sputum. New England Journal of Medicine. 2002; 346:1892–1899. [PubMed: 12063374]
23. O'Connor T, O'Donnell A, Heurley M, Bredin C. Allergic bronchopulmonary aspergillosis: a rare cause of pleural effusion. Respirology. 2001; 6:361–363. [PubMed: 11844130]
24. Shah A, Agarwal A, Chugh I. Hilar adenopathy in allergic bronchopulmonary aspergillosis. Annals of Allergy, Asthma, and Immunology. 1999; 82:504–506.
25. Cattelan A, Loy M, Tognan S, Rea F, Sasset L, Cadrobbi P. An unusual presentation of invasive aspergillosis after lung transplantation. Transplant. 2000; 13:183–186.
26. Mehrad B, Paciocco G, Martinez F, Ojo T. Spectrum of Aspergillus infection in lung transplant recipients: case series and review of the literature. Chest. 2001; 119:169–175. [PubMed: 11157600]
27. Westney G, Kesten S, Hoyos Ad, Chapparro C, Winton T, Maurer J. Aspergillus infection in single and double lung transplant recipients. Transplantation. 1996; 61:915–919. [PubMed: 8623160]
28. Cahill B, Hibbs J, Savik K, et al. Aspergillus airway colonization and invasive disease after lung transplantation. Chest. 1997; 112:1160–1164. [PubMed: 9367451]
29. Nathan S, Shorr A, Schmidt M, Burton N. Aspergillus and endobronchial abnormalities in lung transplant recipients. Chest. 2000; 118:403–407. [PubMed: 10936132]
30. Singh N, Husain S. Aspergillus infections after lung transplantation: clinical differences in type of transplant and implications for management. Journal of Heart and Lung Transplant. 2003; 21:258–266.
31. Singh N, Patterson D. Aspergillus infections in transplant recipients. Clinical Microbiology Reviews. 2005; 18:44–69. [PubMed: 15653818]
32. Stevens D, Schwartz H, Lee J, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. New England Journal of Medicine. 2000; 342:756–762. [PubMed: 10717010]
33. Leon E, Craig T. Antifungals in the treatment of allergic bronchopulmonary aspergillosis. Annals of Allergy, Asthma, and Immunology. 1999; 82:511–517.
34. Paterson D, Singh N. Invasive aspergillosis in transplant recipients. Medicine. 1999l; 78:123–138. [PubMed: 10195093]
35. Kubak BM. Fungal infection in lung transplantation. Transpl Infect Dis. 2002; 4:24–31. [PubMed: 12486789]
36. Scherer M, Fieguth H, Aybek T, Ujvari Z, Moritz A, Wimmer-Greinecker G. Disseminated Aspergillus fumigatus infections with consectutive mitral valve endocarditis in a lung transplant recipient. J Heart Lung Transpl. 2005; 24(12):2297–2300.
37. Shlobin OA, Dropulic LK, Orens JB, Mcdyer JF, Conte JV, Yang SY, Girgis R. Mediastinal mass due to Aspergillus fumigatus after lung transplantation: a case report. J Heart Lung Transpl. 2005; 24(11):1990–1993.
38. Mehrad B, Paciocco G, Martinez FJ, Ojo TC, Iannettoni MD, Lynch JP 3rd. Spectrum of Aspergillus infection in lung transplant recipients. Chest. 2001; 119:169–175. [PubMed: 11157600]

a



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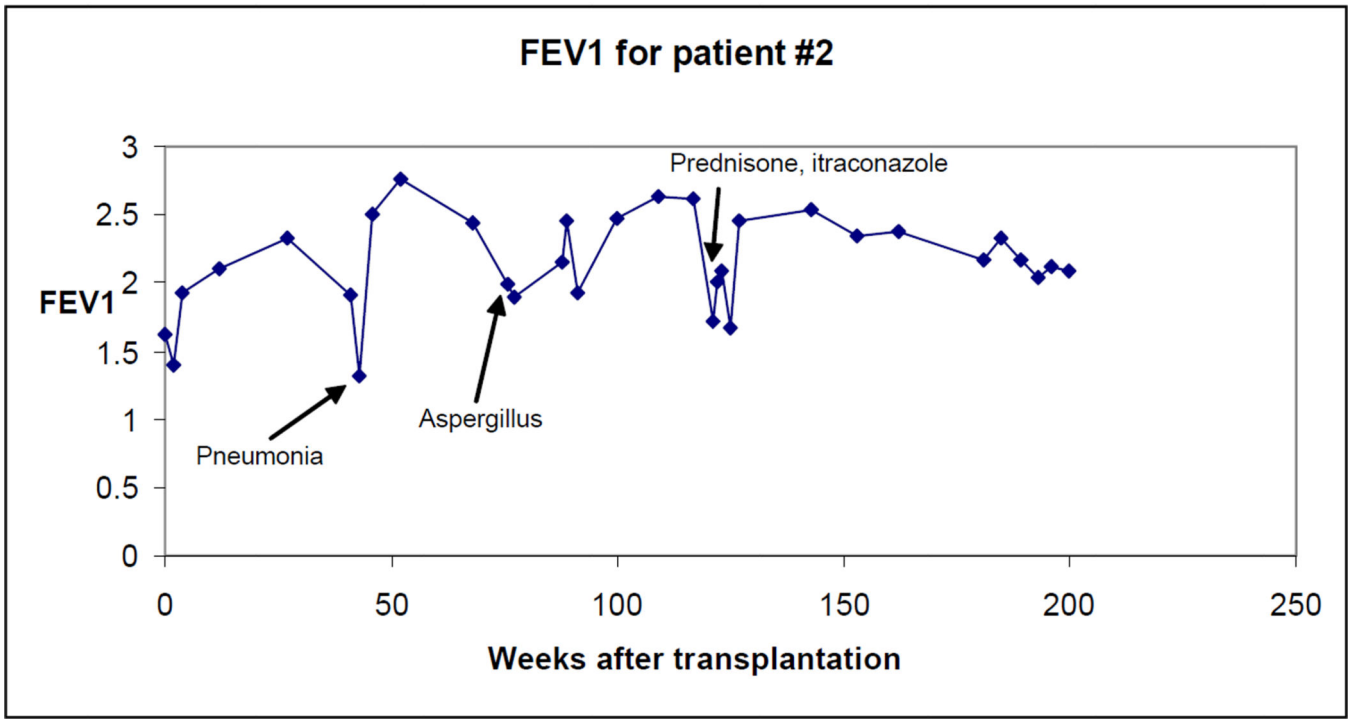

c

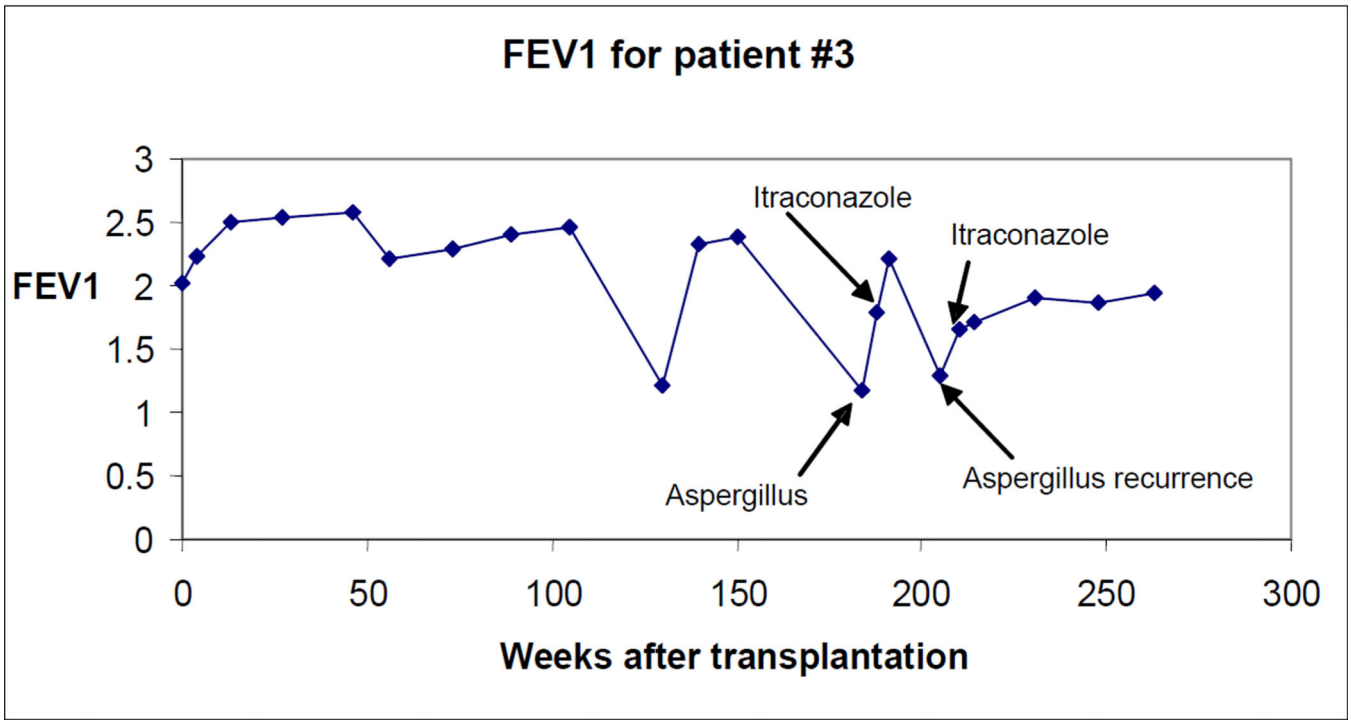

Figure 1.

Course of FEV1 in three subjects with central airways obstruction secondary to *Aspergillus fumigatus*. a) patient #1, b) patient #2; c) patient #3.

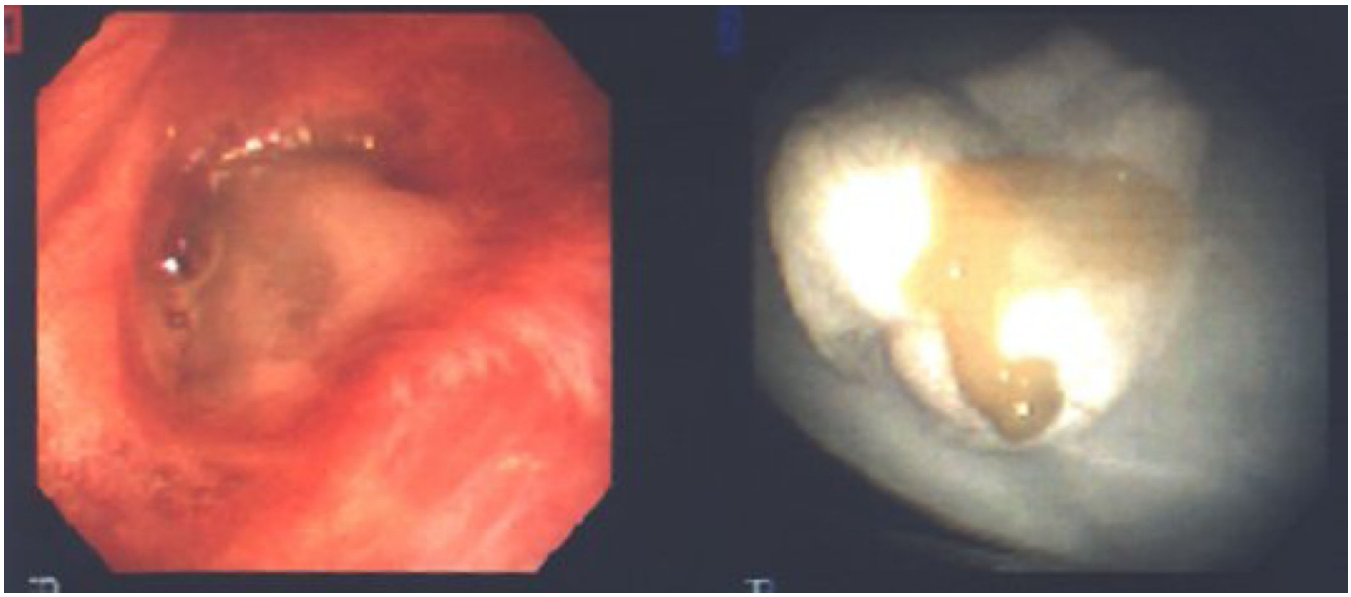

Figure 2.
Bronchoscopic images of occluded right mainstem bronchus with large mucus plug laden with *Aspergillus* species.