

A Case of Allergic Bronchopulmonary Aspergillosis Associated With Hematopoietic Stem Cell Transplantation Due to Chronic Granulomatous Disease

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Summary: Allergic bronchopulmonary aspergillosis is an immunologic pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus*. This disorder is most commonly seen in patients with poorly controlled asthma and cystic fibrosis. It is rarely reported in chronic granulomatous disease patients; however, there are no cases reported with hematopoietic stem cell transplantation in the English literature. Herein, we report a patient with chronic granulomatous disease who had hematopoietic stem cell transplantation and subsequently developed allergic bronchopulmonary aspergillosis.

Key Words: chronic granulomatous disease, allergic bronchopulmonary aspergillosis, corticosteroid, treatment

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Aspergillosis of the respiratory tract has diverse manifestations that range from hypersensitivity disorders to rapidly invasive disseminated disease. These can be classified into 3 distinct clinical categories: saprophytic colonization, allergic aspergillosis, and invasive aspergillosis. Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitive lung disease, due to bronchial colonization by *Aspergillus fumigatus* that occurs in susceptible patients, with a prevalence of 2% to 15% in western countries.¹ It is most commonly seen in patients with asthma and cystic fibrosis (CF). Rarely, ABPA occurs in patients with bronchiectasis, chronic granulomatous disease (CGD), hyperimmunoglobulin E syndrome, and in lung transplant recipients.² Herein, we report a CGD case of a patient who had hematopoietic stem cell transplantation (HSCT) and subsequently developed ABPA.

CASE

A five and a half year old female patient with CGD was admitted to our hospital for HSCT. She was diagnosed at 1 year of age, after retropharyngeal abscess. Her parents had a consanguineous marriage. The patient had chronic pulmonary findings due to previous infections before HSCT in her thorax high-resolution computed tomography (HRCT). The patient received reduced toxicity myeloablative conditioning (treosulfan, 16 g/m²/d for 3 days; fludarabine, 30 mg/m²/d for 5 d; ATG-Fresenius, 10 mg/kg/d for 3 d) and, subsequently, peripheral blood stem cell-derived

HSCT from a full-match unrelated donor. Cyclosporin-A and mycophenolate mofetil were given for graft versus host disease prophylaxis. Voriconazole and acyclovir prophylaxis were administered. Unmanuplated peripheral blood stem cell containing 8.7×10^6 cells/kg CD34⁺ cells was given. On the fifth day of the transplantation, she had fever (38.7°C). On physical examination, a specific fever origin was not detected. Complete blood count revealed a hemoglobin level of 10.4 g/dL, white blood cell count of $30/\text{mm}^3$, absolute neutrophil count of $0/\text{mm}^3$, and platelet count of $37,000/\text{mm}^3$. The biochemical tests were within normal limits. Serum C-reactive protein level was high (9.2 mg/dL). Tests for possible pathogens including cultures and/or stains of blood and sputum for viruses, fungi, parasites, acid-fast bacilli, and bacteria were negative. Meropenem was initiated empirically. On the third day of fever, teicoplanin and amikacin was added to the therapy. Filgrastim was started on day +8.

On day +11, neutrophil engraftment occurred. Cough and tachypnea (respiratory rate, 42/min) developed on day +13. HRCT of the chest showed peribronchovascular, irregular nodular opacities on the lower lobe of the right lung, bilateral diffuse subsegmental atelectasis, and bilateral pleural effusion (Fig. 1). Bronchoalveolar lavage was not specific. Mycological culture was negative. Caspofungin was added to voriconazole therapy. On day +31, the patient still had fever.

She had itchy eruption, disseminated hyperemia, productive cough with mucopurulent and brown sputum, respiratory distress with dyspnea, tachypnea (respiratory rate 48/min), and wheezing. She complained of chest pain and easy fatigability, and physical examination showed intercostal retraction. Chest auscultation revealed bilateral rhonchi and crackles. Heart rate was 120/min, blood pressure was normal, and oxygen saturation was 92%. Chest

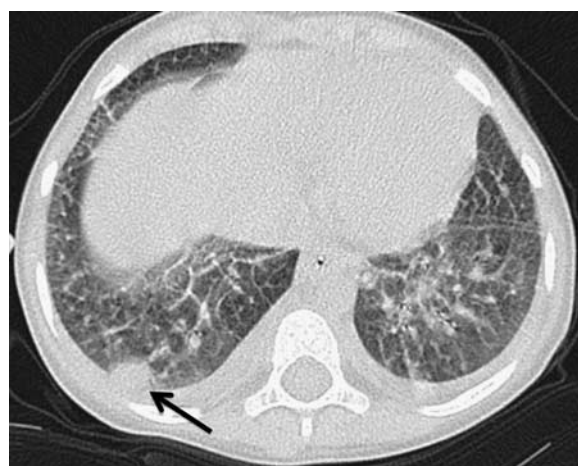


FIGURE 1. HRCT of the chest showing peribronchovascular nodular opacities on the lower lobe in the right lung (arrow), bilateral diffuse subsegmental atelectasis, and bilateral pleural effusion. HRCT indicates high-resolution computed tomography.

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x-ray showed bilateral reticular pulmonary infiltration. Serum galactomannan antigen was positive, while *A. flavus*-specific antigen was negative. Unfortunately, *A. fumigatus*-specific antigen test could not be analyzed in our center. Complete blood count revealed a hemoglobin level of 13 g/dL, white blood cell count of 18,400/mm³, absolute neutrophil count of 11,500/mm³, total eosinophil count (TEC) of 2,910/mm³, and platelet count of 131,000/mm³. Total immunoglobulin (Ig) E was 2968 IU/mL. We diagnosed “probable” ABPA with these clinical, radiologic, and laboratory findings.³ The patient was given methyl prednisolone 1 mg/kg/d for ABPA and liposomal amphotericin-B was replaced with caspofungin. On the 24th hour of methyl prednisolone, the fever diminished and the TEC reduced dramatically (60/mm³). On the second day of steroid treatment (day +38), HRCT was repeated, and pneumothorax, smaller sized but cavitary fungal nodules, and minimal pleural effusion on the right side were detected (Figs. 2A, B). On day +43, the auscultation findings totally recovered. Dose tapering was started on the eighth day of steroid treatment. The total IgE levels were found to be 1500 and 127 IU/mL on the 31st (day +67) and 40th (day +77) days of steroid treatment, respectively. Steroid treatment ended at 8 weeks. The patient is in the 156th day now with full donor chimerism. Her chest x-ray is normal. TEC is 70/mL, and total IgE is 137 IU/mL. Unfortunately, respiratory function test could not be performed due to patient noncooperation. The patient did not have any problems with voriconazole prophylaxis.

DISCUSSION

ABPA was first described by Hinson et al⁴ in 1952 in the UK. The exact prevalence of this disease is still not known, and this is most likely due to the lack of a uniform diagnostic criterion and standardized tests. It is mostly observed in CF and asthmatic patients.² It is rarely reported in CGD patients; however, there are no cases reported with HSCT in the English literature.

The underlying pathologic mechanism of ABPA is not fully understood. It is primarily the result of an abnormal host immune response to *Aspergillus* antigens. Host immunologic responses are central to the pathogenesis of ABPA, which is defined as a hypersensitivity disorder induced by *Aspergillus* species.⁵ It was proposed that ABPA develops in genetically susceptible patients because of increased frequency and/or activity of *A. fumigatus*-specific T-helper 2 (Th2) CD4⁺ cells. The Th2 cytokines lead to total and *A. fumigatus*-specific IgE synthesis, mast cell degranulation, and promotion of a strong eosinophilic response.²

In ABPA, it is hypothesized that defects in innate and adaptive immunity cause persistence of *A. fumigatus*.³ Many of these genetic defects have also been documented in ABPA complicating CF. HLA-DRB1 and HLA-DQB1 alleles have previously been associated with ABPA susceptibility. Muro et al⁶ showed that in the HLA-DRB1*07:01, DRB1*15:01 and DQB1*06:02 associated with ABPA susceptibility, while DQB1*02:01 associated with possible protection. Our patient had HLA-DRB1*07:01.

Patients with ABPA generally present with poorly controlled asthma, wheezing, hemoptysis, and productive cough. Other symptoms include low-grade fever, weight loss, malaise, and fatigue. Expectoration of brownish black mucus plugs is seen in only 31% to 69% of patients.⁷ Our patient had all these symptoms. The key criterion for diagnosis is an elevated *Aspergillus*-specific IgE, supported by an elevated total IgE, detectable *Aspergillus*-specific IgG, eosinophilia, and positive skin prick tests for *Aspergillus* (where available).⁸

The serum total IgE level is a useful test in both diagnosis and follow-up of ABPA. Patterson et al⁹ suggested a cut-off value of > 2500 ng/mL (> 1042 IU/mL). Subsequently, they proposed cut-offs of <1000 ng/mL for “ABPA probably

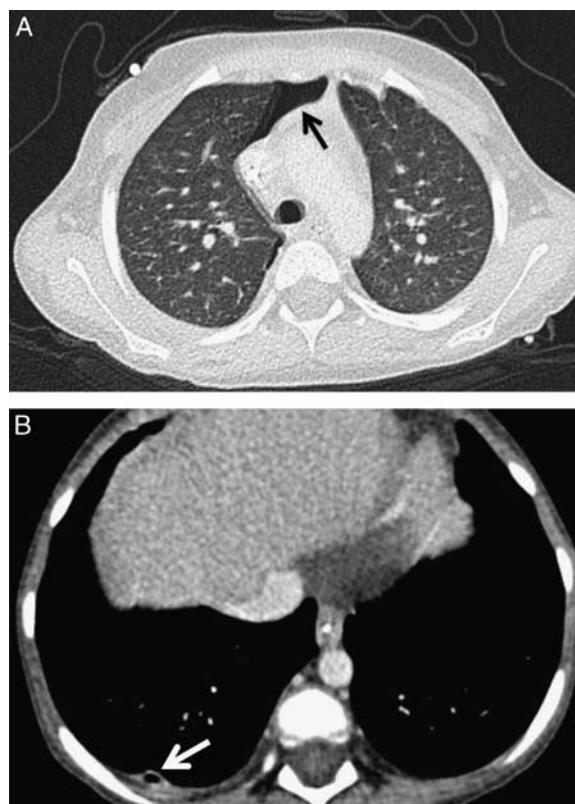


FIGURE 2. Follow-up HRCT of the patient. Pneumothorax (A), smaller sized (black arrow) but cavitary fungal nodules (white arrow), and minimal pleural effusion on right lung (B). HRCT indicates high-resolution computed tomography.

excluded” and > 2000 ng/mL (833 IU/mL) for “further serological studies required.”¹⁰

After treatment, serum IgE levels start declining, but, in most patients, they do not reach normal values.¹¹ Repeated measurements of IgE levels are required to determine the “new” baseline value for an individual patient during remission. The serum IgE also represents an important tool in the follow-up of patients, and an increase in IgE levels may signify an impending exacerbation. At the beginning, the total IgE level was > 2500 IU/mL, but, on the 40th day of steroid therapy, total IgE reduced to normal limits. It is important to determine high levels of *A. fumigatus*-specific IgE and serum precipitins (IgG) against *A. fumigatus* for diagnosis.¹² Unfortunately, we could not establish both tests.

A peripheral blood eosinophil count > 1000 cells/μL has been considered a major criterion for diagnosis of ABPA. However, a recent study found that only 40% of patients with ABPA presented with TEC > 1000 cells/μL at diagnosis.¹³ TEC was > 2000 cells/μL in our patient.

Typically, bronchiectasis may be present in patients with CF or asthma. Uncommon radiologic manifestations include miliary nodular opacities, perihilar opacities simulating hilar lymphadenopathy, pleural effusions, and pulmonary masses.³ The primary diagnosis of our patient was neither CF nor asthma, and she was diagnosed with typical invasive fungal infection on the basis of radiologic findings. Referring to EORTC diagnostic criteria, our patient had 4 “host factors,” 2 “clinical criteria,” and 1 “mycological criterion;” hence, we diagnosed the patient as having “probable” invasive fungal infection.¹⁴

Culture of *A. fumigatus* in sputum is supportive but not diagnostic of ABPA, because the fungus can also be grown in other pulmonary diseases due to the ubiquitous nature of the fungi. In ABPA, the rates of culture positivity range from 39% to 60%, depending on the number of specimens examined.⁷ We speculate that we did not have a positive sputum culture for *A. fumigatus* due to voriconazole prophylaxis.

The management of ABPA consists of anti-inflammatory therapy such as systemic glucocorticoids to suppress the immune activity, and use of antifungal agents to attenuate the fungal load in the airways.¹⁵ Oral corticosteroids are currently the treatment of choice for ABPA, although there are no well-designed trials of steroids in ABPA. There are no data to guide the dose and duration of glucocorticoids, and different regimens of glucocorticoids have been used. Inhaled corticosteroids achieve high concentrations in the tracheobronchial tree with minimal systemic side effects. Itraconazole is an efficient and commonly used azole-derivate antifungal agent, except in HSCT CGD patients, who are immunosuppressed. As well as itraconazole, voriconazole and posaconazole are also successfully used agents. However, in our case, we had a sustained fever episode under voriconazole therapy, and ABPA had developed, although caspofungin was added to voriconazole. With initiation of steroid therapy and replacement of caspofungin with amphotericin, clinical and radiologic improvement was observed. Therefore, we believe that in relatively immune competent patients, narrow-spectrum antifungal agents may be efficient. However, wide-spectrum antifungal agents should be considered for patients with HSCT.

We suggest that, for patients with primary immune deficiency disorders such as CGD, and HSCT patients (especially after engraftment), ABPA should be kept in mind.

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