Successful Treatment of Chronic Pulmonary Aspergillosis With Isavuconazole

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We report the case of a 77-year-old woman followed up in our Allergy Department for nonatopic severe persistent asthma. Between 1975 and 2004, she had experienced frequent exacerbations, which were treated with systemic corticosteroids. She had been admitted to hospital on several occasions and was diagnosed with corticosteroid-induced osteoporosis. When she was diagnosed with asthma 40 years ago, her FEV_1 was 80%, although this decreased to 70% in 2009. Her FEV_1/FVC was <70% after therapy with bronchodilators. A chest computed tomography (CT) scan performed in 2010 showed bronchiectasis in the right upper and middle lobes, with thickening of the septa at the same sites and centrilobular nodules associated with occupation of the small airway. At this time, allergic bronchopulmonary aspergillosis (ABPA) was ruled out based on the Rosenberg-Patterson criteria.

The patient was diagnosed with high-grade serous ovarian carcinoma in February 2016. She was referred to the oncology department and underwent chemotherapy with paclitaxel, carboplatin, and bevacizumab. Six months later she presented with fever and symptoms of respiratory tract infection, and a chest CT scan showed multiple bilateral consolidations with an air bronchogram and lung nodules in the middle and lower lobes, some of them with central cavitation (Supplementary Figure). *Aspergillus* grew abundantly in bronchoalveolar lavage (BAL) fluid culture. The total serum IgE level was 24.50 kU/L. Skin testing with *Aspergillus* was positive (3×5 mm), specific IgE to *Aspergillus fumigatus* was 0.56 kU_A/L, specific IgG to *A fumigatus* was 51.9 mgA/L, and the blood eosinophil count was 400/µL. Testing for galactomannan in BAL fluid was negative. The patient was diagnosed with chronic pulmonary aspergillosis (CPA), and treatment with intravenous voriconazole was started at 6 mg/kg bid for 3 days before being switched to the oral formulation (300 mg bid) on an outpatient basis. One month later, voriconazole was discontinued because she experienced hallucinations. Given the adverse effects to voriconazole, the patient was prescribed oral posaconazole 300 mg per day for an additional 2 months. During the third month of treatment with antifungal therapy, pulmonary function testing showed stable mild obstruction, and a major improvement in the images in the CT scan was observed, although there were persistent patchy ground-glass opacities in both lower lobes, as well as consolidations.

In December 2017, the patient had increased sputum production, chest tightness, dyspnea, and wheezing despite maintenance treatment with high doses of inhaled fluticasone, formoterol, and montelukast (she had not taken antifungals for the previous 11 months). Additionally, frank worsening of serum marker levels was observed (total IgE 512 kU/L, specific IgE to *A fumigatus* 4.12 kU_A/L, IgG to *A fumigatus* 103 mgA/L, eosinophilia 300/µL). Serum galactomannan was negative. Pulmonary function testing revealed a loss of 300 mL in FEV_1. A third chest CT scan showed a 2-cm lesion with a solid central zone and ground-glass periphery (halo sign) in an apical segment of the upper right lobe, bilateral apical pleural thickening, and extensive calcification of bronchial walls.

The case was evaluated together with the Infectious Diseases Department, and the patient was diagnosed with ABPA. Given that the CT scan findings suggested more invasive aspergillosis (Supplementary Figure), treatment with antifungals—but not corticosteroids—was considered. Because of the patient's poor tolerance to voriconazole and the risk of pharmacological interactions between azoles and concomitant treatment with chemotherapy, oral treatment with isavuconazole was prescribed (200 mg tid for 2 days, followed by 200 mg qd for 4 months). The patient reported an improvement in her symptoms. A decline in serum markers was observed (total IgE, 63.7 kU/L; specific IgE to *A fumigatus*, 1.25 kU_A/L; IgG to *A fumigatus*, 72 mgA/L; eosinophilia, 100/µL (Supplementary Table). A chest CT scan was performed after 3 months of treatment with isavuconazole, revealing marked resolution of pre-existing lesions, with persistence of thickening of the bronchial walls, bronchiectasis, and septal thickening in both apexes.

We considered there to be an overlap between CPA and ABPA based on the combination of nodules on the chest images, positive culture results for *Aspergillus*, specific IgG to *A fumigatus*, and the exclusion of *Pseudomonas* species or mycobacterial infections (for >3 months) [1]. In addition, the Rosenberg-Patterson criteria were fulfilled in the second infectious respiratory process [2].

We emphasize that the clinical spectrum of disease caused by *Aspergillus* differs according to the host-fungus interaction [3]. Patients with chronic lung diseases have a high risk of aspergillosis and can develop invasive disease under treatment with corticosteroids or neutropenia [4]. Such was the case we describe, where the patient had chronic asthma, bronchiectasis, and a neutropenic risk associated with cancer treatment.

It is important to prevent tissue invasion by *Aspergillus* in neutropenic patients, since the mortality of invasive disease is >50% [4].

Treatment is first with itraconazole, followed by voriconazole and posaconazole. Treatment and management of CPA in patients with chronic obstructive diseases and reduced pulmonary reserve are harder than those of patients who do not have these diseases, and early discontinuation of antifungal therapy may lead to recurrence or exacerbation [3]. Therefore, most cases of CPA require long-term treatment with azoles, which often leads to adverse effects (eg, liver toxicity, hypertension, heart failure, neuropathy, and precancerous lesions) [3].

Isavuconazole is a broad-spectrum antifungal azole approved by the United States Food and Drug Administration for the treatment of invasive fungal diseases (aspergillosis, mucormycosis) in patients who cannot tolerate other azoles. Isavuconazole has a lower risk of pharmacologic interactions than other members of the azole family [1,5].

Isavuconazole was recently reported to be a good treatment option in ABPA [6], a disease for which the patient in the present report fulfilled the criteria. Since she had experienced hallucinations related to voriconazole and because isavuconazole does not interact with cancer treatment, we prescribed this agent and recorded optimal results.

We report a case of ABPA in the course of CPA, with radiological findings of pulmonary angioinvasion that responded successfully to isavuconazole without adverse events. There is evidence to support isavuconazole as first-line therapy for invasive aspergillosis, without the need for therapeutic drug monitoring of plasma concentrations, and for patients who cannot tolerate other azoles [1,6,7]; however, evidence in favor of this approach in cases of CPA remains insufficient [8,9]. More evidence would be helpful when recommending isavuconazole in patients on long-term therapy. We found isavuconazole to be a suitable option for patients with ABPA/CPA and obstructive pulmonary disease and, therefore, with an increased risk of recurrence of CPA. Treatment should be with long-term oral antifungals. Approaches with minimum adverse effects are desirable.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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