

Chronic Pulmonary Aspergillosis Successfully Treated With Isavuconazole

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A 77 years-old female followed-up in our allergy department for non-atopic severe persistent asthma, with frequent exacerbations from 1975 until 2004 treated with systemic corticosteroids, hospital incoming in multiple times and diagnosis of corticosteroid-induced osteoporosis. From 1975 until 2004 treated with systemic corticosteroids, hospital incoming in multiple times and diagnosis of corticosteroid-induced osteoporosis. Forty years ago when asthma diagnosis was made her pulmonary function was FEV1 80% and since 2009 it decreased to 70% and the FEV1/FVC is <70% after bronchodilators inclusive. In 2010 a chest computed tomography (CT) scan showed bronchiectasis in the right upper and middle lobes with thickening of the septa in these same locations and nodules in relation to the occupation of small airway. At this time, Allergic Bronchopulmonary Aspergillosis (ABPA) was ruled out by Rosenberg criteria's.

On February 2016 high-grade serous ovarian carcinoma was diagnosed, a patient was referred to Oncology and underwent chemotherapy with paclitaxel, carboplatin, and bevacizumab. Six months later she presented fever and symptoms of respiratory tract infection, a chest CT scan showed multiple bilateral consolidations with air bronchogram and lung nodules in medial and lower lobes, some of them with central cavitation (Figure 1). *Aspergillus* grew abundantly on the culture of bronchoalveolar lavage (BAL). Total serum Immunoglobulin E (IgE) level was 24.50KU/l, *Aspergillus* skin testing was positive (3x5mm), specific IgE to *Aspergillus fumigatus* (*Af*) was 0,56KU/l, specific IgG to *Af* was 51,9mgA/l and blood eosinophils count of 400cels/uL. Galactomannan (GM) on bronchoalveolar lavage fluid was negative. A diagnosis of Chronic Pulmonary Aspergillosis (CPA) was established and treatment with intravenous voriconazole was started at 6mg/kg twice a day (BID) during 3 days and then it was changed to oral presentation, voriconazole 300mg BID on an outpatient basis. One

month later, voriconazole was discontinued because she experienced hallucinations. Given the patient's secondary effects to voriconazole, she was prescribed oral posaconazole 300mg per day for 2 additional months. On the third month of treatment with antifungal therapies Pulmonary Function Tests (PFTs) showed stable mild obstruction and an important improvement of the images in the CT scan has been observed although there were persistent opacities, in ground-glass, and patched distribution in both lower lobes and also some consolidations.

On December of 2017, the patient had increased sputum production, thorax tightening, dyspnoea and wheezing despite its maintenance treatment with high doses of inhaled fluticasone, formoterol, and montelukast (she did not take any antifungal since 11 months ago). Additionally, clear worsening of serum markers was observed (total IgE 512KU/l, specific IgE to *Af* 4.12KUA/l, IgG to *Af* 103mgA/l, eosinophilia 300cells/uL). The serum-GM was negative. On repeat PTFs, a loss of 300mL in FEV1 was obtained. A third chest CT scan showed a 2cms lesion with a solid central zone and periphery in ground glass (halo sign) in apical segment of upper right lobe appeared, and bilateral pleuroapical thickening and extensive calcification of bronchial walls.

The case was evaluated together with the Infectious Diseases Department and the patient was diagnosed from ABPA, given the CT scan findings suggesting more Invasive Aspergillosis (IA) see Figure 1 on supplementary material, treatment with antifungals was considered, without steroids. Because of patient's poor tolerance to voriconazole, and the risk of pharmacological interactions between azole and concomitant treatment with chemotherapy, oral treatment with isavuconazole was prescribed, 200mg three times a day for 2 days, followed by 200mg once daily during 4 months. Patient related improvement in her symptoms. A decline in serum markers was observed: total IgE 63.7 KU/l, specific IgE to *Af* 1.25 KUA/l, IgG to *Af* 72 mgA/l,

eosinophilia 100cells/ul (see table on supplementary material). A chest CT scan was performed after three months of isavuconazole treatment, revealing marked resolution of pre-existing lesions persisting only thickening of the bronchial walls, bronchiectasis and the septal thickening in both lung apices.

We presented an overlap between CPA and ABPA, the combination of nodules on thoracic image, positive *Aspergillus* infection demonstrated by culture, specific IgG to *Af* and the exclusion of *Pseudomonas* or mycobacterial infections (for >3 months) [1] were present at the same time as fulfilling Rotemberg's Criteria on the second infectious respiratory process [2].

The idea we would like to emphasize is that different clinical spectrum of disease caused by *Aspergillus* can be observed according to the host-fungi interaction [3]. Patients with lung chronic diseases have a high risk of aspergillosis and they can develop invasive disease under treatment with corticosteroids or neutropenia [4]. This is the case of this patient with chronic asthma, bronchiectasis and neutropenic risk associated with oncological treatment.

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

On the other hand, azoles are first-line treatment, itraconazole, followed by voriconazole and posaconazole. Treatment and management of CPA in patients with chronic obstructive diseases and the reduced pulmonary reserve are harder than patients without these diseases and early stopping of antifungal therapy may lead to recurrence or exacerbation [3]. Therefore, the majority of the CPA cases will need long-term treatment with azoles what leads often to secondary effects (liver toxicity, hypertension, heart failure, neuropathy, precancerous lesions, etc) [3].

Isavuconazole is a broad-spectrum antifungal azole approved by Food Drug Administration to treat invasive fungal diseases (aspergillosis, mucormycosis), in patients with intolerance to other azoles. Compared to other azoles, Isavuconazole has less risk of pharmacologic interactions [1,5].

In a recent publication, Isavuconazole has been reported as a good treatment option in ABPA[6], a disease for which our patient fulfilled criteria. Since she had presented hallucinations related to treatment with voriconazole and because isavuconazole does not present interaction with oncological treatment, we prescribe this treatment with optimal results.

We report ABPA in the evolution of CPA with radiological findings of pulmonary angio-invasion that successfully respond to isavuconazole without adverse events. There's some evidence to support isavuconazole as first-line therapy for IA, without the need for therapeutic drug monitoring of plasma concentrations, and for those patients that cannot tolerate other azoles [1,6,7], but there is not enough evidence in cases of CPA yet [8,9]. All over, more evidence as the present case is useful to recommend isavuconazole in patients on long-term therapy.

We found isavuconazole as an azole drug option, for patients with ABPA/CPA and obstructive pulmonary disease and therefore with an increased risk of CPA relapse, where long-term oral antifungal therapy is required and minimum secondary effects are desirable.

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