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Omalizumab as add-on therapy in patients with asthma and allergic bronchopulmonary aspergillosis

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TO THE EDITOR:

Allergic bronchopulmonary aspergillosis (ABPA) is characterized by a pulmonary hypersensitivity reaction to *Aspergillus* spp. ABPA primarily affects immunocompetent patients with atopic asthma and patients with cystic fibrosis.[1] *A. fumigatus* is the most common etiologic agent of ABPA. The prevalence of ABPA in patients with asthma ranges from 1.0% to 3.5%. In patients with corticosteroid-dependent asthma, the prevalence of ABPA is 7-28%. At our facility, the prevalence of ABPA is 19%.[2]

Omalizumab is a humanized monoclonal antibody approved for use in Brazil for the treatment of difficult-to-treat allergic asthma and refractory chronic spontaneous urticaria. Omalizumab has also been used off label for the treatment of diseases in which IgE has a relevant pathophysiological role, including ABPA and anaphylaxis.

In patients with ABPA, omalizumab appears to reduce the numbers of exacerbations and hospitalizations, as well as the need for systemic and inhaled corticosteroids, thus improving quality of life.[3,4] However, only a few studies have examined the use of omalizumab in asthma patients with ABPA without cystic fibrosis.[3,5,6] Controversies regarding the role of omalizumab in patients with ABPA prompted us to report the following case.

In 1994, a 53-year-old female patient who had had asthma since childhood was admitted to the Immunology Department of the Federal University of Rio de Janeiro Clementino Fraga Filho University Hospital, located in the city of Rio de Janeiro, Brazil. Although she had been under treatment with budesonide (800 µg/day) and formoterol (24 µg/day), she presented with uncontrolled asthma. She often needed systemic corticosteroid therapy and antibiotic therapy for asthma exacerbations and respiratory infections.

Laboratory tests showed a total IgE of 780 IU/mL (reference value, < 100 IU/mL), a peripheral eosinophilia of 5% (305 cells/mm^3; reference value: 100-300 cells/mm^3), and positive *A. fumigatus* precipitins. Skin prick testing was positive to *A. fumigatus*, with a wheal of 4 mm in diameter, positive and negative controls being 8 mm and 2 mm, respectively. Intradermal testing to *A. fumigatus* was positive (8 mm).

A chest X-ray showed bibasilar "tramline" infiltrates. A noncontrast HRCT scan of the chest showed diffuse pulmonary hyperinflation, peribronchial thickening, and pleural thickening, with no signs of bronchiectasis. Spirometry showed moderate obstructive lung disease with reduced FVC, as well as positive bronchodilator test results, but no normalization of FVC.

In 1996, the patient presented with difficult-to-treat asthma, a positive skin prick test to *A. fumigatus*, high total IgE levels, and positive *A. fumigatus* precipitins, but without bronchiectasis, being diagnosed with allergic asthma and serologic ABPA.

The patient had been receiving continuous systemic corticosteroid therapy for 18 years (mean dose, 40 mg/day). Attempts to reduce the dose to ≤ 20 mg/day were unsuccessful. During that period, the patient had infectious complications, hypertension, osteoporosis, and Cushing's syndrome.

Approximately 17 years after being diagnosed with ABPA, the patient presented with a total IgE of 450 IU/mL and an eosinophil count of 5% (245 cells/mm^3). Spirometry revealed very severe obstructive lung disease (FEV_1, 24% of predicted; FVC, 53% of predicted; and FEV_1/FVC, 45%), with negative bronchodilator test results. Static lung volume measurements showed significant air trapping that persisted after bronchodilator administration. A noncontrast HRCT scan of the chest showed an increased anteroposterior chest diameter, scattered air trapping, pleural thickening, peripheral reticular opacities in the upper lobes, ectatic bronchi with unevenly thickened walls, centrilobular nodules, and bronchiolar filling with a tree-in-bud pattern, as well as opacities in the lower lobes, suggesting mucoid impaction and ABPA with bronchiectasis (Figure 1).

In December of 2012, despite treatment, the patient remained classified as being a stage IV (corticosteroid-dependent) ABPA patient. Because of refractoriness to standard treatment, she was started on omalizumab (at a dose of 300 mg every 15 days). Thereafter, she presented with controlled asthma and stage II ABPA (i.e., disease remission), and systemic corticosteroid therapy was discontinued.

At this writing, the patient was receiving treatment with omalizumab (300 mg every 15 days) in combination with budesonide (800 µg/day), formoterol (24 µg/day), and beclomethasone (500 µg/day). Emergency department visits were no longer needed. There was a significant improvement in quality of life. However, acute exacerbations of chronic rhinosinusitis remain common.

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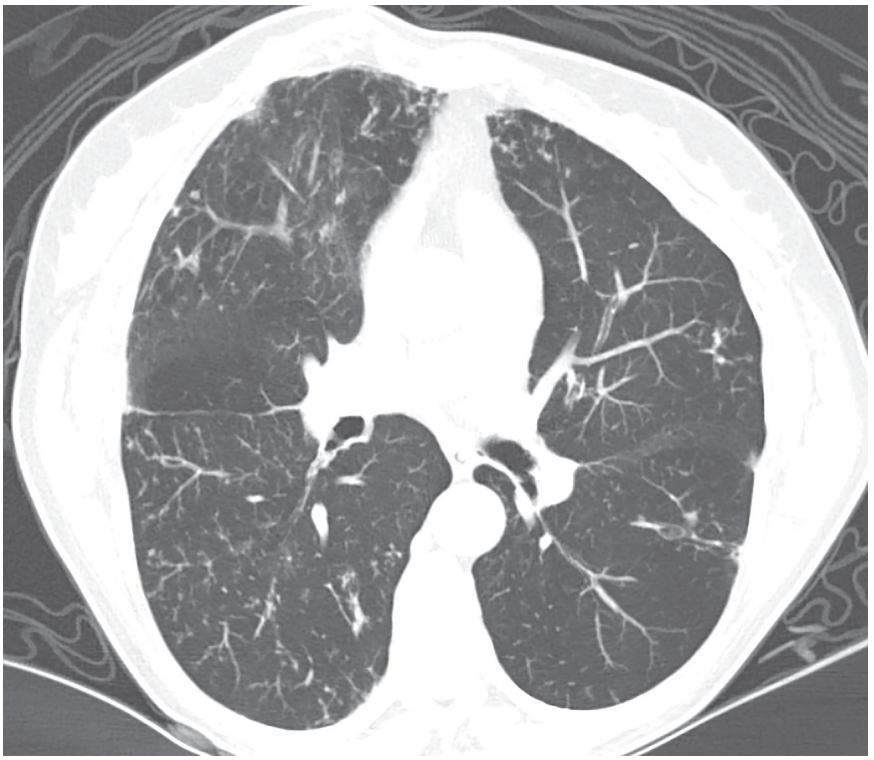

Figure 1. HRCT scan of the chest showing an increased anteroposterior chest diameter, scattered air trapping, pleural thickening, and peripheral reticular opacities in the upper lobes. Note ectatic bronchi with unevenly thickened walls, centrilobular nodules, and bronchiolar filling with a tree-in-bud pattern, as well as opacities in the lower lobes, suggesting mucoid impaction and allergic bronchopulmonary aspergillosis with bronchiectasis.

Table 1. Spirometric parameters.

Year	1994					2012					2014				
	Pre-BD		Post-BD		%	Pre-BD		Post-BD		%	Pre-BD		Post-BD		%
Parameter	n	% p	n	% p	variation	n	% p	n	% p	variation	n	% p	n	% p	variation
FVC, L	1.64	44.0	2.07	56.0	26.0	1.40	53.4	1.40	53.4	0.0	1.87	72.6	1.92	74.3	2.4
FEV_1, L	0.73	23.0	1.08	34.0	47.0	0.53	24.0	0.60	27.3	13.6	0.77	35.6	0.80	37.0	4.0
FEV_1/FVC	0.45	53.0	0.52	61.0	16.0	0.37	45.0	0.40	48.3	7.5	0.41	49.1	0.42	49.8	1.6
$FEF_{25-75\%}$, L/min	0.34	9.0	0.55	15.0	62.0	0.19	7.5	0.24	9.6	29.0	0.23	9.5	0.27	11.2	18.7

BD: bronchodilator; n: absolute value; and % p: percentage of predicted value.

A comparison between data collected in 2012 and 2014 (i.e., before and after treatment with omalizumab) showed improved lung function (FEV_1 and FVC; Table 1). However, improved lung function following treatment with omalizumab is uncommon in the literature. Pérez-de-Llano et al.[5] followed 18 adult patients with ABPA (16 patients with asthma and 2 patients with cystic fibrosis) for a mean period of 16 weeks and found improvement in daily asthma symptoms and FEV_1, as well as a reduction in systemic corticosteroid use. Tillie-Leblond et al.[6] followed 16 patients with asthma and ABPA for 12 months and found a reduction in the number of exacerbations and in the dose of systemic corticosteroids, with no significant changes in lung function.

Before treatment with omalizumab, total IgE levels and peripheral eosinophil levels were 511 IU/mL and 7% (266 cells/mm^3), respectively. After one year of treatment with omalizumab, total IgE levels and peripheral eosinophil levels decreased to 477 IU/mL and 2% (108 cells/mm^3), respectively.

Total IgE levels were found to have decreased after initiation of treatment with omalizumab. This finding is inconsistent with the literature, given that total IgE levels are expected to remain high throughout the treatment period because of formation and prolonged clearance of immune complexes. However, the fact that ABPA includes stages of remission and exacerbation might explain the variation in total IgE levels.

Eosinophils also decreased. Given that the patient had been receiving long-term systemic corticosteroid therapy, it is possible that eosinophils were underestimated before treatment with omalizumab. Therefore, the fact that eosinophil levels decreased

after initiation of treatment with omalizumab is even more significant.

Improved clinical status and laboratory tests provide further evidence that omalizumab is beneficial in patients with ABPA. Omalizumab had a corticosteroid-sparing effect and improved asthma symptoms and asthma control, allowing discontinuation of systemic corticosteroid. Other studies have shown the positive effects of omalizumab as add-on therapy in patients with refractory ABPA.[3,5-7]

Although omalizumab can be used as add-on therapy in such patients, further studies involving a larger sample size are needed in order to determine the actual role of omalizumab in such patients, as well as its effective dose and duration of treatment.

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