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CASE REPORT

Anti-IgE therapy for allergic bronchopulmonary aspergillosis

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Allergic bronchopulmonary aspergillosis (ABPA) is a severe type of asthma. Some cases are resistant to treatment, even with regular use of antiasthmatic drugs and antifungal agents. The diagnosis of ABPA was made in a 40-year-old patient with ABPA according to the Rosenberg-Patterson criteria. Symptoms were not controlled despite regular use of antiasthmatic drugs, daily systemic steroids, and antifungal agents. Omalizumab, administered in an attempt to stabilize these uncontrolled symptoms, was effective with no adverse events. Our experience suggests omalizumab is a potential candidate drug for controlling steroid-dependent ABPA.

Introduction

The global prevalence of bronchial asthma in the adult population is approximately 4% and has been increasing in recent years.[1] Approximately 5% of patients experience severe asthmatic symptoms.[1] Allergic bronchopulmonary aspergillosis (ABPA) is a severe type of allergic asthma that occurs in approximately 10% of patients with severe asthma.[2]

ABPA, a complex clinical entity that results from an innate allergic immune response to *Aspergillus fumigatus* (AF), is mostly seen in patients with allergic asthma or

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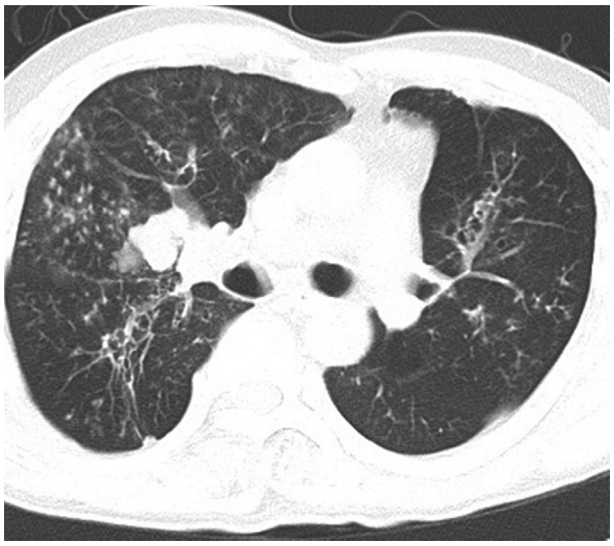

Figure 1. Chest computed tomography obtained at the time of diagnosis of allergic bronchopulmonary aspergillosis.

cystic fibrosis (CF).[3] Sensitization of the allergic host to AF leads to activation of Th2 lymphocytes, which play a key role in allergic diseases, including asthma, by recruiting inflammatory cells like mast cells and eosinophils.[4] The Rosenberg-Patterson criteria are most often used to diagnose ABPA.[5]

ABPA management starts with the avoidance of AF, with antiasthmatic drugs and itraconazole (ITCZ) also being effective in some cases.[6] Systemic prednisolone (PSL) also can be administered in severe cases. Recently, reports have described positive results with the administration of omalizumab, an anti-immunoglobulin (Ig) E drug, in adult patients with severe allergic asthma with or without CF.[7,8]

In this report, we describe an Asian case of non—CF-related ABPA given anti-IgE therapy for longer than 30 months.

Case Report

The current case was a 51-year-old Asian man in whom ABPA was diagnosed at the age of 40 years. He had never received a diagnosis of CF and had no familial history. At the time of diagnosis, his percentage forced expiratory volume in 1 second (FEV1.0) was 58.8%, reversible to 71.1% (253 mL in absolute value) after inhalation of a short-acting beta-agonist. All Rosenberg-Patterson diagnostic criteria were met, including bronchiectasis with pulmonary infiltrates, particularly in the right upper lobe (Fig. 1). At the time of diagnosis, his peripheral blood eosinophils were 1,358/mm^3, total IgE level was 1,500 IU/mL, and AF-specific IgE was 9.24 IU/mL. Precipitating antibody against AF antigen was also found. The patient took PSL regularly (10—20 mg/day) to control severe symptoms in addition to other asthmatic medications (fluticasone 800 μg/day, salmeterol 100 μg/day, pranlukast 450 mg/day, and theophylline 200 mg/day). We could not taper the PSL dose because of frequent exacerbations. Oral ITCZ (200 mg/day) was also administered for 6 months, but did not reduce the annual exacerbation rate and was discontinued because of resulting liver damage (even with the reduction of ITCZ to 100 mg/day). Because of frequent exacerbations, we began administering 375 mg of omalizumab every 2 weeks starting at age 50 years. Asthmatic symptoms improved after 2 months. After 4 months, we evaluated the frequency of exacerbations, the Asthma Control Test (ACT) score, pulmonary function, fraction of exhaled nitric oxide (FeNO), peripheral blood eosinophils, total IgE, and blood AF-specific IgE levels. The frequency of major exacerbations was reduced from three to zero per 4 months, the ACT score changed from 10 to 23, FeNO dropped from 43 ppb to 23 ppb, peripheral blood eosinophils changed from 1,011/mm^3 to 988/mm^3, total IgE elevated from 677 IU/mL to 972 IU/mL, and AF-specific IgE elevated from 7.73 IU/mL to 10.09 IU/mL. According to the patient's daily asthma self-assessment chart, frequency of daytime or nighttime symptoms was reduced from nine to three per fortnight, usage of a short-acting beta-agonist was reduced from five to one per fortnight, and asthma-related absentee rate improved from one incident to zero per 4 months. During this treatment course, the patient was not hospitalized for exacerbations, although his FEV1.0% did not change from 54.1%.

After 12 months of treatment, the skin-prick test became negative, serum total IgE decreased to 609 IU/mL, and AF-specific IgE declined to 6.07 IU/mL (Table 1). With levels of other antiasthmatic drugs remaining the same, we were able to taper the daily PSL dose from 10 mg/day to 5 mg/day without incident. After 30 months of omalizumab treatment, the exacerbation rate, ACT score, FeNO, peripheral blood eosinophils, total IgE, and AF-specific IgE were maintained at good levels without additional PSL administration.

Discussion

We have described an Asian case of ABPA without CF. The patient met the ABPA diagnostic criteria with proximal bronchiectasis, elevated serum IgE, serum precipitating antibodies to AF, positive skin testing to AF, and had FEV1.0

Table 1 Changes in laboratory and clinical findings after omalizumab treatment

	Prior to treatment	After 4 months	After 12 months
Eosinophils (/mm^3)	1011	988	964
Total IgE (IU/mL)	677	972	609
AF-specific IgE (IU/mL)	7.73	10.09	6.07
ACT score	10	23	23
FEV1.0 (L)	1.89	1.96	1.91
%FEV1.0	54.1	55.9	54.7
FeNO (ppb)	43	23	25
Skin test to AF	Positive	Positive	Negative

ACT = Asthma Control Test; AF = *Aspergillus fumigatus*; FeNO = fraction of exhaled nitric oxide; FEV1.0 = forced expiratory volume in 1 second; Ig = immunoglobulin.

less than 60% of the predicted value. Systemic PSL treatment therapy was maintained prior to, during, and after the administration of omalizumab. Omalizumab treatment was effective and resulted in no adverse events. We were able to taper systemic PSL doses, and asthmatic symptoms were dramatically improved. Skin tests for AF were negative after omalizumab administration. In addition, AF-specific IgE titers also were decreased. Daily symptoms showed amelioration, despite a lack of change in pulmonary function assessments, such as %FEV1.0. Patient characteristics such as age, asthma severity, and duration of asthmatic symptoms may account for the lack of change in %FEV1.0 following omalizumab treatment.[9]

Tillie-Leblond et al[7] recently reported the effectiveness of omalizumab in 16 adult patients with ABPA and without CF. The details of our patient treated with omalizumab essentially correspond to those of the patients reported: reduction of daily PSL dose and fewer exacerbations of asthmatic symptoms per year, but no changes in %FEV1.0. Adding to the literature, we used the skin tests for AF to measure the effect of omalizumab in our case. A novel observation in the current study is that skin tests for AF were useful as markers for the effectiveness of omalizumab in

Table 2 Summary of past case reports

	Case no.	Age/ sex	Ethnic background	Oral PSL[#]	IgE (IU/mL)	Omalizumab dose settings	Dosing period	Reduction or discontinuation of PSL	Clinical outcome	Ref.
Without CF	1	44 M	Hispanic American	20 mg	702	375 mg every 2 wk	24 mo	Reduction	Effective	19
	2	55 M	Hispanic American	20 mg	586	375 mg every 2 wk	24 mo	No reduction	Effective	19
	3	44 F	African American	+	4362	375 mg every 2 wk	12 mo	Reduction	Effective	20
	4	45 M	Caucasian	+	1128	375 mg every 2 wk	12 mo	Reduction	Effective	20
	5	56 M	Caucasian	+	565	375 mg every 2 wk	12 mo	Reduction	Effective	20
	6	58 F	African American	+	863	375 mg every 2 wk	12 mo	Reduction	Effective	20
	7	53 F	Not described	7.5 mg	3090	375 mg every 2 wk	12 mo	Reduction	Effective	21
With CF	1	12 F	Not described	50 mg	5200	300 mg every 2 wk	6 wk	Discontinued	Effective	11
	2	12 M	African American	20 mg	805	300 mg every 2 wk	18 mo	Discontinued	Effective	12
	3	12 M	Caucasian	1 mg/kg	2894	375 mg every 2 wk	18 mo	Discontinued	Effective	12
	4	17 M	Caucasian	10 mg	530	300 mg every 2 wk	8 mo	Discontinued	Effective	12
	5	13 F	Not described	+	947	300 mg every 2 wk	11 mo	Discontinued	Effective	13
	6	14 M	Not described	+	4261	375 mg every 2 wk	4 mo	Discontinued	Effective	14
	7	14 F	Not described	+	1526	375 mg every 2 wk	4 mo	Discontinued	Effective	14
	8	14 M	African American	5 mg	261	375 mg every 2 wk	11 mo	Discontinued	Effective	15
	9	15 F	Not described	7.5 mg	248	300 mg every 4 wk	12 mo	Reduction	Effective	16
	10	13 M	Caucasian	+	1092	450 mg every 4 wk	18 mo	Discontinued	Effective	17
	11	12 M	Caucasian	—	1782	450 mg every 2 wk	6 mo	Not on systemic steroids previously	Effective	17
	12	14 M	Not described	+	4388	300 mg every 4 wk	15 mo	Discontinued	Effective	18
	13	15 M	Not described	+	2884	300 mg every 4 wk	17 mo	Discontinued	Effective	18

[#] Average dose of daily PSL.
CF = cystic fibrosis; F = female; M = male; PSL = prednisolone.

ABPA.[10] According to past reports, many cases were able to discontinue systemic PSL treatment completely, but in our case only a PSL dose reduction was feasible. From the past case reports, all patients with ABPA and CF were younger than 20 years and 11 of 12 cases were able to discontinue systemic PSL (Table 2).[11–18] However, all patients with ABPA and without CF were oral PSL-dependent and were only able to reduce or maintain the dose of oral corticosteroids after the omalizumab treatment.[19–21] This implies that patients with CF may have a better chance of discontinuing systemic PSL than patients with non–CF-related ABPA. Also, it is possible that patients with non–CF-related ABPA may benefit from starting omalizumab therapy prior to becoming PSL dependent. We do not believe that omalizumab was ineffective in our case because asthmatic symptoms did show amelioration. In addition, adrenal gland function may be altered in patients with ABPA because of prolonged administration of PSL. This might explain the difficulty with PSL withdrawal for elderly patients. It is noteworthy that most patients with ABPA and CF who were able to discontinue systemic PSL were much younger than patients with ABPA and without CF. These differences may reflect various patient characteristics, such as age, CF complications, race, diminished pulmonary function, and the period from the diagnosis of asthma or ABPA until treatment.

Determining the omalizumab dose and dosing period might be difficult in ABPA cases. In many Asian countries and the United States when omalizumab was distributed for the first time, it can only be administered when IgE levels are between 30 IU/mL and 700 IU/mL in adults, and the maximum dose is 375 mg every 2 weeks. In the European Union, omalizumab can be administered to a maximum of 1,500 IU/mL and the maximum dose is 600 mg every 2 weeks. These differences result in treatment limitations for asthmatic patients with high levels of IgE, like those patients with ABPA. When immunosuppressive agents such as PSL are administered, we often see a decrease in total IgE level. This may lead to an underestimation of the dose of omalizumab required for treatment. In addition, PSL administration usually reduces total IgE titers, but in some cases there is no decrease in AF-specific IgE titers in clinical practice. This raises the possibility that AF-specific IgE titers should be considered when determining the most appropriate doses of anti-IgE therapy for patients with ABPA. From past case reports, CF-related cases were observed up to 18 months, whereas non–CF-related cases were observed for 24 months. In our case, we were able to continue omalizumab treatment for more than 30 months without any adverse event. Some past cases showed deterioration after discontinuation of omalizumab treatment.[20] Because most non–CF-related cases were not able to discontinue systemic PSL during the omalizumab treatment, discontinuation of omalizumab could lead to an unstable control of asthma. Dose setting and dosing period in patients taking PSL remains challenging, and further studies are needed to resolve these problems.

The safety of administration of omalizumab to patients with ABPA is a major concern. In addition to the risk of anaphylaxis, the United States Food and Drug Administration advisory committee recently suggested that cardiac and thromboembolic events may occur with increased frequency in patients using omalizumab.[22] At this time, based on the limited evidence of its benefits, omalizumab treatment is not uniformly recommended for all ABPA cases. However, when a patient cannot tolerate the high toxicity of PSL, as in our case, omalizumab administration may be an option. For our patient and in published reports, there were no obvious adverse events. Prospective studies are needed to corroborate these largely retrospective findings. Treatment remains unsatisfactory in many ABPA cases. Although new agents offer promise, properly controlled trials of their safety and efficacy are required.

In conclusion, when ITCZ efficacy is limited for the patient, omalizumab could be an alternative treatment with the potential to reduce the long-term side effects of systemic PSL. Well-designed prospective studies are needed to fully assess the efficacy and toxicity of omalizumab in patients with ABPA.

Conflicts of interest

All contributing authors declare no conflict of interest.

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