

Allergic Bronchopulmonary Aspergillosis in a 2-Year-Old Asthmatic Boy With Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked

Mihoko Ohshima, MD,¹ Masaki Futamura, MD,² Yoshiro Kamachi, MD, PhD,¹
Komei Ito, MD, PhD,² and Tatsuo Sakamoto, MD, PhD^{1*}

Summary. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) is caused by impaired function of CD4⁺CD25⁺ regulatory T cells that play an important role in controlling exaggerated Th2 responses. The pathogenesis of allergic bronchopulmonary aspergillosis (ABPA) appears to be closely associated with the Th2 response. We report the first case of ABPA in a 2-year-old asthmatic boy with IPEX, this being an unusually young age for the development of ABPA. **Pediatr Pulmonol.** © 2009 Wiley-Liss, Inc.

Key words: *Aspergillus fumigatus*; CD4⁺CD25⁺ regulatory T cells; childhood asthma; immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

INTRODUCTION

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) is caused by impaired function of CD4⁺CD25⁺ regulatory T (Treg) cells that have a forkhead box protein 3 (FOXP3) mutation.¹ Severe allergic diseases, including dermatitis, food allergies, and asthma, often occur in IPEX patients, because Treg cells play an important role in controlling exaggerated Th2 responses.^{1,2} The pathogenesis of allergic bronchopulmonary aspergillosis (ABPA) appears to be closely associated with the Th2 response.³ We describe the first case of ABPA in a 2-year-old asthmatic boy with IPEX.

CASE REPORT

Since the age of 1 month, the patient had a severely eczematous rash involving the entire body, eosinophilia (>6,000/ μ l), an elevated total serum IgE level (>5,000 IU/ml), and elevated food-specific IgE levels. Bone marrow aspirate showed markedly increased eosinophils and eosinophil precursors. However, he had no symptoms of enteropathy, endocrinopathy or autoimmune hematologic diseases such as hemolytic anemia and thrombocytopenia, which are characteristic features of IPEX.¹ Lymphocyte differential and mitogen (PHA and con A)-stimulated lymphocyte blastogenesis were normal. The patient was diagnosed as having IPEX based on the identification of a

mutation within the DNA-binding domain of FOXP3 (1150G > A, Ala384Thr), which has been previously reported.⁴ The identical mutation was detected in his elder brother, who had dermatitis and eosinophilic enteropathy, and in both of his maternal male cousins, who had severe dermatitis with an elevated total serum IgE level, and who died of sepsis. The patient developed asthma at the age of 8 months; he had frequent exacerbations requiring systemic glucocorticosteroids despite regular nebulized budesonide (1.5 mg/day) treatment.

At 2 years and 9 months of age, the patient was hospitalized because of an asthma exacerbation and treated with frequently inhaled procaterol and intravenous

¹Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan.

²Department of Allergy, Aichi Children's Health and Medical Center, Obu, Japan.

*Correspondence to: Tatsuo Sakamoto, MD, PhD, Department of Pediatrics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. E-mail: tatsuos@med.nagoya-u.ac.jp

Received 11 August 2008; Revised 29 December 2008; Accepted 29 December 2008.

DOI 10.1002/ppul.20992
Published online in Wiley InterScience
(www.interscience.wiley.com).

prednisolone (2 mg/kg/day) for 3 days. During tapering of the prednisolone dose, he developed a barksy cough, wheezing, and a low-grade fever that gradually worsened. Inspiratory coarse crackles were heard throughout both lungs, and his oxygen saturation was decreased (<94%). Plain chest X-rays showed bilateral infiltration, mainly in the inferior lobes, and chest computerized tomography showed a ground-glass appearance distributed diffusely in the lungs, without central bronchiectasis. The patient's total serum IgE level (15,071 IU/L) and CAP-RAST to *Aspergillus fumigatus* (3.15 UA/L) (Phadia, Uppsala, Sweden) were several times higher than those that had been present in the preceding 6 months. In addition, CAP-RAST to recombinant Asp f 2, Asp f 4, and Asp f 6, which have been recognized to bind specifically to IgE in ABPA,⁵ became positive. Precipitating and IgG antibodies specific to *A. fumigatus* (Nippon Chemiphar, Tokyo, Japan) were measured using the Ouchterlony method and an enzyme-linked immunosorbent assay, respectively. However, neither of them was significantly increased. *Aspergillus*-specific galactomannan was detected in the serum (Platelia *Aspergillus*; Sanofi Diagnostics Pasteur, Chaska, MN). However, *A. fumigatus* DNA, measured using polymerase chain reaction technology, and β -1,3-D-glucan were not found in the serum, indicating that invasive aspergillosis was not likely. The patient was diagnosed as having ABPA according to the criteria for the diagnosis of seropositive ABPA without bronchiectasis in asthmatic patients.³ The patient was treated with prednisolone, 2 mg/kg/day, and demonstrated immediate marked improvements in respiratory symptoms and

roentgenographic infiltrates (Fig. 1). Serum *Aspergillus*-specific galactomannan also disappeared within 7 days.

DISCUSSION

In the present case, the pathogenesis of ABPA appears to have been closely associated with the Th2 response but not Arthus reactivity to *A. fumigatus* antigens, since precipitating antibodies against *A. fumigatus* were not found in the serum. IPEX impairs activity that normally controls the exaggerated Th2 response, suggesting that such impaired function may be at least partially responsible for the development of ABPA. This may be supported by the unusually young age of development of ABPA in this patient.⁶ Interestingly, Montagnoli et al.⁷ showed that respiratory infection with *A. fumigatus* caused infiltration of eosinophils and Th2 lymphocytes into the lungs, with elevated serum IgE levels in *Aspergillus*-sensitized mice, and that Treg cells were important for the prevention of such allergic reactions. However, this is the first case report of ABPA in IPEX patients. In addition, ABPA in this patient has not recurred in over 4 years since the original onset of ABPA, although he has required nebulized budesonide (2 mg/kg) daily after cessation of oral prednisolone. This raises the possibility that ABPA in this patient simply occurred because of his having asthma and is unrelated to IPEX, although the question is insoluble at this time. Fuchizawa et al.⁸ found that IPEX patients with missense mutations of FOXP3, such as the present patient, are clinically milder than those with a frame shift mutation, who show typical IPEX symptoms, characterized by the early onset of multiple autoimmune diseases. In conclusion, regardless of the heterogeneity of IPEX phenotype and genotype, and no matter how young they may be, the management of asthmatic patients with IPEX should include measures to prevent the development and exacerbation of ABPA.

REFERENCES

1. Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked: forkhead box protein 3 mutations and lack of regulatory T cells. *J Allergy Clin Immunol* 2007;120:744–750.
2. Torgerson TR, Linane A, Moes N, Anover S, Mateo V, Rieux-Laucat F, Hermine O, Vijay S, Gambineri E, Cerf-Bensussan N, Fischer A, Ochs HD, Goulet O, Ruemmele FM. Severe food allergy as a variant of IPEX syndrome caused by a deletion in a noncoding region of the FOXP3 gene. *Gastroenterology* 2007;132:1705–1717.
3. Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2002;110:685–692.
4. Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. *J Med Genet* 2002;39:537–545.
5. Kurup VP, Banerjee B, Hemmann S, Hemmann S, Greenberger PA, Blazer K, Cramer R. Selected recombinant *Aspergillus fumigatus*

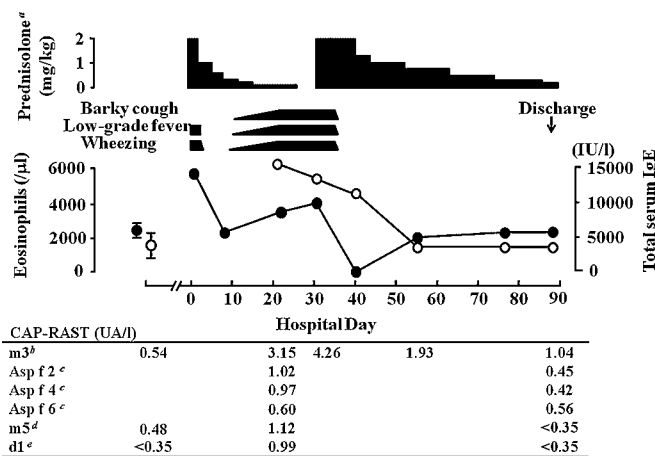


Fig. 1. Profile of the patient's clinical symptoms, laboratory data, and treatment for allergic bronchopulmonary aspergillosis (ABPA) during his hospital admission. Open circles indicate total serum IgE levels, and closed circles indicate the blood eosinophil count. ^aDose of systemic glucocorticosteroids equivalent to prednisolone. ^b*Aspergillus fumigatus* crude extract. ^cRecombinant major allergens of *A. fumigatus*. ^d*Candida albicans* crude extract. ^e*Dermatophagodes pteronyssinus* crude extract.

- allergens bind specifically to IgE in ABPA. Clin Exp Allergy 2000; 30:988–993.
6. Mastella G, Rainisio M, Harms HK, Hodson ME, Koch C, Navarro J, Strandvik B, McKenzie SG. Allergic bronchopulmonary aspergillosis in cystic fibrosis. A European epidemiological study. Epidemiologic Registry of Cystic Fibrosis. Eur Respir J 2000; 16:464–471.
 7. Montagnoli C, Fallarino F, Gaziano R, Bozza S, Bellocchio S, Zelante T, Kurup WP, Pitzurra L, Puccetti P, Romani L. Immunity and tolerance to *Aspergillus* involve functionally distinct regulatory T cells and tryptophan catabolism. J Immunol 2006;176:1712–1723.
 8. Fuchizawa T, Adachi Y, Ito Y, Higashiyama H, Kanegane H, Futatani T, Kobayashi I, Kamachi Y, Sakamoto T, Tsuge I, Tanaka H, Banham AH, Ochs HD, Miyawaki T. Developmental changes of FOXP3-expressing CD4⁺CD25⁺ regulatory T cells and their impairment in patients with FOXP3 gene mutations. Clin Immunol 2007;125:237–246.