

Allergic bronchopulmonary aspergillosis and common variable hypogammaglobulinemia in an adult male patient: Case report

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Allergic bronchopulmonary aspergillosis (ABPA) is an inflammatory disease of the airways, which occurs in some patients with asthma and which represents an exaggerated immunologic response to *Aspergillus fumigatus*. If undiagnosed, it can cause considerable morbidity, with bronchiectasis and fibrotic lung disease. Such patients have high titers of serum IgE, elevated IgE anti-*Aspergillus* antibody levels, and high titers of IgG anti-*Aspergillus* antibodies, which can be detected by a variety of methods.^{1,2}

Common variable hypogammaglobulinemia is a disease that often has its onset in adulthood. It is most commonly associated with frequent infections of the sinuses and the tracheobronchial tree. It can occur in both men and women and is often associated with excessive morbidity. The diagnosis can be made by the demonstration of low levels of serum IgG. In some patients, IgG subclass or specific antibody deficiency is its major manifestation, although total IgG levels can be normal. Confirmation of the diagnosis requires the demonstration of the inability to produce specific IgG antibodies to protein or polysaccharide antigens.

We present the case of an adult with both disease entities.

CASE HISTORY

CEK is a 72-year-old black man with hypertension, insulin-dependent diabetes mellitus, and a long history of allergic respiratory disease and bronchial asthma. He has shown strongly positive skin test reactions to several tree pollens, timothy grass, ragweed, several molds, and *Dermatophagoides pteronyssinus* and has been receiving immunotherapy for his atopic diseases. He never smoked, and though he was exposed to chemicals in his occupation as a laboratory technician, he never had occupational asthma. For most of his adult life, he had steroid-dependent

Abbreviation used

ABPA: Allergic bronchopulmonary aspergillosis

asthma, usually requiring 5 mg of prednisone per day, in addition to theophylline and β -agonists, for control. Several times per year he would have asthma attacks that would require 2- to 3-week bursts of high-dose prednisone. At times he would complain of increased cough and sputum production. In 1990, he was seen for evaluation of recurrent bronchopneumonia, at which time he demonstrated severe obstructive lung disease and a positive immediate hypersensitivity skin test response to *A. fumigatus*. At that time, review of some of his previous and current chest radiographs revealed recurrent pulmonary infiltrates. Sputum cultures were positive for *A. fumigatus*, and a serum IgE value was 432 ng/ml. The diagnosis of ABPA was made, and he was treated with prednisone for several months. The IgE levels declined to 139 ng/ml, and the dose of prednisone was tapered down to 5 mg per day. At the time the diagnosis was made, serum assays were carried out at Northwestern University Allergy-Immunology Laboratory (Table I), where elevated IgE and IgG anti-*A. fumigatus* antibodies were detected by ELISA.³ His disease remained in remission for approximately 2 years, and since then he has had episodic flares.

This patient also gave a history of recurrent respiratory infections over a period of 20 years. These were primarily episodes of sinusitis, which were difficult to treat and usually required prolonged courses of antibiotics, in addition to periodic episodes of pneumonia and bronchitis. Review of old medical records showed that these had been illnesses attributed to infections in an allergic asthmatic subject. He had no complications of diabetes, and there were no infections other than those of the sinobronchial tree.

Physical examination revealed a well-developed, well-nourished man with hyperinflated chest but no distress. Pertinent findings included the presence of lymphatic tissue in both the cervical and tonsillar areas. Chest auscultation revealed a mild, high-pitched wheeze on deep expiration. There was no clubbing or cyanosis. Heart sounds were normal, and results of abdominal and skin examinations were unremarkable. Chest x-ray films revealed some pulmonary hyperaeration but no acute disease. A high-resolution computed tomographic scan

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TABLE I. ABPA assessment

Total IgE = 132 ng/ml
Precipitating antibody to <i>A. fumigatus</i> : Negative
Specific antibody to <i>A. fumigatus</i>
Index for IgE antibody = 3.11
Index for IgG antibody = 5.00

Studies were conducted at The Allergy-Immunology Laboratory, Northwestern University. Both IgE and IgG indices are elevated per laboratory reference standards.

TABLE II. Immunoglobulin levels

	Patient	Normal range
IgA (ng/ml)	128	70-314
IgM (ng/ml)	81	45-250
IgG total (ng/ml)	454	640-1350
IgG-1 (ng/ml)	281	271-1010
IgG-2 (ng/ml)	97	104-570
IgG-3 (ng/ml)	40	14-133
IgG-4 (ng/ml)	7	0-

of the chest showed mild bullous disease and some bronchial cuffing but no bronchiectasis.

Detailed laboratory studies in 1993 revealed that the patient, in fact, has hypogammaglobulinemia (Table II) with a total IgG level of 454 ng/ml and a somewhat low IgG₂ level. A previous IgG level, in 1989, was also low, at 440 ng/ml. His anti-tetanus antibody level was 0.01 IU/ml (protective >0.1 IU/ml), and his anti-diphtheria antibody level was 0.02 IU/ml (protective >0.10 IU/ml) (Table III). He was immunized with tetanus toxoid and demonstrated a normal postvaccination response with a titer of 0.13 IU/ml (protective). However, specific antibody titers after immunization with Pneumovax demonstrated a failure to produce protective titers to any of 12 polysaccharides except for type 56 (Table III). These data were interpreted as evidence that this patient has clinically important hypogammaglobulinemia with inability to respond to bacterial polysaccharide antigens. He began receiving monthly treatment with intravenous gamma-globulin. Since the onset of this treatment, he has had a dramatic change, with almost no recurrence of respiratory infections; and his asthma and ABPA have been managed by the usual therapy as outlined previously.

The ABPA was initially treated in 1990 with several months of high-dose prednisone. In 1994, he had a flare of ABPA (Table IV) despite his hypogammaglobulinemia, with the IgE rising to 335 ng/ml and with high-titer specific anti-*A. fumigatus*, which led to re-treatment with a brief course of prednisone and a 16-week course of oral itraconazole. The ABPA is now apparently in remission. Serial IgE and IgG levels are presented in Table IV.

DISCUSSION

We present a case of an adult with co-existing ABPA and common variable hypogammaglobuline-

TABLE III. Specific antibody titers

Antigen	Before-immunization	After-immunization
Protein		
Anti-tetanus titer	0.01 IU/ml	0.13 IU/ml
Polysaccharide		
Pneumococcal	<0.3 µg/ml	0.9*
Ab Type 1		
Pneumococcal	<0.3 µg/ml	<0.3*
Ab Type 3		
Pneumococcal	<0.3 µg/ml	<0.3*
Ab Type 4		
(6A/6B) Type 6/26	0.4 µg/ml	1.4*
(6A/6B) Type 8	0.7 µg/ml	1.5*
(9N) Type 9	<0.3 µg/ml	0.8*
(12F) Type 12	0.5 µg/ml	0.7*
(12F) Type 14	1.1 µg/ml	1.1*
(19F) Type 19	<0.3 µg/ml	<0.3*
(23F) Type 23	<0.3 µg/ml	0.4*
(7F) Type 51	1.3 µg/ml	4.3*
(18C) Type 56	0.7 µg/ml	15.8

Ab, Antibody.

*Abnormal result, below reference range, and less than a fourfold increase from prevaccine titer.

TABLE IV. Serial immunoglobulin levels

Year	IgA (ng/ml)	IgG (ng/ml)	IgM (ng/ml)	IgE (ng/ml)
1989	140	440	60	432
1991	—	—	—	272
1992	—	—	—	565
1993	128	454	81	335
1994	—	—	—	443
1994	—	—	—	154
1995	—	—	—	200

mia requiring intravenous gammaglobulin therapy. It is of interest that these two syndromes should be present in one individual, in view of the fact that ABPA is typically regarded as a disease of hypersensitivity in which exaggerated responses involving both IgE and IgG antibodies to *A. fumigatus* antigens are pathogenic in the evolution of the problem. On the other hand, hypogammaglobulinemia is an illness characterized by hyporesponsiveness to microbial antigens, leading to recurrent respiratory infections. The co-existence of both problems in one person is a surprise; one does not know how frequent this combination of illnesses can occur. The patient continues to show strong type I allergy, with positive skin test responses to inhalant allergens, including pollens and dust mites. This is consistent with the notion that IgE and IgG immune responses are regulated indepen-

dently. This patient does have lymphoid tissue and normal lymphocytes and is able to respond immunologically to some types of antigens (Table II); that is, he produces IgG antibody to protein and IgE to pollens, dust mites, and *A. fumigatus*. Therefore it appears that his antibody deficiency is likely to be due to immune dysregulation, a phenomenon that presumably could be involved in ABPA. Alternative to this idea would be the concept that just as autoimmunity may accompany common variable immune deficiency, this case illustrates that hypersensitivity can accompany it as well.

The prevalence of ABPA in the United States has been a source of contention.⁴⁻⁶ Typically, many more cases are reported from the United Kingdom than from the United States, but there appear to be regional areas of the United States, such as the Great Lakes, where more cases are reported than elsewhere in the United States. One may question the role of prolonged intermittent steroid therapy, which this patient had throughout his adult life, in the development of immune deficiency syndrome, but the possible causal relationship of steroids in the development of immune hyporesponsiveness has been argued and is an issue that has not been settled. We cannot determine whether the steroid therapy for his asthma and ABPA played a role in

the development of his immune deficiency syndrome. Recognition of these two clinical entities in a single patient clearly requires a combination of careful clinical follow-up and detailed use of the clinical immunology laboratory to prove the existence of any such syndromes. Once recognized, treatment is usually straightforward, and as seen in our patient, will lead to a marked improvement in the clinical course.

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Hypersensitivity pneumonitis in a patient with hypogammaglobulinemia

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Hypersensitivity pneumonitis (HP) is an inflammatory disease of the lung parenchyma, which occurs in a susceptible host after repeated inhala-

Abbreviation used

HP: Hypersensitivity pneumonitis

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tion of a multitude of antigens.¹ Although immunologically mediated, the relative contributions of cellular versus humoral immunity in the pathogenesis of HP remain undefined. We report here an "experiment of nature," a patient with simultaneous agammaglobulinemia and HP. This case report illustrates that specific antibody is not required for clinical HP and supports the central role of cellular immunity in mediating HP.