

Sensitization to *Aspergillus* species in the congenital neutrophil disorders chronic granulomatous disease and hyper-IgE syndrome

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Background: Hyper-IgE syndrome (HIE) and chronic granulomatous disease (CGD) are congenital immunodeficiency diseases with increased susceptibility to bacterial and fungal infections. Both carry significant morbidity and mortality rates because of invasive infections by *Aspergillus* species. We encountered 2 patients, one with HIE and one with CGD, in whom detection of sensitization to *Aspergillus* species preceded the diagnosis of immunodeficiency. With high-dose systemic corticosteroids for allergic bronchopulmonary aspergillosis (ABPA), an inflammatory disorder caused by sensitization to *Aspergillus* species, pulmonary abscesses developed in the patient with HIE, and the patient with CGD succumbed to an overwhelming *Aspergillus* species-induced pneumonia.

Objective: We sought to assess the prevalence of sensitization to *Aspergillus fumigatus* and the presence of diagnostic criteria for ABPA in patients with CGD and HIE.

Methods: We measured *A fumigatus*-specific serum IgE, IgG, and precipitating antibodies as indicators for *A fumigatus* sensitization in the sera of 18 patients with neutrophil disorders (7 with HIE and 11 with CGD). Hospital records were reviewed for the presence of other diagnostic criteria for ABPA (asthma, elevated total serum IgE concentration, and radiographic abnormalities).

Results: Twelve (67%) of 18 patients were sensitized to *A fumigatus*, as evidenced by precipitating *A fumigatus*-specific antibodies. Six (33%) of 18 patients had serologic evidence of

ABPA. Five of those 6 patients had radiologic abnormalities consistent with a diagnosis of ABPA. One patient with HIE also had asthma, thus fulfilling minimal essential criteria for concurrent ABPA.

Conclusions: Patients with HIE syndrome and CGD have a high incidence of sensitization to *Aspergillus* species. A clinical picture indistinguishable from ABPA may coexist or emerge in patients with CGD or HIE and create a major management dilemma because systemic corticosteroids may accelerate tissue damage and invasive fungal infections. It is important to distinguish individuals with congenital neutrophil disorders from uncomplicated classic ABPA. (*J Allergy Clin Immunol* 1999;1265-72.)

Key words: Allergic bronchopulmonary aspergillosis, *Aspergillus fumigatus*, neutrophil disorder, chronic granulomatous disease, hyper-IgE syndrome, corticosteroids

Chronic granulomatous disease (CGD) and hyper-IgE syndrome (HIE) are primary immune deficiencies with a propensity for suppurative infections caused by a spectrum of bacteria and fungi. The molecular basis of CGD is well understood.¹ Defects in the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system result in decreased production of hydrogen peroxide, superoxide, and oxygen radicals and defective killing of phagocytized organisms by granulocytes. The diagnosis of CGD is confirmed by abnormal in vitro superoxide production of neutrophils, molecular analysis, or both of the NADPH-oxidase enzyme system.²⁻⁴ In contrast, the mechanism underlying the granulocyte dysfunction in HIE is not known.⁵ HIE is diagnosed clinically in the presence of eczematous rash, pneumonia with pneumatocele formation, elevated serum IgE concentrations, and typical dysmorphic features.⁶ *Staphylococcus aureus* is isolated most commonly in both diseases, but *Aspergillus fumigatus* is a major cause of morbidity and mortality.⁶⁻¹⁴

The standard treatment for CGD and HIE involves continuous oral antibiotic prophylaxis with cotrimoxazole. IFN- γ has been shown in a placebo-controlled trial to be effective in reducing the numbers of infections in patients with CGD and is administered routinely.^{15,16} It may also have a role in treating HIE.^{17,18}

Recent data obtained from genetically engineered X-CGD GP91^{phox-/-} mice indicate that there is increased

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Abbreviations used

ABPA:	Allergic bronchopulmonary aspergillosis
CGD:	Chronic granulomatous disease
CT:	Computed tomography
HIE:	Hyper-IgE syndrome
NADPH:	Reduced nicotinamide adenine dinucleotide phosphate

susceptibility to invasive infection with *Aspergillus* species in these animals compared with their normal litter mates but also an abnormally high and prolonged inflammatory reaction to sterile *Aspergillus* material.¹⁹ There are no reports in the literature to date investigating the prevalence of sensitization to *Aspergillus* species in CGD and other neutrophil disorders in humans.

Both hypersensitivity pneumonitis and allergic bronchopulmonary aspergillosis (ABPA) are manifestations of a heightened immune response to *Aspergillus* species. Hypersensitivity pneumonitis presents as an eosinophilic pneumonia. ABPA results from an altered host response to a noninvasive colonization of bronchial mucus by *A fumigatus*, leading to a T-cell driven eosinophilic inflammation of the airways with mucus plugging and bronchial wall destruction, which results in bronchiectasis. ABPA is diagnosed in classic cases by the presence of up to 8 criteria.²⁰ The 5 minimal essential criteria include asthma, a positive immediate hypersensitivity skin test reaction to *Aspergillus* species, current or previous pulmonary infiltrates, central bronchiectasis, and an elevated total serum IgE concentration (>1000 ng/mL [416 IU/mL]). Additional criteria are peripheral blood eosinophilia (>1000/mm³), precipitating antibodies to *A fumigatus*, and increased quantities of serum IgG and IgE antibodies to *A fumigatus*. Seropositive ABPA²¹ has been defined in patients who fulfill these criteria but do not have evidence of bronchiectasis, as determined by high-resolution chest computed tomography (CT) scanning. ABPA occurs in patients with asthma and cystic fibrosis. The treatment is aimed at altering the inflammatory response and involves a course of prednisone, 0.5 mg/kg daily for 2 weeks and then every other day for 2 months before it is tapered.²¹ Antifungal agents have been administered as treatment of ABPA but have been ineffective as sole therapy and currently are not standard treatment.^{22,23}

In the normal host, resistance to infection by *Aspergillus* species is 2-fold. First, alveolar macrophages ingest and kill inhaled fungal spores through nonoxidative mechanisms. Second, neutrophils attack germinating hyphae by using oxygen-dependent pathways.²⁴ In vitro data suggest that the nonoxidative anticonidial activity of macrophages in CGD is normal, possibly providing some protection¹⁹; however, this activity is suppressed by therapeutic concentrations of glucocorticoids in experiments with *Aspergillus* and *Nocardia* spores.²⁵

Recently, a patient with hyper-IgE syndrome was

given a diagnosis of ABPA, and another with chronic granulomatous disease was given a diagnosis of hypersensitivity pneumonitis before the diagnosis of immune deficiency had been made. The diagnoses were established by clinical, serologic, and radiographic criteria. High-dose corticosteroid treatment was given in both, resulting in worsening disease in one and death from invasive aspergillosis in the other. These 2 patients formed the rationale for exploring the sensitization to or disease from *Aspergillus* species in all patients with CGD and HIE followed at our institution.

METHODS

Case report 1

The patient is a 35-year-old bank accountant who was referred for immunologic evaluation in 1997 by an infectious disease specialist. In 1992, the patient was found to have a lung abscess of the left upper lobe caused by *S aureus*, which was surgically excised in 1993. Over the following years, the patient had recurrent right upper lobe infiltrates and hilar adenopathy and required repeated therapeutic bronchoscopic removal of impacted mucoid material from the right upper lobe bronchus. Fungal elements were seen on microscopy, and cultures of the recovered material grew *A fumigatus*. The biopsy showed no evidence of neoplasm. He was diagnosed with ABPA on the basis of the culture that grew *A fumigatus*, intermittent right upper lobe infiltrates, and elevated total serum IgE and serum anti-*A fumigatus* IgE and anti-*A fumigatus* IgG antibodies. He was treated with high-dose prednisone, which was tapered over several weeks. Several recurrences of the right upper lobe infiltrates were treated with courses of prednisone. In early 1997, the patient had hemoptysis and a right upper lobe abscess, which was drained percutaneously. All cultures were without growth.

The patient's past medical history revealed that he had mild reversible pulmonary obstruction and had been treated with inhaled steroids for asthma for approximately 10 years. He also had several episodes of pneumonia between the ages of 20 to 25 years, which were attributed to possible aspiration after excess alcohol consumption and which were treated as an outpatient with good results. Between the ages of 25 and 32 years, he had been relatively free of symptoms, with the exception of occasional episodes of cough and wheezing. There were no other family members with atopy, asthma, unusually severe or frequent infections, or premature deaths. At the time of presentation, he was a healthy appearing young male in no distress, and he was afebrile. His vital signs were within normal limits. There was no clubbing, no cyanosis, and no tenderness over the maxillary and frontal sinuses. Decreased breath sounds on the right, without audible crackles or wheezing, were noted. A left thoracotomy scar was present. There was no lymphadenopathy and no hepatosplenomegaly. His white blood cell count was 10,100/mm³ with 39% eosinophils. His total serum IgE concentration was 1900 ng/mL. His neutrophil NADPH oxidase activity was assayed by flow cytometry²⁶ and was normal. On the basis of these findings and the history of *S aureus* lung abscesses, the diagnosis of HIE syndrome was made.

Case report 2

A 24-year-old woman presented with cough, fever, and dyspnea for 1 day. She had been doing some work in the yard, exposing her to composted leaves on the day before. Her past medical history was significant for elevated total serum IgE concentration and repeated staphylococcal skin infections for which she received prophylactic antibiotic treatment with dicloxacillin until the age of 10 years for a presumptive diagnosis of HIE syndrome. At age 17, she stopped

antibiotic treatment and remained asymptomatic until this presentation. She also had a history of milk allergy as a child, seasonal rhinitis, and a herpes simplex infection of the left leg, which responded to topical acyclovir treatment. She had no history of previous pneumonia, asthma, or exercise intolerance. On presentation, she was febrile to 101°F. She had no clubbing and was not visibly cyanotic. Bilateral basilar rales were noted on auscultation. Pulse oximetry revealed a resting O₂ saturation of 93% on room air, which decreased to 87% after walking. A chest radiograph showed bilateral diffuse infiltrates. She was hospitalized and underwent bronchoscopy. The bronchial biopsy specimen showed marked eosinophilia, no granuloma, and no evidence of fungal or bacterial elements. Her sedimentation rate was 130 mm/h, and a complete blood cell count showed a white blood cell count of 13,000/mm³ with 15% eosinophils; the total serum IgE concentration was elevated to greater than 5000 IU/mL, and she had precipitating antibodies to *Aspergillus flavus* and *Aspergillus niger*, but not *A fumigatus*. The differential diagnosis included ABPA or hypersensitivity pneumonitis, for which she was treated with high-dose (1 mg/kg body weight) prednisone. She underwent defervescence, improved clinically, and was discharged from the hospital after 3 days. After 2 weeks, prednisone was tapered, but fever and dyspnea recurred, and therefore the prednisone was intensified. The chest radiograph now showed an increase in the bilateral diffuse infiltrates with confluent areas in the upper lobes. One month into the course, *A fumigatus* was cultured from sputum. The chest radiograph and computed chest tomography scan showed an increase of the diffuse infiltrations, and she was readmitted to the hospital for open lung biopsy. The biopsy specimen showed necrotizing granuloma with fungal hyphae. Amphotericin B was started. On the third postoperative day, she died from respiratory failure. The diagnosis of autosomal CGD was made retrospectively when another sibling, who presented with a lung abscess was found to have CGD by means of an abnormal nitroblue tetrazolium reduction test.

Patients and serum

The diagnosis of CGD was made on the basis of family history, abnormal results in the nitroblue tetrazolium reduction test,³ chemiluminescence,² flow cytometry,²⁶ and, in some cases, molecular analysis.⁴ The diagnosis of HIE was made on the basis of the presence of elevated IgE levels, history of suppurative staphylococcal pulmonary infections, and eczematous skin rash⁵ as minimal clinical criteria. ABPA was considered present when the patient had, at a minimum, the following: (1) asthma, (2) current or previous compatible pulmonary infiltrates, (3) elevated total serum IgE levels (>416 IU/mL), (4) elevated (>2.0) index for serum IgE and IgG antibodies to *A fumigatus*, and (5) central bronchiectasis. None of the patients underwent immediate hypersensitivity skin testing.

Patients followed in the Immunodeficiency Clinic at Mount Sinai Medical Center New York who had the diagnosis of CGD (Table I) or HIE (Table II) were included in the study. Serum samples were obtained after informed consent during routine clinic visits and stored at -70°C until analysis. Clinical data and radiology reports on the patients were obtained from inpatient and outpatient records, and available chest radiographs, CT scans of the lung, or both were reviewed.

Fungal serologic studies

Quantitation of total serum IgE concentration, determination of serum IgG and IgE antibodies to *A fumigatus* by ELISA, and determination of precipitating antibodies for *A fumigatus* by double-gel diffusion analysis were performed on serum samples. Sera were concentrated 5-fold by a Minicon Concentrator (Amicon Co, Danvers, Mass) before precipitin testing. *A fumigatus* source material

for precipitation testing and ELISA was obtained from Dr V. Kurup (Medical College of Wisconsin, Milwaukee, Wis). It is a mixture of 3 reactive strains of *A fumigatus*. Serum IgG and IgE antibodies to *A fumigatus* were determined by ELISA, as previously described.²⁷ The isotypic antibody determinations used an index for comparison with an asthma serum pool, which consisted of patients with asthma and immediate-type cutaneous reactivity (3-4+ prick reaction) to *A fumigatus* in whom ABPA was excluded. The serum antibody index was calculated as follows: antibody index equals antibody activity (optical density) to *A fumigatus* in test serum divided by antibody activity to *A fumigatus* in pooled asthma sera. An index of 2 or greater, based on previous series, was considered consistent with ABPA and is at least 4 SDs greater than the asthma mean for the IgG-*A fumigatus* assays and 6 times the asthma mean for the IgE-*A fumigatus* assay.²⁷ The interassay coefficient of variation has been 8% for pooled sera from asthma patients (1:10 dilution) and 14% for IgG-*A fumigatus* (1:1000 dilution).

RESULTS

Eighteen patients with either CGD or HIE were studied, 11 with CGD (mean age, 16 ± 11.7 years; 9 male and 2 female subjects) and 7 with HIE (mean age, 35 ± 14 years; 4 male and 3 female subjects). All male patients with CGD had the X-linked form of the disease, as determined by family history, molecular analysis, or both. A compilation of the clinical courses and outcomes of the patients is shown in Table I and Table II.

From the 18 patients studied, 12 (67%, 10 of 11 with CGD and 2 of 7 with HIE) were sensitized to *A fumigatus*, as evidenced by the presence of precipitating *A fumigatus*-specific antibodies. In 2 patients with CGD who were 10 years of age or younger, 2 consecutive sera identified a rise in anti-*A fumigatus* isotypic antibody production over time. The only patient with CGD without precipitating antibodies to *A fumigatus* was the youngest (2 years of age) patient.

Six patients (33%, 4 of 11 with CGD and 2 of 7 with HIE) had serologic evidence for ABPA with an elevated total serum IgE concentration, increased serum IgE and IgG antibodies to *A fumigatus*, and precipitating antibodies to *A fumigatus*. Bronchiectasis was identified in 5 of those patients, which was consistent, by current criteria, with the presence of ABPA with central bronchiectasis in those 5 and ABPA without central bronchiectasis in the other patient.²¹ Two additional patients had elevated total serum IgE concentrations and either elevated serum IgE or IgG antibodies to *A fumigatus* in the presence of bronchiectasis in 1 patient, suggesting a diagnosis of ABPA with central bronchiectasis in one and ABPA without central bronchiectasis in another additional patient.

DISCUSSION

In CGD and HIE, invasive pulmonary *Aspergillus* infections are one of the more common disease manifestations.^{5-8,10} *Aspergillus* infections can cause pneumonia, disseminated interstitial disease, and granulomata in CGD and carry a significant mortality rate.^{9,28} In HIE syndrome *Aspergillus* infections may produce lung

TABLE I. Aspergillus sensitization in 11 patients with CGD

Patient No.	Age (y)/sex	Chest CT/radiography	Current medication	Clinical course and outcome
1	2/M	ND	IFN- γ , cotrimoxazole	Liver abscess with <i>S aureus</i> at 1 year of age
2	4/M	Chest radiograph: diffuse infiltrates	—	<i>A fumigatus</i> -induced pneumonia; died from <i>Pseudomonas cepacia</i> -induced sepsis
3	5/M	Chest radiograph: RUL infiltrate; chest CT: normal	IFN- γ , cotrimoxazole	Protracted RUL pneumonia, failure to thrive, colitis, chorioretinitis
4	6/M	Chest CT: bilateral masses, positive air bronchograms and hilar adenopathy, right chest wall erosion and fistula	—	<i>A fumigatus</i> pneumonia, serratia osteomyelitis, liver abscess, tooth abscess, corneal ulcer, RML pneumonia with fistula, <i>Trichophyton tonsurans</i> from RUL, <i>Candida</i> species-induced endocarditis and -retinitis, <i>Trichosporon inku</i> m and yeast from BAL; died from overwhelming sepsis
5	10/M	Not available	IFN- γ , cotrimoxazole	Doing well
6	16/M	Chest radiograph: increased heart size and interstitial markings, bronchiectasis, cavitary lesion, RML discoid atelectasis	IFN- γ , cotrimoxazole, occasional steroids for granulomatous inflammatory bowel disease	<i>A fumigatus</i> -induced pneumonia, regional enteritis, rectal abscess
7	19/F	Chest radiograph: RUL cavity, RUL and RML infiltrates	IFN- γ , cotrimoxazole	Congenital hypothyroidism, recurrent pneumonia, eczema
8	22/M	Not available	IFN- γ , cotrimoxazole, itraconazole	Skin abscesses, unspecified fungal pneumonia, <i>A fumigatus</i> -pneumonia, numerous hospitalizations with pneumonia, gastrointestinal bleeding
9	23/F	Chest radiograph/CT: bilateral diffuse infiltrates in upper lobes, hilar adenopathy	—	See case report 2; acute respiratory distress and fever, treated with prednisone, pulmonary necrotizing granulomatous inflammation and <i>A fumigatus</i> -induced pneumonia; succumbed to ARDS
10	33/M	Chest radiograph: increased interstitial markings, nodular densities, LLL + LUL infiltrate, honeycombing	IFN- γ , cotrimoxazole	Liver and pulmonary abscesses, <i>A fumigatus</i> , <i>Mycobacterium</i> , <i>M gordonae</i> , <i>Klebsiella</i> species, <i>Candida</i> species, PCP, <i>Enterobacter</i> species- and <i>Pityrosporum</i> species-induced pneumonia, groin adenitis with <i>Serratia</i> species
11	36/M	Chest radiograph: fibrotic change	IFN- γ , cotrimoxazole	<i>A fumigatus</i> -induced pneumonia, lung abscess, retropharyngeal abscess, lymphadenitis, seizure disorder

Ten (90.8%) of 11 patients with CGD are sensitized to *A fumigatus*, as evidenced by the presence of precipitating *A fumigatus*-specific antibodies. Four (36%) of 11 patients fulfill all serologic criteria for ABPA (patients 4, 5, 7, and 10). Three of those patients also have bronchiectasis, which is a consistent criteria for ABPA (patients 4, 7, and 10). One additional patient fulfills serologic ABPA criteria, but has an *A fumigatus*-specific IgE index slightly below the cut-off of 2 (patient 2). IgG and IgE antibodies to *A fumigatus* were determined by ELISA. The serum antibody index was calculated as follows: antibody index equals antibody activity (OD) to *A fumigatus* in test serum divided by antibody activity to *A fumigatus* in pooled asthma sera. An index of 2 or greater is considered significant, which is consistent with ABPA and is at least 4 SDs greater than the asthma mean for the IgG-*A fumigatus* assays and 6 times the mean for the IgE-*A fumigatus* assay.²⁷ The asthma serum pool consists of pooled sera from patients with asthma and immediate-type cutaneous reactivity (3-4+ prick reaction) to *A fumigatus* in whom ABPA was excluded. NA, Not applicable; ND, not done; RUL, right upper lobe; RML, right middle lobe; BAL, bronchial lavage; ARDS, adult respiratory distress syndrome; FVC, forced vital capacity; FEF_{25-75%}, forced expiratory flow, midexpiratory phase; DLCO, pulmonary CO diffusion capacity; LLL, left lower lobe; LUL, left upper lobe; PCP, pneumocystis carinii pneumonia.

*Total IgE at first measurement and subsequent level obtained a year or more later.

†Precipitins to *A flavus* and *A niger*, but not *A fumigatus*, were found. Two consecutive measurements of antibodies were performed on 4 patients to follow titers with time intervals of 3 months to 8 years.

‡This IgG-anti-*A fumigatus* index and IgE-anti-*A fumigatus* were measured by a commercial laboratory and given as SDs from normal controls (IgG-a-*A fumigatus*, reference range <2) and as RAST class (IgE-anti-*A fumigatus*, reference range class 1).

abscesses and erosion of pulmonary vasculature, leading to hemoptysis.¹¹ In contrast, in ABPA *Aspergillus* species serve as an immune stimulant, but tissue invasion does not occur.

Our results illustrate that patients with HIE and CGD have a high level of sensitization to *Aspergillus* species, which has resulted in clinical, serologic, and radiologic

findings consistent with criteria used to diagnose ABPA. These findings have the potential to lead to diagnostic, therapeutic, or both types of difficulties for a number of reasons. First, high concentrations of total serum IgE, a criterion for ABPA, are characteristic of HIE but are also common in CGD; 6 of 11 of our patients with CGD had elevated serum total IgE concentrations. Recurrent

Total IgE (ng/mL)*	<i>A fumigatus</i> index IgE	<i>A fumigatus</i> index IgG	Precipitating antibody to <i>A fumigatus</i>	Precipitating antibody to <i>Candida</i> species	Bronchiectasis	Pulmonary function test	Eosino- philia	History of <i>A</i> <i>fumigatus</i> - induced pneu- monia
74	1.6	1.35	—	—	NA	ND	NA	NA
1241	1.74	2.31	+	—	—	ND	—	+
37	1.2	1.63	+	—	—	ND	—	—
605, 1633	4.04, 7.87	4.11, 7.76	+	+	+	ND	+	+
2335, 2784	1.48, 3.51	3.12, 2.26	+, ‡	—, —	—, —	ND	NA	—
43, 28	1.42, 1.56	1.93, 1.69	+	—	+	ND	—	+
1199	3†	3.1†	+	ND	+	ND	—	—
26, 110	2.09, 2.43	2.51, 4.64	+	—	NA	ND	—	+
5919	ND	ND	++	ND	—	FVC 68%, FEV ₁ 71%, FEF _{25/75} 93%, DLCO 64%	+	+
3912, 1079	6.26, 6.03	5.99, 4.76	+	—	+	ND	+	+
<24	2.43	2.76	+	+	—	ND	NA	+

Aspergillus infections are found in both conditions, leading to a phenotypic overlap between these disorders.²⁹⁻³² Second, milder forms of these neutrophil deficiencies may result in a delay in the recognition of the immune defect.^{12,33} Evidence of sensitization to *A fumigatus* may be detected first and, especially in those patients with concurrent asthma, may lead to an earlier diagnosis of

ABPA. An additional problem is that although a diagnostic test is available for CGD, there is no laboratory test to confirm the diagnosis of HIE. However, lung abscesses typically are not found in patients with ABPA and, if present in a subject with serologic evidence of *Aspergillus* sensitization, should suggest a revision of diagnosis and, potentially, a change in treatment.

TABLE II. *Aspergillus* sensitization in 7 patients with HIE

Patient No.	Age (y)/sex	Chest CT/radiography	Current medication	Clinical course and outcome
12	20/F	Not available	IFN- γ , otrimoxazole, intravenous immunoglobulin	Sinusitis, pneumonia, septic arthritis and <i>S aureus</i> -induced sepsis, gingivitis, hypergammaglobulinemia with no response to pneumococcal or measles, mumps, rubella vaccination
13	25/M	Chest radiograph: RLL infiltrate; chest CT: infiltrate and cavity, LUL bronchiectasis, RLL mucoid impaction	—	Recurrent pneumonia, bronchiectasis, RML lobectomy, hemoptysis, bronchial artery embolization, pseudomonas sepsis, IgA nephropathy; died from pulmonary hemorrhage
14	32/F	Chest radiograph: right pleural thickening	Cotrimoxazole	Severe eczema, furunculosis, cellulitis of the ear
15	35/M	Chest radiograph: intermittent infiltrates, RUL bronchial mass, scattered densities, multiple bronchiectasis	IFN- γ , prednisone, inhaled steroids, cotrimoxazole, itraconazole	See case report 1: LUL resection, mucoid impaction, repeated right-sided lung abscesses while receiving systemic corticosteroids
16	35/M	Chest CT: bilateral bronchiectasis	—	Brain, skin, skull, joint + pulmonary abscesses, granulocyte transfusions, pulmonary hemorrhage, bronchial artery embolization, HIV, LLL resection; died from HIV, leukencephalopathy
17	40/F	Chest CT: bilateral peripheral and central bronchiectasis, cavity, RUL infiltrates	IFN- γ , cotrimoxazole	Chronic bronchitis, sinusitis, pulmonary cavity, esophageal candidiasis, gastroesophageal reflux, malabsorption
18	60/M	Not available	Cotrimoxazole	<i>S aureus</i> -induced pneumonia, frequent upper respiratory infections, folliculitis on forearms

Two (28%) of 7 patients with HIE are sensitized to *A fumigatus* evidenced by the presence of precipitating *A fumigatus*-specific antibodies. Both fulfill all serologic criteria for ABPA and also have bronchiectasis, which is consistent with a diagnosis of ABPA (patients 13 and 15). One additional patient fulfills serologic ABPA criteria but has an *A fumigatus*-specific IgG index slightly below the cut-off of 2 (patient 16). For methods, see legend to Table I.

NA, Not applicable; ND, not done; RLL, right lower lobe; LUL, left upper lobe; RML, right middle lobe; RUL, right upper lobe; FVC, forced vital capacity; FEF_{25-75%}, forced expiratory flow, midexpiratory phase; LLL, left lower lobe.

*Total IgE at first measurement and subsequent level obtained a year or more later.

In classic ABPA the diagnosis is usually considered clinically in a patient with unremitting asthma or asthma not responsive to the usual treatment modalities and confirmed or excluded by means of respective laboratory, clinical, and radiologic tests.

In 17 of the 18 cases discussed here, a suspicion for ABPA would not have been raised on clinical grounds. The findings consistent with ABPA were made in retrospect, and corticosteroid treatment for *Aspergillus* pulmonary sensitization was not contemplated. The exception to this is case 1, a patient who presents a diagnostic and therapeutic challenge because he appears to exemplify an overlap between HIE and ABPA. In this case the diagnosis of ABPA was suspected secondary to resistance to asthma therapy, bronchial mucoid impaction, and radiologic findings and was confirmed by serologic analyses. HIE was subsequently diagnosed on the basis of recurrent lung abscesses, hemoptysis, and an elevated total serum IgE concentration that occurred during and

despite therapy for ABPA, even though typical facial features, scoliosis, cutaneous abscesses, and delayed dentition, features of the majority of patients with HIE, were not present.⁶ After HIE had been diagnosed and after the patient began receiving dicloxacillin treatment alone, he still had marked symptoms of asthma and *Aspergillus* spore-laden bronchial casts removed by bronchoscopy. Adding low doses of oral prednisone, IFN- γ , and itraconazole, his clinical condition has stabilized. This overlap between HIE syndrome and ABPA may be comparable with patients with cystic fibrosis who also may have ABPA, which is presumed to occur because of a state of sensitization to *Aspergillus* species in a patient with underlying bronchiectasis.²⁰

In ABPA, clearing of pulmonary infiltrates can be achieved with 1 to 2 weeks of daily prednisone (1 mg/kg body weight) followed by alternate-day administration and slow taper. The latter route avoids serious infections in patients without immune deficiency disorders. In

Total IgE* (ng/mL)	<i>A fumigatus</i> index IgE	<i>A fumigatus</i> index IgG	Precipi- tating antibody to <i>A fumigatus</i>	Precipi- tating antibody to <i>Candida</i> species	Bronch- iectasis	Pulmonary function test	Eosinophilia	History of <i>A fumigatus</i> - induced pneumonia
63360, 22464	0.85, 1.0	0.89, 0.87	—	—	NA	ND	+	—
41,040	6.76	5.82	+	+	+	Report: restriction, no reversibility	+	—
5280, 4644	1.03, 0.91	0.94, 1.13	—, —	—	—	ND	—	—
1990	6.11	4.53	+	—	+	FVC 85%, FEV ₁ 66%, FEF _{25-75%} 36%, FEV ₁ 15.5%	+	—
1153	0.89	4.92	—	—	+	ND	—	—
1613	1.8	1.27	—	+	+	FVC 69%, FEV ₁ 55%, no rever- sibility	+	—
12,504	0.94	0.86	—		NA	ND	NA	—

CGD, prednisone is usually reserved for rare cases of life-threatening urinary or gastrointestinal obstructions resistant to broad-spectrum antibiotic treatment.³⁴ In vitro data suggests that residual host defense mechanisms against *Aspergillus* species in CGD may be suppressed by therapeutic concentrations of corticosteroids.¹⁹ As for the case described here, the use of high-dose systemic corticosteroids can be especially deleterious for patients with CGD. Moreover, the absence of clinical suspicion for ABPA in all of our patients with CGD and the availability of laboratory methods to diagnose CGD warrant a separation of these patients from those with classic ABPA. Primarily, patients with CGD should be excluded from a diagnosis of ABPA to avoid adverse outcomes from therapeutic corticosteroids. CGD and HIE appear sufficiently rare compared with the occurrence of ABPA in patients with asthma, such that the authors would not suggest that an immunodeficiency needs to be ruled out in every patient with classic ABPA. However, this study illustrates the

importance of considering the diagnosis of a congenital immune defect in a patient with a pulmonary *Aspergillus* infection in whom tissue invasion with abscess formation or cavitory lesions have occurred.

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