A 58-Year-Old Man with Respiratory Insufficiency After a 50-Year History of Hypersensitivity Pneumonitis and Pulmonary Aspergillus Infections

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A 58-year-old man was referred to our Department for Pediatric Immunology after a 50-year history of recurrent episodes of dyspnea with fever, night sweat, weight loss, and bronchial obstruction. The patient’s history in early childhood was unremarkable except for recurrent tonsillitis followed by tonsillectomy and a severe atopic dermatitis. However, at the age of 8 years, after threshing molding grain on his father’s farm, long-term hospitalization and antifungal treatment were necessary due to suspected pulmonary aspergillosis. Over the next 30 years, he suffered frequently during the harvest season from episodes with dyspnea and night sweat, which ended spontaneously after a few days and were interpreted as “summer flu.” From the age of 38 years, he developed recurrent episodes of severe dyspnea, mostly after contact with molding agents, which necessitated repeated hospitalizations. After presentation with weight loss, night sweat, respiratory symptoms, and diffuse pulmonary opacities, miliary tuberculosis was ruled out. High serum levels of IgE-antibodies (600 IU/mL), immediate cutaneous hyperreactivity reaction (“scratch test”), and increased specific IgE antibodies (36 kU/L) against Aspergillus fumigatus, transient diffuse opacities on the chest radiograph and bronchial hyperreactivity led to the diagnosis of allergic bronchopulmonary aspergillosis (ABPA), which fulfilled 5 of the 8 Patterson Criteria. ABPA is characterized by a late-phase inflammatory response to the antigens of colonizing A fumigatus and may also affect patients with asthma and those with cystic fibrosis.

Typically, markedly elevated Aspergillus-specific and total IgE levels, and eosinophilia can be found. Clinical features are wheezing, pulmonary infiltrates, bronchiectasis, and fibrosis. In our patient, intermittent funigistic (amphotericin B, flucytosine, itraconazole, voriconazole) and systemic as well as inhalative corticosteroids resulted in transient amelioration.

When the patient was 39 years old, in addition to ABPA, hypersensitivity pneumonitis was diagnosed based on inspiratory crackles and on diffuse nodular and striated patchy opacities on the chest radiograph, diffusion impairment in pulmonary function testing (diffusing capacity of the lung for carbon monoxide [DLCO] 66% predicted), positive precipitating IgG antibodies against Aspergillus spp, lymphocytosis (54%), and eosinophilia (6%) in bronchoalveolar lavage fluid. These findings were in line with the diagnostic criteria for hypersensitivity pneumonitis published by Cormier and Schuyle. Hypersensitivity pneumonitis is an interstitial lung disease in response to a type III allergy to a large variety of inhalative antigens with the symptoms of dyspnea, flu-like symptoms, cough, chest pain, and diffusion impairment, which starts a few hours after antigen exposure. Histopathologic examinations usually reveal interstitial granulomas and peribronchial mononuclear cell infiltration with giant cells. Corticosteroid treatment and antigen avoidance are the treatment options. In our patient, long-term inhalative (beclomethasone 50 µg twice a day) and systemic corticosteroid treatment (methylprednisolone up to 64 mg/d by mouth, minimum prednisolone 5 mg/d) was initiated.

Due to ongoing clinical impairment, an open lung biopsy specimen was taken at the age of 47 years from the left lung (segments S2 and S3). The surgeon described the lung as being interspersed with palpable dense infiltrations. Histopathologic analyses revealed interstitial inflammation, fibrosis, and multiple epithelioid cell granulomas, which correspond to the palpable dense infiltrations and, in addition, few necrotizing capillaries. The culture of the biopsy specimen grew A fumigatus. These results were interpreted as compatible with hypersensitivity pneumonitis but also raised the suspicion of necrotizing granulomatous vasculitis. Wegener granulomatosis and Churg-Strauss syndrome were largely ruled out by negative autoantibodies (perinuclear/cytoplasmic anti-neutrophil cytoplasmatic antibodies [p/c-ANCA], anti-nuclear antibodies [ANA], and anti double-stranded DNA antibodies [anti-dsDNA antibodies]). At the ages of 54 and 56 years, partial resections of the right and left upper lung lobes were necessary, and the histopathologic analyses revealed new Aspergillus infiltrates. At the age of 57 years, corticosteroid-induced osteoporosis was diagnosed, but the patient could not be taken off corticosteroids because of rapid pulmonary deterioration after an attempt at tapering them.

The patient’s brother had a history of repeated skin abscesses that started in adolescence. At the age of 47 years, the brother had to change his profession as a beer brewer, because a suspected
allergy to malt and corn dust had led to a combined obstructive and restrictive ventilation disorder. Inhalative corticosteroids and bronchodilators allowed him normal daily routine activities. Two liver abscesses caused by Staphylococcus aureus occurred at the age of 51 years.

In both patients, dihydrorhodamine 123 testing and chemiluminescence showed a strongly reduced but not completely absent production of reactive oxygen species (ROS) by neutrophils. Ensuing genetic analyses revealed a homozygous splice mutation (c.1000+2 thymine -> guanine, nomenclature Human Mutation 15: 7-12, 2000) in the NCF2 gene encoding the p67phox component of the NADPH oxidase enzyme complex. The results were typical for autosomal-recessive chronic granulomatous disease (AR-CGD). In the family history, there was no indication of consanguinity as an explanation for the manifestation of this rare AR-CGD mutation.

CGD is a genetic immunodeficiency caused by defects in 1 of the 4 components of the NADPH oxidase enzyme complex. The more rare autosomal recessive forms of CGD affect p67phox, p47phox, or p22phox of the NADPH oxidase, whereas the most common gp91phox defect shows an x-linked inheritance. Patients with CGD are prone to severe infections with certain microorganisms (such as Aspergillus spp or S aureus). In CGD, a complete defect in ROS production is often associated with certain microorganisms. In contrast, patients with residual ROS production may have a delayed onset of disease or less severe infections or even be affected by granulomas that affect different organ systems as the lung or the gastrointestinal or urogenital tracts, which may lead to a delayed diagnosis, as was the case in our index patient and his brother.

Other constellations that have led to a very delayed diagnosis of CGD were a somatic mosaic in the gene encoding for gp91phox in one women, who had an onset of symptoms at the age of 60 years, or several cases of female patients with conductor status of x-linked gp91phox defective CGD and age-related skewing of lyonization, that had led to an onset of symptoms in later life.

In the course of disease, persisting inflammation in patients with CGD, due to recurrent infections and their incomplete intracellular obliteration, result in the formation of granulomas and fibrosis, thereby leading to chronic organ destruction, as documented in the granulomatous lung disease of our index patient (Figure 2). The typical radiologic signs of chronic CGD manifestations that can be seen on this computed tomography are granulomas, air-space consolidations, scarring and fibrosis, emphysematous changes, tracheobronchiectasis, and enlargement of the pulmonary artery as a sign for pulmonary arterial hypertension. Radiologic signs, therefore, may be very similar to allergic bronchopulmonary aspergillosis with its typical radiologic signs of fleeting pulmonary alveolar opacities, centrilobular nodules, bronchiectasis, and, in chronic disease, also pulmonary fibrosis and cavitation.

Another important differential diagnosis is hypersensitivity pneumonitis with its typical radiologic signs of upper-zone or lower-zone predominance or with diffuse infiltrates on chest radiograph, ground-glass infiltrates, nodular opacities, and fibrosis on high resolution computed tomography.

Continuous prophylactic antibiotic and immunosuppressive treatment with azathioprine and systemic low-dose corticosteroids, trimethoprim-sulfamethoxazole, and itraconazole helped to stabilize the patient’s physical condition, but the effect on the extensive granulomatous lung disease was very limited. The patient presented at an age of 58 years with extensive irreversible restrictive lung damage, pulmonary heart disease, and continuous need for oxygen supply. IFN-γ has not been prescribed for...
reasons of ambiguous evidence and considerable adverse effects, especially in older patients and due to contradicting results of its prophylactic efficacy, especially in European centers. Bone marrow transplantation was declined because of the advanced, irreversible impairments that augmented the risk for such profound interventions and the high risk of recurrence of *A fumigatus* infections under the necessary immunosuppressive regimen.

We drew the following conclusions from our case:

1. CGD should be suspected in individuals with severe, repeated fungal infections who demonstrate inadequate response to antimicrobial treatment and always in invasive Aspergillosis.

2. Patients with CGD with residual ROS production can present with symptoms that are also found in allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. The set of symptoms shared by these different diseases can be a provocation of acute symptoms and an extensive inflammatory process after contact with molding materials. All 3 diseases may present with episodes of dyspnea and obstructive pulmonary disease, such radiologic changes as mentioned above, precipitating antibodies against *A fumigatus*, and interstitial lung disease that leads to restrictive pulmonary impairment. Typically, transient amelioration occurs with corticosteroid treatment and often, especially in ABPA and CGD, with fungistatic treatment.

3. Granulomatous restrictive pulmonary disease and invasive pulmonary aspergillosis are highly suspicious of CGD. Other symptoms of CGD can be the following: any *Aspergillus* and severe *S aureus* infection, recurrent skin and organ abscesses, abdominal symptoms that result from granulomatous intestinal or urogenital obstruction, granulomatous colitis, or Crohn-like inflammatory bowel disease.

4. In principle, available treatment options for CGD comprise continuous prophylactic antibiotics, antimycotics, and subcutaneous IFN-γ. Especially in cases with recurrent granuloma formation, low-dose immunosuppression with corticosteroids is often necessary. The curative bone marrow transplantation is increasingly successful in healing this life-threatening immunodeficiency. Involvement of clinical centers specialized in the treatment of immunodeficiencies, including patients with CGD, is highly recommended. Early diagnosis and adequate treatment of primary immunodeficiencies are important to prevent chronic organ damage and infectious complications.

**FIGURE 2.** Computed tomography of the thorax, showing granuloma, emphysema, intrapulmonary consolidations, abundant reticular scarring (white arrows), traction bronchiectasis, and bronchus dilatation (white asterisk). Status is shown after partial resection of the right and left upper lobe after recurrent pulmonary aspergillosis with residual pleural thickening.
REFERENCES