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## Case Report

## Allergic bronchopulmonary aspergillosis (ABPA) an IgE mediated disease?

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## ABSTRACT

This case is about a 6-year-old boy with cystic fibrosis (CF), suffering from allergic bronchopulmonary aspergillosis (ABPA) with total atelectasis of the left lung. To prove the hypothesis that IgE mediated disease is the major pathomechanism of ABPA, a bronchial provocation with *Aspergillus fumigatus* was performed before and after treatment with omalizumab (OMA). We could demonstrate for the first time that OMA completely suppresses the early allergic reaction (EAR) after bronchial allergen challenge with *Aspergillus*. Moreover, as has been shown by others, our patient showed a marked improvement of FEV<sub>1</sub> without a relapse after tapering systemic steroid treatment.

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## 1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a disease primarily occurring in patients with asthma (1–2%) and cystic fibrosis (5–15%). This disease is characterized by a variety of clinical signs (asthma related events, pulmonary infiltrates and bronchiectasis) and immunologic responses to antigens of *Aspergillus*. Diagnosis is often difficult and classical diagnostic criteria include: asthma, immediate cutaneous reactivity to *Aspergillus*, elevated total IgE, and elevated specific IgE and IgG in response to *Aspergillus*, which may colonize the bronchial trees of patients. Standard therapy targets the eradication of *Aspergillus* with antimycotics, preferentially itraconazole, and the suppression of *Aspergillus*-mediated inflammation by corticosteroids.<sup>1</sup> However, relapses often occur and many patients develop severe side-effects caused by systemic steroid therapy.<sup>2</sup>

The underlying pathological mechanism of ABPA is not fully understood. In particular the role of specific IgE in ABPA is unclear. Some authors propose IgE is an innocent bystander whereas others describe it as the major cause of Th-2 driven disease. Indeed there is increasing evidence that OMA, a recombinant humanized monoclonal antibody (mAb) that binds and neutralizes IgE is effective and may be a corticosteroid sparing treatment in ABPA.<sup>3–5</sup> In keeping with our case we hypothesize that specific IgE plays a major role in ABPA.

## 2. Case report

We report on a 6-year-old boy with CF who suffered from an acute exacerbation and was found to have atelectasis of the left lung in August 2008 as shown in Fig. 1. Bronchoscopy with bronchoalveolar lavage revealed *Aspergillus* in culture. His total IgE (1066 U/ml), specific IgE *Aspergillus* (29.7 U/ml), and eosinophils (2175/μl) were markedly elevated. ABPA was diagnosed and the boy was treated with prednisone (1 mg/kg body weight/day) and itraconazole (8 mg/kg body weight/day) for four weeks as recommended. He gradually improved and prednisone was tapered to 5 mg/daily in September 2008. At that time total IgE was 441 U/ml, specific IgE against *Aspergillus* unchanged, and eosinophils 260/μl. Bronchial methacholine challenge using a short protocol as described,<sup>6</sup> demonstrated severe hyperreactivity and gave further evidence of the asthma-like picture which is often found in ABPA.<sup>7</sup>

To prove the concept that an IgE mediated mechanism is the major cause of ABPA, we performed a titrated allergen provocation test using the APS dosimeter technique (Cardinal Health) as described previously.<sup>8</sup> The doses of inhaled *Aspergillus* allergen were increased according to the following pattern from step 1 to 6: 5, 10, 20, 40, 80, and 160 standardized biological units (SBU, Allergopharma, Rhinebeck, Germany). Thus, the entire protocol delivered cumulative doses of 5, 15, 35, 75, 155, and 315 SBU. FEV<sub>1</sub> was measured 10 min after each step-up. All lung function tests were performed according to the American Thoracic Society guidelines.<sup>9</sup> Inhalation was stopped if FEV<sub>1</sub> dropped >20% compared to baseline values. The allergen dose causing a 20% drop of FEV<sub>1</sub> (PD<sub>20</sub>FEV<sub>1</sub>) was calculated by logarithmic interpolation using an integrated programme. As shown in Fig. 2 the patient developed a significant EAR at a PD<sub>20</sub>FEV<sub>1</sub> of 220 SBU. No late asthmatic reaction occurred

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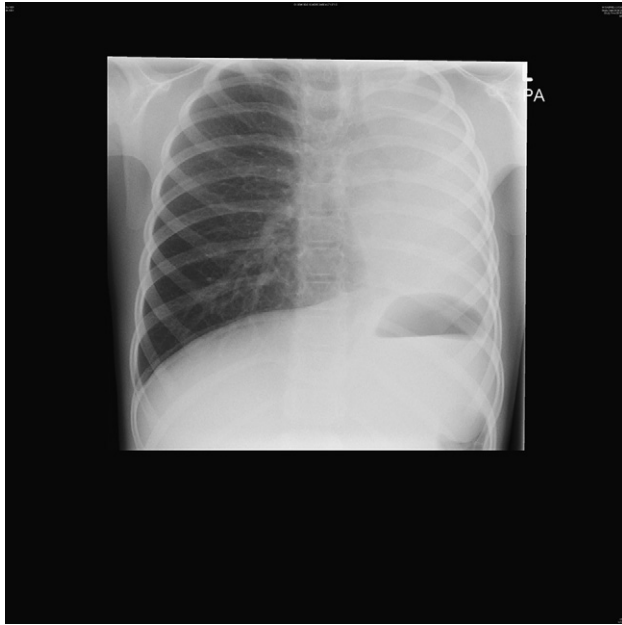


Fig. 1. Total atelectasis of left lung at presentation.

after challenge. Then we initiated treatment with OMA 300 mg s.c. every four weeks. Since OMA has been previously reported to reduce LAR within two weeks and EAR within four weeks,<sup>10</sup> the allergen provocation test was repeated after four weeks of treatment with OMA. No EAR was demonstrated at cumulative provocation dosing up to 315 SBU (Fig. 2). During the next six months the patient had improvement of lung function and showed no relapse under treatment with OMA and itraconazole. However, during colds mild virus induced wheezing was present with a transient drop of FEV<sub>1</sub>, indicating high airway hyperreactivity.

### 3. Discussion

The underlying pathological mechanism of ABPA is not fully understood. ABPA may develop in genetically susceptible CF patients due to HLA-DR2 and DR5 restriction, increased sensitivity to IL-4 stimulation, and increased *Aspergillus* allergen-specific Th-2 CD4<sup>+</sup> T-cell-mediated responses.<sup>1</sup> The importance of a Th-2 mediated immune response was recently highlighted by the finding of increased levels of the Th-2 cytokine TARC (Thymus

activation regulated chemokine).<sup>11</sup> Interestingly the level of TRAC in patients with CF correlates positively with specific IgE to *Aspergillus fumigatus*.<sup>11</sup> In addition, *Aspergillus proteases* play a role in facilitation of antigen transport via chitinases by damaging the epithelial integrity and by a direct interaction with epithelial cell surface receptors, resulting in pro-inflammatory cytokine production and corresponding inflammatory responses.<sup>1</sup>

The role of IgE and mast cell activation is a matter of debate. High total and specific IgE levels, an asthma-like picture and increased airway hyperreactivity are highly suggestive that in the beginning ABPA is just an IgE mediated disease. We have demonstrated for the first time that OMA completely suppresses the EAR after bronchial allergen provocation with *Aspergillus*. Moreover, as has been shown by others, our patient showed a marked improvement of FEV<sub>1</sub> without a relapse after stopping systemic steroid treatment.<sup>3–5</sup>

In children treatment of allergic patients with OMA is limited to IgE levels from 30 to 1300 kU/L. Efficacy of OMA to neutralize high IgE levels >1300 kU/L is unclear.<sup>12</sup> Recently there was a preliminary report that OMA was effective in patients with asthma and high IgE.<sup>13</sup> In addition we have demonstrated the efficacy and safety of OMA in attenuating allergen-induced bronchoconstriction in patients with allergic asthma and pre-treatment IgE levels up to 2000 U/ml.<sup>14</sup> Since ABPA patients usually have high levels of IgE, an alternative therapeutic option could be the reduction of the total and specific IgE by systemic steroids to a treatable level.

In conclusion our case suggests that IgE mediated disease is the major mechanistic pathway of ABPA, and OMA has potential to control ABPA.

### Competing interests

Johannes Schulze has received author and lecture fees from Novartis; Ulrich Zissler has none to disclose; Martin Christmann has none to disclose; Martin Rosewich has none to disclose; Stefan Zielen has participated in advisory board meetings of, and received lecture fees of Novartis.

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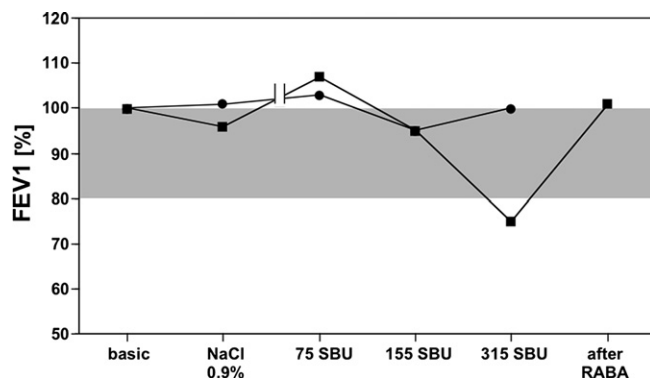


Fig. 2. Bronchial allergen provocation before (■) and after (●) treatment with omalizumab. Squared line: fall of FEV<sub>1</sub> at a PD<sub>20</sub> of 220 SBU *Aspergillus*. Dotted line: course of FEV<sub>1</sub> after a cumulative dose of 315 SBU *Aspergillus*.