Concurrent sensitization to *Aspergillus fumigatus* in tropical pulmonary eosinophilia

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### Abbreviations

TPE: Tropical pulmonary eosinophilia  
SAFS: Severe asthma with fungal sensitization  
ABPA: Allergic bronchopulmonary aspergillosis  
IgE: Immunoglobulin E  
IgG: Immunoglobulin G  
HRCT: High resolution computed tomography  
MMRC: Modified Medical Research Council  
FVC: Forced vital capacity  
FEV1: Forced expiratory volume in 1 second

### Abstract

Tropical pulmonary eosinophilia (TPE) is characterized by lung tissue and peripheral blood eosinophilia. Serum total IgE is also markedly increased in TPE. However, an association with asthma or other hypersensitivity conditions has not been described. During the diagnostic workup of three patients eventually confirmed to have TPE, hypersensitivity to the fungus, *Aspergillus Fumigatus* was found. However, there was no evidence of diseases of aspergillus hypersensitivity such as severe asthma with fungal sensitization (SAFS) and allergic bronchopulmonary aspergillosis (ABPA). This association however raises the possibility of a future risk of these potentially serious allergic respiratory manifestations.

### Introduction

Tropical Pulmonary Eosinophilia (TPE), one of the eosinophilic lung diseases, is a hypersensitivity response to microfilariae of the parasites, *Wuchereria bancrofti* and *Brugia malayi* [1]. Criteria for diagnosis include residence in an endemic area for filariasis, symptoms of recent onset of paroxysmal nocturnal cough with or without sputum, absolute blood eosinophil count of 2000/μl or above, absence of circulating microfilaria in blood, and successful clinical and hematological remission with diethylcarbamazine therapy [2,3]. Though it usually responds well to treatment, recurrence and a chronic state characterized by interstitial fibrosis have been described in TPE [1]. It is characterized by a marked elevation of serum Immunoglobulin E (IgE) levels [4]. Specific IgE antibodies to filarial antigens have also been demonstrated in TPE [5]. However, these immunological features notwithstanding, it is not labeled as an atopic disease and neither familial nor genetic predisposition, or any association with any allergic disorder has ever been documented.

### Cases reports

#### Case 1

A 25 years old nonsmoker male presented with intermittent cough, mainly nocturnal, with minimal mucoid sputum, breathlessness and wheeze for the last six months. He had also developed an evening rise of...
A diagnosis of TPE with aspergillus hypersensitivity was made. Diethylcarbamazine (100 mg t.i.d. for 21 days) was prescribed. There was a marked clinical response and after three weeks the eosinophils came down to 15% in a total white cell count of 9,900/mm³. Post-treatment spirometry was within normal limits with FEV₁ increasing to 89% of predicted and FVC to 85% of predicted.

Case 3

A 28 years old male presented with insidious-onset progressive breathlessness (MMRC grade 2) for the past one year with occasional wheezing and essentially dry cough. On examination, vital signs were in the normal range and chest auscultation revealed bilateral vesicular breath sounds with end-expiratory wheeze. The total cell count was 19,900 with 30% eosinophils. A plain chest radiograph revealed no abnormality and spirometry showed a FEV₁/FVC ratio of 76% with a FVC of 2.93 L (82% of predicted) and FEV₁ of 2.22 L (72% of predicted) with lack of response to inhaled bronchodilator. Total serum IgE was 21056 IU/ml. Specific IgE levels against Aspergillus fumigatus were raised, being 0.45 IU/L. Specific IgG against Aspergillus fumigatus was negative. Peripheral blood smear was negative for microfilariae. Filarial antigen was detected in peripheral blood. A diagnosis of TPE with aspergillus hypersensitivity was established. The patient was treated with a three weeks course of diethylcarbamazine.

The clinical and laboratory data of the patients is summarized in Table 1.

**Discussion**

TPE is a variant of filariasis that results from a hypersensitivity response to microfilariae of the parasites, *Wuchereria bancrofti* and *Brugia malayi* [1-3]. It is endemic in many of the tropical and subtropical areas of South America, Africa, Asia, and Oceania [9]. The predisposing factors for the development of TPE are not well understood, although there is evidence that host immune response to a filarial antigen, γ-glutamyl transpeptidase, confers an increased risk of developing TPE [10].

The most notable, hitherto unreported, observation in the three cases of confirmed TPE presented here, was the evidence of sensitization to the fungus, *Aspergillus Fumigatus*. In *vivo* (skin tests) and in *vitro* methods (serum IgE estimations) are used to detect aspergillus hypersensitivity and because of differences in sensitivity, the two methods are considered complimentary. Either or both may be diagnostic of aspergillus sensitization [11]. In the present study, specific IgE against *Aspergillus Fumigatus* levels were increased in all the three cases, skin tests were not considered necessary. Clinically, hypersensitivity to *aspergillus fumigatus* is important as it is associated with two specific expressions of severe asthma, i.e., the Aspergillus-sensitive asthma or SAFS and ABPA [7,8]. Sensitization to aspergillus is a powerful risk factor for severe, including life-threatening asthma in adults [6].

Unlike several eosinophilic lung diseases including Churg Strauss syndrome and chronic pulmonary eosinophilia, association with asthma is not a feature of TPE even though these patients often have wheezing and demonstrate airways obstruction [1-3]. Further, we have also described the presence of bronchial hyperresponsiveness in TPE [12]. Among the cases presented here, there was evidence to support a diagnosis of asthma only in the first patient. However, none of the patients had evidence of SAFS or ABPA. The question whether sensitization to aspergillus poses a future risk of these potentially serious allergic respiratory manifestations remains to be explored. Although,
Case Report

only a short treatment of three weeks with diethylcarbamazine is the recommended therapy [1-3], many patients with TPE have subsequent relapses and continue to have breathlessness and wheezing. The marked increase in IgE production that characterizes TPE certainly raises the possibility of development of other hypersensitivities including that to aspergillus, as documented in this report. In view of these important clinical implications, we suggest that cases of TPE should be investigated for allergies, including that to aspergillus.

Table 1. Clinical and laboratory data of patients.

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
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<tr>
<td>Duration of symptoms (months)</td>
<td>6</td>
<td>24</td>
<td>12</td>
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<tr>
<td>Symptoms</td>
<td>Nocturnal cough with minimal sputum, Grade II exertional dyspnoea with wheeze, low grade fever for five days</td>
<td>Intermittent cough with scanty sputum, Grade II exertional dyspnoea with wheeze</td>
<td>Dry nocturnal cough, Grade I exertional dyspnoea</td>
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<tr>
<td>Positive signs on physical examination</td>
<td>Prolonged expiration with wheeze</td>
<td>No abnormality</td>
<td>End-expiratory wheeze</td>
</tr>
<tr>
<td>Pulse oximetry, SpO2</td>
<td>96%</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Imaging</td>
<td>Diffuse, bilateral, randomly distributed micronodular opacities on radiograph and HRCT chest</td>
<td>Normal radiograph</td>
<td>Normal radiograph</td>
</tr>
<tr>
<td>Spirometry</td>
<td>Mixed pattern: FVC 59% of pred., FEV1 44% of pred., FEV1/FVC 62%; Post-bronchodilator increase in FEV1, 330 ml (16%)</td>
<td>Mild restriction: FVC 76% of pred., FEV1 81% of pred., FEV1/FVC 92%;</td>
<td>Within normal range: FVC 82% of pred., FEV1 72% of pred., FEV1/FVC 76%; Response to bronchodilator not significant</td>
</tr>
<tr>
<td>Blood counts</td>
<td>42,800/mm3 with 48% eosinophils</td>
<td>17,900 cells/mm3 with 41% eosinophils</td>
<td>19,900 cells/mm3 with 30% eosinophils</td>
</tr>
<tr>
<td>Serum IgE (normal &lt; 400 IU/ml)</td>
<td>6,464 IU/ml</td>
<td>19,136 IU/ml</td>
<td>21056 IU/ml</td>
</tr>
<tr>
<td>Filarial antigen in blood</td>
<td>Detected</td>
<td>Detected</td>
<td>Detected</td>
</tr>
<tr>
<td>Serum precipitins against aspergillus species</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Specific IgE against aspergillus species (normal &lt; 0.35 IU/l)</td>
<td>1.6 IU/ml/l</td>
<td>0.75 IU/ml/l</td>
<td>0.45 IU/ml/l</td>
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<tr>
<td>Specific IgG against aspergillus species</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Treatment</td>
<td>Diethylcarbamazine with inhaled budesonide-formoterol</td>
<td>Diethylcarbamazine</td>
<td>Diethylcarbamazine</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Marked improvement in symptoms, radiological resolution, counts 6,300/mm3 with 15% eosinophils, spirometry in normal range</td>
<td>Marked improvement in symptoms, 9,900/mm3 with 15% eosinophils, spirometry in normal range</td>
<td>Marked improvement in symptoms</td>
</tr>
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References