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
FEV_1: 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.

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Riassunto

L'eosinofilia polmonare tropicale (TPE) è caratterizzata da tessuto polmonare e eosinofilia nel sangue periferico. Anche il siero IgE totale è notevolmente aumentato in TPE. Tuttavia, un'associazione con asma o altre condizioni di ipersensibilità non è stata descritta. Durante l'iter diagnostico di tre pazienti, che alla fine si sono rivelati presentare TPE, ipersensibilità al fungo, è stato trovato l'*Aspergillus fumigatus*. Tuttavia, non vi era alcuna evidenza di malattie di *Aspergillus* ipersensibilità come l'asma grave con sensibilizzazione fungina (SAF) e aspergillosi broncopolmonare allergica (ABPA). Questa associazione pone tuttavia la possibilità di un rischio futuro di queste potenzialmente gravi manifestazioni allergiche respiratorie.

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.

During the diagnostic workup of three patients with pulmonary symptoms and marked peripheral eosinophilia, who were eventually confirmed to have TPE, we found evidence of hypersensitivity to the fungus, *Aspergillus Fumigatus*. Sensitivity to aspergillus is of immense clinical importance as it is the basis of serious allergic respiratory diseases including severe asthma with fungal sensitization (SAFS) and allergic bronchopulmonary aspergillosis (ABPA) [6-8]. Due to this unique and hitherto unrecognized association, and the potentially serious outcomes of aspergillus sensitization, we report these cases.

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

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temperature for the last five days. On examination, the vital signs were not remarkable and the resting oxygen saturation was 96%. Chest auscultation revealed bilateral vesicular breath sounds with prolonged expiration and diffuse expiratory wheeze. The total peripheral white cell count was 42,800/mm^3 with 48% eosinophils. The chest radiograph showed micronodular shadows that were found to be randomly distributed in all lobes on high resolution computed tomography (HRCT) of chest (Figure 1). Spirometry showed a mixed pattern of ventilatory impairment: FEV_1/FVC 62%, FVC 3.07 L (59% of predicted) and FEV_1 1.91 L (44% of predicted). After inhalation of salbutamol, the FVC improved to 3.2 L (61% of predicted) and FEV_1 to 2.24 L (51% of predicted). The improvement in FEV_1 was 330 ml and 16%, a significant response. Total serum IgE was 6,464 IU/ml (normal < 400 IU/ml). Specific IgE levels against *Aspergillus fumigatus* were 1.6 IU/L (normal < 0.35 IU/L). Serum precipitins and specific immunoglobulin G (IgG) against *Aspergillus fumigatus* were negative. Filarial antigen was detected in peripheral blood.

A diagnosis of TPE and bronchial asthma with aspergillus hypersensitivity was made and diethylcarbamazine (100 mg t.i.d. for 21 days) was administered along with inhaled budesonide-formoterol inhalation. There was a dramatic response in symptoms and a repeat spirometry showed marked improvement: FEV_1/FVC 86%, FVC 70% of predicted, FEV_1 81% predicted. The total white cell counts dropped to 6,300/mm^3 with 15% eosinophils. The chest radiograph showed complete resolution. The treatment for asthma has continued.

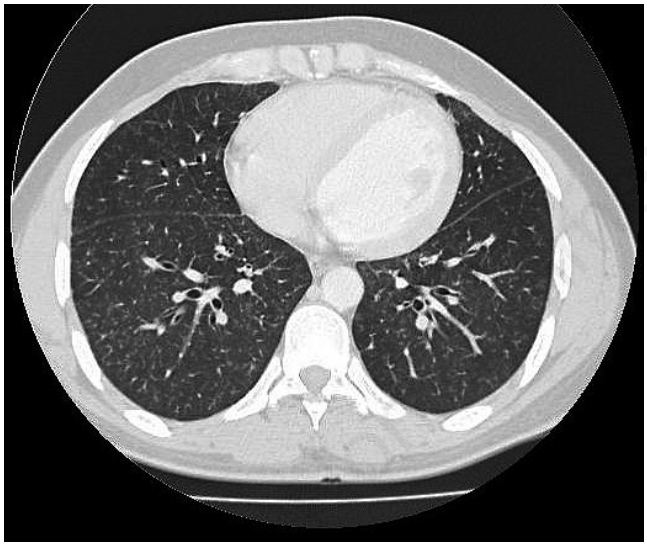

Figure 1. High resolution computed tomography (HRCT) of chest showing bilateral, diffuse, randomly distributed micronodular shadows.

Case 2

A 17 years old nonsmoker boy presented with a two years history of intermittent cough with scanty mucoid sputum, exertional dyspnea (Modified Medical Research Council grade II) and wheezing. Physical examination of the patient was not remarkable. The chest radiograph was normal. Peripheral white cell counts revealed a total of 17,900 cells/mm^3 with eosinophils of 41%. Total serum IgE was 19,136 IU/ml. Filarial antigen was detected in blood. Specific IgE levels against *Aspergillus fumigatus* were 0.75 IU/L (normal < 0.35 IU/L). Serum precipitins and specific IgG against *Aspergillus fumigatus* were negative. Spirometry revealed a FEV_1/FVC ratio of 92%, FEV_1 of 81% of predicted, and FVC of 76% of predicted, a pattern of mild restriction.

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/mm^3. Post-treatment spirometry was within normal limits with FEV_1 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 FEV_1/FVC ratio of 76% with a FVC of 2.93 L (82% of predicted) and FEV_1 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, and 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,

Table 1. Clinical and laboratory data of patients.

	Case 1	Case 2	Case 3
Age (years)	25	17	28
Gender	Male	Male	Male
Duration of symptoms (months)	6	24	12
Symptoms	Nocturnal cough with minimal sputum, Grade II exertional dyspnoea with wheeze, low grade fever for five days	Intermittent cough with scanty sputum, Grade II exertional dyspnoea with wheeze	Dry nocturnal cough, Grade I exertional dyspnoea
Positive signs on physical examination	Prolonged expiration with wheeze	No abnormality	End- expiratory wheeze
Pulse oximetry, SpO2	96%	98%	98%
Imaging	Diffuse, bilateral, randomly distributed micronodular opacities on radiograph and HRCT chest	Normal radiograph	Normal radiograph
Spirometry	Mixed pattern: FVC 59% of pred., FEV_1 44% of pred., FEV_1 /FVC 62%; Post-bronchodilator increase in FEV_1 330 ml (16%)	Mild restriction: FVC 76% of pred., FEV_1 81% of pred., FEV_1 /FVC 92%.	Within normal range: FVC 82% of pred., FEV_1 72% of pred., FEV_1 /FVC 76%; Response to bronchodilator not significant
Blood counts	42,800/mm^3 with 48% eosinophils	17,900 cells/mm^3 with 41% eosinophils	19,900 cells/mm^3 with 30% eosinophils
Serum IgE (normal < 400 IU/ml)	6,464 IU/ml	19,136 IU/ml	21056 IU/ml
Filarial antigen in blood	Detected	Detected	Detected
Serum precipitins against aspergillus species	Negative	Negative	Negative
Specific IgE against aspergillus species (normal < 0.35 IU/l)	1.6 IU/ml /l	0.75 IU/ml /l	0.45 IU/ml /l
Specific IgG against aspergillus species	Negative	Negative	Negative
Treatment	Diethylcarbamazine with inhaled budesonide-formoterol	Diethylcarbamazine	Diethylcarbamazine
Response to treatment	Marked improvement in symptoms, radiological resolution, counts 6,300/mm^3 with 15% eosinophils, spirometry in normal range	Marked improvement in symptoms, 9,900/mm^3 with 15% eosinophils, spirometry in normal range	Marked improvement in symptoms

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.

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