

CLINICAL CASE OF THE MONTH

27-Year-Old Asian Man Presenting With Chronic Nocturnal Cough

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With increased globalization, more people are migrating to the United States (US) for higher education and employment. Consequently, more internationally associated infectious diseases are being diagnosed in the United States. Physicians should be aware of the consequences of this global travel and become familiar with parasitic infections and their clinical manifestations. We report a case of tropical pulmonary eosinophilia in a foreign medical resident from India. Tropical pulmonary eosinophilia should always be included in the differential diagnosis of chronic cough with eosinophilia, especially when dealing with immigrants or when there is a history of recent travel to an endemic area.

CASE

A 27-year-old Indian man presented to the allergy clinic with a four-month history of cough and shortness of breath. Four months prior to the presentation, he noticed upper respiratory symptoms with rhinorrhea and nasal congestion. He reported exposure to a known pertussis case and was prescribed azithromycin. The runny nose and nasal congestion resolved, but the cough persisted. The cough gradually worsened over the next eight weeks and was more frequent during the night. He developed wheezing and post-tussive emesis with these nocturnal coughing spells. The coughing spells were unprovoked and paroxysmal. Despite use of several over-the-counter cough medications, no relief was attained. His primary care provider prescribed fluticasone nasal spray and albuterol inhaler for presumed allergic bronchitis, but he saw no improvement. He denied fever, weight loss, night sweats, and chest pain. He denied recent exposure to anyone with active tuberculosis. His past medical history was significant for two episodes of epididymo-orchitis five years earlier due to presumed filarial infection. Family history was non-contributory. He denied tobacco use and any illicit drug or alcohol abuse. He was a medicine-pediatrics house officer who had migrated to the United States approximately three years earlier. He is in a monogamous relationship with his wife and does not have any pets. He reported travel to India two months prior to the onset of symptoms. While there, he spent four weeks in rural South India. He denied any drug or food allergies.

His vital signs at presentation included: temperature

98.9°F, blood pressure 120/75 mm Hg, heart rate 76/ min, pulse oximetry of 96% on room air, and a body mass index of 23. No physical exam abnormalities were appreciated. He did not have any wheezes or rales on lung auscultation. Laboratory analysis revealed a WBC of $55 \times 10^3/\text{UL}$ ($4.5 - 10.5 \times 10^3/\text{UL}$) and absolute eosinophil count (AEC) of $30 \times 10^3/\text{UL}$ (less than $0.45 \times 10^3/\text{UL}$). Hemoglobin of 15.1 gm/dl, and platelets of $294 \times 10^3/\text{UL}$ were within normal ranges. A comprehensive metabolic panel was normal. A serum IgE was 3,000 IU/ml ($4.2 - 595 \text{ U/mL}$). HIV and T-spot tests were negative, as was a nasopharyngeal swab for pertussis DFA test. Chest X-ray showed mild non-specific interstitial changes at the lung bases. A CT scan of the chest revealed mild peripheral interstitial markings at the bases bilaterally with no focal consolidation.

Based on the patient's history of travel, clinical features, and laboratory findings of a profound eosinophilia and very high IgE levels, a parasitic etiology was suspected. Further workup revealed significantly high titres of serum anti-filarial IgG and IgE antibodies. Pulmonary function testing demonstrated a mild restrictive pattern with no significant post bronchodilator response. A diagnosis of tropical pulmonary eosinophilia was made, and he was treated with diethylcarbamazine (DEC) 2 mg/kg/dose three times a day for three weeks. His cough and dyspnea completely resolved in one week. After three weeks of treatment, his leukocytosis, eosinophilia, and IgE levels normalized, and serum anti-filarial IgG and IgE antibody titres showed significant reduction.

DISCUSSION

Introduction

Tropical pulmonary eosinophilia (TPE) is a common cause of chronic cough in tropical countries where parasitic infections are prevalent due to water and soil contamination. It was first described as "pseudo-tuberculosis condition associated with eosinophilia" in 1940 and as "tropical eosinophilia" in 1943. TPE is a rare, serious manifestation that results from a hypersensitive reaction to microfilariae released by the filarial worms (*Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*).^{1,2} It is usually characterized by pentad of chronic paroxysmal nocturnal non-productive cough, nocturnal wheezing, shortness of breath, elevated serum IgE (>1,000 IU/ml), and peripheral eosinophilia (>3,000/mm³). The detection of high titers of anti-filarial I_E and I_G antibodies, favorable response to DEC treatment, and the absence of microfilaria in the blood confirm the diagnosis.²

Epidemiology

Historically, TPE was exclusively a disease of tropical regions including India, South East Asia, South America, South Pacific Islands, and Africa.³ TPE has been increasingly reported in developed countries due to an increase in global travel. Based on various studies conducted in India, TPE prevalence is shown to be present in 0.5% to 9.9% of all filarial infections.^{4,5} Individuals from non-endemic areas visiting a filarial endemic region are more prone to develop TPE because they lack the natural immunity against filarial infection.² TPE should be considered in any patient returning from an endemic region who presents with "asthma-like" symptoms.⁶

Pathogenesis

Microfilariae are released by adult filarial worms living in the lymphatics. These microfilariae become trapped in the pulmonary circulation where they release their antigenic constituents and produce a local inflammatory response. Antigenic material released from the microfilariae can reach the systemic circulation and cause extrapulmonary manifestations. Bronchoalveolar lavage studies have demonstrated an intense eosinophilic inflammatory process in the lower respiratory tract. The pathogenic hallmark of TPE is the intense immunologic response associated with rapid clearance of microfilariae from the blood.² Eosinophil degranulation products, eosinophil-derived neurotoxin, eosinophilic cationic protein and major basic proteins (MBP) have been found to be responsible for some of the pathology seen in TPE.¹ A profound antibody response to filarial gamma-glutamyl transpeptidase can also be observed in the lungs of patients with TPE.^{4,5}

Diagnosis

The clinical onset of TPE is usually gradual. Affected individuals are generally 20 to 30 years of age, and men

are more affected than women.¹ A history of exposure to a filarial endemic area is essential for the diagnosis of TPE. Pulmonary involvement is a hallmark of this condition.² Patients present with symptoms of cough (90%); paroxysmal cough followed by breathlessness, which is worse at night (70%); mucoid expectoration (50%); exertional dyspnea (45%); and wheezing (28%). Constitutional symptoms include fatigue, occasional weight loss, low-grade fevers, body aches, anorexia, and night sweats.² The physical examination is usually unremarkable in most patients, though bilateral scattered rhonchi may be auscultated. Extrapulmonary manifestations may include lymphadenopathy, hepatosplenomegaly, pericarditis, pericardial effusion, and cor pulmonale.^{4,5} Pleural effusions and mediastinal lymphadenopathy are uncommon.^{1,2}

Laboratory findings typically consist of a marked leukocytosis, an immense eosinophilia, and high serum IgE levels.^{2,4} The erythrocyte sedimentation rate is elevated in 90% of cases. Microfilariae are rarely seen in the peripheral blood.⁵ Stool studies are not very specific and may yield ova of other helminthic parasites, as persons from endemic countries may be simultaneously infected with other worms.² Chest radiographs are normal in 20 - 30% of patients, though radiological findings may include increased bronchoalveolar markings, reticulonodular changes predominantly in mid and lower zones, and miliary mottling often confused with miliary tuberculosis.¹ A CT of the lung is felt to be a more sensitive method for detecting these changes. Bronchoalveolar lavage may reveal eosinophilic alveolitis. Pulmonary function tests predominantly show a restrictive pattern together with a mild-moderate obstructive picture.⁷ Mild arterial hypoxemia (PaO₂ <80 mmHg) may be seen. If treated within the first few years of TPE infection, lung function abnormalities are reversible. Delay in treatment can lead to progressive interstitial fibrosis and irreversible pulmonary impairment.^{1,2}

Differential diagnosis

Helminthic infections are the most common cause of pulmonary-associated eosinophilia in tropical countries.^{8,9} Filarial TPE may be clinically indistinguishable from a TPE-like syndrome caused by other helminths (*ascaris*, *strongyloides*, *paragonimus*, *cysticercosis*, *trichinosis*, and *schistosomiasis*), as anti-filarial antibodies are also elevated in patients with TPE-like syndrome because the filarial antigens cross-react with other helminthic antigens.¹⁰ Detection of the Og4C3 antigen, by either immunochromatography or ELISA, has proven to be a specific and sensitive method for the immunodiagnosis of *Wuchereria bancrofti* infections. This test is unable to detect *Brugia malayi* infections, however.¹⁰ Differentiating TPE from eosinophilic pneumonia due to *Strongyloides stercoralis* is very important because corticosteroids, which are often used in the treatment of TPE, can cause life threatening disseminated strongyloidiasis, particularly in immunocompromised persons.¹¹ Until a specific diagnostic test is available to differentiate filarial TPE from other TPE-like syndromes, the diagnostic criteria described

above should be used to diagnose TPE. Non-helminthic causes of pulmonary eosinophilia should also be included in the differential diagnosis of pulmonary infiltrates with eosinophilia (PIE). These include bronchial asthma, allergic broncho-pulmonary aspergillosis (ABPA), acute eosinophilic pneumonia, chronic eosinophilic pneumonia, idiopathic hypereosinophilic syndrome, Wegener's granulomatosis, lymphomatoid granulomatosis, Churg-Strauss syndrome, some malignancies, and drug hypersensitivity reactions.¹²⁻¹⁴

Management

The standard treatment for TPE is diethylcarbamazine (DEC) at a dose of 6mg/kg/day in three divided doses for three weeks.¹⁵ Agents like ivermectin in combination with corticosteroids are an acceptable alternative.¹³ Most patients show marked symptomatic and radiographic improvement after a standard three-week course of DEC therapy.¹⁶ Twelve to twenty-five percent of untreated or partially treated patients may develop a mild form of interstitial lung disease with chronic respiratory insufficiency.⁵ Treatment with prednisolone significantly reduces lower respiratory tract inflammation and release of oxidants.¹ Relapses occur in 20% of TPE patients. Resistant and relapsed cases require higher dose of DEC (6 - 12 mg/kg per day) for three to four weeks.¹⁵

Prevention of filarial infections can be achieved with mass chemotherapy and vector control. The World Health Assembly has pledged to eliminate lymphatic filariasis as a public health problem by the year 2020. The strategy is to treat the entire population at risk for lymphatic filariasis through yearly, single-dose treatment with a combination of DEC and albendazole in order to cover the reproductive lifespan of adult-stage parasites which lasts four to six years.^{15,17}

Conclusion

TPE is caused by immunologic hyperresponsiveness to the human filarial parasites, i.e., *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. Even though TPE is mostly a disease of developing countries, it is increasingly reported in various other parts of the world due to global travel. Early diagnosis and treatment is important as delay in treatment can potentially lead to chronic respiratory insufficiency. Diagnostic criteria for TPE include: (a) history of exposure to filarial endemic area; (b) symptoms of paroxysmal nocturnal cough and breathlessness; (c) laboratory abnormalities with marked leucocytosis, profound peripheral eosinophilia (>3,000 cells/mm³), elevated serum IgE levels (>1,000 IU/ml); (d) positive serology for serum antifilarial antibodies (IgG and/or IgE); (e) absence of microfilariae in peripheral blood; and (f) a favorable clinical response to DEC. The antifilarial drug, DEC, is the treatment of choice. Eliminating filariasis in endemic areas using WHO recommended mass chemotherapy will eliminate TPE.

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