# Tropical Eosinophilia - The Indian Scene

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*Tropical eosinophilia, an occult form of filariasis, results from immunologic hyperresponsiveness to the human filarial parasites, Wuchereria bancrofti and Brugia malayi. The clinical syndrome is characterised by cough, dyspnoea, nocturnal wheezing and chest discomfort and is occasionally accompanied by constitutional symptoms such as weight loss, anorexia and fever. Chest radiographs show-diffuse reticulo-nodular infiltrates and pulmonary function reveals restrictive ventilatory defect with mild obstruction. Laboratory studies are characterised by marked peripheral blood eosinophilia and high serum levels of IgE and filaria-specific IgG and IgE antibodies. The hallmark of the syndrome is markedly elevated eosinophils in the lower respiratory tract and interstitial lung fibrosis develops if left untreated. Although patients respond rapidly following a standard 3-week course of diethylcarbamazine, there is incomplete reversal-of clinical, hematological, radiological, physiological and pathological changes despite treatment. Therefore other therapeutic modalities such as the addition of corticosteroids to the DEC regimen have to be evaluated in controlled clinical trials.*

## Introduction

Tropical eosinophilia (TE), one of the main causes of pulmonary eosinophilia in tropical countries; is prevalent in filarial endemic regions of the world especially South-East Asia[1]. Even though tropical eosinophilia as a clinical entity was described only in 1940s, the earliest report that conformed to the clinical picture of TE was published in 1916 by Low[2] in a 30-year-old male. Subsequently, Roy and Bose[3] noticed marked leucocytosis and eosinophilia in a group of "asthmatic" subjects who responded to subcutaneous or intramuscular injections of soamin. Frimodt - Moller and Barton[4] in 1940 described a group of sanatorium patients in Madanappalle who had extensive biateral, evenly distributed miliary mottling in chest X-rays resembling miliary tuberculosis. and blood eosinophilia. They termed this condition as "a pseudo-tuberculosis condition associated with eosinophilia". The name "Tropical eosinophilia" was coined in 1943 by Weingarten[5] who accidentally observed that these patients could be treated with neoarsphenamine, as one of his patients with concurrent syphilis was cured of his TE on being given neoarsphenamine for syphilis.

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## Aetiology

Various studies[6,7] had shown that filarial infection is the cause of TE. It has been observed that TE is most frequently encountered in those regions where filariasis is endemic[1,8].

A positive filarial complement fixation test (FCFT) in most patients with TE was described by Dhanaraj[6] and many workers used the positive FCFT and intradermal skin tests using *D.immitis* antigen as a diagnostic test for TE[9]. Webb et all[10] in 1960 demonstrated microfilariae in the lungs, liver and lymph nodes of patients with TE. The microfilariae were sheathed and had the anatomical features of *Wuchereria bancrofti.* Udwadia[8] also had demonstrated microfilariae (indistinguishable from *Brugia malayi)* in open lung biopsy specimens from TE patients. Elevated concentrations of filarial-specific IgE have also been reported in TE[11]. The observation that diethylcarbamazine (DEC), an antifilarial drug, is useful in the treatment[12,13] further supports the hypothesis of a filarial etiology in TE. Experimental studies carried out in human volunteers[14,15] had suggestedthat TE is due to immunologic hyperresponsiveness to human filariasis. Leucocyte adhesion phenomenon[16] and the demonstration that basophils from patients with TE released greater amounts of histamine when cells were challenged with Brugia or Wuchereria antigens than with Dirofilaia antigens[17] provide further evidence that human forms rather than animal filaria are responsible for TE.

## Pathogenesis

Histopathological findings such as widely scattered nodules of varying size (1 to 5mm) over lung surface were first described by Viswanathan[18] and Dhanaraj[19]. Detailed histopathological studies demonstrating eosinophilic, histiocytic and mixedcell type infiltrations were documented by Udwadia[8]. He had clearly shown that pulmonary fibrosis developed in some patients, particularly in those with a long-standing history[8,20]. Poh[21] had noticed mild to moderate thickening of both pulmonary arteries and veins in a patient with TE. The current concept of the pathogenesis of TE suggests that it begins. with a lung parenchymal inflammation in individuals highly sensitized immunologically to filarial parasites. The microfilariae released from lymphatic dwelling adult worm is cleared in the pulmonary circulation and the microfilariae degenerate and release their antigenic constituents which trigger the local inflammaiory and immune processes[10,17,20]. Morphologically, it had been shown that there was evidence of degenerating microfilariae and diffuse inflammation in the lung parenchyma[8,10,22,23]. Therefore, it can be reasonably hypothesized that the clinical and pulmonary physiological abnormalities in TE are at least in part due to accumulation of inflammatory cells in the lung parenchyma.

Bronchoalveolar lavage studies had demonstrated that TE was characterized by intense eosinophilic inflammatory process in the lower respiratory tract[24]. The concentration of eosinophils in the epithelial lining fluid (ELF) of the tower respiratory, tract was many fold greater than that in the blood, suggesting that eosinophils accumulate selectively in the lung parenchyma. Electron microscopic examinations disclosed marked alterations consisting of severe degranulation with loss of both the cores and the peripheral portions of the granules. These findings suggest that eosinophils are in an activated state. The significant negative correlation of lung eosinophils with transfer factor[25] is, therefore, compatible with the hypothesisthat the toxic mediators liberated- by activated eosinophils are responsible for the injury to the lung parenchyma in TE. Polyclonal IgE and parasite - specific IgG, IgM and IgE antibody levels in epithelial lining fluid (ELF) were significantly higher in TE patients[25]. Treatment with DEC 6 - 14 days later showed a dramatic fall in the levels of ELF parasite-specific IgG and IgE antibodies without corresponding changes in either the serum antibody levels or ELF polyclonal immunoglobulin levels. Immunoblot comparison of the antigen recognition pattern of ELF and serum antibodies demonstrated a general similarity in parasite antigen recognized. Thus. a profound antibody response to filarial infection is found in the lungs of patients with TE, suggesting that these filaria specific antibodies play an important role in the pathogenesis of this disorder[25].

## Clinical features and management

TE is predominantly seen in males and between the ages of 15 and 40 years[1]. Udwadia[8] had classified the clinical manifestations into 6 forms. They are respiratory form which is the commonest form, alimentary form, general form. lymphatic form, mixed form and asymptomatic form with only peripheral eosinophilia. Respiratory form is characterised by cough, dyspnoea and nocturnal wheezing, occasionally associated with fever, anorexia and weight loss. Clinical examination may reveal rales and rhonchi. Leucocytosis with an absolute increase in eosinophils in the peripheral blood is the hallmark of TE[4,5]. Microfilariae are rarely seen in the peripheral blood[8]. Sputum shows clumps of eosinophils and Charcot-Leyden crystals[5]. Radiological features in TE include miliary mottling, prominent hila with increased vascular markings. In patients with long-standing history. lung fields may show reticulations and in a few cases honeycombing[2O]. Chest radiographs may be normal in 20-30% of patients with TE[8]. Before treatment, the main physiological abnormality in acute TE was a reduction in the carbonmonoxide transfer factor[21,27] which was found to be due to reduction in membrane diffusing capacity (Dm)[28]. Mild to moderate obstructive ventilatory defect was seen in 30% of cases and restrictive defect in 50-70%[20,29]. Arterial hypoxemia ($PaO_2$ < 80 mm Hg) was observed in 42% of acute TE patients, but 36% had only mild hypoxemia ($PaO_2$, 70-80 mm Hg)[29,30].

The diagnostic criteria, of TE, therefore, include history of past orpresent residence in the endemic areas of filariasis, respiratory symptoms, pulmonary infiltrates, peripheral blood eosinophils > 2000 cells/$mm^3$ and high serum antifilarial IgG. Initially, the treatment of TE was with arsenic and was abandoned because of its toxicity[5]. Later on, diethylacarbamazine (DEC), a piperazine derivative with antifilarial activity was found to be the drug of choice[12,13,31] and it is cheap and least toxic. The recommended schedule of treatment with DEC is 6mg/kg body weight for 3 weeks[32,33]. Most individuals with TE respond to DEC within 1 to 3 weeks with a progressive reduction in symptoms, clearing of the chest X-rays, reduction in the blood eosinophil count, and improvement in lung function. Relapses occurred in 20% of patients followed up for 5 years[8]. Earlier workers[34] had shown that steroids were also effective in the treatment of TE. The new antifilarial drug, Ivermectin given in a dosage of 200 ug/kg/day for 2 days was found to be ineffective in TE (Personal observations-unpublished.

## Course of disease

It had been shown previously that acute tropical eosinophilia left untreated could develop into chronic interstitial lung disease'. Studies conducted to know the fate of those patients who were treated "successfully" with a standard three weeks course of DEC had revealed that most patients had shown a marked symptomatic improvement, but peripheral blood eosinophilia (> 2000 cells/cc) persisted in 52%, radiographic abnormalities in 44%, cough in 22% and chest signs in 8%[29]. Significant improvement was noticed in almost all aspects of lung function including blood gases, but the mean values for forced expiratory volume in one second ($FEV_1$), transfer factor (TLCO), transfer coefficient (KCO) and membrane diffusing capacity(Dm) continued to be significantly lower than predicted values[20,21,29]. At one month the obstructive defect was persistent in 14% and the restrictive in 16%. Reduced transfer factor and transfer coefficient persisted in 62% and 54% respectively. There was also a marked decrease of the lung eosinophils[35] following the treatment. However, a mild macrophage-eosinophilic alveolitis was presisting at one month despite treatment=. Thus, there was incomplete reversal of clinical, hematological, radiological, physiological and pathological changes in TE one month after starting a 3-week course of diethylcarbamazine[29,35].

The observation that there is incomplete recovery in TE[29] suggests the possibility that the disease can persist despite DEC therapy and lead to chronic dyspnoea with restrictive functional impairment. Majority of patients evaluated 12±2 months later following a standard 3-week course of DEC for acute TE[36] had mild, pesistent symptoms referable to the lung, chest X-ray abnormalities, blood eosinophilia and elevated serum IgE and filarial specific IgG[35]. On the average, lung function was consistent with the presence of chronic, mild interstitial lung disease. When the inflammatory cells from the lower respiratory tract were examined, there was a persistent eosinophilic alveolitis[36]. A one year follow up study of 50 patients had' revealed that

chronic eosinophilic alveolitis in 35% and diffusion defect in 51% could occur at 12 months despite treatment[37]. Evaluation of the lower respiratory tract inflammatory cells recovered from post-DEC - treated individuals demonstrated spontaneous release of exaggerated amounts of $O_2$ and $H_2O_2$ compared to normal subjects[36]. Treatment with prednisone significantly reduced the lower respiratory tract eosinophil inflammation and the release of oxidants[38].

These findings suggest that standard treatment as practiced currently ie one course DEC (6 mg/kg/body weight) for 3 weeks is inadequate for a cure in TE. Therefore, other modalities of treatment such as long-term DEC with or without corticosteroids have to be evaluated in a controlled clinical trial.

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