Review Article

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Tropical pulmonary eosinophilia - A review

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Tropical pulmonary eosinophilia (TPE) is a syndrome of wheezing, fever and eosiniphilia seen predominantly in the Indian subcontinent and other tropical areas. Its etiological link with *Wuchereria bancrofti* and *Brugia malayi* has been well established. The pathogenesis is due to an exaggerated immune response to the filarial antigens which includes type I, type III and type IV reactions with eosinophils playing a pivotal role. Peripheral blood eosinophilia is usually striking with levels over 3000/µl being common. High serum levels of IgE and filarial-specific IgE and IgG are also found. The pathology may vary from an acute eosinophilic alveolitis to histiocytic infiltration depending on the stage of the disease. While earlier studies had suggested that the disease runs a benign course, more recent work has shown that untreated TPE could result in a fair degree of respiratory morbidity. Pulmonary function tests may show a mixed restrictive and obstructive abnormality with a reduction in diffusion capacity. The bronchoalveolar lavage (BAL) eosinophil count has a negative correlation with the diffusion capacity. Treatment consists of diethylcarbamazine (DEC) for at least three weeks. Despite treatment with DEC, about 20 per cent of patients may relapse. Steroids have shown to have a beneficial effect but the exact dose and duration is yet to be confirmed by randomized controlled trials. A specific and easily available marker is required for TPE in order to distinguish it from other parasitic and non-parasitic causes of pulmonary eosinophilia.

Key words Cough - DEC - fibrosis - filarial antigen - microfilariae - tropical pulmonary eosinophilia - wheezing

Historical background

First described in 1940 and labelled as "pseudotuberculosis with eosinophilia"[1], the term tropical pulmonary eosinophilia (TPE) was first coined by Weingarten in 1943[2] to a syndrome of wheezing, fever, eosinophilia and bilateral mottling of the lungs. This was followed by a series of reports describing similar conditions from the tropical regions such as the Indian subcontinent[3-6].

The pathology, pathogenesis, links with the *Wuchereria* antigen and the *Brugia malayi* antigens and effectiveness of diethylcarbamazine (DEC) as therapy were subsequently described. TPE was initially thought to be a benign self-limiting condition. It is now an accepted fact that though TPE does not end fatally, it does and can scar the lung badly.

Epidemiology

TPE is endemic in areas with filarial endemicity. It is most commonly found in regions of the Indian subcontinent, South East Asia, South America and Africa[7-9]. It is found in less than 1 per cent of filarial infections and occurs as a hypersensitivity reaction to

the microfilariae. In India, it is mostly found around the coastal regions from Maharashtra to Kerala and West Bengal to Tamil Nadu[7]. The prevalence of TPE in various settings in India has varied from 0.5 per cent among children in Tamil Nadu[10] to 9.9 per cent among jail inmates in Patna[11]. Some cases have been reported from non-endemic countries such as Japan[12], Netherlands[13], United Kingdom[14] and Australia[15], probably as a result of travel to or immigration from endemic areas. In fact, persons travelling to endemic areas may be more prone as they lack natural immunity to filarial antigens[16].

Clinical features

TPE occurs mostly in young males with a male-female ratio of 4:1 and in an age group between 15-40 yr[18]. It may involve multiple body systems but predominantly affects the lungs[7]. Udwadia[7] reported in his study that about 7 per cent of patients had only non-pulmonary manifestations. The respiratory symptoms are chiefly cough, breathlessness, wheezing and chest pain. Symptoms are mostly nocturnal but may also occur during the day[7,17]. Sputum production is in scanty quantities and may be viscous and mucoid. Sputum eosinophilia is often present[7]. Chest pain may be due to rib fractures caused by excessive vigorous coughing.

Rare pulmonary presentations include consolidation, cavitation[18], pneumothorax[19] and bronchiectasis[20].

Systemic symptoms include fever, weight loss, fatigue and malaise. Extrapulmonary manifestations include lymphadenopathy and hepatosplenomegaly[17]. Cor pulmonale does not occur and ECG changes are non-specific[21]. Neurologic involvement is not known. Wheezes and crackles may be found on examination although 20 per cent of patients may have no findings on examination[7]. Laboratory findings are characterized by a striking eosinophilia >3000/µm and may rise as high as 80,000/µm[16,17,22]. Eosinophil count may show diurnal fluctuations and may paradoxically be lowest during the night when the symptoms are at their worst (probably due to sequestration of eosinophils within the lungs). Blood eosinophils may show cytoplasmic vacuoles and degranulation. Erythrocyte sedimentation rate (ESR) is usually elevated in 90 per cent of the cases. High serum levels of IgE and filarial-specific IgE and IgG are found[8,9,23]. In a study by Neva *et al*[24], serum IgE level was 2355 ng/ml which reduced (but did not normalize) to about 600ea - 1000 ng/ml after 8-12 days of treatment. Wb E34 penicillinase and *W. bancrofti* microfilarial excretory secretory (Wb mf ES) antigen detect filarial antibody in 35 per cent of cases of TPE (which rises to almost 81% in the presence of microfilaraemia)[25].

Aetiology

TPE occurs as an unusual hypersensitivity response to the filarial antigens of *W. bancrofti* and *B. malayi*. This conclusion has been arrived at based on various histopathological and immunological studies.

Evidence for filarial infection as a cause of TPE

(i) Danaraj *et al*[26,27] and Danaraj and Schacher[28] showed a positive complement fixation test to *Dirofilaria immitis* antigen in the form of an alcohol-based extract indicating that tropical eosinophilia may well be a systemic manifestation of sensitivity to the filarial antigen.

(ii) Several studies[7,29,30] showed the presence of microfilariae in the lungs of patients of tropical eosinophilia. Webb *et al*[29] found the microfilariae to be sheathed and showed the anatomical features characteristic of *W. bancrofti*, and also reported therapeutic responses to DEC.

(iii) Topographical distribution of endemic filariasis in India coincides with the incidence of tropical eosinophilia. Filariasis is common along the greater part of the Western coast of India particularly the coastal strip around Maharashtra, Goa and Kerala, along the whole of the Eastern coast of India, in West Bengal, Bihar, Orissa, parts of Karnataka and Andhra Pradesh as also in parts of Madhya Pradesh and Uttar Pradesh. Tropical eosinophilia is also very common in all the above mentioned parts of the country[7]. Also, the response to DEC which is filaricidal is further evidence to support this.

There have been isolated reports of TPE occurring by animal filarial infection[31-34]. However, this seems to be extremely rare.

Pathology

The first histopathological descriptions on TPE were reported by Viswanathan in 1947[35]. The first series of open lung biopsies was reported by Udwadia and Joshi in 1964[36]. They detected parasites in only three of the 26 biopsies. The histopathological reactions observed were mainly classified into three types:

(i) Acute eosinophilic infiltration, eosinophilic bronchopneumonia and eosinophilic abscesses.

(ii) Mixed cell type of infiltrate (*i.e.* eosinophils and histiocytes) with generally well-marked fibrous tissue formation between six months to two years.

(iii) Histiocytic infiltration and fibrosis beyond two years in the natural history of the disease. Fibrosis occurred early in the natural course of the disease. It was usually interstitial but also peribronchial and perivascular in distribution. It is slowly progressive. Later in the natural course, the lung is badly scarred with a restrictive pattern. However, it is never as crippling as in idiopathic pulmonary fibrosis (IPF). Although symptoms and eosinophilia usually resolve within one month of treatment with DEC, the lung biopsies demonstrate incomplete histological regression.

Natural history - Correlation of the clinical features with the lung functions and histopathology

Initially it was felt that TPE was, by and large a benign, self-limiting condition. TPE does not kill the patient and hence may be classified as "benign". However, Udwadia and Joshi[36] showed that in TPE, the lung could be badly scarred and a fair degree of respiratory morbidity could occur. There is definite correlation between the histopathological features and the clinical and lung function abnormalities that the patient presents with[7,35,37-40].

(1) The earliest histopathological response is a histiocytic infiltrate in the lung parenchyma. The eosinophil is scarce and yet, intriguingly, the patient manifests with cough, breathlessness, wheezing, a few crepitations and an increased peripheral eosinophil count. The wheezing is chiefly due to bronchial spasm as there is no endobronchial obstruction. The crepitations are due to exudates in the alveoli and smaller bronchioles.

(2) Soon after the histiocytic response, there occurs an acute eosinophilic exudate within the lungs. The symptom complex is unchanged. The early features of acute breathlessness (sometimes but not always associated with wheezing) are really due to an alveolitis with involvement of the airways. It is due to hypersensitivity (type 1 immune response) reaction to the microfilariae trapped within the lungs. There is a marked increase in the IgE levels in the blood. Lung function shows a restrictive pattern in a number of patients together with superadded obstruction (in 30% of the cases). The wheezing observed is not only due to bronchial spasm but also due to mucosal oedema, mucosal thickening due to eosinophilic infiltration, and partial blockage of bronchioles produced by clumps of eosinophils and shedded mucosa. We now have the fully developed clinical syndrome which if untreated shows spontaneous remissions and relapses; the peripheral eosinophilia often increases.

(3) Later in the natural history, from six months to two years, patients come with breathlessness on exertion instead of the episodic dyspnoea so often seen in the first three months. The histopathology now shows a mixed cell reaction (histiocytes, epitheloid cells, lymphocytes and eosinophils). Lung function shows more "restriction" and less "obstruction". The disease is still recognized by the well-marked peripheral eosinophilia.

(4) Still later (at 2-5 years from onset), untreated patients show well-marked pulmonary fibrosis. Breathlessness on exertion is the dominant feature. There are more histiocytes and lymphocytes and scattered foci of eosinophils along with fibrous bands. In some of these patients, the eosinophilia progressively wanes and if the patient had not been observed in the early phase of the disease, it could be indistinguishable from other causes of lung fibrosis.

(5) It is possible that some patients in the tropics who were labelled as "bronchitis" or having a degree of "pulmonary fibrosis" may well be end stage of TPE. Lung functions now show a clear restrictive pattern. The degree of pulmonary disability is nowhere what we see in interstitial lung disease. This is because the fibrosis is patchy and not progressive. Generally, patients do not get cor-pulmonale unless they are fairly heavy smokers.

(6) An accurate assessment of the frequency of pulmonary disability in TPE would be difficult to ascertain; it would certainly be a small minority if one were to consider all patients of TPE. However, if one were to consider only patients of TPE with a history of 2-5 years duration who were untreated or had an incomplete response to DEC, the number left with considerable disability would be significant[7].

(7) Waning of peripheral eosinophilia on follow up: It has been observed that some patients with frequent relapses showed lesser and lesser degrees of increase in the absolute eosinophil count in the peripheral blood with each relapse; this was associated with an incomplete response in their respiratory symptoms and signs to DEC. Waning of the peripheral eosinophil count could present a problem in diagnosis for the end result in the natural history would then be characterized by respiratory disability with a peripheral eosinophil count which is far less than what is usually seen in tropical eosinophilia. The relation of such an end result

(when seen for the first time) to tropical eosinophilia may then be impossible to determine[7,36,37].

Pathogenesis and immunology

Mature gravid human filarial parasites, living in the lymphatics periodically release microfilariae which are trapped within the pulmonary microcirculation. As a result, microfilaraemia is rarely observed in TPE[7]. The degenerating microfilariae release their antigenic constituents which triggers an immune response[41]. The presence of cough, breathlessness, wheezing, peripheral eosinophilia and pulmonary infiltrates points to a hypersensitivity reaction. There is a severe eosinophilic inflammation involving the lower airways. The dual role of the eosinophil *i.e.* destruction of microfilariae, and lung damage by release of eosinophilic granule components gives it a central role in the pathogenesis of TPE. Activated eosinophils release eosinophil degranulation products, eosinophil derived neurotoxin (EDN), eosinophilic cationic protein (ECP) and major basic proteins (MBP)[42]. EDN has been found to be increased in bronchoalveolar lavage (BAL) of patients with TPE compared to controls[43]. Major basic protein-2 (MBP-2) has been postulated to be a useful biomarker for eosinophilic diseases such as TPE[44]. MBP has been reported to be associated with airway hyper-reactivity which is one of the presenting symptoms of TPE[45]. In a study by Pinkston *et al*[42], BAL from acute untreated TPE revealed a striking eosinophilic alveolitis. When individuals with acute TPE were treated with DEC, there was a marked decrease in lung eosinophils and improvement in lung functions. A study by Rom *et al*[46] also showed that there was a mild persistent inflammation despite a three week course of DEC leading to chronic dyspnoea due to restrictive lung disease. The BAL showed a persistent eosinophilic alveolitis and increased amounts of free radicals and oxidants.

It has been proposed that interleukin (IL)-4 induces while interferon (IFN)-gamma suppresses filarial-induced airway hyper-reactivity[47]. The immune response includes type 1, type III and type IV hypersensitivity reactions[7,39,40,48,49].

There is a profound antibody response in the lower airways in patients with TPE. Nutman *et al*[41] showed strikingly elevated total IgE in the lower respiratory tract epithelial lining fluid (ELF) along with high levels of filarial-specific IgG, IgM, and IgE. When these patients were re-evaluated after 6-14 days of therapy with DEC, there was marked reduction in ELF parasite-specific IgG and IgE, which corresponded to the clinical response. Immunoblot comparison of the antigen recognition patterns of ELF and serum antibodies demonstrated a general similarity in parasite antigens recognized.

The Bm23-25, an IgE inducing antigen of the infective L3 stage larvae of *B. malayi* has been detected in patients with TPE[50,51]. There is molecular mimicry between this antigen and the human gamma-glutaryl transpeptidase present on the surface of the pulmonary epithelium[52,53]. In BAL studies IgE against Bm23-25 has been detected[50]. This may hence play an important role in the pathogenesis of TPE.

Untreated or partially treated TPE may progress to interstitial lung disease (ILD)[7,17,39,40,54] with the role of mononuclear cells, macrophages, histiocytes, platelets and eosinophils in maintaining inflammation and inducing fibrosis under investigation. Recovery of lymphocytes and macrophages from BAL is more likely to correlate with impaired lung volumes[38]. The inflammatory response, although mostly confined to the lung may affect other organs such as liver, spleen, lymph nodes. If microfilariae succeed in running the gauntlet of the pulmonary circulation, they reach the systemic circulation and can set up an eosinophilic reaction chiefly in the reticuloendothelial system (liver, spleen, lymph nodes) and rarely in the muscle and the gastrointestinal tract[7,29,55,56].

Chest imaging findings

About 20 per cent of patients with TPE may have a normal chest radiograph[7]. The main radiological features include reticulo-nodular shadows more in the mid to lower zones and miliary mottling which make differentiation from miliary tuberculosis often difficult[7,57,58]. Computerized tomography (CT) scan often reveals bronchiectasis, air trapping, lymphadenopathy, cavitation, consolidation or pleural effusions in addition to the miliary mottling and interstitial shadows[59]. Radiologic findings very often regress on treatment with DEC but many patients may show residual changes[60].

Lung function changes

Spirometry is usually mixed restrictive and obstruction which may be mild to moderate in degree[7,37,61-65]. In a study by Kuppurao *et al*[66] the mean values of expiratory flow rates were significantly decreased in untreated TPE and while there was improvement with treatment, it was still below normal

at one month. Udwadia[7] had reported a pure restrictive pattern on spirometry in 70 per cent patients and mixed disorder in 30 per cent. Vijayan *et al*[67] also reported a low transfer factor for carbon monoxide (TLCO) as measured by the single breath method. This reduction in TLCO is due to deceased area for diffusion although pulmonary capillary blood volume is normal. Most lung functions including TLCO improve on treatment with DEC but may not return to normal. The patients who had frequent relapses or responded poorly to DEC were more likely to have impaired lung functions with progress to interstitial fibrosis.

A study by Vijayan *et al*[38] showed a negative correlation between BAL eosinophil count and TLCO and transfer coefficient (KCO) in patients with TPE but not forced vital capacity (FVC). The alveolar macrophage count had a negative correlation with FVC but not TLCO, while the BAL lymphocyte count had a negative correlation with total lung capacity (TLC) leading them to conclude that lymphocytes and macrophages were more damaging to the lung. Blood gas analysis has shown mild arterial hypoxaemia in about 41 per cent of patients with untreated TPE[68]. This may be due to a ventilation-perfusion mismatch as observed on V/Q scanning[69].

Differential diagnosis

Eosinophilia in tropical countries is mostly caused by a hypersensitivity reaction to helminthes[70-73]. While TPE due to hypersensitivity to filarial antigen is commonest, eosinophilia may also be due to roundworm[74], *Toxocara*[75], strongyloides[76] and hookworm[77]. Non-infectious causes mainly include bronchial asthma, allergic bronchopulmonary aspergillosis, acute and chronic eosinophilic pneumonia, Churg-Strauss syndrome, idiopathic hypereosinophilic syndrome, and drug reactions[78,79].

Patients with a TPE like syndrome due to other helminthes may have serological tests which cross-react with filarial antigens[80]. Hence, there is a need for more specific tests which can differentiate filarial TPE from other causes of TPE like syndrome. An ELISA test detecting the Og4C3 antigen is sensitive and specific for *W. bancrofti* infections[81-83] but fails to detect *B. malayi* infection. A sandwich ELISA detecting antibodies to recombinant antigen Bm-SXP-1 has been found useful to detect *B. malayi* infection[84].

Until a more specific and sensitive test is commercially available, the following criteria may be useful in distinguishing filarial TPE from non-filarial TPE like syndromes – *(i)* history suggestive of nocturnal symptoms mainly cough and dyspnoea, *(ii)* pulmonary infiltrates on chest radiograph, *(iii)* leukocytosis with peripheral eosinophilia > 3000/µm, *(iv)* elevated serum IgE and filarial specific IgG and IgE, and *(v)* clinical improvement with DEC[16,17,23].

It is important to rule out other causes of TPE-like syndromes such as strongyloidosis as use of steroids in these cases may cause disseminated infection[85].

Management

Weingarten, in 1943[2], had described the successful treatment of TPE with neoarsphenamine. However, by the late 1950s and early 1960s, DEC had completely replaced arsenic compounds in the treatment of TPE[86,87]. Initially Baker *et al*[86] had recommended a 7-10 day course of DEC at a dose of 5 mg/kg/day. However, Udwadia[7] found that the response to treatment was better when the drug was used for four weeks. About 4-5 per cent of the patients may not respond to DEC. In chronic patients with a long duration of symptoms, the drug may be ineffective even in up to 20-40 per cent cases, probably due to already established fibrosis[7]. Many studies[46,60,88] have demonstrated incomplete response to treatment with a standard three week course of DEC with a persistent lower respiratory inflammation and oxidative stress. Steroids have been shown to have a beneficial effect[17] but the exact dose and duration in combination with DEC is yet to be determined by randomized controlled trials.

Relapse

In the only follow up study of patients for five years, the relapse rate was found to be almost 20 per cent after DEC therapy[7]. As a result, monthly courses at 2-3 month intervals for 1-2 years have been suggested. In a few patients, DEC was not found to be as effective in successive relapses as it was in the original episode leading to chronic respiratory impairment and also the degree of peripheral eosinophilia decreased with successive relapses[7].

Prevention

The World Health Assembly aims to eliminate lymphatic filariasis as a public health problem by 2020[89]. The WHO strategy aims at preventing transmission of microfilaria through mosquito bites. The goal is to treat the population at risk for lymphatic filariasis through a once yearly combination of DEC (6 mg/kg) and albendazole (400 mg) for 4-6 years (*i.e.* the reproductive life span of the filarial parasite)[90,91]. A

study from Egypt has reported encouraging results for this strategy[92].

Conclusion

TPE is caused by a type 1 hypersensitivity reaction to filarial antigens (*W. bancrofti* or *B. malayi*). It presents as an eosinophilic alveolitis with an airway component. With the passage of time, the presenting symptom is breathlessness on exertion and the lung shows a mixed cell reaction. Later on in untreated patients well-marked fibrosis occurs. Lung function shows increasing restriction. The peripheral eosinophilia may wane so that the end result may not be recognized as TPE unless the patient was observed in the early part of the natural history. DEC produces remission but a mild inflammatory state persists and almost 20 per cent patients may relapse in five years. The role of steroids in the treatment of TPE needs to be studied through randomized controlled trials. Strategies to minimize transmission as well ensure effective treatment and reduce relapses need to be tested and put in place. We need an easily available and specific marker for filarial TPE in order to distinguish the pulmonary eosinophilic manifestations of filarial infection from those due to other parasitic infections (ascariasis, ankylostomiasis and strongyloidosis), as also from non-parasitic causes of pulmonary eosinophilia. Once such a diagnostic modality is available, the term tropical pulmonary eosinophilia may turn out to be obsolete and replaced by specific aetiology-induced eosinophilia.

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