Re-examination of the diagnostic criteria of tropical pulmonary eosinophilia

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There is no agreement on the minimum absolute eosinophil count essential for the diagnosis of tropical pulmonary eosinophilia (TPE) at present. The aim of this study was to determine this figure as well as to evaluate the other diagnostic criteria of TPE.

The response to diethylcarbamazine (DEC) was tested in 98 patients [of whom 79 (80.6%) completed the study] by means of clinical scores, lung function tests and the absolute eosinophil counts.

The minimum absolute eosinophil count necessary for the diagnosis of TPE was found to be 3300 for two reasons. Firstly there was a marked fluctuation in the mean percentage change of the absolute eosinophil count after treatment with DEC, when it was below 3225 cells mm⁻³, while the mean percentage reduction showed a remarkable stability when the eosinophil count exceeded 3600. Secondly there was a marked difference in the response to DEC in patients whose eosinophil counts were above and below these values.

All patients who had eosinophil counts greater than 3600 responded to DEC and were diagnosed as cases of TPE. All of them were from filarial endemic areas. The total eosinophil count decreased by a mean of 92.5%, 3 months after administration of DEC.

The sensitivities of the following tests in TPE were as follows: filarial antibody test (FAT) 30%, radiological changes 45.5%, erythrocyte sedimentation rate (ESR) 80%. The radiological changes and the ESR, but not the FAT, were helpful in differentiating TPE from those patients with TPE-like symptoms but with lower eosinophil counts, e.g. those with asthma.

Patients with cough who had eosinophil counts of between 53 and 2000 cells mm⁻³, showed elevated filarial antibody levels in a significant number of cases when compared to asymptomatic subjects. (P < 0.001). Five of them responded to DEC. Three of these had filarial antibody in their serum and one had bilateral mottling on chest X-ray. These results suggest that atypical cases of TPE may exist.

Our study has shown that the diagnosis of TPE rests on the following criteria: cough worse at night; residence in a filarial endemic area; the eosinophil count greater than 3300 cells mm⁻³, clinical and haematological response to DEC. The diagnosis is supported by radiological changes and elevated ESR. The FAT is of little value.

The clinical benefit and the improvement in lung function which follows the administration of DEC was sustained up to a minimum period of 15 months.

Introduction

Tropical pulmonary eosinophilia is one of the many syndromes with pulmonary infiltrates and peripheral blood eosinophilia (PIE). It is an interstitial lung disease thought to result from immunological hyperresponsiveness to the human lymphatic dwelling filarial parasites Wuchereria bancrofti and Brugia malayi (1) although other non-filarial helminth-induced PIES resembling tropical pulmonary eosinophilia have been described recently (2). Beaver proposed the following criteria for the diagnosis of tropical pulmonary eosinophilia (TPE); eosinophilia over 2000 mm⁻³, cough/breathlessness at night, radiological evidence of lung striations/mottling at bases, elevated erythrocyte sedimentation rate, a high titre of complement fixation and a cure with arsenic or diethylcarbamazine (DEC) (3).

Donohugh suggested four major criteria, or three major and three minor criteria, for the diagnosis of this condition (4). The major criteria are cough and dyspnoea which are worse at night, an eosinophil count of over 2000 cells mm⁻³, a positive filarial complement fixation test and a clinical and haematological response to DEC. The minor criteria are residence in an endemic filarial area for several months, presence of the illness in a young adult male, expiratory rhonchi with inspiratory crepitations, chest film showing diffuse mottling along with increased hilar and basal markings, elevated erythrocyte sedimentation rate
and accompanying non-specific symptoms such as malaise, fatigue, anorexia and weight loss.

The detection of filarial antibodies by the complement fixation test, which is obsolete, has been replaced by the indirect immunofluorescent test (FAT) (5), while many minor criteria are non-specific.

There is no agreement on the minimum absolute eosinophil count necessary for diagnosis of TPE. Some authors specify a count of 2000 eosinophils mm$^{-3}$ (3,4,6) while others refer to a count of 3000 eosinophils mm$^{-3}$ (7,8,9). We have observed patients who have symptoms consistent with TPE and show circulating filarial antibodies but with normal or slightly raised eosinophil counts, who respond to DEC. Thus atypical cases of TPE probably exist. It is therefore necessary to determine the therapeutic response of DEC in relation to the degree of eosinophilia and to re-examine the diagnostic criteria of TPE.

**Patients and Methods**

The study population consisted of 98 patients of both sexes between the ages of 12 and 74 years (mean 31 years). All of them had cough and an eosinophil count ranging from 53 to 49 840 cells per mm$^3$. They were referred to one of the authors (J.H.L.C.) from the outpatients department, Chest Hospital, Welisara, Sri Lanka. All except three were from filarial endemic areas. All patients were given DEC 150 mg three times a day for 10 days.

The following patients were excluded from the study: children under 12 years of age; patients with cough or dyspnoea of less than 2 weeks duration; those who had taken DEC during the previous year or were on steroid therapy; patients with past or present pulmonary tuberculosis or with chronic lung disease; chronic alcoholics; patients with chronic renal disease; or those with abnormalities of the central nervous system.

A detailed history was obtained from each patient and a clinical examination was carried out at the onset as well as on each follow-up visit. Clinical symptoms were graded and given the following scores: 1. absence of symptoms; 2. able to carry out normal work or having undisturbed sleep in spite of symptoms; 3. symptoms interfering with normal work or sleep; 4. complete incapacitation (unable to get out of bed). The mean of all post-treatment clinical scores, forced vital capacity (FVC) and absolute eosinophil counts observed during follow-up were recorded as the mean post-treatment clinical score, mean FVC and mean eosinophil count, respectively, in each patient. The deviation from the pre-treatment values was calculated for these three parameters.

The following lung function tests were carried out at the time of each clinical examination: peak expiratory flow rate (PEFR); forced expiratory volume in 1s (FEV$_1$); and forced vital capacity (FVC). The FEV$_1$/FVC ratio was calculated in each case. Other investigations carried out were chest X-ray; white blood cell and differential count; erythrocyte sedimentation rate (ESR); indirect immunofluorescent assay for filarial antibodies (FAT) (using *Wuchereria bancrofti* antigen) (5); direct smear and culture for fungi in sputum; and detection of antibodies against *Aspergillus fumigatus*, *Histoplasma capsulatum*, *Rhodotorula dermatitidis*, *Coccidiodes immitis* and *Candida albicans* in serum.

All patients were followed up at the end of 1,3,6,9,12 and 15 months and investigations were carried out according to the schedule outlined in Table 1.

The ESR was considered raised if it was over 14 mm in the first hour in men and over 20 mm in women (10). To assess the presence of filarial antibodies in asymptomatic individuals living in the same localities, tests were carried out on serum samples of 51 such individuals.

The response to DEC was considered satisfactory if two or more of the following parameters were fulfilled: mean percentage reduction in the absolute eosinophil count of more than 70% (Fig. 1) increase in FVC of more than 10%, reduction in the mean clinical score of more than 40%.

**STATISTICAL ANALYSIS**

The SND test (Z-test) was used to compare the sensitivity of the FAT, radiological changes and elevated ESR between patients with TPE and other groups as well as to examine the relationship between a raised ESR and radiological abnormalities in TPE. The Student’s $t$-test was used to assess the response of patients to DEC, (reduction in clinical score, increase in FVC, reduction in eosinophil count in relation to the pre-treatment eosinophil count) as well as to assess the mean clinical scores and FVC of the patients with TPE at different periods following treatment with DEC.

<table>
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<tr>
<td><strong>Pre-treatment</strong></td>
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<td>White blood cell count</td>
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<tr>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>Lung function tests</td>
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**Results**

All 98 patients had cough, which was nocturnal in 90 (91.8%), while 78 (81.1%) had wheezing and 84 (85.7%) had shortness of breath. The absolute eosinophil counts of the 79 (80.6%) who completed the study ranged from 53 to 49,460 cells mm$^{-3}$ (mean 10,635.6). Of these 79 patients, 21 had an eosinophil count of less than 2000. Five of the 21 responded to DEC, three of them showed filarial antibodies and one had radiological evidence of mottling.

The laboratory findings in patients were classified according to their eosinophil counts: less than 2000 (group A); 2001-3500 (group B); > 3500 (group C); and asymptomatic subjects (group D), as indicated in Table 2. The positivity of the FAT in patients with TPE (group C) as well as in patients in group A was significantly greater when compared to asymptomatic subjects. (group D) ($P<0.01$ and 0.001, respectively) but did not show a significant difference between groups A and C. On the other hand, the ESR was significantly greater in patients in group C when compared to patients in groups A ($P<0.001$) and B ($P<0.05$). Radiological abnormalities were significantly greater in patients in group C compared to group A ($P<0.05$) but not group B ($P=0.43$). Of the patients with TPE who showed radiological abnormalities, 94.4% had a raised ESR, which was a significant correlation ($P<0.05$). Forty-five of the 51 cases of TPE were examined for evidence of fungal infection. On direct smear, *Candida albicans* was detected in the sputum in five cases and on culture in three cases. However, the serological tests for fungal antibodies were negative in all cases.

Patients in groups A and B showed statistically equivalent responses to DEC with regard to the three parameters used to assess the response to DEC, namely a mean percentage

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**Table 2. Laboratory findings in different groups of patients and asymptomatic subjects**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient category</th>
<th>FAT positive $n/total$ (%)</th>
<th>Chest X-ray changes$^1$ $n/total$ (%)</th>
<th>Elevated ESR $n/total$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Patients with absolute eosinophil counts between 0 and 2000 cells mm$^{-3}$ (probable asthmatics/atypical cases of TPE)</td>
<td>8/21*** (38.1%)</td>
<td>1/11 (9.1%)</td>
<td>6/16(37.5%)</td>
</tr>
<tr>
<td>B</td>
<td>Patients with absolute eosinophil counts between 2001 and 3500 cells mm$^{-3}$</td>
<td>1/6(16.6%)</td>
<td>1/4 (25%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>C</td>
<td>Patients with eosinophil counts of over 3500 cells mm$^{-3}$ (TPE)</td>
<td>15/50*** (30%)</td>
<td>20/44* (45.5%)</td>
<td>40/50* ** (80%)</td>
</tr>
<tr>
<td>D</td>
<td>Asymptomatic subjects</td>
<td>4/51 (7.8%)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

$^1$Increased vascular markings, multiple nodules/mottling.
ND, Not done.

Significance ($P<0.05$):* group C vs. group A; ** group C vs. group B; *** groups C/A vs. group D.
reduction in the eosinophil count, reduction in the mean clinical score and increase in FVC respectively. On the other hand, the response to DEC of patients in groups A and B was significantly different to that of group C with regard to the mean percentage reduction in eosinophil count, and the reduction in the mean clinical score. Although there was an increase in FVC, this did not appear to be significant (Table 3).

All 51 patients who had eosinophil counts over 3500 responded to DEC. They all showed a mean percentage reduction of the eosinophil count of over 70%; 48 (94-1%) showed a reduction of the mean clinical score of over 40% and 39 (76-5%) had an increase in FVC of over 10%. Therefore, these 51 cases were diagnosed as cases of TPE. All of them were from the filarial endemic areas of Sri Lanka. They included 42 men (82.4%) and nine women (17.6%). Their ages varied from 12 to 74 years, with a mean of 33.4 years. In this group of patients, 50 (98%) had nocturnal cough and 11 (21%) gave a history of fever, while a family history of asthma was present in 41.2% of cases. The lungs signs included rhonchi in 70% and rhonchi and crepitations in 22%, while the lungs were clear in 8%. The absolute eosinophil counts ranged from 3600 to 49 840 mm$^3$ (mean, 15 582.2; SD, 11 258.4). Lung function tests in patients with TPE showed a restrictive defect in 76% and an obstructive pattern in 24%. There was a relatively uniform reduction in the absolute eosinophil count, after administration of DEC, when the eosinophil count exceeded 3600 mm$^3$. When the eosinophil count was less than 3225 cells mm$^{-3}$, there was a marked fluctuation of the mean percentage change in the count (Fig. 1). The total eosinophil count decreased by 92.5%, 3 months after administration of DEC.

The mean of the clinical scores of all the patients with TPE was significantly reduced ($P<0.001$), while the mean of the FVC values was significantly increased ($P<0.001$) after treatment with DEC throughout the entire follow-up period of 15 months.

### Table 3. Response to DEC

<table>
<thead>
<tr>
<th>Group</th>
<th>Absolute eosinophil count</th>
<th>E (%)</th>
<th>C (%)</th>
<th>F (%)</th>
<th>FAT positive n/total (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt;2,000</td>
<td>-75-31</td>
<td>-36-37</td>
<td>20-43</td>
<td>8/21 (38-1%)</td>
<td>5/21 11/21 3/21 2/21</td>
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<tr>
<td>(n = 21)</td>
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<tr>
<td>B</td>
<td>2,001-3,500</td>
<td>-48-15</td>
<td>-40-83</td>
<td>8-35</td>
<td>1/6 (16-6%)</td>
<td>2/7 3/7 2/7 0/7</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>&gt;3,500</td>
<td>-91-19***</td>
<td>-59-53***</td>
<td>36-37</td>
<td>15/50 (30%)</td>
<td>0/51 0/51 16/51 35/51***</td>
</tr>
<tr>
<td>(n = 51)</td>
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</table>

E, Mean percentage reduction of the absolute eosinophil count after DEC
C, Mean percentage reduction of the clinical score after DEC
F, Mean percentage increase in the FVC after DEC
N, Number of parameters that have responded to DEC.
Significance ($P<0.05$): * group C vs. group A; ** group C vs. group B.

Discussion

Some of the features recorded in our study confirmed observations made by previous investigators. Of the cases of TPE, 82.4% were men (7,9). Lung function tests showed an obstructive pattern in 24% of cases, as has been shown previously (12). A positive filarial antibody test was observed in 30% of our patients, which is similar to the rate of 33-3% shown by De Sylva et al. (13). Increased vascular markings and/or multiple nodules or mottling in chest X-rays were seen in 45-5% of patients with TPE. These changes were observed by Jayewardene et al. (14) in 64% of their patients. Our results have shown that the radiological changes and the ESR, but not the FAT, are helpful in differentiating TPE patients from those with TPE-like symptoms but with lower eosinophil counts, such as in asthma. An elevated ESR and changes in the chest X-ray were shown to be correlated, therefore including them as two different criteria may lead to over-diagnosis.

The mean clinical scores and lung function (FVC) were maintained up to the end of the study (15 months after administration of DEC), suggesting that the drug is effective for this period.

Patients in group A showed elevated filarial antibodies in a significant number of cases when compared to asymptomatic subjects ($P<0.001$). Five of them responded to DEC. These included three who had filarial antibodies in their serum and one who had radiological evidence of mottling in both lung fields. These could be either atypical cases of TPE or asthma precipitated by filariasis (13). The fact that 21 out of 51 (41.2%) of our patients with TPE had a family history of asthma suggests that those who have a predisposition to be asthmatic and probably have airway hyperresponsiveness are more likely to develop TPE. Thus, there appears to be a close link between these two diseases.

None of the patients in our group had evidence of cryptogenic pulmonary eosinophilia (15). *Candida albicans* was isolated on direct smear or culture in seven patients with TPE, but a fungal aetiology was excluded by the fact...
that serum samples of these patients did not show antibodies to *Candida albicans*, suggesting that when this organism was present in the sputum, it was probably a contaminant.

Our study unfortunately did not include any patients with eosinophil counts between 3225 and 3660 cells mm\(^{-3}\), thus the cut-off point probably lies between these two values. There is clear evidence that the minimal eosinophil count for the diagnosis of TPE should be 3300 cells mm\(^{-3}\). This is based on two criteria. Firstly, patients who had eosinophil counts between 2000 and 3225 cells mm\(^{-3}\) showed a response to DEC which was similar to those with eosinophil counts below 2000 cells mm\(^{-3}\), while a different response was elicited in patients whose eosinophil counts exceeded 3500 cells mm\(^{-3}\). Secondly, the mean percentage reduction of the absolute eosinophil count showed a remarkable stability when the eosinophil count exceeded 3600 cells mm\(^{-3}\).

The cut-off point in the eosinophil count to distinguish between asthma and TPE is particularly important as studies have shown that there is a significant correlation between the peripheral blood eosinophil count and clinical severity as well as with the risk of mortality in asthma (16,17). Misdiagnosis of an asthmatic with a high peripheral eosinophil count as a case of TPE could therefore have serious consequences.

Our study has shown that the diagnosis of TPE rests on the following criteria: cough worse at night; residence in a filarial endemic area; eosinophil count greater than 3300 cells mm\(^{-3}\); and clinical and haematological response to DEC. The diagnosis is supported by radiological changes and elevated ESR. The FAT is of little value.

References