Pulmonary eosinophilia with and without allergic bronchopulmonary aspergillosis

B J CHAPMAN, S CAPEWELL, R GIBSON, A P GREENING, G K CROMPTON

From the Respiratory Unit, Northern General Hospital, Edinburgh

ABSTRACT Sixty five patients with pulmonary eosinophilia attending one respiratory unit were reviewed. All had fleeting radiographic abnormalities and peripheral blood eosinophil counts greater than 500 x 10^6/l. Eighteen had a single episode and 47 recurrent episodes during a median follow up period of 14 years. Thirty three patients had allergic bronchopulmonary aspergillosis on the basis of a positive skin test response to Aspergillus fumigatus, serum precipitins, or culture of A fumigatus from sputum, or a combination of these. All but seven patients had asthma, six of the seven being in the group who did not have allergic bronchopulmonary aspergillosis. The patients with allergic bronchopulmonary aspergillosis were more often male and had a greater incidence of asthma and an earlier age of onset of asthma than those without aspergillosis. The patients with aspergillosis had lower mean blood eosinophil counts and more episodes of pulmonary eosinophilia and more commonly had radiographic shadowing that suggested fibrosis or bronchiectasis (20 v 7). Pulmonary eosinophilia associated with allergic bronchopulmonary aspergillosis appears to be a distinct clinical syndrome resulting in greater permanent radiographic abnormality despite lower peripheral blood eosinophil counts.

Introduction

The term pulmonary eosinophilia describes a group of disorders in which transient radiographic lung shadows are associated with a raised blood eosinophil count.1 Allergic bronchopulmonary aspergillosis is the most common cause of pulmonary eosinophilia in Britain.2 3 Pulmonary eosinophilia has also been described in association with other fungi,4 an increasing number of drugs,5 the systemic vasculitides,6 7 and the hypereosinophilic syndrome.8 9 Most cases of tropical pulmonary eosinophilia are allergic reactions to filarial infections,10 whereas various helminths have been implicated in more temperate latitudes.11 About 20% of cases of pulmonary eosinophilia in Britain are unexplained and labelled cryptogenic.12 13 Recommended classifications have their limitations, whether based on clinical features,14 aetiology,11 15 16 or anatomical and pathological features.17

There are many published studies on allergic bronchopulmonary aspergillosis, but fewer on pulmonary eosinophilia.12 13 Most studies have originated from secondary and tertiary referral centres, which makes it difficult to estimate the relative frequency of the various underlying conditions. The differences between patients with and without allergic bronchopulmonary aspergillosis are not clear. We therefore reviewed an unselected series of patients with pulmonary eosinophilia attending a primary referral unit during a 20 year period.

Methods

Sixty five patients with pulmonary eosinophilia attending the Northern General Hospital, Edinburgh, during 1966–86 were identified. All had evidence of transient pulmonary shadowing associated with a peripheral blood eosinophil count exceeding 500 x 10^6/l. The patients’ medical records were reviewed for evidence of asthma, atopy, hypersensitivity to Aspergillus fumigatus, clinical features associated with episodes of pulmonary eosinophilia, pulmonary function tests, corticosteroid treatment, radiographic features, and possible aetiological factors other than A fumigatus. Patients with aspergillosma were excluded.

Patients were considered to be asthmatic if there was evidence of airflow obstruction (FEV1 < 70% predicted) and more than 15% variation in FEV1 over
a short period either spontaneously or in response to bronchodilator treatment. Atopy was defined by two or more positive skin prick test responses to common allergens (grass pollens, shrubs, tree mix, house dust, house dust mites, feathers, dog hair, and cat fur), excluding *Aspergillus* species (Bencard). *A. fumigatus* precipitins were identified by an Agar-gel double diffusion technique using *A. fumigatus* antigens I and 11 (Bencard). A diagnosis of allergic bronchopulmonary aspergillosis was made if an immediate skin prick test response to *A. fumigatus* was positive, and if serum precipitins to *A. fumigatus* were present or *A. fumigatus* was cultured from sputum. Bronchiectasis was identified by bronchography (nine patients) or by radiographic shadowing that suggested fibrosis or bronchiectasis with (five) or without (13) a history of chronic cough and sputum.

The results were analysed by the χ² test with Yates’s correction and Wilcoxon’s rank sum test for unpaired data.18

**Results**

Sixty five patients (27 male, 38 female) were identified. There were 247 recorded episodes of pulmonary eosinophilia, 18 patients having single and 47 patients recurrent episodes. The median age at the time of the first episode was 39 (range 12–78) years and the median follow up period 14 (range 1–31) years.

Thirty three patients met the criteria for allergic bronchopulmonary aspergillosis (table 1). The remaining 32 were labelled “non-allergic bronchopulmonary aspergillosis.” Eight of the 32 had an isolated positive skin test response to *A. fumigatus* (table 2). There was no evidence of drug induced pulmonary eosinophilia in any subject. Faecal specimens in 10 patients were negative for cysts, ova, and parasites. One of the 32 non-aspergillosis patients had the Churg-Strauss syndrome and one a hypereosinophilia like syndrome. Two patients had rheumatoid arthritis and two purinoous anaemia and one had sarcoidosis.

Fifty eight patients were asthmatic and seven non-asthmatic. The asthmatic patients had been followed up for longer than the non-asthmatic patients (median 14.5 v 2 years; p < 0.05). Six of the seven non-asthmatic patients did not have aspergillosis; in five of the seven patients episodes of aspergillosis were associated with systemic features (see below). In six patients pulmonary eosinophilia preceded the onset of asthma (interval 1–11, median 9 years).

Patients with allergic bronchopulmonary aspergillosis were more frequently asthmatic, atopic, and male than those without aspergillosis and had lower blood eosinophil counts during episodes of pulmonary eosinophilia (table 3). The onset of asthma occurred at an earlier age in the group with aspergillosis (median 7.5 v 30.5 years; p < 0.01) but age at the first documented episode of pulmonary eosinophilia was similar for the two groups (fig 1). The interval between onset of asthma and onset of pulmonary eosinophila was therefore greater in the patients with allergic bronchopulmonary aspergillosis (median 19 v 11 years; p < 0.05). Patients with aspergillosis also had more episodes of pulmonary eosinophilia (median 5 v 2; p < 0.01: fig 2) and a longer duration of follow up.

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**Table 1** Number of positive results of *Aspergillus fumigatus* tests in the groups with and without allergic bronchopulmonary aspergillosis (ABPA)

<table>
<thead>
<tr>
<th></th>
<th>ABPA (n = 33)</th>
<th>Non-ABPA (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate skin test</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>Serum precipitins</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>24</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 2** Significance of a positive skin test response to *Aspergillus fumigatus* in patients with pulmonary eosinophilia: comparison of clinical and investigative features with allergic bronchopulmonary aspergillosis (ABPA) and "definite" non-ABPA patients (see text)

<table>
<thead>
<tr>
<th></th>
<th>ABPA (n = 33)</th>
<th>Non-ABPA (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspergillus fumigatus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin test positive</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Serum precipitins positive</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Sputum culture positive</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Asthmatic</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Median (range) age of onset of asthma (y)</td>
<td>7.5 (1–61)</td>
<td>29 (2–49)</td>
</tr>
<tr>
<td>Median (range) age of onset of pulmonary eosinophilia (y)</td>
<td>38 (14–78)</td>
<td>41 (22–65)</td>
</tr>
<tr>
<td>Maximum blood eosinophil count during episodes × 10⁹/l (group mean (SD))</td>
<td>2290 (3584)</td>
<td>4774 (3681)</td>
</tr>
<tr>
<td>Number with systemic features during episodes</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Fibrosis or bronchiectasis</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Median (range) duration of follow up (y)</td>
<td>17.9 (1–31.5)</td>
<td>7 (1–18)</td>
</tr>
</tbody>
</table>

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18 Chapman, Capewell, Gibson, Greening, Crompton.
Pulmonary eosinophilia with and without allergic bronchopulmonary aspergillosis

Table 3  Clinical and investigative features of patients with pulmonary eosinophilia with and without allergic bronchopulmonary aspergillosis (ABPA)

<table>
<thead>
<tr>
<th></th>
<th>ABPA (n = 33)</th>
<th>Non-ABPA (n = 32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female</td>
<td>19 : 14</td>
<td>8 : 24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atopic</td>
<td>28</td>
<td>17</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Asthmatic</td>
<td>32</td>
<td>26</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Median (range) age of onset of asthma (y)</td>
<td>7.5 (1–61)</td>
<td>30.5 (2–69)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median (range) age of onset of pulmonary eosinophilia (y)</td>
<td>38 (14–78)</td>
<td>40 (13–67)</td>
<td>NS</td>
</tr>
<tr>
<td>Number developing pulmonary eosinophilia before asthma</td>
<td>2</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum blood eosinophil count during episodes × 10^6/l</td>
<td>2290 (3584)</td>
<td>3526 (3045)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean blood eosinophil count during episodes × 10^6/l (group mean (SD))</td>
<td>1406 (1287)</td>
<td>2858 (2919)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number with systemic features during episodes</td>
<td>4</td>
<td>12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Median (range) duration of follow up (y)</td>
<td>17.9 (1–31.5)</td>
<td>10.1 (1–29)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

There was no seasonal variation in episodes of pulmonary eosinophilia in either group (fig 3). Radiological features consistent with bronchiectasis or fibrosis or both occurred more often in patients with allergic bronchopulmonary aspergillosis than in those without (p < 0.005) (table 4).

The most common systemic features associated with episodes of pulmonary eosinophilia were night sweats, malaise, fever, rashes, and anaemia; they occurred more frequently in the group without allergic bronchopulmonary aspergillosis (44% v 9%; p < 0.005).

Discussion

Pulmonary eosinophilia was associated with allergic bronchopulmonary aspergillosis in 33 of the 65
patients in this unselected series. Eighty per cent of cases of pulmonary eosinophilia were associated with allergic bronchopulmonary aspergillosis in the series of McCarthy and Pepsy and 74% of 62 asthmatic patients in the study of Scadding. Middleton et al also studied 65 asthmatic patients with pulmonary eosinophilia, of whom 54 were fully investigated for allergic bronchopulmonary aspergillosis and 59% were considered to have the disease. The differences between these figures probably reflects referral to secondary or tertiary referral centres, though a changing pattern of pulmonary eosinophilia during the last 15–20 years cannot be excluded. The increased use of oral and perhaps inhaled corticosteroid drugs during this period may have had an effect.

The diagnostic criteria used to define allergic bronchopulmonary aspergillosis remain controversial. In Britain the three essential criteria have generally been asthma, pulmonary eosinophilia, and a positive immediate skin prick test response to an extract of *A fumigatus*. In the United States, however, serum precipitating antibodies to aspergillus antigens, a raised serum total IgE concentration, and when possible the appearance of proximal bronchiectasis on a bronchogram would also be required. In this study we chose to modify the UK criteria by insisting on the additional presence of either serum precipitating antibodies to *A fumigatus* or *A fumigatus* in the sputum as a positive skin prick test response alone may simply be a manifestation of atopy. Thirty three of the 65 patients fulfilled our criteria, and 41 met the UK criteria. The clinical and haematological features of the eight patients with pulmonary eosinophilia with a positive skin test response alone resembled the patients who did not have aspergillosis more closely than those with aspergillosis. In seven patients the positive skin test response may have been due to atopy. We suggest that the established UK criteria for the diagnosis of allergic bronchopulmonary aspergillosis are inadequate, and should be modified to include the presence of serum aspergillus precipitins.

Asthma appears not to be an essential feature for the diagnosis of allergic bronchopulmonary aspergillosis.

### Table 4 Radiographic signs suggesting fibrosis and bronchiectasis in patients with pulmonary eosinophilia with and without allergic bronchopulmonary aspergillosis (ABPA)

<table>
<thead>
<tr>
<th></th>
<th>ABPA (n = 33)</th>
<th>Non-ABPA (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchogram proved</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Clinical features</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Chest radiographs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>of bronchiectasis</td>
<td>20</td>
<td>7*</td>
</tr>
</tbody>
</table>

*p < 0.005.
Pulmonary eosinophilia with and without allergic bronchopulmonary aspergillosis

Glancy. One of the patients with aspergillosis in the present study did not have asthma, confirming other reports. Glancy et al reported that three of their 11 non-asthmatic patients subsequently developed asthma two, four, and 10 years after the onset of pulmonary eosinophilia. In our series six patients developed asthma up to 11 years after the first recorded episode of pulmonary eosinophilia.

Most of our patients with allergic bronchopulmonary aspergillosis were male, of predominance to pulmonary eosinophilia. Evidence was noted whether pulmonary eosinophilia occurred in patients with allergic broncho-pulmonary aspergillosis. Clinical immunology: (1) Clinical features. Clin Allergy 1971;1:261–86.


Syndromes whose underlying pathogeneses remain unclear.

References


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