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A Young Male with Asthma and Eosinophilia

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Case history

A 22-year-old male with a 7-year long history of bronchial asthma, presented with worsening of asthma and fever of 20-days duration. The patient was well controlled on budesonide metered dose inhalations (400 µg/day) and rarely ever required to take salbutamol inhalations. For the past 20 days, the patient was experiencing increasing breathlessness requiring multiple, frequent dosing of salbutamol inhalations with little relief. He also complained of fever which was high grade, continuous, associated with cough and production of mucoid expectoration for the past 20 days. There was no orthopnoea, haemoptysis, joint pains, rash, no history of ingestion of any drug, nor any urinary or bowel complaints. There was a strong history of atopy in the patient's mother – she suffered from allergic rhinitis. Examination revealed a conscious, febrile male with pulse 98/minute and regular, BP 130/80 mmHg, and temperature 38.6°C. Respiratory examination revealed tachypnoea- (RR-28/minute) and bilateral widespread wheezes. There were no crackles or any other added sounds. The cardiovascular, abdomen, and neurological examination were unremarkable. Investigations revealed- Hemoglobin- 12.4 g/dl, total leukocyte count – 12,800/cu mm, differential count – P70, L20, E10, absolute eosinophil count –3,800/cu mm. Stool examination did not reveal any parasite (ova or cysts). The rest of the biochemical parameters including the liver and kidney function tests were normal. The chest X-ray revealed pulmonary infiltrates in the right mid- and lower zones – Figure 1.

The laboratory investigations of the patient are summarised in Table II. The CECT of the chest revealed bronchial thickening, mucous plugging, and central bronchiectasis – Figure 2.

Table I : Pulmonary infiltrates with eosinophilia.

Known aetiology :

- Allergic broncho pulmonary aspergillosis
- Parasitic infestations
- Drug reactions

Unknown aetiology :

- Loeffler's syndrome
- Acute eosinophilic pneumonias
- Chronic eosinophilic pneumonias
- Allergic granulomatosis of Churg- Strauss
- Hypereosinophilic syndrome

Question 1. What are the diagnostic possibilities that you will consider in this patient?

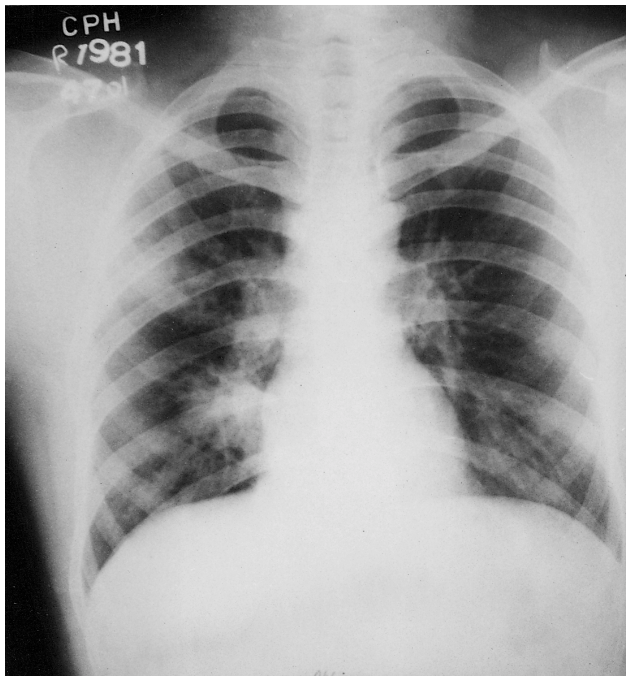

Fig. 1. *Chest X-ray revealing infiltrates in the right mid and lower lung fields.*

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Question 2. **What further investigations will you do to confirm your diagnosis?**

Question 3. **What is your final diagnosis?**

Answer 1.

The presence of eosinophilia and pulmonary infiltrates occurs in a group of disorders called eosinophilic pneumonias or pulmonary infiltrates with eosinophilia (PIE). It includes a group of disorders – some of known, and some with unknown aetiology - Table I[1].

Table II : Investigations of the patient.

- Serum Ig E levels – 2,825 IU/ml (Ref: 0-100 IU /ml)
- Serum precipitins to *Aspergillus fumigatus* (gel diffusion) – Positive
- CECT of Chest: Bronchial thickening, central bronchiectasis of right lung (Fig.2)

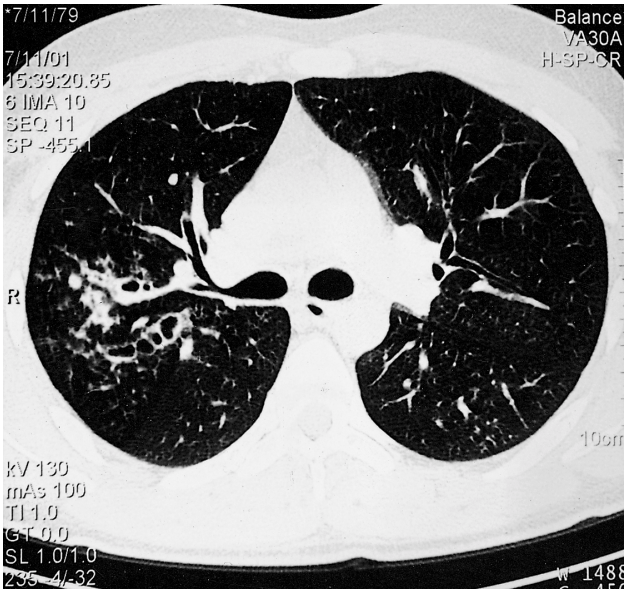

Fig. 2. *CECT of chest revealing central bronchiectasis.*

Filariasis, ascaris, ancylostoma sp., toxocara sp., and *Strongyloides stercoralis* are the chief parasitic causes of PIE. There was no evidence of any parasite, ova/cyst in the stool examination of this patient.

Nitrofurantoin, sulfonamides, penicillins, thiazides, tricyclic antidepressants, hydralazine, isoniazid, PAS are among the important drugs implicated in drug-induced eosinophilic pneumonias. The present patient did not give history of consumption of any of the above drugs.

Acute eosinophilic pneumonia is a disease of unknown aetiology that presents as an acute febrile illness of < 7 days duration with severe hypoxaemia, pulmonary infiltrates, and eosinophilia. There is no history of asthma in these patients. Chronic eosinophilic pneumonia has a more protracted course over several weeks to months with significant constitutional symptoms in addition to peripheral lung infiltrates. The present patient had a short illness of 20 days.

Hyper-eosinophilic syndrome is characterised by an absolute eosinophil count of > 1,500/cu mm lasting > 6 months. Additionally, cardiac involvement – tricuspid valve involvement, restrictive cardiomyopathy, endomyocardial fibrosis may be seen.

The two important conditions of pulmonary infiltrates associated with eosinophilia and asthma are:

1. Allergic broncho-pulmonary aspergillosis (ABPA).
2. Churg -Strauss disease.

The allergic granulomatosis of Churg Strauss syndrome is a multisystem vasculitis that is characterised by asthma, allergic rhinitis, eosinophilia, and systemic vasculitis involving the liver, kidney, heart, nervous system, and spleen in addition to the lungs. The vasculitis usually begins as cutaneous lesions or as a sensori-motor neuropathy[2]. The hallmark of the disease is the demonstration of angiitis and extravascular necrotising granulomas with eosinophilic infiltration in the biopsies from the involved organs. The present patient did not have any multi-organ involvement or vasculitis on examination or investigations.

So the most likely possibility is allergic bronchopulmonary aspergillosis (ABPA).

Answer 2.

In view of ABPA being the most likely diagnosis in this patient, the following investigations should be done to confirm the diagnosis:

1. Serum Ig E levels.
2. Serum precipitins to *Aspergillus fumigatus*
3. Ig E antibody specific for *Aspergillus fumigatus*

4. High resolution CT of the chest
5. Culture of Aspergillus from the sputum

Answer 3.

The diagnostic criteria for the diagnosis of ABPA are summarised in Table III. Most authors are in agreement that six of the seven primary criteria should be present for a definitive diagnosis of ABPA[3,4]. In this patient, the wheal and flare skin reactivity could not be tested due to the non-availability of the test. The rest 6 of the primary criteria were present confirming the diagnosis of ABPA.

Table III : Diagnostic criteria for ABPA.

Primary criteria:

- Bronchial asthma
- Peripheral blood eosinophilia
- Immediate skin reactivity to Aspergillus antigen
- Elevated serum Ig E
- Transient/Fixed pulmonary infiltrates
- Precipitating antibodies against Aspergillus antigen
- Central bronchiectasis

Other criteria :

- History of brownish plugs in the sputum
- Culture of *Aspergillus fumigatus* in sputum
- Increased Ig E/Ig G antibody specific for *Asp. fumigatus*

In a recent publication, Patterson *et al*[5] have summarised the clinical, laboratory, and serological findings as a basis for the diagnosis and have listed the relative importance of these in establishing a diagnosis of ABPA. The clinical or lab. findings include: asthma, eosinophilia, fleeting pulmonary infiltrates, and central bronchiectasis (CB). ABPA with central bronchiectasis is classified as ABP–CB, etc. The presence of CB is the most sensitive of these and its presence makes the diagnosis as "ABPA almost certain". The 4 serological parameters include: Precipitins against *A.fumigatus*, IgE antibodies > 2 times asthma control, IgG antibody > 2 times asthma control, and total S. IgE > 1,000 ng/ml. All 4 positive tests make ABPA established; 3 positive tests – ABPA likely; and 2 positive tests – ABPA possible. The third assessment is the establishment of a 50-75 % decline in the total S. IgE after treatment with prednisone, which is consistent with the diagnosis of ABPA.

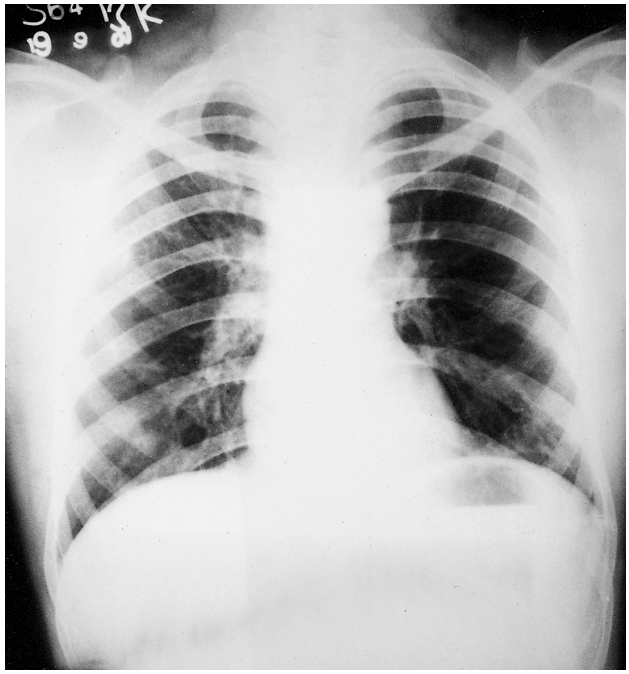

Fig. 3. *Clearing of the X-ray infiltrates after treatment.*

In the present patient, the presence of CB makes the diagnosis of ABPA almost certain. Though all the 4 serological tests could not be performed, the 2 positive tests lend further credence to the diagnosis.

Final diagnosis : Allergic bronchopulmonary aspergillosis (ABPA)

Discussion

Hinson *et al*[6] in the United Kingdom first described ABPA in 1952. Since then it has been reported worldwide. Reports of ABPA from India are also present, though no large series of cases exists[7,8].

The exact pathogenesis of ABPA is still unclear. ABPA is thought to be a reaction to inhaled Aspergillus in an atopic individual. Consequent upon reaching the bronchi, the fungus causes host sensitisation and an immunological response that involves type 1, type 3, and possibly type 4 hypersensitivity reactions[9]. The type 1 response is Ig E mediated and is responsible for the raised serum Ig E, eosinophilia, and the positive skin reaction to Aspergillus antigen. The type 3 response results in severe bronchial

inflammation leading to bronchiectasis and increased secretion of mucus with mucus plugging.

ABPA is recognised to have 5 different stages[5]:

Stage 1 – acute stage

Stage 2 – stage of remission

Stage 3 – recurrent exacerbations

Stage 4 – corticosteroids dependant asthma with exacerbations of ABPA

Stage 5 – fibrotic lung disease.

Patients with acute ABPA generally present with fever, cough with expectoration, and typically, a worsening of asthma. On a chest X-ray, hyperinflation, fleeting pulmonary infiltrates, consolidation, parallel lines and ring shadows, 'tooth paste shadows', 'gloved finger shadows', and band appearance-describing the mucus plugging of the bronchi, and segmental atelectasis have been described[10]. The radiological hallmark is the central bronchiectasis on CECT of the chest that is a disease-defining criterion.

The mainstay of therapy in ABPA is systemic corticosteroids. The exact duration of therapy is unclear but generally long term therapy for several months is recommended. Recently, oral itraconazole has been found in some uncontrolled studies, to be beneficial in the treatment of ABPA though the exact duration of therapy is still undefined[11,12].

The learning points from this case are summarised in the following table.

Learning points

- Presence of peripheral eosinophilia, pulmonary infiltrates in a patient of bronchial asthma should prompt a search for ABPA
- Central bronchiectasis on the CECT of the chest is a radiological hallmark of the disease.
- Immediate wheal and flare response to Aspergillus antigen, serum precipitins, elevated Ig E are the other disease defining criteria for ABPA
- Long-term steroids are the mainstay of treatment.

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