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# *Aspergillus fumigatus* and lung disease

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**Summary**

**The range of clinical presentations of lung diseases associated with *Aspergillus* spp. is great. The conditions are very frequently misdiagnosed but errors should be avoided if the possibility of a fungal cause is considered and simple immunological tests undertaken. Often no more than skin-prick tests and serum precipitins need to be done. In many cases, fungus is not isolated from the sputum and negative results do not exclude the possibility of *A. fumigatus* as the causal agent. Treatment often results in marked clinical improvement and there is evidence that suppression of recurrent episodes of bronchopulmonary aspergillosis prevents progressive lung damage.**

## Introduction

Lung involvement relating to *Aspergillus* spp. is important for several reasons. The clinical presentations are of many different types. This fact has led to difficulties and misunderstandings in terminology with consequent misdiagnosis. Many of the syndromes are progressive and there is some evidence that prophylactic treatment is useful. Thus the correct diagnosis is of practical importance. The fact that the same inhaled agent induces many different clinico-pathological syndromes, suggests that multiple factors are involved in pathogenesis and that host-dependent propensities to different types of tissue response may have an important and determining role.

## Classification

A summary of some of the more frequent syndromes seen in medical practice is shown in Table 1.

TABLE 1. Lung disease associated with *Aspergillus* spp.

1. A commensal in sputum
2. An allergen in bronchial asthma
3. Transient shadows with blood eosinophillia (acute bronchopulmonary aspergillosis)
   a. Non-segmental shadows
   b. Segmental shadows
   c. Bronchial obstruction with the development of mucocele
4. Persisting shadows
   a. Upper lobe shrinkage
   b. Widespread proximal bronchiectasis with peripheral shadows
   c. Widespread peripheral bronchiectasis
5. Extrinsic allergic alveolitis
   a. Acute (very rare with *A. fumigatus*)
   b. Chronic (reported with *A. clavatus*)
6. Fungus ball aspergilloma
   a. Simple
   b. With evidence of hypersensitivity
7. Invasive aspergillosis. Especially in immunosuppressed individuals

## Commensal

The incidental identification of *A. fumigatus* in random sputum samples is not uncommon. The frequency of this finding probably varies with the local environment, perhaps also with the climate. It has been reported in up to 10% of random samples but this figure may be exceptionally high. When *A. fumigatus* occurs as a commensal no host response occurs and all immunological tests are negative.

## *A. fumigatus* in asthma

A positive immediate skin-prick test to *A. fumigatus* was found in 13% and 16% respectively, in 2 fairly large asthma clinics where the same range and preparations of antigens were used. Immediate skin responses to *Aspergillus* spp. are usually found in atopic individuals having positive responses to other common allergens, but are occasionally found in isolation. In individuals with such skin reactions specific IgE antibodies to *A. fumigatus* can be identified and bronchial challenge tests show an immediate type of reaction. In some individuals, a dual skin reaction is seen (i.e. a response at 10 min and 4–6 hr) and, in these, a comparable dual response is seen following inhalation challenge.

## *A. fumigatus* and transient lung shadows

Typical acute bronchopulmonary aspergillosis

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may be defined as a condition characterized by a blood eosinophilia, transient radiographic shadows associated with an immediate skin reaction to *A. fumigatus* (McCarthy and Pepys, 1971). In many patients IgG antibody may be identified in neat or concentrated serum using simple precipitin tests or *in vitro* RAST (radioallergosorbent test) or ELISA (enzyme-linked immunoabsorbent antibody) techniques.

Typical non-segmental (i.e. shadows not corresponding to anatomical boundaries of the lung) transient shadows are most commonly found in atopic individuals, usually in association with asthma and usually associated with sputum eosinophilia. The pathology of these lesions is essentially that of an eosinophilic pneumonia. The patient may complain of little in the way of symptoms but may suffer some fever or exacerbation of asthma. Rubbery plugs may be found in the sputum and from these the fungus may be isolated. However in many instances identification of the fungus in the sputum is difficult and reliance cannot be placed on direct isolation of the organism to establish the diagnosis. Characteristically the total serum IgE is considerably elevated and is associated with a moderate blood eosinophilia (i.e. about $0{\cdot}800–1{\cdot}500 \times 10^9$/l).

Segmental shadows occur when a mucus plug blocks a segmental bronchus. Although such shadows may occur alongside the transient infiltrates described above, they may also occur in isolation. In the latter instance the patient may have very little in the way of symptoms. Lesions may occur in the absence of atopy or asthma, and in the absence of sputum or blood eosinophilia. These cases obviously present diagnostic problems but the presence of precipitins or of positive skin tests, or isolation of the fungus from the sputum may indicate the correct diagnosis. The immunological features in cases of mucus impaction may be less complete than in typical bronchopulmonary aspergillosis. In particular, blood and sputum eosinophilia may not be prominent.

Sputum obstruction may be massive in size giving a 'gloved finger' pattern representing a grossly dilated bronchial tree having the appearance of a mucocele. Such an appearance may be seen without collapse of the more peripheral lung, ventilation presumably being maintained through collateral airflow.

### *A. fumigatus* and chronic shadows

The pathology underlying any of the types of transient shadowing described above, may result in permanent bronchiectasis and peripheral lung fibrosis. The patterns of bronchiectasis and associated lung damage vary. Most typically proximal bronchi are dilated but the peripheral bronchial tree is patent and normal. In other cases, however, widespread non-specific saccular or tubular bronchiectasis is seen. These cases are often associated with extensive peri-bronchial shadowing due to secondary infection and possibly also to continuing local hypersensitivity responses. The latter is suggested by the substantial clearing sometimes seen following treatment with corticosteroids.

Uncommonly, patients are seen having a radiographic pattern of very widespread peripheral bronchiectasis affecting smaller airways, and this at first sight gives a nodular appearance on the radiograph.

In some individuals the radiograph shows bilateral contracted upper lobes and the diagnosis is frequently confused with chronic tuberculosis. Appropriate immunological tests, however, will distinguish the 2 conditions. Specific IgE and IgG antibodies to *A. fumigatus* can normally be demonstrated and the presence of these supports the clinical observation that these cases are the chronic consequence of repeated transient shadows of the upper lobe. A negative tuberculin test is also helpful in suggesting an alternative cause for apical scarring.

Cases with persisting shadows have to be distinguished from other types of widespread bronchiectasis and in these the pattern of cytophilic antibodies may be a helpful distinguishing feature (Assem and Turner-Warwick, 1976). The features of chronic bronchopulmonary aspergillosis has recently been reviewed in a series of 50 personal cases seen by Malo, Hawkins and Pepys (1977).

### Extrinsic allergic alveolitis

Granulomatous lesions of the lung without an associated blood eosinophilia of the farmer's lung type are very uncommonly related to *A. fumigatus* although the condition has been described in malt workers exposed to high doses of *A. clavatus*. Although a late 6-hr skin reaction and a late response seen on bronchial challenge testing, together with circulating precipitins suggests that pathogenesis may depend upon an Arthus' reaction, such a reaction is also found in bronchopulmonary aspergillosis where the histology in the lung is distinctive (namely, an eosinophilic pneumonia). Thus, factors in addition to the Arthus' response must be invoked to explain the distinctive histological features of bronchopulmonary aspergillosis and extrinsic allergic alveolitis relating to *Aspergillus* spp.

### Aspergilloma

*A. fumigatus* not infrequently infests pre-existing cavities and areas of destroyed lung. The fungus ball with its surrounding air-cap produces a characteristic radiographic appearance, but this is not in-

variable. Local invasion may occur in a damaged area of the lung without a definitive fungal mass. These cases frequently give rise to diagnostic problems. Whether an aspergilloma is radiographically typical or not, the immunological characteristic is the same; multiple precipitin lines are readily identified when serum is reacted with an appropriate antigen in a double diffusion Ouchterlony system.

Some patients having a typical aspergilloma develop systemic symptoms of malaise, fever and weight loss, and treatment of these with corticosteroids is often successful. The suggestion that such systemic symptoms were due to hypersensitivity reactions to fungus was proposed by Davies and Somner (1972). This suggestion is supported by the fact that the pattern of cytophilic antibodies identified (IgE and IgG) is very similar to that found in bronchopulmonary aspergillosis (Assem and Turner-Warwick, 1976). In other instances, however, systemic symptoms, fever and weight loss, are due to secondary anaerobic contamination.

**Invasive aspergillosis**

This frequently fatal condition usually arises as a complication in immunosuppressed individuals – either those receiving immunosuppressant drugs or very high doses of corticosteroids or those with lymphomas or other malignant tumours. The widespread extending shadows have to be distinguished from pulmonary involvement, from the underlying disease, and from other opportunist infections. Fibreoptic bronchoscopy and transbronchial biopsies now enable the correct diagnosis to be made in many cases.

**Treatment**

A full discussion on treatment is not possible in this short review. Evidence has been published demonstrating the reduction in relapses in acute bronchopulmonary aspergillosis using maintenance doses of corticosteroids (Saferstein *et al.*, 1973) and in view of the progressive nature of this disorder continuous steroids may have to be considered. The dose required to suppress shadows is, however, difficult to ascertain because the latter frequently occur in asymptomatic individuals.

Inhalation of antifungal agents so far has a limited place because the amount of fungus in many hypersensitivity reactions is very small. Where fungus balls occur, little inhaled agents can be expected to reach the fungal mass.

There are many other approaches to treatment of aspergillomata. Many fungus balls remain unaltered in size in asymptomatic patients over very many years and require no treatment at all. Others, especially those where the shadow is enlarging or developing haemoptysis, can be resected. In cases where compromised lung function prevents resection, evacuation of the contents of a fungus-filled cavity can result in substantial improvement. In some personal cases followed over several years, the fungus does not necessarily return even when the cavity remains open. Where life-threatening haemoptysis occurs, bronchial artery embolization may be life-saving.

**References**

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