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## Unilateral wheeze caused by pseudomembranous aspergillus tracheobronchitis in the immunocompromised patient

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### Abstract

**Unilateral wheeze in the immunocompromised patient with unremitting fever may be the first localising sign of aspergillus tracheobronchitis. Two such cases are presented.**

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With the improved range of antibacterial and antiviral agents currently available, fungal infection has become a more common cause of mortality in the immunocompromised host. Superficial fungal infections, particularly candida, can be prevented or treated with various drugs including fluconazole. However, deep seated fungal infections are a major problem, particularly invasive aspergillosis for which prophylaxis is difficult, so the cornerstone of a successful outcome is early diagnosis and treatment. The diagnosis of invasive pulmonary aspergillosis is based upon clinical features and radiographic evidence with confirmation by culture or microscopy of bronchoalveolar lavage fluid or biopsy of lung tissue. In invasive aspergillus tracheobronchitis, however, where the disease is confined to the airways with only superficial mucosal invasion, the diagnosis is typically delayed because of insidious onset, non-specific signs and symptoms, and lack of radiographic abnormalities.<sup>1-3</sup>

We report two cases of aspergillus tracheobronchitis in which unilateral wheeze was a

distinctive physical sign preceding any radiographic abnormalities. It is therefore suggested that, in immunocompromised patients with apparent infection not responding to broad spectrum antibiotics, such a sign should raise the suspicion of aspergillus tracheobronchitis and prompt early bronchoscopy and culture to clarify the diagnosis.

### Case reports

#### PATIENT 1

A 57 year old man presented with a six week history of weight loss, anorexia, non-productive cough, and pyrexia. The spleen was considerably enlarged with mild hepatomegaly and minimal lymphadenopathy. There was a peripheral blood pancytopenia and a diagnosis of diffuse immunoblastic non-Hodgkin's lymphoma was made following splenectomy. Cultures were sterile but fever persisted, despite broad spectrum antibiotics, until initiation of cytotoxic chemotherapy including corticosteroids. He required ventilation briefly for a dramatic cyanotic hypothermic reaction immediately after his second pulse of chemotherapy and recovered in 48 hours. However six days later, when neutropenic, he became pyrexial and dyspnoeic and, on auscultation of the lungs, was noted to have left sided expiratory wheeze with basal crackles. The chest radiograph remained normal, blood cultures were sterile, but sputum grew an alpha haemolytic streptococcus. Despite antibiotics his respiratory function deteriorated, and at bronchoscopy two days later thick white plaques forming a pseudomembrane were seen in the trachea and left main bronchus and its divisions with almost complete obliteration of their lumen. The right bronchial tree appeared relatively clear. Microscopy of bronchial secretions and brushings revealed numerous hyphal elements and culture confirmed the presence of *Aspergillus fumigatus*. Despite initiation of high dose (1 mg/kg/day) intravenous and nebulised amphotericin B he died from respiratory insufficiency within 24 hours. Post-mortem examination was not performed.

#### PATIENT 2

A 61 year old man presented with a four week history of weight loss, polyarthralgia, night sweats, and pyrexia. There were no focal

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signs of infection and cultures were sterile. Fever persisted despite broad spectrum intravenous antibiotics. He was neutropenic ( $0.37 \times 10^9/l$ ) and thrombocytopenic ( $32 \times 10^9/l$ ) but bone marrow aspirate and trephine biopsy had normal appearances. Soluble IgG immune complexes were identified in the serum and antibody tests against dsDNA were positive. A diagnosis of a systemic lupus erythematosus-like disorder was made and, in an unsuccessful attempt to improve neutrophil and platelet counts, intravenous IgG was given (0.8 g/kg). He was subsequently given oral prednisolone (0.25 mg/kg/day) with immediate resolution of pyrexia and, after five days, a rise in neutrophils to  $2.5 \times 10^9/l$ . He then became progressively confused and dyspnoeic and, although left sided expiratory wheeze was noted on auscultation, the chest radiograph was normal. Hypoxia ensued and bronchoscopy revealed white fungal plaques in the trachea, carina, and left bronchial tree. The right main bronchus contained a few plaques but its subdivisions appeared clear. Microscopy and culture of bronchial washings yielded *Aspergillus fumigatus*. Steroids were discontinued and intravenous amphotericin B (1 mg/kg/day), flucytosine (120 mg/kg/day), and oral itraconazole (600 mg/day) commenced, but he died from respiratory failure five days later. Postmortem examination revealed the typical appearances of aspergillus tracheobronchitis with a sloughing, ulcerating tracheobronchitis (figure) and occasional bronchopneumonic patches, devoid of fungal hyphae, in adjacent lung parenchyma. Histological examination of the heart, liver, and spleen revealed no fungal elements.

Tracheal appearances at autopsy (after removal of slough) showing remarkable erythema and ulceration down to carina.



## Discussion

Invasive aspergillosis is commonly fatal and in 90% of cases is manifest by significant pulmonary involvement.<sup>2,4</sup> The commonest radiological features of pulmonary infiltration are nodular parenchymal disease or cavitating disease with pathological findings of necrotising bronchopneumonia or haemorrhagic pulmonary infarction.<sup>1,2</sup> However, about 7–10% of pulmonary cases manifest as invasive aspergillus tracheobronchitis.<sup>1–3</sup> Within this spectrum of disease the mildest form is tracheobronchitis with mucosal inflammation and mucous secretions containing *Aspergillus*.<sup>5</sup> Another mild form is obstructing bronchial aspergillosis recently described in AIDS.<sup>6</sup> Progression to ulceration has been seen in lung transplant recipients,<sup>5</sup> but multifocal disease with ulceration and formation of a pseudomembrane is more typical in the host with significant neutropenia and underlying malignancy, often haematological.<sup>1,3,7–9</sup> Although most cases described are caused by *Aspergillus fumigatus*, other fungal genera have produced a similar pattern of disease including *Candida* species and members of the Mucorales family.<sup>3</sup> As with the more invasive patterns of aspergillus infection diagnosis is often late, but in aspergillus tracheobronchitis this may be delayed further because of the lack of radiographic pulmonary infiltrates as shown in the two cases presented.

It has been suggested that aspergillus tracheobronchitis is more common in mild to moderately immunosuppressed patients which may explain the endobronchial localisation without extension to bronchopneumonia.<sup>1</sup> Typically the fungal colonies form plaques lining the bronchi resulting in a necrotising bronchitis. This may form a pseudomembrane causing significant airway narrowing which could result in wheeze which may be monophonic. The bronchitis is initially focal and may then result in unilateral wheeze. However, in its later stages ulceration and pseudomembrane formation are usually widespread, affecting both sides of the bronchial tree, when bilateral wheeze may be heard. The presence of wheeze has been documented in some reports<sup>3,8–10</sup> but no comment has been made on its diagnostic significance, often being the first indication of localised endobronchial pathology.

Both cases described here were neutropenic and had received corticosteroids and broad spectrum antibiotics. Patient 1 also had an underlying malignancy and had undergone recent splenectomy. Both were therefore archetypal subjects for developing this uncommon pattern of infection. Disappointingly, in patient 2 prompt recognition of the clinical features and early bronchoscopy failed to prevent fatal respiratory insufficiency despite intensive systemic therapy. This may reflect the ineffectiveness of systemic antifungal drugs on extensive endobronchial disease in the face of continuing host immunosuppression, and it may be that removal of the fungal plaques and pseudomembrane at bronchoscopy are

critical if a favourable outcome is to be achieved.<sup>7</sup> Antifungal treatment is problematic as no studies have addressed this subgroup of patients specifically. Certainly the milder variants of aspergillus tracheobronchitis have been successfully treated with oral itraconazole,<sup>5,6</sup> but those with pseudomembranous disease are more advanced and are thus a much greater therapeutic challenge.

In consideration of the above we recommend that, in the clinical setting of unremitting fever despite broad spectrum antibiotics in an immunocompromised patient, the presence of wheeze, particularly in the absence of a history of chronic airways disease, should raise the possibility of endobronchial disease and prompt early bronchoscopic examination.

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## Pulmonary nodules due to reactive systemic amyloidosis (AA) in Crohn's disease

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### Abstract

**Multiple nodules of AA (reactive systemic) amyloid were identified at necropsy in the lungs of a patient with Crohn's disease. No other organs were involved. Nodular pulmonary amyloidosis is usually caused by deposition of AL (primary) amyloid.**

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Nodular pulmonary amyloidosis is an infrequent manifestation of amyloid disease.<sup>1</sup> In this report multiple nodules of amyloid were identified at necropsy within the lungs of a patient who had active Crohn's disease but no amyloid deposits at other sites.

### Case report

A 75 year old woman presented with a two month history of diarrhoea and two stone weight loss. She had features of congestive cardiac failure and her chest radiographs showed diffuse basal shadowing only, obscuring any further disease. Three days after hos-

pital admission the patient sustained a fatal cardiac arrest.

There was no history of drug ingestion and no significant past medical history, but she was a heavy smoker.

At necropsy no lesions of the tongue or skin were seen. Recent myocardial infarction was confirmed and each pleural cavity contained 500 ml of clear effusion fluid. The lungs were oedematous, together weighing 1480 g. Throughout both lungs, but predominantly in the bases, there were 12 well circumscribed nodules of firm, brown, waxy material up to 3 cm in diameter. There was a terminal ileitis and patchy colitis with a cobblestone mucosal pattern and areas of fibrous stenosis.

Histological examination showed that the pulmonary nodules were composed of amyloid with scattered foci of calcification and ossification. They stained pink with Congo red eliciting apple-green dichroism in polarised light (figure). Staining was abolished by pretreatment of the sections with potassium permanganate. Immunohistochemical examination with the avidin-biotin complex method showed positive staining for amyloid A component (Dako, UK). The ileum and colon showed features of active Crohn's disease.

Congo red staining of all major organs (including myocardium, kidney, bladder, liver, spleen, small and large intestine, adrenal, thyroid, and pancreas) revealed no evidence of amyloid deposition.

### Discussion

Nodular pulmonary amyloidosis is an uncommon but recognised manifestation of amyloid

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