Chronic Necrotizing Pulmonary Aspergillosis Mimicking Bronchocentric Granulomatosis

Victor Tron and Andrew Churg
Department of Pathology and UBC Health Sciences Centre Hospital, University of British Columbia, Vancouver, B.C., Canada

SUMMARY
We present a case of slowly progressive Aspergillus infection occurring in a partially immunocompromised host. The histologic pattern mimicked bronchocentric granulomatosis as seen in allergic bronchopulmonary aspergillosis, but the clinical history, spread of disease in the face of steroid therapy, peculiar granulomatous response to the organisms, and large numbers of organisms present suggest that this was really a case of chronic necrotizing pulmonary aspergillosis. These entities must be distinguished because their therapy, prognosis, and clinical significance are totally different.

Introduction
A variety of clinical and pathologic forms of Aspergillus infection occur in the lung. Colonization of pre-existing cavity (fungus ball), pneumonia caused by invasive Aspergillus organisms, and the tissue manifestations of allergic bronchopulmonary aspergillosis are well known. Recently, Binder et al.¹ and Gefter et al.⁵ have suggested that an additional form of low grade invasive aspergillosis exists. Binder et al.¹ have christened this disease "chronic necrotizing pulmonary aspergillosis" (CNPA) and defined it as an indolent cavitating process in the lungs due to invasion of lung tissue by a fungus of the Aspergillus species. Gefter et al.⁵ used the term "semi-invasive" pulmonary aspergillosis and a fairly similar definition. Binder et al.¹ reviewed the literature and found 22 previously reported cases which they believed were examples of chronic necrotizing aspergillosis. The disease typically appeared in patients with some, but usually limited, impairment of host defenses¹,⁶,¹¹. CNPA requires treatment with anti-fungal agents and some patients are cured by such regimens.

The pathologic features of this process are uncertain. The descriptions of the cases reported and reviewed by Binder et al.¹ suggest the presence of large numbers of organisms with limited tissue invasion and a marked giant cell granulomatous response; the latter is an unusual finding in Aspergillus infections in the lung and usually is seen in bronchocentric granulomatosis (allergic bronchopulmonary aspergillosis). We report a case which appears to represent chronic necrotizing pulmonary aspergillosis, but which pathologically is an excellent mimic of bronchocentric granulomatosis.

Case Report:
The patient was a 55 year old male who presented with rapidly progressive weakness, low grade fever and cerebellar ataxia. A CT scan revealed multiple cerebral lesions, consistent with metastases, for which he was treated with Decadron (4 mg PO qid) for two months before admission. The initial chest radiograph was read as normal. He had no history of asthma.

On admission, the patient was drowsy and weak, with a temperature of 38.2 °C. Examination of the chest revealed dullness in the left apex. Chest radiograph showed an ill-defined left upper lobe infiltrate which over two weeks progressed to a mass-like consolidation. An initial blood count showed an elevated WBC (18,200) with polymorphonuclear cells and 32% lymphocytes.

Shortly after admission, bronchoscopic examination of the left upper lobe revealed mild chronic inflammation; culture grew Aspergillus fumigatus. A needle aspiration of the mass confirmed an Aspergillus infection. Amphotericin B and 5-FU were started approximately three weeks after admission. There was some symptomatic relief but little resolution of the radiographic find-
A diagnosis for the pulmonary process was pursued by means of a large wedge biopsy of lung; a brain biopsy confirmed metastatic adenocarcinoma. Antifungal therapy and steroid therapy were then discontinued. He died 4 days later, 46 days after admission.

Pathologic Finding:

Grossly, the lung specimen revealed many whitish-yellow nodules measuring from 2–3 mm in diameter. Multiple histological sections showed a peculiar pattern of fungal abscesses (Fig. 1–5). These consisted of collections of typical Aspergillus hyphae, often arranged in a radial pattern, located within large and small airways. The hyphae were often associated with a polymorphonuclear but not an eosinophil response, and were surrounded by multi-nucleated giant cells. In some instances only well formed granulomas with giant cells but no polymorphonuclear cells surrounded the fungi. Elastic tissue stain confirmed that the fungi were primarily located within airways, but invasion into the airway walls and in some areas destruction of the airway wall were present. However, fungi were never found in tissue away from airways, nor was there evidence of vessel invasion.

Fig. 2. Involvement of a small airway by the inflammatory process; elastic stain confirmed that this structure is indeed an airway. Note the granulomatous response in the airway wall and the isolated granuloma near the airway (X 64).

Fig. 1. Low power view showing destruction of the wall of a large airway (X 40).

Fig. 3. Higher power view of small airways showing prominent granulomatous response (X 160).
Fig. 4. Silver methenamine stain showing relatively large numbers of organisms in 3 adjacent airways. This pattern of airway involvement is very reminiscent of bronchocentric granulomatosis except for the large number of organisms present (×64).

Fig. 5. Silver methenamine stain showing radial arrangement of fungal hyphae. Note that the hyphae extend into the airway wall (×64).

Discussion

This case presents an unusual pathologic pattern of Aspergillus lung infection which probably corresponds to one form of the clinical entity of chronic necrotizing aspergillosis, but which is histologically very similar to bronchocentric granulomatosis (BCG). When Aspergillus organisms are present, BCG is one of the tissue manifestations of allergic bronchopulmonary aspergillosis. However, a number of features indicate that this patient did not have allergic bronchopulmonary aspergillosis: 1) There was no history of asthma; 2) There was no blood or tissue eosinophilia at the time the disease process was active; 3) Numerous fungi were present in the lung and were often arranged in the typical radial pattern seen in invasive aspergillus infections, particularly in hosts with serious degrees of immunodeficiency. By contrast, in BCG fungal organisms are usually scanty; 4) Fungi invaded the airway walls, a phenomenon which is rare in BCG; 5) The disease appeared and progressed in the face of high dose steroid therapy, a regimen which ordinarily suppresses allergic bronchopulmonary aspergillosis.

As noted, the histologic features of CNPA are mentioned in passing by Binder et al. and Gefter et al. Some of the pathologic descriptions simply mention invasion of tissue, but some also document a multinucleate giant cell type of granulomatous response, a finding which is distinctly uncommon in invasive aspergillus infections. However, a granulomatous response to Aspergillus spores may be produced in rabbits by intratracheal instillation, and a similar response has been described in the past in humans in patient who probably did not have aspergillosis and who Binder et al. believe (retrospectively) had CNPA.

The clinical setting (immunosuppression), the time course, and the progression in the face of steroid therapy suggests that our case represents CNPA, despite the fact that it is an excellent histologic mimic of BCG. However, careful observation of the large numbers of fungi, the arrangement of the organisms, and the limited tissue invasion should raise the possibility of another diagnosis. Because BCG requires steroid therapy while CNPA requires antifungal therapy, this distinction is critically important for patient management.
References


Key words: Granulomatosis response – Steroid therapy – Immunocompromised host aspergillosis – Bronchocentric granulomatosis

Victor A. Tron MD, c/o A. Chung, Department of Laboratory Medicine, University of British Columbia, 2211 Wesbrook Mall, Vancouver, B.C. Canada V6T 1W5

Letters to the Case

W. Jones-Williams
Cardiff, UK

The authors present an interesting case which raises a number of problems including that of semantics. Is Chronic Necrotising Pulmonary Aspergillosis (CNPA) an entity, or merely a variant of the continuum of pulmonary aspergillosis. The commonly recognised forms of aspergillosis include allergic bronchopulmonary aspergillosis (ABPA), invasive pulmonary aspergillosis (IPA), mycetoma (M) and tuberculoid aspergillosis.

Let us first consider bronchocentric granulomatosis (BCG). Clee et al.1 in an excellent recent review, consider that BCG is a morphological diagnosis as the clinical, immunological, and radiological features are inconsistent. BCG is characterised by necrotising granulomatous inflammation centred on usually peripheral bronchi. The bronchi are obstructed by necrotic eosinophilic mucoid debris with palisading histocytes and foreign body giant cell reaction replacing the bronchial lining. It is emphasised that BCG results from any persistent intra-luminal insult, often with proximal bronchial obstruction. When BCG is caused by Aspergillus, asthma is a feature with well marked tissue and peripheral eosinophilia and, usually, scanty fungi and recognised as ABPA. In non-asthmatic subjects, BCG shows no eosinophils, polymorphs are prominent and, commonly, no causative agents can be detected. Similar features may result from inhalation of hydatid fluid2 following obstruction by proximal carcinoma1, and, rarely, rheumatoid lung disease3.

Clinically IPA occurs in severely immunosuppressed patients causing a fulminant diffuse and often focal pneumonitis and can affect normal lung. Eosinophils are prominent (eosinophilic pneumonia) and fungi easily found. Vascular invasion is common with blood spread to distant sites. Progression of the disease leads to cavitation containing fungal balls.

Mycetoma, fungal balls, result from an indolent saprophytic Aspergillus infection of preformed cavities. How-