CASE REPORT

BRONCHIOLITIS OBLITERANS ORGANIZING PNEUMONIA CAUSED BY CAPSULE-DEFICIENT CRYPTOCOCCOSIS

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Abstract. A 67-year-old diabetic man presented with progressive multifocal myeloradiculopathy for 6 months, with no pulmonary symptoms. A chest x-ray and CT scan of the lungs revealed bilateral multiple nodular infiltrates in the right upper lobe and the lower lobes bilaterally, mimicking metastases. A thoracoscopic lung biopsy demonstrated bronchiolitis obliterans organizing pneumonia caused by capsule-deficient cryptococcosis.

INTRODUCTION

The pathologic spectrum of pulmonary cryptococcosis is wide, largely depending on host immunity. It ranges from granulomatous pneumonia and granulomatous inflammation at one end, to infection with minimal host response and massive proliferation of the organisms in the interstitium, capillaries or alveolar spaces at the other end (McDonnell and Hutchins, 1985; Shibuya *et al*, 2001). Unusual presentations that have been reported, include massive pulmonary involvement occurring in an apparently immunocompetent host, endobronchial lesions, inflammatory pseudotumors, cryptococcal empyema and bronchiolitis obliterans organizing pneumonia (BOOP) (Carey *et al*, 1991; Luhr and Svane, 1991; Mulanovich *et al*, 1995; Mahida *et al*, 1996; Silachamroon and Shuangshoti, 1998). A review of the literature found only one reported case of cryptococcosis associated with BOOP. We present here another case of this rare form of pulmonary cryptococcosis, caused by a capsule-deficient organism.

CASE REPORT

A 67-year-old man with diabetes mellitus (DM), hypertension, and two-vessel coronary artery disease presented with back pain radiating to both legs for 6 months, with weakness and muscle wasting of the left upper and lower extremities for 2 months. He had no chest complaint. Physical examination confirmed the weakness, and muscle wasting. Cranial nerve VII involvement of lower motor neuron type was also noted. A CT scan of the chest showed multiple lung nodules, 0.5-1.5 cm in diameter, on the anterior segment of the right upper lobe close to the pleura, and multiple nodules in the basal segments of the lower lobes bilaterally. Neither mediastinal adenopathy nor pleural effusion was observed.

The clinical impression was progressive multifocal myeloradiculopathy with multiple lung nodules, with lung metastasis to be ruled out. The neurological deficit was thought to be from an infiltrative disease in the subarachnoid space due to an immune process or malignancy. A work up for primary tumor and tumor markers was negative. Fine needle aspiration of the lung mass suggested inflammatory and reparative processes without malignancy. Lung biopsy was performed.

Pathology

A thoracoscopic lung biopsy yielded a piece of lung tissue, 4.5x1.7x1.2 cm in size. Bisection showed an ill-defined gray-white consolidated area 1.5x1 cm in size. Hematoxylin-eosin (H&E) stained sections display lobular distribution of mixed air space-interstitium inflammatory pro-

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cesses. There was scattered loose fibromyxoid tissue proliferation within the terminal bronchioles and alveolar ducts (Fig 1). The alveolar spaces contained varying amounts of foamy, non-foamy and multinucleated histiocytes, lymphocytes and plasma cells without neutrophils or eosinophils (Fig 2A). Similar inflammatory cells were present in the center of some fibromyxoid plugs (Fig 2B). Within a few alveolar spaces, vague granuloma-like aggregates of macrophages were seen. Widened alveolar septa were lined by mildly hyperplastic type II pneumocytes and infiltrated by lymphocytes and plasma cells. Spherical yeast cells, 4 to 15 µ in diameter, with thin light basophilic cell walls were found in the cytoplasm of macrophages within the alveolar spaces and in some fibromyxoid plugs. A few

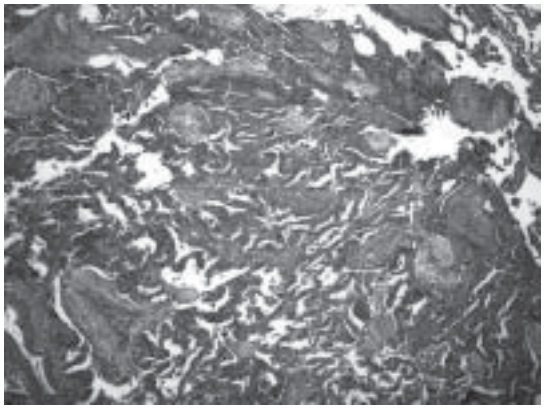

Fig 1–Open lung biopsy demonstrated bronchiolitis obliterans organizing pneumonia characterized by scattered loose fibromyxoid organizing tissue plugs in terminal air spaces (hematoxylin-eosin, original magnification x 100).

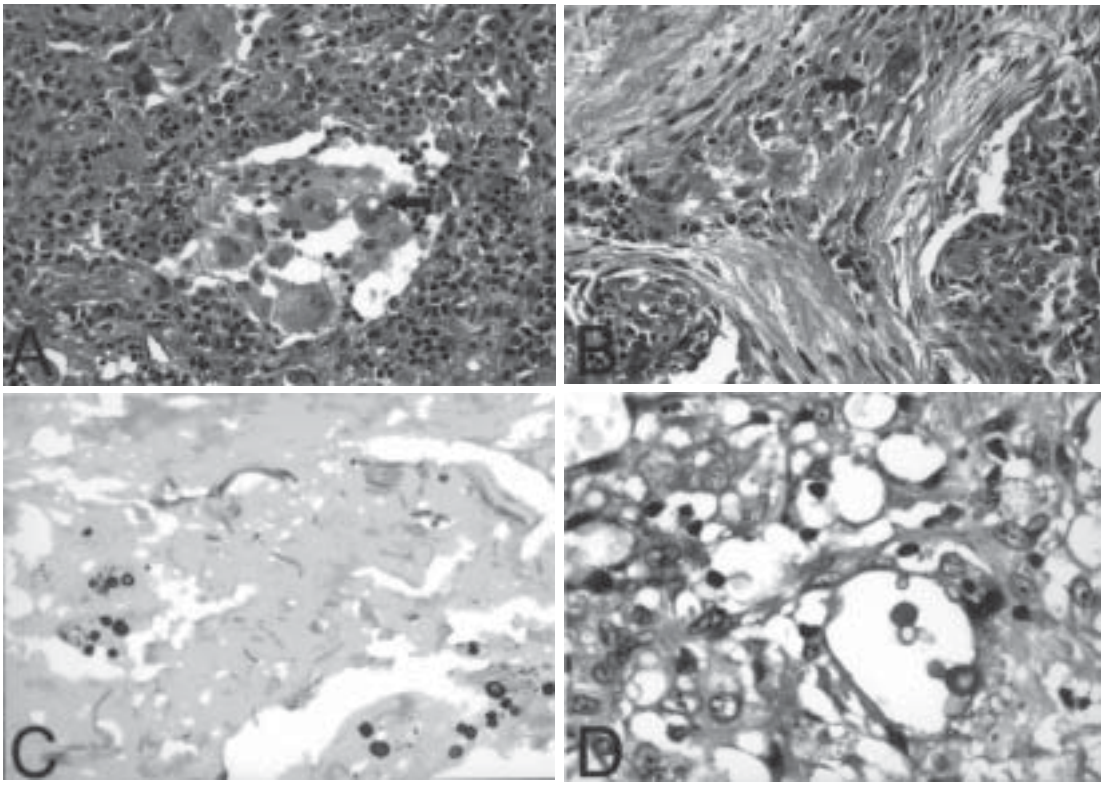

Fig 2–Pathologic features, high magnification (A) Lymphocyte and plasma cell infiltration in alveolar septa and infiltration of histiocytes, lymphocytes and multinucleated histiocytes in alveolar spaces. Note few small round spaces of organisms in the cytoplasm of histiocytes (arrow) (hematoxylin-eosin, original magnification, x 200). (B) Organizing fibromyxoid tissue containing lymphocytes and histiocytes in the center. Organism in a multinucleated cell is shown (arrow). (hematoxylin-eosin, original magnification, x 200). (C) Silver stain highlighting the organisms in the cytoplasm of alveolar macrophages (Gomori methenamine silver stain, original magnification x 200). (D) Narrow-based budding yeasts with mucinous capsule are rarely seen (Mayer's mucicarmine, original magnification x 400).

budding yeasts with narrow bases were identified. The organisms were not easily seen in H&E sections, and surprisingly were highlighted more by Gomori's methenamine silver (GMS) stain (Fig 2C). Mayer's mucicarmine stain revealed very few organisms with mucinous capsules (Fig 2D).

The patient received amphotericin B, which was later changed to fluconazole due to renal toxicity. Serum and CSF for cryptococcal antigen were negative. There were no abnormalities on the immunologic work up other than DM. A CD4 lymphocyte level was normal. On follow-up 2 months after admission, the patient was experiencing improvement of the pain but still had mild weakness and decreased pinprick sensation of the left leg. The exact cause of the myeloradiculopathy is still unclear. The patient revealed that he had raised pigeons during the past one year.

DISCUSSION

BOOP is regarded as a response to acute and subacute lung injury at the level of the terminal airways (Katzenstein, 1997). The findings of BOOP are occasionally seen as non-specific minor components of other processes, such as usual interstitial pneumonia, non-specific interstitial pneumonia, or hypersensitivity pneumonitis, and can be a reaction found near a primary lesion, such as a tumor or granuloma. BOOP has many etiologies, including inhalation of toxic substances, connective tissue diseases, drugs, and infections by bacteria and viruses. The term cryptogenic organizing pneumonia is given only after the exclusion of other possible causes. The treatment of cryptogenic organizing pneumonia is prolonged administration of corticosteroids, therefore, it is important to rule out infectious etiologies before making such a diagnosis.

Pulmonary cryptococcosis causing BOOP is very rare. Only one case had been reported (Carey *et al*, 1991). The BOOP pattern is occasionally seen in cryptococcosis, and represents a non-specific reaction around the main pathology, such as an area of granulomatous inflammation (Addis, 1996). By obtaining a large piece of lung tissue, the BOOP pattern was verified as the main pathology in this case. However, the BOOP pattern presented here exhibited minor deviations from the classic BOOP pattern, in that there were relatively more lymphocytes and plasma cells in the alveolar septa, more alveolar macrophages, frequent multinucleated giant cells, and the presence of few vague granuloma-like histiocyte aggregates in alveolar spaces. Since the yeast and the inflammatory cell reaction to them were seen in the alveolar tissue as well as within the organizing fibromyxoid tissue plugs, cryptococcus was regarded as the cause of the BOOP pattern.

The lack of pulmonary symptoms, limited numbers of organisms, infrequent budding yeasts and free organisms, and the obvious response of the histiocytes and lympho-plasma cells reflects the immune competency of the host. The mucinous capsule of cryptococcus is known to be an important virulence factor. It helps the organism to evade phagocytosis by macrophages and can suppress cellular and humoral mediated immune responses (Addis, 1996). It is not known why the host response in this case was BOOP rather than the usual granulomata. Our hypothesis is that, the capsule deficient form is more rapidly cleared by the host immune system than the capsular form, thus, the organisms were not present long enough to bring on the delayed type hypersensitivity reaction and the formation of granulomata. The patient's diabetes may have resulted in the sub-optimal immune response which hindered granulomatous inflammation. As a result, the histiocyte-rich pneumonic response occurred with interstitial pneumonitis, instead of granuloma developed, and the injured bronchiolo-alveolar tissue was subsequently repaired in the BOOP pattern.

The diagnosis of cryptococcosis can be difficult in cases of capsule-deficient cryptococci and in old fibrogranulomata, in which long standing and degenerating organisms frequently lack a carminophilic capsule (Chandler and Watts, 1996). Both can show small mucin-negative yeast cells that have to be distinguished from histoplasmosis (Binford and Dooley, 1976). In most situations, there are some mucin positive organisms and an obvious variation in size

with cryptococcosis. Another mycosis that enters the differential diagnoses is blastomycosis. Although, the organisms in blastomycosis may be weakly stained for mucin, they are larger, have thicker cell walls, multiple nuclei and broad-based budding. Rhinosporidiosis, although mucin positive, is easily distinguished from cryptococcosis, due to its characteristically large sporangia with endospores.

In conclusion, we presented here a case of capsule-deficient cryptococcal infection causing a BOOP pathological pattern. Documented cryptococcosis was the possible etiology of the BOOP. Although, it is rare for any fungus to produce BOOP, a routine GMS stain is recommended when an atypical BOOP pattern is encountered.

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