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Massive pleural effusions in cryptococcal meningitis

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Summary

Cryptococcal infection uncommonly presents with pulmonary manifestations and even more rarely so as massive bilateral effusions. Pleural involvement is usually associated with underlying pulmonary parenchymal lesions and is unusual while on antifungal therapy. We report a patient with cryptococcal meningitis who, while on intravenous 5-flucytosine and amphotericin B, developed life-threatening bilateral massive pleural effusions with evidence of spontaneous resolution, consistent with prior hypothesis of antigenic stimulation as the cause of pleural involvement.

Keywords: cryptococcosis; pleural effusions

Cryptococcus neoformans infection usually presents as chronic meningitis and is increasingly recognised in immunocompromised patients.¹ Serious underlying illnesses or treatment with corticosteroids and/or immunosuppressants predispose to disseminated cryptococcosis. Pleural effusions are unusual and may be diagnosed with a positive cryptococcal antigen test.¹ We report a case of massive bilateral pleural effusions occurring in an apparently immune-competent woman with cryptococcal meningitis.

Case report

A 30-year-old previously well woman presented with severe persistent bitemporal and occipital headaches of six weeks duration. There were associated symptoms of night sweats and vomiting but no other constitutional symptoms. She was a non-smoker and had had no prior illness. Medical examination and magnetic resonance imaging of the brain performed at the beginning of the illness at another hospital were unremarkable. On the day of admission to our hospital, she developed diplopia and had a generalised tonic-clonic seizure. She was drowsy but afebrile and had bilateral papilloedema and lateral rectus palsies. Computed tomography (CT) of her brain

was normal. Her cerebrospinal fluid (CSF) showed lymphocytosis (240 cells/dl), high protein level (59 mg/dl), normal glucose and chloride levels, elevated pressure of 37.8 cmH₂O and was positive for cryptococcal antigen (titre 1:256) and culture-positive for *Cryptococcus neoformans*. Her chest X-ray was normal. She tested negative for HIV I and HIV II antibodies.

She was commenced on intravenous amphotericin B (0.5 mg/kg/day) and 5-flucytosine (180 mg/kg/day) for cryptococcal meningitis. On day 8 of therapy, a ventriculoperitoneal shunt was inserted to relieve the increasing CSF pressure (>60 cmH₂O) which was associated with worsening papilloedema and visual loss. On day 10, she was still febrile and had become extremely dyspnoeic overnight; unable to recline from a sitting position. The chest radiograph at this stage revealed bilateral massive pleural effusions, greater on the right side. Thoracentesis was performed and an intercostal chest tube was left in-situ on the right. Clear pleural fluid amounting to over 3.5 litres was drained over the next three days. Pleural fluid analysis revealed a protein concentration of 2.5 g/dl (serum protein 78 g/dl), lactate dehydrogenase (LDH) 23 IU/l (serum LDH was 218 IU/l), white cell count 230 cells/dl with 91% polymorphs. The pleural fluid was culture and smear negative for pyogenic micro-organisms, mycobacterium and fungus but was positive for cryptococcal antigen. Blood cultures were also negative.

The massive left effusion resolved spontaneously and the right chest drain was removed after 8 days with no further recurrence of the effusion. A repeat chest radiograph while on antifungal therapy was clear but the CT scan of the thorax showed a cavitating infiltrate in the left lower lobe.

The patient made an uneventful recovery after 11 weeks of amphotericin and 5-flucytosine therapy and was functionally normal when last seen. Further questioning revealed she had been living two doors away from a pigeon breeder for the last 3 years. She was discharged on oral fluconazole 400 mg daily but was lost to follow-up.

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Discussion

Cryptococcus neoformans infection is now more commonly recognised in immunocompromised hosts especially in those with the acquired immunodeficiency syndrome but may occur even in healthy individuals.² Despite the respiratory tract being the major port of entry, pulmonary manifestations are infrequent or mild and chronic meningitis is the commonest mode of manifestation.¹ Pleural cryptococcosis is seldom reported and was thought to connote dissemination in the immunocompromised hosts but later evidence appears to dispute this.³ It has been postulated that the release of antigen rather than organism growth is responsible for pleural manifestations. Pleural effusions, if present, are almost always associated with underlying lung parenchymal lesions which may manifest as subpleural nodules, interstitial infiltrates, pulmonary masses, miliary nodules, focal or widespread alveolar consolidation and lymphadenopathy.⁴ Pleural effusions occurring after commencement of treatment has been reported but are exceptionally rare.¹

There have been very few documented cases of massive pleural effusions.⁵ Our case is of interest as she developed massive bilateral effusions whilst on intensive antifungal chemotherapy. The release of cryptococcal antigens as the stimulus for the pleural effusions appear to be an attractive explanation for the sudden massive accumulation of fluid in this case. The spontaneous resolution of the massive left

Learning points

- pleural involvement is unusual in cryptococcosis but may manifest as massive bilateral effusions while on antifungal therapy
- pleural cryptococcosis may be reliably diagnosed by cryptococcal antigen test on the pleural fluid
- clinical and radiological involvement of the lung and pleura should be sought in cases of cryptococcal meningitis

pleural effusion without additional therapy concurs with previously reported observations.⁶

Normally, diagnosis may be achieved by pleural biopsy, culture and/or detection of cryptococcal antigen in the pleura or pleural fluid. The fluid itself may be haemorrhagic or serosanguinous in nature and tends to be lymphocytic in cellular response. Our case is unusual as her pleural fluid demonstrated neutrophilic pleocytosis. Protein levels range from 2.5 to 5.7 g/dl.³ Treatment is with amphotericin, frequently administered with 5-flucytosine for synergistic effect, especially in the severely immunodeficient patients. Fluconazole alone has received widespread acceptance for less severe infections. Some isolated bronchopulmonary infections have done well without treatment. Likewise, isolated pleural disease may also resolve spontaneously in immunocompetent individuals with localised thoracic disease.

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