Case report

Cryptococcal pneumonia in HIV

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Case 1

A 42-year-old black man was diagnosed with cryptococcal meningitis in February 2008, 1 month after starting antiretroviral therapy (CD4 count nadir 78 cells/mm^3). He completed 2 weeks of intravenous amphotericin B and continued on maintenance fluconazole. A serum cryptococcal latex agglutination titre (CLAT) at diagnosis was >1:4 096. In June 2008 he was referred to the respiratory clinic with 8 months of dyspnoea, 5 months' loss of weight and night sweats, and a cough productive of small amounts of white sputum for the past month. The referring hospital had started empiric amphotericin B for cryptococcal pneumonia on the basis of his symptoms, a failure to demonstrate *Mycobacterium tuberculosis* or *Pneumocystis jirovecii* on sputum microscopy, and the fact that while on amphotericin B in February 2008 he had noted a slight improvement in his respiratory symptoms. Bilateral fine reticulonodular infiltrates were evident in both mid-zones on chest X-ray (Fig. 1) and his serum CLAT was elevated at 1:2048. Despite recommencing intravenous amphotericin B, there was no response to therapy after 5 days, precipitating referral for bronchoscopy.

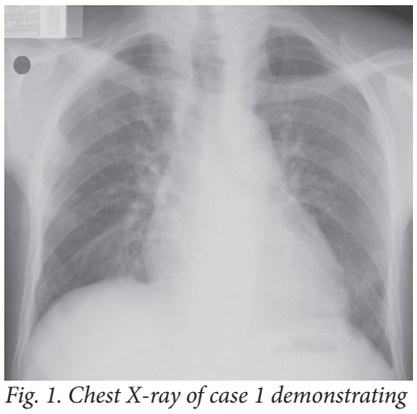

Fig. 1. Chest X-ray of case 1 demonstrating fine reticulonodular infiltrates in the lower zones.

On examination he was thin and wasted, with finger clubbing, bilateral parotidomegaly and small, generalised lymphadenopathy. There was no evidence of mucocutaneous Kaposi's sarcoma. His respiratory rate was 24 breaths/min with soft breath sounds but no added sounds. Sputum microscopy was again negative for *M. tuberculosis* and *P. jirovecii*. Transbronchial biopsies identified numerous yeast forms of *Cryptococcus neoformans* invading the lung parenchyma (Fig. 2), confirming the diagnosis of cryptococcal pneumonia.

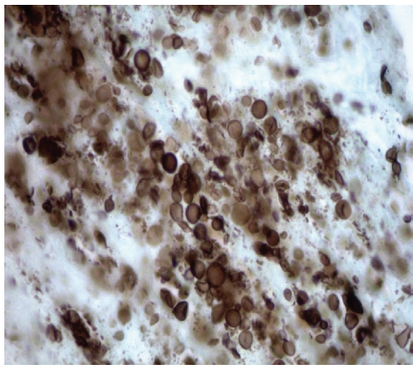

Fig. 2. Grocott stain of lung tissue obtained by transbronchial biopsy.

Case 2

A 47-year-old antiretroviral-naïve woman with HIV was referred to the respiratory clinic complaining of mucoid cough for 6 months. She experienced left-sided pleuritic chest pain, grade 2 dyspnoea and loss of weight in excess of 10 kg. She was comfortable at rest with a respiratory rate of 22 breaths/min. There was dullness, soft breath sounds and inspiratory crackles in the left base posteriorly. Investigations revealed a CD4 count of 44 cells/mm^3 and her chest X-ray showed interstitial infiltrates with fine nodularity more pronounced in the right lower zone than on the left (Fig. 3). Empiric TB treatment was commenced, but stopped once sputum culture confirmed a non-tuberculous mycobacterium rather than *M. tuberculosis*. Without a firm diagnosis, she was referred for bronchoscopy. Transbronchial biopsy showed lung parenchyma diffusely infiltrated by cryptococci (Fig. 4).

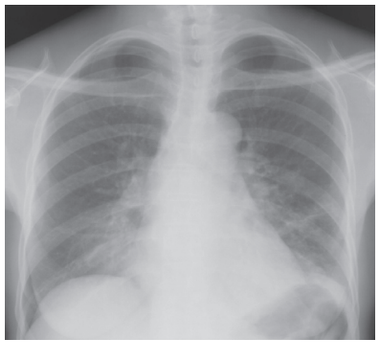

Fig. 3. Chest X-ray of case 2 demonstrating fine reticulonodular infiltrates in the lower zones.

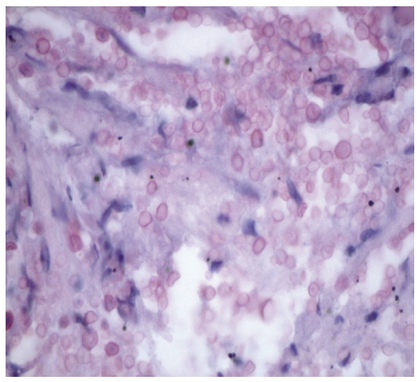

Fig. 4. Transbronchial biopsy of case 2 demonstrating numerous encapsulated fungi on mucicarmine stain.

Case 3

An antiretroviral-naïve 28-year-old woman with a CD4 count of 290 cells/mm^3 developed her first episode of pulmonary tuberculosis in 2003. One year later she was again treated for culture-confirmed pulmonary tuberculosis. Three months into treatment, a left lower lobe lung abscess caused by *Streptococcus viridans* was diagnosed. She was referred to our clinic for assessment of a non-resolving right lower lobe infiltrate following 8 months of TB treatment. Her only symptoms were those of an intermittent dry cough and grade 2 dyspnoea. There were reduced breath sounds with inspiratory crackles and bronchial breathing in the right base posteriorly. Chest X-ray confirmed right lower lobe consolidation (Fig. 5) and she proceeded to bronchoscopy. A histopathological diagnosis of *P. jirovecii* pneumonia was made on transbronchial lung biopsy and she was treated for 3 weeks with high-dose co-trimoxazole. However, the right lower lobe infiltrate persisted on chest X-ray, precipitating a repeat bronchoscopy. This time cryptococci were demonstrated on transbronchial biopsies. Sadly, by the time she returned to our clinic for the results of the second biopsy, she had developed signs of meningitis confirmed on cerebrospinal fluid sampling as cryptococcal meningitis. Despite prompt admission and starting intravenous amphotericin B, the patient died 3 weeks later.

In summary, these cases demonstrate the varying temporal relationships between the presentation of cryptococcal pneumonia and meningitis. Case 1 represents a patient previously treated for cryptococcal meningitis who subsequently developed cryptococcal pneumonia; case 2 a patient who developed cryptococcal pneumonia

in the absence of any meningitis; and case 3 a patient who developed cryptococcal pneumonia prior to the development of meningitis.

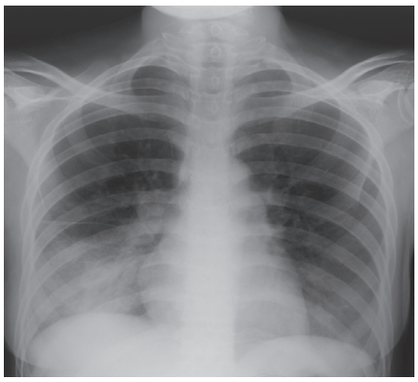

Fig. 5. Chest X-ray of case 3 demonstrating alveolar infiltrates in the right lower zone.

Discussion

Cryptococcal pneumonia is caused by the yeast *C. neoformans* found in soil contaminated by pigeon droppings. It shares many pathogenetic traits with tuberculosis. Both are acquired by aerosol spread to the lungs, where subclinical infection most often occurs. Thereafter, depending on the state of host immunity, infection may be cleared, remain in a latent form in the lungs, or disseminate to extrapulmonary sites, which in the case of cryptococcus, typically involves the meninges.[1]

Cryptococcal pneumonia accounts for up to 15% of AIDS-related pneumonia in North America and has been noted to occur in up to 40% of cases with cryptococcal meningitis.[2] In South Africa, Wong *et al.* found that 7% of autopsied miners (a group with a high prevalence of HIV) had evidence of cryptococcal pneumonia, 47% of which had concomitant meningitis.[3] Of these cases, only 1.2% were correctly diagnosed in life and 30% were misdiagnosed with TB. This highlights the complexity of diagnosing cryptococcal pneumonia and raises serious concerns over whether many infections are being missed. Symptomatology and chest X-ray changes are often nonspecific in cryptococcal pneumonia and the relative contribution of cryptococcal pneumonia may be overshadowed by co-morbid respiratory tract opportunistic infections, such as *P. jirovecii* pneumonia, as in case 3.

Clinical features

The spectrum of cryptococcal pneumonia ranges from entirely asymptomatic to the development of acute respiratory failure. The most common symptoms are fever, fatigue and weight loss, with cough productive of scanty mucoid sputum, and dyspnoea occurring in up to 71% and 50% respectively.[2-5] Chest pain is less frequently reported and haemoptysis is rare. The radiological patterns are equally variable, the commonest finding being diffuse interstitial infiltrates which mimic TB or *P. jirovecii* pneumonia. Other patterns include consolidation, ground-glass opacification, lymphadenopathy and pleural effusions, all of which are features of either TB or *P. jirovecii* pneumonia.

Diagnosis

Our 3 cases exemplify the challenge of diagnosing cryptococcal pneumonia. Culture from bronchoalveolar lavage and histology from transbronchial biopsies are the gold standard tests. Sputum culture performs variably.[2,5] A reliable non-invasive diagnostic test would be of great benefit. CLAT, which denotes extrapulmonary dissemination, has been evaluated. A titre of >1:8 in serum had a sensitivity and specificity of >95% for predicting patients with symptomatic pulmonary cryptococcosis in one study.[7] Studies of the utility of CLAT from bronchoalveolar lavage have shown promising results in the same study.[7] Analysis of CLAT from induced sputum by Bottone and colleagues recorded 2/9 patients with proven cryptococcal pneumonia having a positive sputum CLAT.[8] We are currently evaluating the utility of sputum CLAT in our setting of high HIV and TB prevalence in South Africa.

Recommendation

In this case series, all diagnoses of cryptococcal pneumonia were made following flexible fibreoptic bronchoscopy. In a resource-limited setting, this facility is most often unavailable. Clinicians need to consider pulmonary cryptococcosis as a diagnosis in all HIV patients with new pulmonary infiltrates and advanced HIV disease, particularly in those for whom a diagnosis of tuberculosis or *P. jirovecii* pneumonia has been excluded or in whom an empiric trial of therapy fails to resolve the clinical presentation. In this situation, we advocate the use of serum CLAT to diagnose disseminated cryptococcosis, raising the probability of cryptococcal pneumonia. A lumbar puncture to exclude CNS dissemination should also be performed if the serum CLAT is positive. Pulmonary cryptococcosis in HIV-infected patients should be treated as per the recommended guidelines,[9,10] i.e intravenous amphotericin B for 2 weeks followed by oral fluconazole at 400 mg daily to 10 weeks followed by maintenance therapy 200 mg daily. Fluconazole may be discontinued once the CD4 count remains >200 cells/mm^3 for at least 6 months.[9] In the case of symptomatic patients whose serum CLAT is negative as are tests for TB and *P. jirovecii* pneumonia, we currently advocate referral for flexible fibreoptic bronchoscopy and transbronchial biopsies.

Conclusion

Our case series highlights the challenge of diagnosing cryptococcal pneumonia in HIV-positive patients. A high index of suspicion should be maintained in the patient with a low CD4 count and pulmonary infiltrates in whom investigations for other opportunistic infections are negative. The use of a serum CLAT should aid in diagnosing disseminated cryptococcosis and alert clinicians to the possibility of underlying cryptococcal pneumonia. The utility of sputum CLAT in the setting of high HIV/TB co-infection needs further evaluation.

References

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Inflammatory myopathy, malignancy and steroid unresponsiveness – an interesting case

L VARKEL, Y VALLIE

JS, a 58-year-old man, was diagnosed with an inflammatory myopathy on the basis of: proximal weakness, elevated creatinine kinase (CK) (7 000) and a myopathic picture on electromyography. He was commenced on prednisone and his CK fell to 3 900, with some improvement in weakness.

At follow-up, the patient had weight loss, worsening weakness and dysphagia.

Further history revealed a significant smoking history and change in bowel habit. Inflammatory myopathy was confirmed histologically and common malignancies were excluded by chest and abdomen CT, endoscopic gastrointestinal assessment and prostate evaluation.

We added methotrexate to his therapy with a slow, but positive response.

Discussion

Up to 75% of patients with an inflammatory myopathy are steroid-unresponsive, requiring additional immunosuppression such as methotrexate or azathioprine.[1] Other reasons for non-response include alternative diagnoses, such as inclusion body myositis, or an underlying malignancy.

The association between inflammatory myopathies and malignancy is greatest in dermatomyositis, with a 3-fold increase in malignancy. Polymyositis confers a 30% increased risk. The risk of a malignancy is greatest within the first 5 years of diagnosis and may not be present at time of diagnosis.[2]

A consensus-guiding malignancy search suggests an age-specific examination: endoscopic assessment and chest and abdominal studies in all patients, mammography and pelvic examination in females and prostate evaluation in males. Assessment for malignancy is critical in steroid-unresponsive patients.[3]

In summary, we present a patient with steroid-unresponsive polymyositis where an underlying malignancy was excluded.

References

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