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Disseminated cryptococcosis presenting as mediastinal and hilar lymphadenopathy in an immunocompetent patient

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Abstract

We herein report a rare case of disseminated cryptococcosis presenting as mediastinal and hilar lymphadenopathy in a young immunocompetent man. A previously healthy 26-year-old man presented with persistent headache and nonproductive cough. Chest computed tomography indicated mediastinal and hilar lymphadenopathy. Cryptococcal lymphadenitis and meningitis was confirmed by endobronchial ultrasound-guided transbronchial needle aspiration and central spinal fluid examination, respectively. He received liposomal amphotericin B and flucytosine followed by fluconazole and finally improved.

Introduction

Cryptococcosis is a potentially life-threatening invasive fungal infection and is often associated with disseminated disease. It mainly occurs in immunocompromised hosts such as acquired immunodeficiency syndrome patients and less frequently in immunocompetent patients [1]. The most commonly affected sites in immunocompetent hosts are the lungs and central nervous system, while the lymph nodes usually remain unaffected. We herein report a case of disseminated cryptococcosis presenting as hilar and mediastinal lymphadenopathy in an apparently immunocompetent young man.

Case Report

A previously healthy 26-year-old man who worked as a freight forwarder at an international airport had developed a high fever and nonproductive cough following a persistent headache for a month. He was a non-smoker but a social drinker. Antibiotics were administered based on the suspicion of pneumonia at a local hospital, but they were ineffective. As such, he was referred to our hospital for further evaluation.

The patient's body temperature was 38.3°C. On physical examination, a stiff neck and palpable lymph nodes were absent. A chest auscultation revealed a normal vesicular breathing sound without any crackles.

Blood tests showed elevated white blood cell counts (11,700 cells/μL) and C-reactive protein levels (6.8 mg/dL). Chest X-Ray and computed tomography revealed a right hilar and mediastinal lymphadenopathy, and partial atelectasis of the right lung without apparent parenchymal abnormalities (Fig. 1A, C, and D).

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed for diagnosis. Subcarinal and right interlobar nodes were biopsied without any complications. The culture tests of obtained specimens were negative. Pathological examination demonstrated epithelioid cell granulomas with multinucleated giant cells and many yeast-like organisms (Fig. 2A). These organisms were positive for Grocott, periodic acid-Schiff/Alcian blue and mucicarmine stains (Fig. 2B–D).

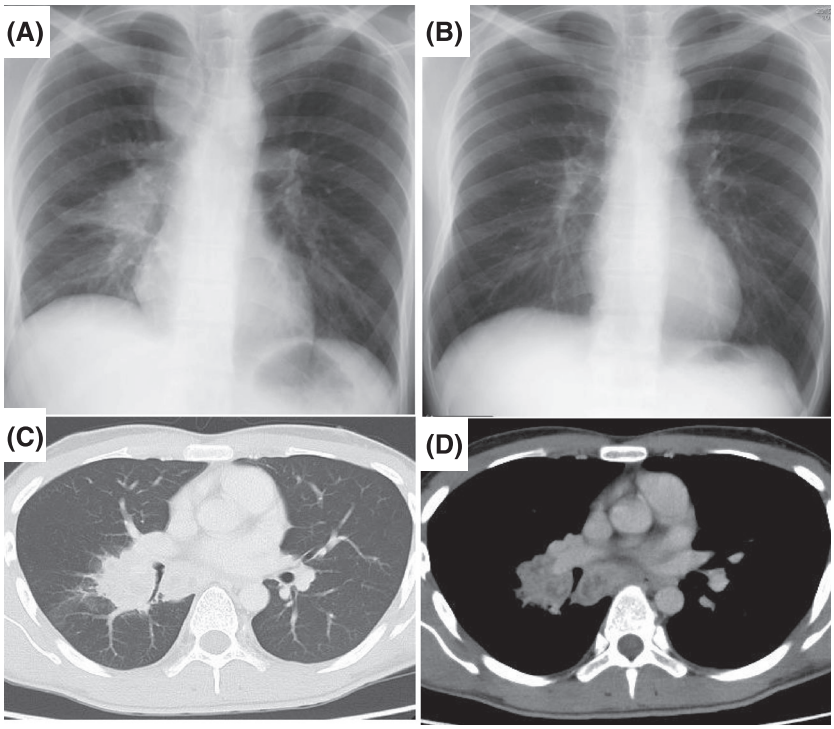

Figure 1. (A, C, D) A chest X-ray and computed tomography showed mediastinal and hilar lymphadenopathy with focal necrosis and partial atelectasis of the right lung. (B) The follow-up chest X-Ray three months after treatment initiation demonstrated a significant reduction in lymphadenopathy and disappearance of atelectasis.

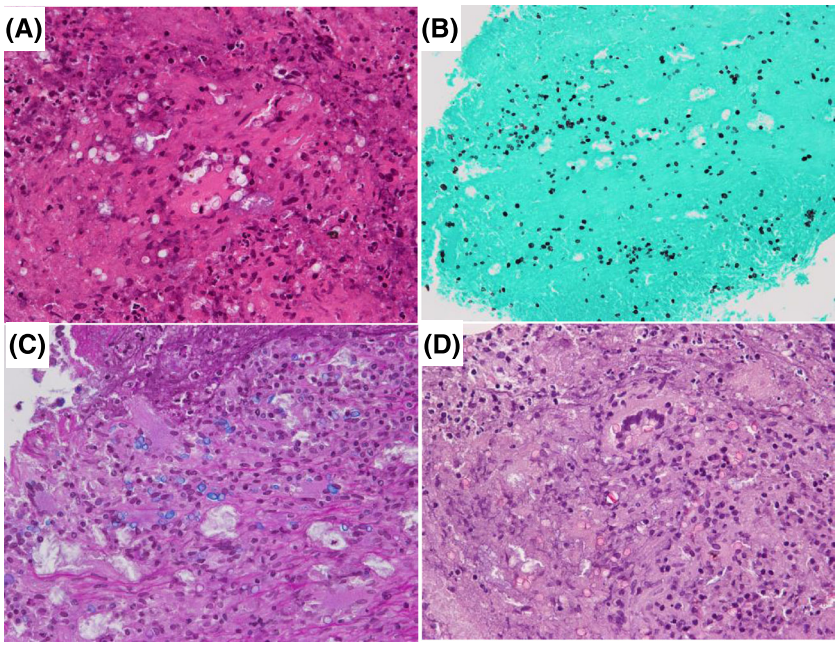

Figure 2. Pathological findings. (A) A specimen showed epithelioid cell granulomas with multinucleated giant cells and many yeast-like organisms (hematoxilin and eosin, ×100). These microorganisms were positive for the Grocott (B), periodic acid-Schiff/Alcian blue (C), and mucicarmine stain (D).

A serum cryptococcal antigen test was negative and blood culture revealed no organism growth. Cerebrospinal fluid (CSF) analysis revealed high white blood cell counts (170 cells /μL, lymphocyte dominant) and protein levels (63 mg/dL) but normal pressure (15 cmH_2O) and glucose levels (50 mg/dL). A cryptococcal antigen and culture of CSF was negative. Magnetic resonance imaging of the head presented normal findings. Serologic testing to assess his immune status revealed no abnormalities: negative results of human immunodeficiency virus (HIV) and human T-cell leukemia virus type 1 antibodies, and normal levels of glucose, immunoglobulins, complements, and cluster of differentiation 4 (CD4) cell counts.

The patient was suspected to suffer from disseminated cryptococcosis with lymphadenitis and meningitis from the results of pathologic and CSF analysis. The patient received 5 weeks of intravenous liposomal amphotericin B and 3 weeks of oral flucytosine followed by oral fluconazole. His symptoms subsequently improved, and a follow-up examination demonstrated significant reduction in lymphadenopathy, disappearance of atelectasis (Fig. 1B) and normalized CSF cell counts. The fungi were identified as *Cryptococcus neoformans* var. *grubii* by genetic analysis using pathologic specimens after treatment initiation.

Discussion

Cryptococcus is a basidiomycetous yeast ubiquitous in the environment. It is a major human fungal pathogen and includes two medically important species, *C. neoformans* and *C. gattii*. *C. neoformans* is further divided into *C. neoformans* var. *grubii* and *C. neoformans* var. *neoformans*. *C. neoformans* var. *grubii* is the causative agent for the majority of the cases of cryptococcosis, while the other subtypes are far less clinically prevalent. These microorganisms are typically a threat to immunocompromised patients (e.g. HIV-infected patients, patients with long-term glucocorticoid therapy or patients after organ transplantation), but a number of immunocompetent cases have also been described.

Cryptococcal infection develops after inhalation of fungal spores. The host's immune status determines the dissemination and clinical course of infection. In immunocompetent hosts, these microorganisms tend to be localized without dissemination, and pulmonary lesions mainly present as solitary or multiple nodules [2]. Lymph node involvement is rare and is usually part of the disseminated disease or an immune reconstitution inflammatory syndrome in HIV-infected individuals.

The diagnosis of cryptococcosis is usually based on isolation of the fungus from cultured clinical specimens, but it requires several days and a large amount of samples. The detection of cryptococcal capsular antigen in serum and CSF specimens by latex agglutination is one of the most helpful adjunct techniques to diagnose cryptococcosis because of its excellent sensitivity. On rare occasions, false-negative antigen detection could be caused by unencapsulated *Cryptococcus* [3], or the prozone phenomenon resulting from excess antibodies that interfere with proper formation of the antigen-antibody lattice network [4]. Although the reason for a negative antigen result in our case study was not fully elucidated, the occurrence of unencapsulated *Cryptococcus* was improbable because we confirmed the presence of capsule in pathological specimens by periodic acid-Schiff and mucicarmine stain.

We successfully diagnosed cryptococcal infection by EBUS-TBNA and molecular analysis. The feasibility and accuracy of molecular methods using EBUS-TBNA specimens have been well established in thoracic malignancies [5]. Molecular analysis has a high diagnostic yield and can distinguish between *Cryptococcus* and the other yeast-like fungi [6]. In uncommon situations where the cryptococcal antigen is not detected, such as in our case study, and the fungus does not grow or is seen only in pathological sections, molecular methods are useful in the diagnosis.

In our case study, the reason as to why an apparently immunocompetent patient acquired cryptococcal infection was unclear. It is possible that he had been exposed to a large number of fungal spores due to his job hazard of handling various cargoes from all over the world as a freight forwarder. Rosen et al. previously reported that anti-granulocyte-macrophage colony stimulating factor autoantibodies were associated with some cases of cryptococcal meningitis in otherwise immunocompetent patients [7].

The Infectious Diseases Society of America published a clinical practice guideline for the management of cryptococcal disease [1]. It recommends amphotericin B plus flucytosine followed by fluconazole for cryptococcal meningoencephalitis and severe pulmonary cryptococcosis in immunocompetent patients. We started initial treatment according to these recommendations. The patient had a good clinical course and continued oral fluconazole in the outpatient department.

In conclusion, mediastinal and hilar lymphadenopathy are rare presentations of disseminated cryptococcosis in immunocompetent patients. Physicians should recognize its unlikely but nonetheless possible occurrence and develop therapeutic strategies. EBUS-TBNA and molecular analysis is useful when the diagnosis cannot be established by conventional methods.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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