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Pulmonary coinfection by *Pneumocystis jiroveci* and *Cryptococcus neoformans*

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ABSTRACT

We communicate the diagnosis by microscopy of a pulmonary coinfection produced by *Cryptococcus neoformans* and *Pneumocystis jiroveci*, from a respiratory secretion obtained by bronchoalveolar lavage of an AIDS patient. Our review of literature identified this coinfection as unusual presentation. Opportunistic infections associated with HIV infection are increasingly recognized. It may occur at an early stage of HIV-infection. Whereas concurrent opportunistic infections may occur, coexisting *Pneumocystis jiroveci* pneumonia (PCP) and disseminated cryptococcosis with cryptococcal pneumonia is uncommon. The lungs of individuals infected with HIV are often affected by opportunistic infections and tumours and over two-thirds of patients have at least one respiratory episode during the course of their disease. Pneumonia is the leading HIV-associated infection. We present the case of a man who presented dual *Pneumocystis jiroveci* and cryptococcal pneumonia in a patient with HIV. Definitive diagnosis of PCP and *Cryptococcus* requires demonstration of these organisms in pulmonary tissues or fluid. In patients with < 200/microliter CD4-lymphocytes, a bronchoalveolar lavage should be performed. This patient was successfully treated with amphotericin B and trimethoprim sulfamethoxazole. After 1 week the patient showed clinical and radiologic improvement and was discharged 3 weeks later.

1. Introduction

Cryptococcosis has dramatically increased in frequency as a result of the pandemic of human immunodeficiency virus (HIV) infection and an enlarging population of other immunocompromised individuals. The main morbidity in cryptococcal infection comes from the dissemination of the fungus beyond the confines of the lung. *Cryptococcus neoformans* (*C. neoformans*) var *neoformans* is strongly tropic for the central nervous system (CNS), and the vast majority of clinically recognized infections involve the meninges[1]. This meningeal disease so overshadows the pulmonary disease that most physicians do not even think of the lung as an organ involved by the *Cryptococcus*. In fact, in most patients with cryptococcal meningitis, the chest radiograph is either normal, or at most, has an incidental pulmonary focus. People with weakened immune systems, such as those suffering from AIDS, are generally more susceptible to this kind of infection[2].

The severe immunosupression that affects AIDS patients makes them susceptible to numerous infections, called "opportunistic" due to the poor pathogenicity of their etiologic agents or the immunologic deterioration of the host. These infections may occur in joint form, appearing as generalized infections or just localized in certain organs. *Pneumocystis jiroveci* (*P. jiroveci*), recently incorporated in the Fungi Kingdom, is responsible for the pulmonary pneumocystosis (PCP), considered as one of the most frequent opportunistic infections in AIDS patients. Its clinical picture becomes evident when the $CD4^+$ T limphocyte count is < 200 cells/μL[3].

Although a biopsy may need to be performed in complicated patients, bronchoalveolar lavage (BAL) is an important adjunct to the diagnosis of pulmonary and disseminated infections. Culture is the gold standard for diagnosis in many instances, but cytologic and morphologic analysis is often diagnostic. Although newer molecular and antigen techniques may be applied to BAL samples, the role of such tests is yet to be defined for many pathogens[1].

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2. Case report

A 42-year-old man with a history of pulmonary tuberculosis had been diagnosed with HIV seropositive 1 year ago and treated with Atripla for the last 2 months. He was admitted with a 1-week history of asthenia, dyspnea and fever. Blood gases showed acute respiratory failure and his white blood cell count was 3 180/mm^3, with 50/mm^3 lymphocytes. Chest X-ray and CT scan revealed upper peripheral bilateral interstitial infiltrates and an alveolar infiltrate in the right lower lobe. *P. jiroveci* and *C. neoformans* were found in both BAL and transbronchial biopsy specimen. The wet mount microscopy of the sample' concentrate by centrifugation revealed the presence of typical "honeycombs structures", pathognomonic of *P. jiroveci* pneumonia (PCP), and abundant capsulated yeasts, compatible with *C. neoformans* (Figure 1A). Grocott stain applied to hot fixed smears of the BAL sample revealed capsulated yeasts and cysts of *P. jiroveci* (Figure 1B). Treatment with liposomal amphotericin B (6 mg/kg/day) and trimethoprim-sulphamethoxazole (320-1 600 mg/8 h) was started. The patient was transferred to the intensive care unit because of refractory respiratory failure and non-invasive intermittent positive-pressure ventilation was started. After 1 week the patient showed clinical and radiologic improvement and was discharged 3 weeks later.

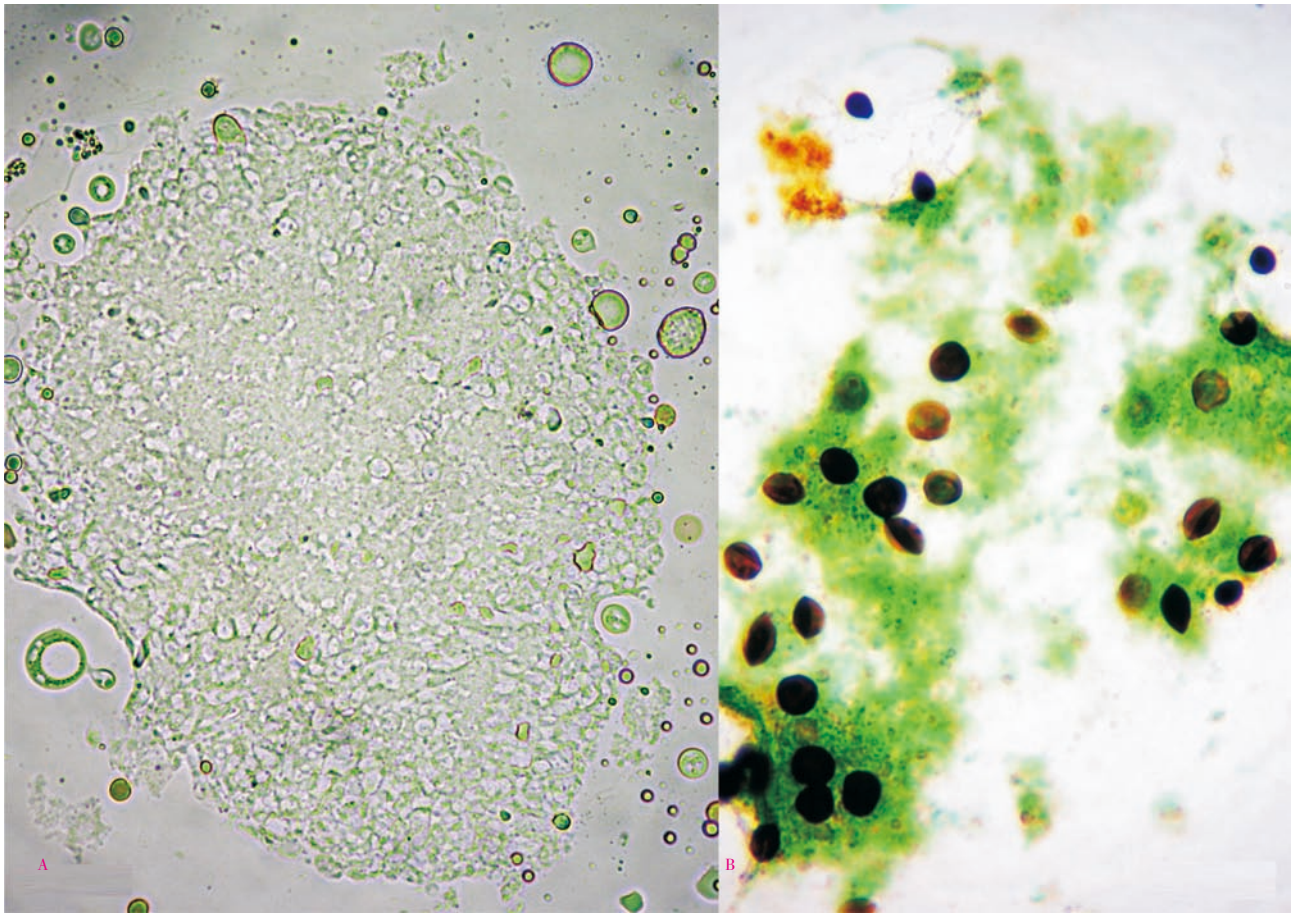

Figure 1. Observations of the smear of BAL sample.
A: Foamy exudate and capsulated yeasts in fresh microscopy of BAL concentrate (1 000×); B: Cysts of *P. jiroveci* and capsulated yeasts in a smear of BAL concentrate stained with Grocott (1 000×).

3. Discussion

Pulmonary disease is a major source of morbidity and mortality in HIV-infected persons. PCP has decreased substantially during the last ten years, but in the United States it remains the most common disorder that announces the onset of AIDS. In contrast, tuberculosis is by far the most important AIDS-associated indicator disease in developing countries, such as Argentina. The clinical presentation of pulmonary tuberculosis varies with the state of immunity. Community-acquired acute bacterial pneumonia is a common HIV-linked complication throughout the world. Pneumonia occurs at all levels of immune suppression but increases in frequency as CD4 counts decrease[1].

The coinfection of *P. jiroveci* with other microbial agents *i.e.* bacteria, mycobacteria, fungi or protozoa, is infrequently diagnosed by microscopy in respiratory samples submitted to our laboratory. About 10% of these samples correspond to associated infectious diseases, as it was determined by cultures in a previous work performed by us and other authors with a similar cohort[2,3]. This case has been the first case of coinfection by *P. jiroveci* and other fungi, bacteria, mycobacteria or protozoa diagnosed by microscopy, with the methodology habitually employed

in our laboratory[4]. Over two-thirds of all HIV-infected individuals have an associated pulmonary disease. The following causes are frequently observed: bacterial infection (*Streptococcus pneumoniae*, *Haemophilus influenzae* and mycobacteria), protozoal infection (*P. jiroveci*), fungal infection (*C. neoformans* and *Histoplasma capsulatum*), viral infection (cytomegalovirus), tumors (Kaposi's sarcoma) and pneumonitis[5]. Pulmonary cryptococcosis is rare in the immunocompetent patient.

Pulmonary infection by *C. neoformans* has been reported in immunocompetent and immunocompromised patients. Pulmonary cryptococcosis most commonly occurs in AIDs patients, those undergoing cytotoxic chemotherapy, those receiving other immunomodulating agents such as corticosteroids, transplant recipients, or patients with hematologic malignancy. Although the lungs are the portal of entry for *Cryptococcus*, pulmonary disease is relatively uncommon. Most patients, particularly those who are immunocompromised, present with meningoencephalitis. Local pulmonary infection may be seen in patients with higher CD4 cell counts or in immunocompetent patients, who most often present with isolated pulmonary nodules[6,7].

In summary, AIDS individuals have increased susceptibility to a range of infections which are uncommon in the normal host. An understanding of the individual's immune defect provides important information about the range of organisms that this individual may be susceptible to[8]. For diagnosis of patients' immune status, imaging techniques, and microbiological, cytological and histological examination of respiratory secretions and biopsy material are important. Infection with *P. jiroveci* remains common as a cause of respiratory disease in HIV-infected patients, mainly in those without prophylaxis[9]. Though life threatening, pneumocystis pneumonia is a treatable infection and therefore, a rapid and accurate diagnosis is mandatory. Clinically these patients present with respiratory symptoms and/or signs suggestive of pulmonary infection like cough, dyspnoea, fever or an abnormal chest radiograph. These signs and symptoms may also be observed in other opportunistic infections in patients with AIDS or other immunocompromised states[10]. Due to nonspecific clinical and chest film presentations as well as frequent coinfections, definite diagnosis should be carried out in all HIV infected patients with pulmonary infections[11,12]. Because these opportunistic pulmonary infections remain a significant problem in HIV-infected patients, early bronchoscopy with BAL in those patients treated with presenting respiratory symptoms and/or abnormal Chest X-ray should be considered in order to diagnose and treat these opportunistic infections promptly. The diagnostic yield from BAL is high in immunocompromised patients with respiratory complaints[13]. In severely immunosuppressed hosts with PCP, including patients with HIV/AIDS, coexisting lung infection is not an uncommon occurrence. It is reported in up to 40% of cases in some series. Organisms such cytomegalovirus, *C. neoformans*, herpes simplex, and bacteria have been identified in or grown from lung tissue from patients with PCP[14]. Dual pulmonary infection caused by both *P. jiroveci* and *C. neoformans* has been only rarely reported[15]. The precise contribution of *C. neoformans* infection to PCP is uncertain. Prognosis depends on immunological status and underlying comorbidities[16].

Conflict of interest statement

We declare that we have no conflict of interest.

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