

**CASE REPORT**


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**PULMONARY COINFECTION BY *Pneumocystis jiroveci*,  
*Cryptococcus neoformans* AND CYTOMEGALOVIRUS IN HIV  
PATIENT WITHOUT ANTIRETROVIRAL TREATMENT**

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**ABSTRACT**

Pulmonary diseases are among the main causes of morbidity and mortality in HIV patients. Here, we present the fatal case of a 30 year-old AIDS patient, who did not undergo antiretroviral treatment, presenting pulmonary coinfection by *Pneumocystis jiroveci*, *Cryptococcus neoformans* and cytomegalovirus diagnosed in the postmortem histological examination. Concurrent pulmonary infection by these three agents is not common and, to date, apparently had not been reported in the literature.

**KEY WORDS:** HIV; *Pneumocystis jiroveci*; *Cryptococcus neoformans*; cytomegalovirus; pulmonary infection.

**INTRODUCTION**

Highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) infection dramatically reduced AIDS-related morbidity and mortality; however, opportunistic lung infections remain a major cause of hospitalization in these patients, due to decreased CD4 T lymphocyte counts (Brooks et al., 2009; Brasil, 2013).

Most common lung diseases are those caused by fungi such as cryptococcosis usually caused by *Cryptococcus neoformans*, histoplasmosis caused by *Histoplasma capsulatum* and pneumocystosis, caused by *Pneumocystis jiroveci*, which leads to intra-alveolar pneumonitis due to alveolar occupation by exudate, thickening of the alveolar membrane, inflammation of parenchyma, and subsequently edema and fibrosis (Thomas & Limper, 2004; Thomas & Limper, 2007).

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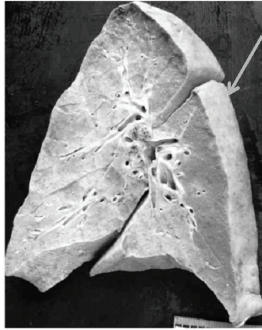
In addition to pneumocystosis, patients with HIV/AIDS commonly present complications caused by opportunistic viruses such as cytomegalovirus (CMV). Infection may remain latent, hardly recognized by the immune system, being one of the major causes of morbidity and mortality in HIV patients worldwide (Fielding et al., 2011; Soderberg-Naucler, 2006).

Pulmonary coinfection by *Pneumocystis jiroveci* and *Cryptococcus neoformans* is considered uncommon, although it has already been reported in the literature (Javier et al., 2012). There are some reports of HIV patients with Pneumocystis pneumonia associated with cytomegalovirus, but they are also uncommon (Polaczek et al., 2014). Here, we present a case of a patient with AIDS without antiretroviral treatment with pulmonary coinfection by *Pneumocystis jiroveci*, *Cryptococcus neoformans* and Cytomegalovirus diagnosed in the postmortem histological exam. Concurrent pulmonary infection by these three agents is not common and, to date, apparently had not been reported in the literature.

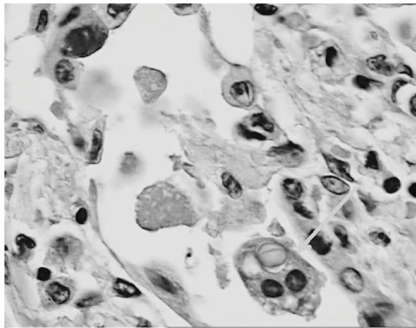
## CASE REPORT

A 30 year-old white man, farmer, married, reported one month of hyporexia and insomnia, watery diarrhea for 15 days, fever for 6 days, dyspnea and nausea for 5 days. His HIV rapid test was positive, subsequently confirmed by serology. His medical history was meaningless. On physical examination, there were no fever, no pulmonary or cardiac abnormalities. He presented pain during left hypocondric palpation and lip lesions of *Herpes simplex* virus. Chest X-Ray showed a bilateral thin interstitial infiltrate around the pulmonary hilum and bases. Sulfamethoxazole/trimethoprim for *P. jiroveci* pneumonia was started. No infectious agents were found in the stool tests. After 15 days of hospitalization, he presented the first fever episode, while diarrhea and dyspnea persisted. In the 19<sup>th</sup> day of hospitalization, a chest X-ray showed parenchymal opacities in both hemithoraces. Sputum exam was negative for acid-fast bacilli. Hemoculture was positive for *C. neoformans* and fluconazole was started. Two days later, liquor was also positive for this agent. Amphotericin B was started. Patient presented worsening of dyspnea, cyanosis and was intubated, after which he presented cardiorespiratory arrest and died. Antiretroviral treatment was not initiated.

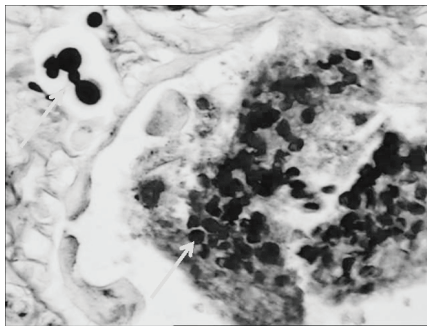
Necropsy was performed and the cause of death was fungal septicemia with disseminated cryptococcosis in the lungs (Figure 1 and 3), lymph nodes, spleen, liver, brain, cerebellum, kidneys, adrenal glands, pancreas, heart, smooth intestine, prostate, thymus and skin. Cytomegalovirus inclusions were present in the lungs (Figure 2) and adrenal glands. *P. jiroveci* was found in the alveolar spaces (Figure 3). Therefore, the lungs were coinfecting with three different agents, a rare finding even in HIV patients.



*Figure 1.* Arrow indicates bilateral diffuse consolidation of pulmonary lobes (Left lung, 800 g).



*Figure 2.* In high magnification, one alveolar space with CMV intracellular inclusions surrounded by a clear halo that gives the appearance of “owl’s eye” (arrow, down right) (HE, 1280x).



*Figure 3.* Using Grocott methenamine silver stain at high magnification, *Pneumocystis jirovecii* in lung have the appearance of crushed ping-pong balls (arrow). *C. neoformans* organisms in an adjacent alveolus (arrow upper left) (Grocott, 1280x).

## DISCUSSION

In Brazil, examinations, drug distribution, health professionals training and monitorization of HIV-positive patients are covered by the Unified Health System, with no costs to patients (Greco & Simão, 2007). Unfortunately, most cases of death due to HIV/AIDS are related to late diagnosis and lack of adherence to highly active antiretroviral therapy, HAART (Ewings et al., 2008). Young men with lower socioeconomic status tend to discontinue treatment. Another important aggravating factor for HIV/AIDS patient survival is the difficulty in accessing health services (Brito et al., 2006; Travassos et al., 2002; Lopes et al., 2012). The present case is of a 30-year-old male farmer who was diagnosed with an HIV infection only on hospitalization and died after 21 days. According to the clinical history and socio-epidemiological characteristics, this patient had several risk factors for early death due to HIV/AIDS infection (Lopes et al., 2012).

Cryptococcosis is one of the leading opportunistic fungal infections in patients with HIV/AIDS (Castro-Jiménez et al., 2011) and *C. neoformans* is responsible for more than 90% of the cryptococcosis cases (Fircative et al., 2018). Infection occurs by inhalation of yeasts from the environment, which reach lung alveoli causing primary pulmonary infection, usually asymptomatic or with mild symptoms. Infection is usually controlled by immune response involving macrophages, T helper lymphocytes and cytokines such as tumor necrosis factor (TNF), gamma-interferon and interleukin-2. However, in immunosuppressed people, yeasts can grow and spread (Shao et al., 2005). Fungal plasmatic spread occurs in the minority of cases and usually in patients with advanced AIDS characterized by high viral load and low CD4 cell counts (Kiertiburanakul et al., 2012). This was the cause of death of this patient, which is uncommon. Extrapulmonary cryptococcosis is considered an AIDS-defining disease and usually occurs in patients without HAART (Mirza et al., 2003; Center for Disease Control, 2002).

Cytomegalovirus is a prevalent herpesvirus that in most cases, after infection, remains latent in the host, and can be reactivated when the cell-mediated immune system is depressed (Cannon et al., 2010). Cytomegalovirus infection in HIV patients is associated with faster disease progression as well as increased risk of bacterial and fungal superinfections (Johnstone et al., 2014). As this patient died from cryptococcus septicemia, coinfection with cytomegalovirus may have contributed to fungal spread.

*P. jiroveci* is one of the most common agents of opportunistic respiratory infections in HIV patients, also considered an AIDS-defining disease. It presents tropism to type I alveolar epithelium cells, causing an inflammatory reaction that can result in respiratory failure (Truong & Ashurst, 2018).

Conventional chest X-ray is often the only image technique available for first line investigation in clinical practice, as in this case. In AIDS patients,

despite atypical manifestations with overlapping features in a multifactorial disease, this image resource is accurate for diagnosing common complications (Allen et al., 2010). Therefore, it is important to be aware of the particular features of each agent, as there may hypothetically be individual diseases and be forewarned that even with nonspecific images, in very severe cases, it is empirically necessary to cover the most frequent agents.

Imaging findings of cryptococcal pneumonia are varied and nonspecific. Reticular or reticulonodular infiltrates are the most common pattern in immunocompromised hosts (McGuinness, 1997). In around 30% of them, there are multiple or solitary nodules up to 4 cm in diameter; and another less frequent feature in AIDS-related diseases compared to immune competent hosts, is cavitation, which usually appears during mild immune suppression (Wallace et al., 1998). Less-frequent manifestations include miliary nodularity, ground-glass opacification, consolidation, adenopathy, effusions and chest wall abscesses (McGuinness, 1997).

Pulmonary CMV impairment has varied radiographic findings, which overlaps other AIDS-related diseases, especially pneumocystosis (McGuinness, 1997). Features include perihilar and lower zone interstitial infiltrates, ground-glass opacification, nodules (varying from miliary to 3 cm) and effusions; highlighting that a small airway disease may be the sole manifestation of infection. A useful tip, although not applicable to the case reported, is that CMV should be considered over *P. jirovecci* when ground-glass opacification is associated with nodularity and effusion, especially in patients with CD4 counts under 50 (Waxman et al., 1997).

In pulmonary pneumocystosis, the classic appearance is bilateral symmetric perihilar or diffuse interstitial opacification, which may be reticular, finely granular or ground-glass in appearance and some patients, despite treatment, will progress to coarse reticular opacification and fibrosis (Boiselle et al., 1999).

Therefore, as the first chest radiograph showed a bilateral thin interstitial infiltrate around the pulmonary hilum and bases, and *P. jirovecci* is the most common individual pathogen to cause this appearance, it indicates at least initially, pneumocystosis, but also the possible radiologic manifestation of fungi (especially *Cryptococcus*), mixed infections, tuberculosis and atypical mycobacteria (Schlossbauer et al., 2007). In this case, possible *Cryptococcus* as described above. The image on the 19<sup>th</sup> day of hospitalization showed parenchymal opacities in both hemithoraces, a nonspecific finding that would suggest no particular hypothesis, but as the patient's clinical condition deteriorated, in spite of medication, broadening the spectrum of treatment to cover possible coinfections, such as CMV, would be in order, without ruling out the hypothesis of poor evolution of pneumocystosis.

Fungal pneumonia is an important cause of morbidity and mortality among HIV/AIDS patients and without adequate treatment, this opportunistic infection can progress rapidly (Kaur et al., 2017). The clinical evolution of the case under study is according to the literature, since the patient was subsequently diagnosed with an HIV infection, which made treatment response difficult.

Pulmonary coinfection by *P. jiroveci* and cytomegalovirus is indicative of severe immunosuppression, related to a poor prognosis (Shah et al., 2017; Yu et al., 2017). This co-infection has been reported in some studies (Shah et al., 2017; Jacobson et al., 1991; Bozzette et al., 1992). Coinfection of *P. jiroveci* and *C. neoformans* is considered uncommon but has also been reported in the literature (Boonsarnsuk et al., 2009; Javier et al., 2012; Desai et al., 2016). There are few reports of cytomegalovirus and *C. neoformans* coinfection in HIV/AIDS patients (Lemert et al., 1996).

A limitation in this case report is the absence of CD4 cell count. However, it was certainly low, since the patient had an AIDS-defining disease (Center for Disease Control, 2002). Some studies associate the risk of developing opportunistic infections with CD4 cell cut-offs. Levels below 200 cells/ $\mu$ L have a higher risk of fungal pneumonia. Levels below 100 cells/ $\mu$ L indicate a higher risk of *Cryptococcus* infection related to meningitis and lung disease, and levels below 50 cells/ $\mu$ L lead to higher risk of cytomegalovirus infection. As the patient reported had pulmonary infection by *P. jiroveci*, *C. neoformans* and cytomegalovirus, his CD4 cell count can be inferred as below 50 cells/ $\mu$ L. Another limitation is the impossibility of adding the chest X-ray image in this study as only the X-ray description was available in the patient's medical record.

In conclusion, the patient studied presented several risk factors for early death due to HIV/AIDS infection, as he had *P. jiroveci*, *C. neoformans* and Cytomegalovirus coinfections. Late diagnosis, lack of antiretroviral therapy and co-infections led to rapid disease progression. Concomitant pulmonary infection with *P. jiroveci*, *C. neoformans* and cytomegalovirus has apparently not been reported in the literature.

Thus, this report may help clinicians in cases with poorly defined disease profiles, which can interfere in clinical diagnosis and impair rapid and effective therapeutic intervention, culminating in an unfavorable prognosis.

Facing a patient who does not respond well to usual therapy, the presence of more than one agent is a possibility. Has the clinician really managed to cover all possible diagnoses? These points are fundamental as, in this case, the possibility of Cytomegalovirus infection was not evaluated for clinical diagnosis or treatment purposes. This report further reinforces the role of autopsy as a tool for better understanding the comorbidities that can affect HIV/AIDS patients.

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