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Histoplasma capsulatum and *Mycobacterium avium* co-infection in an immunocompromised patient: Case report and literature review

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ABSTRACT

We report a case of fungal and mycobacterial co-infection in an immunosuppressed patient from Southern Brazil. Histoplasmosis was diagnosed in an AIDS patient admitted to the hospital with nonspecific respiratory signs. However, 4 months post hospital discharge, the patient worsened and a co-infection with *Mycobacterium avium* was detected. Physicians must consider and investigate a broad spectrum of diseases which can occur as co-infections and which share the same clinical symptoms and signs in immunosuppressed patients.

1. Introduction

Patients immunocompromised by human immunodeficiency virus (HIV) infection are at increased risk of opportunistic diseases, even with the advance of antiretroviral therapy, which represent a better prognosis for these patients [1]. Among the main opportunistic agents are *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, *Cryptococcus neoformans*, *Toxoplasma gondii*, cytomegalovirus, *Histoplasma capsulatum* and *Mycobacterium avium* [2].

Advanced and more accurate diagnosis techniques directed at the large diversity of pathogens that can infect HIV-AIDS patients, have indicated that co-infections can occur more frequently than previously expected. Thus, a full diagnostic investigation is necessary to find the correct treatment and improve the prognosis [1]. *H. capsulatum* and *M. tuberculosis* co-infection in HIV patients has been described, however, co-infection reports of *H. capsulatum* and non-tuberculous mycobacteria, such as *M. avium*, in these patients are scarce in the literature [3]. Therefore, we report a case of histoplasmosis and mycobacteriosis by *M. avium*, in a HIV/AIDS patient from southern Brazil and perform a bibliographic review to report all cases of this co-infection described thus far.

2. Case

A 52 year-old man, living on a farm, with HIV infection diagnosed in 2007, was admitted to the University Hospital Dr. Miguel Riet Corrêa Jr., Rio Grande, Rio Grande do Sul, Brazil (UH-FURG) in January 2017, reporting loss of appetite, nausea, vomiting and weight loss of 10 kg in the previous four months. The patient had a history of poor adherence to and abandonment of antiretroviral therapy several times. He was a smoker since age 13 and an alcoholic for 25 years.

Given his medical history, his symptoms of asthenia, adynamia, night sweats, fever and productive cough, and the high tuberculosis endemicity of the region, an investigation for *M. tuberculosis* infection was performed. Negative microscopy and liquid culture (BD BACTEC MGIT™ - BD Medical, United States of America) of three sputa made a diagnosis of tuberculosis unlikely. Unfortunately, the investigation had to be interrupted since the patient left the hospital without medical consent.

Four months later (May 2017, Day 0), he was again hospitalized

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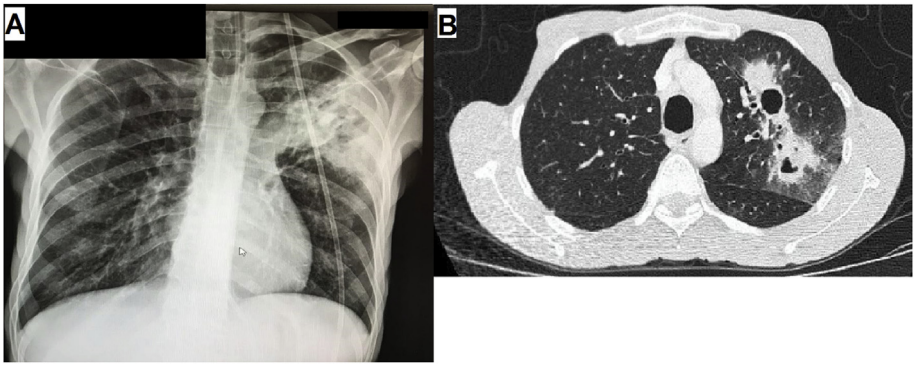

Fig. 1. A. Chest radiograph (May 2017, Day 0) showing bilateral ground-glass pattern and left upper lobe bronchiectasis. B. Chest computed tomography shows consolidation area in the left upper lobe with two cavities, the largest 4 cm, and bronchiectatic areas, ground glass attenuation areas and septal thickening.

with the same symptomatology previously reported. Laboratory tests showed immunosuppression (LTCD4+ cells = 20 cells/mm^3 and HIV viral load of 178,304 copies), and several laboratory abnormalities, such as anemia (hemoglobin of 6.9 g/dL and hematocrit of 21.3%), leukopenia (leukocytes of 2760/mm^3), increase in serum ferritin (1389 ng/mL) and in inflammatory markers (erythrocyte sedimentation rate of 120 mm and C-reactive protein of 82.2mg/L). A bilateral ground-glass pattern and a consolidation area in the left upper lobe with two cavities (the largest 4 cm) and bronchiectasis areas were detected in the computed tomography of the chest, as well as hepatosplenomegaly (Fig. 1).

On this occasion, three more sputum smear samples were negative for *M. tuberculosis* infection, as well as for fungal and bacterial. *Cryptococcus* antigen tested by latex agglutination was also negative. On the other hand, histoplasmosis was diagnosed via a serum positive immunodiffusion test and urinary antigen test (both kits from IMMY®, Immuno-Mycologics, Oklahoma, United States). The patient was given amphotericin B deoxycholate (1mg/kg/d) intravenously, showing clinical improvement after 14 days of antifungal therapy (weight gain, decreased cough, resolution of fever). Then he was discharged with prescriptions for itraconazole (400mg/d) and antiretroviral therapy (tenofovir, lamivudine, efavirenz) and sulfamethoxazole-trimethoprim, and azithromycin prophylaxis. The patient did not return for follow-up appointments at Infectology Service (UH) for three months.

In September 2017 (Day 120), and he was hospitalized again with productive cough with mucopurulent sputum, hemoptysis, daytime fever, weight loss (6 kg). Diffuse wheezing was noted on respiratory auscultation. He was in the day 96 of itraconazole and no cutaneous lesions or other physical examination abnormalities were detected. His blood lymphocyte CD4$^+$ count was 74 cells/mm^3 and HIV viral load was 1815 copies/mL. The chest radiograph showed consolidation areas in the left upper lobe with lower density than the previous image on May 2017 (Day 0) (Fig. 2).

His sputum was cutured for mycobacteria, and grew in two consecutive samples non-tuberculosis mycobacteria, identified as *M. avium* by sequencing of the hsp65 gene. Therapy with clarithromycin, ethambutol, streptomycin, and levofloxacin, as per the Health State Department of Brazil [4] recommendations, was introduced. He was maintained on itraconazole therapy for histoplasmosis treatment, and antiretrovirals for HIV therapy. In January 2018 (Day 240), the patient returned to UH-FURG asymptomatic, and had been adherent to treatment. His blood parameters were improved (hematocrit of 30.1%, hemoglobin of 10.0 g/dL, leukocytes of 6310/mm^3, erythrocyte sedimentation rate of 21 mm and C-reactive protein of 5.42mg/L), including an undetectable HIV viral load.

3. Discussion

A bibliographic search was performed in the PubMed database, using the descriptors "AIDS and *Histoplasma capsulatum* and *Mycobacterium avium*", to collect articles referring to *H. capsulatum* and *M. avium* coinfection. Table 1 show the seven studies found in this search, which described 15 cases of *H. capsulatum* and *M. avium* coinfection in HIV patients.

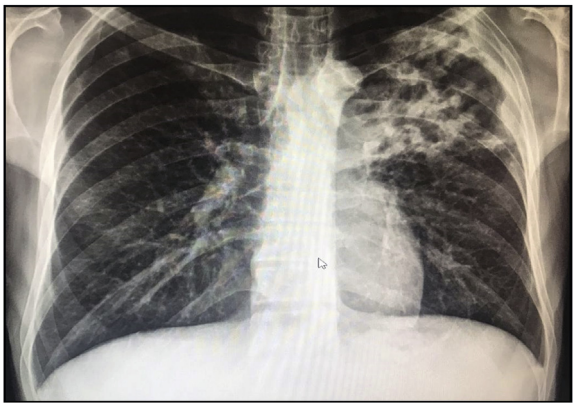

Fig. 2. Chest X-ray (September 2017, Day 120) showing consolidation area in the left upper lobe, paraseptal thickening and bronchial thickening in the peripheral region.

Opportunistic co-infection diseases in HIV patients are widely described in the literature, however, *H. capsulatum* and *M. avium* coinfection is hardly mentioned, with only seven reports of this co-infection in a period of 38 years [5–11]. There are many diagnostic challenges, owing to nonspecific and overlapping symptoms for both diseases [3]. Our report is the first with a premortem diagnosis of this co-infection, with survival, in a Brazilian patient.

Intense investigation is necessary to uncover the etiologies in co-infections [12–14]. In this case, one of the most sensitive tests (95%) [15] for disseminated histoplasmosis (galactomannan antigen detection) and semi-automatized liquid culture for mycobacteria with molecular identification, yielded the diagnoses. Then correct treatment favored the patient outcome, adding antibacterial therapy to the antifungal therapy already started. The molecular identification enabled a treatment specific for nontuberculous mycobacteria, whereas the therapeutic scheme used for *M. tuberculosis* would not have been efficacious [3,16].

Once established, the progression of a systemic infection, such as histoplasmosis or mycobacteriosis, will each lead to depression of, or exhaustion of, cell-mediated immunity; thus one infection may make establishment of a second infection more likely. Co-infections in HIV patients often do not have a favorable outcome, owing to the lack of clinical suspicion and consequently a late diagnosis. This is illustrated in our literature review, emphasized by the high mortality rate [3,5–11]. Considering the emergent importance of histoplasmosis in

Table 1
Cases of H. capsulatum and *M. avium* coinfection in HIV patients reported in scientific literature.

Case	Year	Country	Age (years), sex	Clinical Presentation	Histoplasmosis Diagnosis method	Treatment	Outcome	Reference
1	1980	USA	30, Male	Disseminated	Culture	Ketoconazole, isoniazid, ethionamide, ethambutol	Died	[5]
2	1981	USA	26, Male	Disseminated	Serological and Culture	Amphotericin B, rifampin, ethambutol, cycloserine, streptomycin	Died	[6]
3	1981	USA	30, Male	Disseminated	Serological and Culture	Amphotericin B, isoniazid, rifampin, ethambutol, cycloserine, ethionamide	Died	[6]
4, 5, 6, 7, 8	1983–1987	USA	NDA	Disseminated	Histopathology or culture	Ketoconazole and amphotericin B	NDA	[7]
9	1996	USA	30, Male	Disseminated	NDA	Clarithromycin, ethambutol, and itraconazole, rimethoprim-sulfamethoxazole, zidovudine-lamivudine, nelfinavir	Recovered	[8]
10	2015	USA	32, Male	Disseminated	Culture	Amphotericin B, itraconazole, clarithromycin, ethambutol	Recovered	[9]
11, 12, 13, 14	2015–2017	Mexico	NDA	Disseminated	Histoplasma urinary antigen and culture	NDA	NDA	[10]
15	2018	Brazil	52, Male	Pulmonary	Culture post mortem	Not treated	Died	[11]

*NDA: No data available.

HIV patients on Latin America, particularly Brazil [13,14,19], it is important that clinicians are knowledgeable about the availability of rapid diagnosis tests, such as *Histoplasma* antigen detection.

Our patient was likely exposed to infection with both pathogens (*H. capsulatum* and *M. avium*) during his farm occupation, which provides contact with soil contaminated by chicken and pig excrement [17,18]. Due to the fact that a diversity of co-infection can be caused by environmental pathogens, immunocompromised patients should be advised about the risks of exposure to such infection sources, and to take preventive measures. Pertinent to this is the “one-health concept”, in which environment, animals and humans can share potential pathogens [20].

Declaration of competing interest

All authors declare that they have no conflicts of interest pertaining to this work.

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