The diagnosis of multiple opportunistic infections in advanced stage AIDS: when Ockham’s Razor doesn’t cut it

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ABSTRACT

In the advanced stage of AIDS, the diagnosis of the opportunistic infections may be challenging due to the high risk of performing invasive diagnostic methods in a patient with a critical clinical condition, as well as the correct interpretation of the results of microbiological exams. One of the challenges for the diagnosis and treatment of the opportunistic infections is that they may occur concomitantly in the same patient and they may mimic each other, leading to a high discrepancy between clinical and autopsy diagnoses. We describe the case of a 52-year-old man who was hospitalized because of weight loss, anemia, cough, and hepatosplenomegaly. During the investigation, the diagnosis of AIDS was made, and the patient developed respiratory failure and died on the fourth day of hospitalization. At autopsy, disseminated non-tuberculosis mycobacteriosis was found, affecting mainly the organs of the reticuloendothelial system. Also, severe and diffuse pneumonia caused by multiple agents (\textit{Pneumocystis jirovecii}, \textit{Histoplasma capsulatum}, suppurative bacterial infection, non-tuberculosis mycobacteria, and cytomegalovirus) was seen in a morphological pattern that could be called “collision pneumonia.” The lesson from this case, revealed by the autopsy, is that in advanced AIDS, patients often have multiple opportunistic infections, so the principle of Ockham’s razor—that a single diagnosis is most likely the best diagnosis—fails in this clinical context.

Keywords
Acquired Immunodeficiency Syndrome; Mycobacterium; Pneumocystis; Histoplasma; Cytomegalovirus

CASE REPORT

A 52-year-old male patient with a past of alcoholism and smoking (50 pack-years), attended the emergency department with a 6-month history of progressive and painful abdominal distension, weight loss, coughing, and lower limbs edema. On admission, the physical examination revealed a pale patient with normal vital signs. The peripheral oxygen saturation was 96\% detected by pulse oximetry. Pain was present in the right upper abdominal quadrant along with hepatomegaly and splenomegaly, which measured 10 cm below the left costal margin. Pronounced edema in the lower limbs and rales in the basal lung areas were
present. The initial laboratory work-up revealed severe anemia and thrombocytopenia (Table 1).

The patient was initially treated with blood components transfusion (packed red blood cells and platelets). An abdominal ultrasound revealed a spleen size of 21.0 cm in its longest axis, with lesions consistent with infarctions, and multiple heterogeneous hepatic nodules. Chest radiography taken on the first day of hospitalization showed mediastinal enlargement and consolidations in both upper pulmonary lobes (Figure 1A). The patient was kept in isolation due to the hypothesis of disseminated tuberculosis with pulmonary involvement, according to the clinical and radiological findings; a sputum examination for acid-fast bacilli was requested. The serology testing for HIV infection was positive (enzyme-linked immune assay [ELISA] and Immunoblot), but the patient was not aware of his HIV status. On the third day

Table 1. The patient’s laboratory tests

| Parameter        | Result | RV                        | Parameter        | Result | RV                        |
|------------------|--------|---------------------------|------------------|--------|---------------------------|
| Hemoglobin       | 3.5    | 12.3-15.3 g/dL            | Glucose          | 24     | 70.0-100.0 mg/dL          |
| Hematocrit       | 11.6   | 36.0-45.0%                | ALT              | 21     | 9.0-36.0 U/L              |
| Platelets        | 13     | 150-400 x10^3/mm^3        | AST              | 114    | 10.0-31.0 U/L             |
| Leukocytes       | 10.3   | 4.4-11.3 x 10^3/cells/mm³ | Venous pH        | 7.41   | 7.32-7.42                 |
| Bands            | 18     | 1.0-5.0%                  | HCO₃             | 16.4   | 22.0-26.0 mmol/L          |
| Segmented        | 92     | 45.0-70.0%                | Amylase          | 49     | 28.0-100.0 U/L            |
| Lymphocytes      | 4      | 18.0-40.0%                | Total proteins   | 4.2    | 6.0-8.0 mg/dL             |
| CRP              | 72.6   | <5.0 mg/L                 | Albumin          | 1.3    | 3.0-5.0 mg/dL             |
| Urea             | 84     | 5.0-25.0 mg/dL            | Total bilirubin  | 1.05   | 0.3-1.2 mg/dL             |
| Creatinine       | 0.95   | 0.4-1.3 mg/dL             |                  |        |                           |

ALT = alanine aminotransferase; AST = aspartate aminotransferase, CRP = C-reactive protein, RV = reference value.

Figure 1. A – Chest radiography taken on the first day of hospitalization showing mediastinal enlargement, consolidation in the right superior and middle lobes, and sparse interstitial and alveolar infiltrates in the remaining fields; B – Gross examination of the right lung: diffuse consolidation (hepatization of the lung). Note the adhesions of the visceral pleura to the diaphragm and to the soft tissues of the chest are partially fixed.
The microscopic exam exhibited extensive pneumonia with diffuse alveolar damage (septal congestion and necrosis, alveolar edema and hemorrhage, and hyaline membranes) involving the visceral pleura (Figure 2). Most of the lung samples showed alveolar spaces filled with foamy exudates associated with some multinucleated giant cells (Figure 3), with foci of calcification (Figure 4), sparse

 AUTOPSY FINDINGS

On external examination, the body weighed 69.0 kg and measured 178.0 cm (body mass index: 21.47 kg/m²), with moderate edema in the lower limbs, and poor dentition. At the opening of the chest cavity, 300 mL of serosal pleural effusion from each hemithorax were drained. Both lungs were congested and increased in volume. The right lung weighed 1,488.0 g (mean reference value [mRV]: 455 g) and the left 1,012.0 g (mRV: 402 g). On sectioning, the parenchyma showed edema and had hepatization with friable areas and adhesions to the thoracic soft tissues (Figure 1B).

Figure 3. Micrography of the lung. The typical pneumocystosis foamy alveolar exudate associated with some multinuclear giant cells, type II pneumocytes hyperplasia, thickened alveolar septum, and an alveolar epithelial cell with cytoelastic cytopathic changes (arrow) (H&E, 300X).
areas of granulomatous inflammatory reaction surrounding foamy exudate or calcifications (Figure 5), and with parenchymal microscopic necrotic cavities (Figure 6).

The Grocott’s stain revealed cup-shaped yeasts, measuring 4–6 µm, some with the central intracystic bodies, compatible with *P. jirovecii* in the foamy alveolar exudates (Figure 4, inset). In some areas of the lungs, the pneumonia was represented by alveolar spaces filled with histiocytes with many tiny yeasts (0.5-1.5 µm) in the cytoplasm, consistent with *H. capsulatum* acute pneumonia (Figures 2, 7, 8A, and 8B). Different areas

Figure 4. Micrography of the lung. Foci of plate-like dystrophic calcification within the typical pneumocystosis foamy alveolar exudate (H&E, 300X). The inset shows typical *P. jirovecii* cup-shaped yeasts, measuring 4-6 µm, some with the central intracystic bodies at Grocott’s stain (400X).

Figure 5. Micrography of the lung. Pneumocystosis with two histologic patterns in the same field: on the left the typical foamy alveolar exudate, lined by an alveolar septum with type II pneumocyte hyperplasia, and an alveolar cell with cytomegalovirus cytopathic changes (arrow); on the right, a granulomatous reaction, surrounding foci of dystrophic calcifications (H&E, 300X).

Figure 6. Micrography of the lung. Severe pneumocystosis characterized by confluent foamy exudate, forming a “cystic” parenchymal cavitation in the center. At the periphery, alveoli filled by foamy exudate can be seen (arrowheads) (H&E, 300X).

Figure 7. Micrography of the lung. Alveolar macrophages with tiny *Histoplasma capsulatum* yeasts in their cytoplasm (arrow), admixed in the typical pneumocystosis foamy alveolar exudate. Note an alveolar epithelial cell with cytomegalic cytopathic changes (arrowhead), septal congestion, alveolar hemorrhage, and a discrete mixed inflammatory exudate in the alveolar space (H&E, 300X).
of both lungs had remarkable suppurative pneumonia, forming abscesses, but the Gram stain was negative (Figure 2). Enlarged alveolar macrophages and epithelial cells with nuclear eosinophilic inclusion surrounded by a clear halo were observed, which were spread in all lung fields (Figures 3, 5, 7). These were consistent with pulmonary CMV infection, which was confirmed by immunohistochemistry (using mouse anti-CMV cocktail of DDG9 and CCH2, Diagnostic BioSystems). Finally, rare foci of histiocytes were found with engorged and bluish cytoplasm due to the presence of numerous acid-fast bacilli in the alveolar septa and peribronchiolar space, which were infiltrating the hilar lymph nodes (Figures 8C and 8D).

The liver was increased in volume, weighing 2,792.0 g (mRV: 1,650 g), with a congested surface on sectioning; the parenchyma had the “nutmeg” aspect and scattered yellowish nodules, with poorly defined borders (Figure 9A). At histology, the liver parenchyma was infiltrated by sheets of many round and bluish histiocytes in the portal tracts, lobules, and sinusoids, occasionally forming loose granulomas with rare multinucleated giant cells with numerous acid-fast bacilli (Figures 9B-9D). The spleen was also increased in volume, measured 22.0 cm in the longest axis, and weighed 2,688.0 g (mRV: up to 150 g). The splenic surface had an opaque capsule, with foci of adhesions to the greater omentum, with subcapsular yellowish

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**Figure 8.** Micrography of the lungs. A – Area of acute histoplasmosis pneumonia, showing numerous alveolar macrophages with small yeasts forms in their cytoplasm (H&E, 300X); B – The Grocott’s stain shows small nucleated yeasts within the alveolar macrophages (1,000X); C and D – Scarce peribronchiolar areas and alveolar septa infiltrated by engorged macrophages, with pale bluish cytoplasm (arrows in C), with plenty acid-fast bacilli in the cytoplasm (arrows in D) (C: H&E, 300X; D: Ziehl-Neelsen, 400X).
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areas (Figure 10A). On sectioning, the parenchyma was congested and friable; with areas of white–yellowish wedge-shaped infarctions, forming abscesses, measuring up to 7.5 cm in its major axis (Figure 10B).

Histologically, there was diffuse infiltration of the splenic parenchyma by sheets of round and bluish histiocytes, with some giant multinucleated cells, which affected the arterial walls, and caused vasculitis, endothelial necrosis, thrombosis, and consequently ischemic necrosis (Figures 10C and 10D). The exuberant histiocytic inflammatory reaction seen in the liver and spleen was also observed in the intestines (Figures 11A and 11B), kidneys (Figures 11C and 11D), bone marrow (Figure 12A), periadrenal soft tissues (Figure 12B), and lymph nodes collected from different chains (Figures 12C and 12D). The Ziehl–Neelsen stain revealed plenty of acid-fast bacilli within the histiocytes’ cytoplasm; this was also positive at Brown–Brenn (Gram-positive), Grocott’s, and periodic acid–Schiff (PAS) stains, which is compatible with the diagnosis of disseminated non-tuberculous mycobacteriosis. The remaining organs were unremarkable.

**DISCUSSION**

The case described herein represents a patient with long-lasting complaints of cough, weight loss and gastrointestinal symptoms, and a history
of alcoholism and smoking, who was found to be seropositive for HIV. The patient was in the late stage of the infection, with multiple opportunistic infections (pneumocystosis, histoplasmosis, pulmonary CMV and disseminated non-\(M. tuberculosis\) mycobacteriosis), severe anemia, and low serum albumin (Table 1). Also, the patient acquired nosocomial bacterial infections, such as pneumonia and bloodstream infections, due to \(S. aureus\) and \(P. aeruginosa\), leading to a rapid and refractory septic shock state, and death due to multiple organ failure.

The Brazilian public health system is internationally recognized as a good model for the treatment of HIV/AIDS infection.\(^1\) Despite this, cases of late-stage diagnosed HIV infection (or late entry, defined as peripheral CD4+ T cells <350 cells/\(\mu\)L, the presence of AIDS-defining diseases, or death attributed to HIV at the diagnosis) represent a problem in the healthcare of people living with HIV/AIDS (PLHA) in Brazil.\(^1\) Granjeiro et al.\(^2\) described that between 2003 and 2006, 115,369 cases of HIV/AIDS were reported in Brazil, with 58.6% of these cases diagnosed in the advanced stage of HIV infection, and 29% were diagnosed after death attributed to AIDS. However, improvements have been achieved in Brazil in recent years. In 2015, 25% of the new cases of HIV infection were considered as late entry in the health system, a percentage that has been decreasing since 2009.\(^3\)
In Brazil, there are few data about opportunistic diseases that affect the PLHA. The annual national report on the AIDS epidemic does not disclose the frequency and geographical distribution of the opportunistic infections diseases. However, it is known that in Brazil tuberculosis is the leading cause of mortality among the population with AIDS, and approximately 10% of new tuberculosis cases have the HIV coinfection.

There are few Brazilian studies about autopsies in the PLHA population. They mostly covered the first 20 years of the AIDS epidemic and were restricted to a single hospital center; few of them describe the immediate cause of death and the pathologic findings in the different body systems. The discrepancy between clinical and postmortem diagnosis is about 50%. Pulmonary involvement by opportunistic agents can reach more than 80% of autopsied cases and coinfection by multiple agents occurs in some cases, especially involving P. jirovecii, M. tuberculosis and CMV.

In the present case, we found four concomitant opportunistic agents in the patient’s organs, one of which caused multisystem disease: the non-tuberculosis mycobacteria. Although it was not isolated in culture, the Ziehl–Neelsen stain demonstrated mycobacteria in the histiocytes’ cytoplasm. This infiltrated several organs, especially those of the reticuloendothelial system, in a histopathological and histochemical pattern consistent with M. avium-intracellulare infection. The negative RT-PCR for M. tuberculosis in the tracheal secretion reinforces the diagnosis of
atypical mycobacteriosis as the COBAS TaqMan MTB RT-PCR has a high accuracy to detect *M. tuberculosis* complex with 95.2% sensitivity and 91.6% specificity for the smear-positive respiratory specimens. In this autopsy, the lungs were the most affected organs; therefore, they are considered to be the main site of injury that led to the patient’s death. A severe and diffuse pneumonia with five different infectious agents was found, which morphologically could be called "collision pneumonia," alluding to the collision tumor, where two tumors with different histogenesis exist in the same organ. The pneumocystosis was severe, affecting all lung fields, with foci of calcification, parenchymal microscopic cavities, and granulomatous reaction surrounding the foamy alveolar exudate; these morphological findings are rare, and are only described in 2%–3%, 2%, and 5%, respectively, in pulmonary biopsies from patients with AIDS. In a series of 13 cases, Lee et al. proposes that the calcification found in pneumocystosis results from the degeneration of *P. jirovecii* cystic forms. Dystrophic calcification foci may have elongated, conchoidal, "bubbly" or plate-like aspects, and may be associated with viable cystic forms of the fungus and with parenchymal fibrosis. The calcification can occur in individuals with or without treatment or prophylaxis for pneumocystosis, without any hypercalcemic conditions, and may not be detected by radiological images. *H. capsulatum* was found only in the lungs, within the cytoplasm of macrophages (histiocytomycotic pattern). The macrophages filled the alveolar spaces, and this pneumonia elicited a moderate neutrophilic inflammatory response. These

**Figure 12. A to D –** Micrography showing aspects of non-tuberculous disseminated mycobacteriosis: sheets of engorged and bluish histiocytes infiltrating the bone marrow (A). The periadrenal fat tissue (B, arrows and inset) and an anthracotic thoracic lymph node (C, arrow). The Ziehl–Neelsen stain in all these sites revealed plenty of acid-fast bacilli within histiocytes’ cytoplasm (D). (A, H&E, 100X; B, H&E, 100X; C, H&E, 100X; D, Ziehl–Neelsen, 100X).
Findings indicate acute *Histoplasma* pneumonia in an immunocompromised host.\(^\text{11}\) The pulmonary CMV infection was observed in some isolated alveolar epithelial cells and macrophages. No endothelial CMV lesions, ischemic necrosis, or inflammatory reaction surrounding cytomegalic cells were seen in any of the lung fields. Finally, an extensive suppurative pneumonia was found in our patient, but no bacterial agents were found through histochemical stains.

Brazilian autopsies series on AIDS population describe the frequency of the opportunistic infections. Atypical mycobacteriosis occurred between 1.7%\(^\text{9}\) and 6%, and tuberculosis occurred between 14% and 28%.\(^\text{9,10,18}\) The frequency of pneumocystosis was 8%\(^\text{10}\) to 27%\(^\text{18}\) and was associated with *M. tuberculosis* in 25% of cases\(^\text{12}\) and with CMV in 16%.\(^\text{6}\) Histoplasmosis occurred in 1.7%\(^\text{18}\) to 13%\(^\text{19}\) and may not be clinically suspected in up to 80% of cases.\(^\text{13}\) CMV is a frequent opportunistic agent found in autopsies of Brazilian AIDS patients, ranging from 1.8%\(^\text{9}\) to 46.6%.\(^\text{6}\) However, the pathogenic role of CMV may be uncertain, as the CMV infection does not always correspond to the CMV disease. CMV can cause miliary pneumonitis, diffuse interstitial pneumonitis, hemorrhagic pneumonia, isolate nodules, or infect isolated cells, without provoking an inflammatory reaction,\(^\text{19-21}\) as found in this autopsy. Cury et al.\(^\text{8}\) reported that in Brazil, CMV pneumonitis was recorded in 8 (8.7%) among 92 autopsied AIDS cases. Finally, Soeiro et al.\(^\text{18}\) described bacterial bronchopneumonia in 91% of cases in autopsies of AIDS patients who died due to respiratory failure.\(^\text{18}\) These data are consistent with the results of Nichols et al.,\(^\text{22}\) who found that in 46 autopsies of adults with AIDS, 83% were bacterial infections, having as the main etiological agents *S. aureus*, *P. aeruginosa*, and *Enterococcus*.\(^\text{22}\)

In medicine, it is common to use a single diagnosis to explain a conjunction of signs and symptoms. This medical reasoning is based on the principle of Ockham, also known as the “law of parsimony” or the “principle of simplicity,” determined by the English Franciscan friar and philosopher William Ockham (1287-1347).\(^\text{23}\) The theorem *Numquam ponenda est pluralitas sine necessitate*, translated into English as *Plurality ought never to be posed without necessity*\(^\text{23}\) can be interpreted in several ways.

### Table 2. Current methods for definitive diagnosis of non-tuberculosis mycobacteria, *Pneumocystis jirovecii*, *Histoplasma capsulatum* and cytomegalovirus (CMV) infections

| **Etiologic agent** | **Diagnostic methods** |
|---------------------|-----------------------|
| **Non-*M. tuberculosis* mycobacteria**\(^\text{27}\) | Microscopic examination of sputum, tissues and cytologic preparations with Ziehl–Neelsen, Kinyoun, Carbol-Fuchsin, or auramine-rodamine stains. Culture of tissues and fluids (MAC is a slowly growing mycobacteria) in solid media (middlebrook 7H10 and 7H11 agar) or liquid medium (BACTEC). Nucleic acid probes in sputum smears or culture growth. Polymerase chain reaction (PCR) of respiratory samples, fluids and tissues. |
| **Pneumocystis jirovecii** (definitive diagnosis)\(^\text{28}\) | Microscopic visualization of the cystic or trophic forms of *P. jiroveci* in respiratory secretions (sputum, bronchoalveolar lavage and endotracheal aspirates) and tissues. Stains: Gomori-methenamine silver, cresyl violet, Gram-Weigert and toluidine blue O stain the cell wall of the cystic form. Giemsa and Diff-Quick detect both the cystic and trophic forms. Immunofluorescent staining with fluorescein-labeled monoclonal antibodies in respiratory secretions. PCR of respiratory fluids (mainly bronchoalveolar lavage). |
| **Histoplasma capsulatum**\(^\text{29}\) | Culture (with lysis-centrifugation technique) of blood, respiratory secretion, fluids, and tissues. Cytology and histopathology (hematoxylin-eosin, methenamine silver, and periodic acid-Schiff stains) of fluids and tissues. Antigen detection (enzyme immunoassay) in serum, respiratory secretion, and cerebrospinal fluid. Antibody detection (immunodiffusion, complement fixation, and enzyme immunoassay tests) in serum. PCR and loop-mediated isothermal amplification assay (LAMP) in fluids and tissues. |
| **Cytomegalovirus**\(^\text{30}\) | Serologic tests (enzyme immunoassays, indirect, and anticomplement immunofluorescence assays and other methods): detect anti-CMV immunoglobulin (Ig)M and IgG. CMV antigenemia: fluorescently labeled monoclonal antibodies specific to the pp65 CMV protein in peripheral blood leukocytes. CMV DNA viral load (blood, serum): quantification by real-time PCR tests. Histopathology: cytopathic effect in infected cells (cytomegaly, eosinophilic nuclear inclusion surrounded by a clear halo, cytoplasmatic inclusions) on hematoxylin-eosin stain and immunohistochemical staining of tissue samples. CMV culture (conventional or shell vial): blood, tissue, and other body fluids. |
However, when we find ourselves at the bedside, facing a severely immunocompromised patient with AIDS, it is not always possible to maintain parsimony and simplicity. In the present case, on first impression, one might think that a disseminated mycobacteriosis associated with AIDS could explain the whole clinical picture. However, the autopsy showed four opportunistic infectious agents in the lung, two of which were not considered clinically (CMV and *H. capsulatum*). Multiple simultaneous opportunistic infections, diagnosed at autopsy in patients with advanced AIDS, were described in large autopsies series during the first decade of the pandemic in different regions of the world.24-26

Given the severe clinical condition of patients with AIDS in an advanced stage, the best practice is to adopt the medical reasoning based on the antithesis of Ockham’s principle—the “Saint's triad”—which says that several pathologies can coexist in the same case.23 Thus, different opportunistic infections can coexist simultaneously, acting in synergy, and contributing to the immediate cause of death of a patient with AIDS. Such cases require proper diagnostic investigation for etiologic agents (see Table 2) and prompt administration of broad-spectrum antimicrobials. Nevertheless, it must be considered that the patient’s clinical condition may hamper invasive diagnostic measures, and empirical (and “aggressive”) antibiotic therapy can cause serious adverse effects, such as hypersensitivity reaction, hepatotoxicity, and renal dysfunction. Consulting experienced infectious diseases specialists in the management of patients with advanced AIDS can help in deciding on the best diagnostic and therapeutic approach.

**CONCLUSION**

We have described the autopsy of a 52-year-old male patient who was hospitalized to investigate weight loss, anemia, and hepatosplenomegaly. The AIDS diagnosis was made during the patient’s hospital stay, but he died on the fourth day due to severe pneumonia, which was secondary to multiple opportunistic agents. The death was attributed to HIV infection at the diagnosis. The recent increase of new cases of HIV infection observed in Brazil—especially among men aged between 20 and 29 years who are diagnosed in the late stage—may allow physicians to again observe clinical scenes similar to those at the beginning of the AIDS pandemic in the early 1980s, when multiple simultaneous opportunistic infections compromised multiple systems in the same patient, with a high rate of fatal outcomes. Frequently, such infections are not diagnosed in the premortem period; therefore, autopsy plays an important role, not only to elucidate a single case but also to provide valuable information for epidemiological surveillance. More Brazilian studies are needed regarding opportunistic infections in AIDS to inform the attending physicians about the epidemiology of these diseases in different regions of the country, thereby helping them to make the correct diagnostic and therapeutic decisions. It must be kept in mind that in the case of late-stage AIDS (i) multiple opportunistic infections (similar to neoplasia and other entities) can occur concomitantly in the same individual; (ii) AIDS-defining illnesses can mimic each other; and (iii) the rate of discrepancy between premortem and postmortem diagnoses is high in this population.7-10

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