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CASE REPORT

Co-infection with Mycobacterium tuberculosis and *Mycobacterium avium* in an HIV-positive patient – Case Report

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Introduction: The association between Mycobacterium tuberculosis and the Human Immunodeficiency Virus can accelerate the deterioration of immunological functions. The risks are even more accentuated in the situation of a Non-tuberculous Mycobacterium and Mycobacterium tuberculosis co-infection.

Case presentation: We present the case of a 59-year-old male patient, who was admitted at the hospital with non-specific symptoms. Further investigations reveal a remarkable particularity about the case: The infection with Mycobacterium tuberculosis was urogenital, whereas the one with Non-tuberculous mycobacteria was pulmonary.

Conclusion: Both Mycobacterium tuberculosis and Non-tuberculous strains can exist within the same infection, posing great difficulties for diagnosis, as well as the treatment scheme.

Keywords: *Mycobacterium tuberculosis*, *Mycobacterium avium*, HIV, co-infection

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Introduction

Tuberculosis (TB), a disease caused by strains of the *Mycobacterium Tuberculosis Complex (MTC)*, is transmitted from person to person [1]. The association between the etiological agent of tuberculosis (*Mycobacterium tuberculosis*) and the Human Immunodeficiency Virus (HIV) is a global concern. Their complex and bidirectional interaction has devastating effects on the body and accelerates immunological deterioration, increasing the possibility of latent TB infection activation [2]. Globally, in 2022, there were reported 671000 incident TB cases in HIV-positive patients [3].

Moreover, depending on the stage of CD4 T-cell damage (which has an important role in TB control), HIV-positive patients are at risk of contracting non-tuberculous strains of *Mycobacterium* (NTM), especially if their CD4 T-cell count is less than 50/mm³ [4]. NTM tends to develop an extrapulmonary form, especially for HIV-positive people [5].

The treatment of HIV-TB co-infection is a difficult one, as we must take into account the possible drug interactions as well as the patient tolerance and compliance [6].

Case presentation

The patient is a 59-year-old male who was diagnosed with HIV infection two years ago. His laboratory investigations had revealed severe immunocompromise, with a CD4 T helper lymphocyte count of 5/mm³, and consequently, he received antiretroviral therapy with Biktarvy 50/200/25 mg, increasing the cell count to 26/mm³.

He was admitted to the Infectious Diseases Department of the Mures County Clinical Hospital, presenting with fever (38°C), asthenia, and fatigue. His previous medical history also revealed *Pneumocystis Jirovecii* pneumonia, oropharyngeal candidiasis, and anemia. The previous laboratory investigations revealed a leukocyte count of 4.10x10³/mL (normal values: 4.0-10 x 10³/mL), and hemoglobin levels of 8,7 g/dL (normal values: 12-16 g/dL).

In this case, due to the patient's immunocompromised (HIV clinical-immunological stage: C3), there was a high risk of pulmonary or extrapulmonary tuberculosis. Hence, a series of diagnostic tests were conducted to confirm MTB's presence. Furthermore, pulmonary radiological investigations indicated suggestive lesions for MTB: enlarged pulmonary hilum and accentuated bronchovascular drawing basal bilateral.

Initial diagnostic tests included seromucous sputum microscopic examination with the Ziehl-Neelsen (Z-N) staining, which showed negative results. The GeneXpert MTB/RIF (Cepheid, Sunnyvale, USA) test which aids tuberculosis identification in HIV-positive patients, was negative.

Despite the initial negative findings, the patient's clinical presentation and severe immunocompromise prompted further diagnostic evaluation. After one month, sputum, stool, and urine samples of the patient were processed, yielding negative results both microscopically and in culture.

Two months after admission, another urine sample revealed negative Z-N staining results. Despite this result, after an incubation of 45 days, the culture showed significant bacterial growth, with approximately 30-100 "R" type colonies on Lowenstein-Jensen (L-J) medium. Positive immunochromatographic test results for qualitative detection

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of MTB classified the organisms as Acid-Fast Bacilli (AFB) belonging to the MTB Complex. Antibiotic susceptibility testing revealed resistance to first-line antibiotics (Rifampicin and Isoniazid). Consequently, tuberculostatic treatment (Pyrazinamide, Etambutol, and Vitamin B6) was initiated, leading to the modification of the previously used antiretroviral treatment (Biktarvy®) to Tivicay® and Descovy®. This favorable adjustment allowed the patient to have a steady evolution, demonstrated by the number of CD4 cells, which escalated from 26/mm^3 before the current admission to 48/mm^3.

Cultures of biological specimens play a pivotal role in confirming mycobacterial infections, especially in cases where conventional diagnostic modalities yield inconclusive results, emphasizing the importance of comprehensive diagnostic evaluation. Despite negative microscopic examination, in the same month, the stool sample examined revealed positive culture results after 60 days of incubation. On the L-J medium, the presence of 10 "M" type colonies was observed for specimen A and 5 "M" type colonies for specimen B. The results of the immunochromatographic test (MPT64 Antigen Test) for qualitative detection of MTB were negative. This raised the suspicion that these organisms belonged to the Non-tuberculous strains of *Mycobacterium*.

A new seromucous sputum sample was taken to clarify the diagnosis, revealing positive microscopic results. The two examined specimens, A and B contained 8 AFB per 100 fields. After 45 days, 10 "M" type colonies grew on the L-J culture medium for both A and B specimens. Since the GeneXpert MTB/RIF assay did not detect the presence of an MTB complex, the bacilli were identified as Non-tuberculous *Mycobacterium* species. To verify the results of the culture sample, it was sent to the laboratory of the "Leon Daniello" Pneumophtiziology Clinical Hospital, Cluj-Napoca. Genotype genetic testing and processing by the nitrocellulose hybridization method (LPA) confirmed the previously obtained results and identified the species as *Mycobacterium avium*.

Finally, the last stool sample yielded positive results in microscopic evaluation and culture tests. Positive results in the immunochromatographic test for qualitative detection of MTB (MPT64 Antigen Test) allowed the identification of the organisms as AFB belonging to the MTB complex.

Discussion

HIV-positive individuals, especially those with a CD4 cell count below 50/mm^3 face a greater risk of NTM infections. [7]. Radha Gopalaswamy's study shows the correlation between TB history and NTM exposure [8], facilitating the patient's opportunistic NTM infection.

NTM infections may mimic TB symptoms, requiring further evaluation [9]. Historically, atypical mycobacteria weren't considered a threat due to lack of direct transmission [10]. However, with molecular diagnostic advancements, and increased awareness among clinicians, more cases of NTM are reported. These bacteria often cause lung infections similar to MTB [11]. Despite co-infection making NTM diagnosis challenging, our case presents a remarkable peculiarity: the localization of atypical mycobacteria was pulmonary (detected from sputum samples) and MTB extrapulmonary (detected in urine and faecal samples).

Yu Pang's study identifies lymph nodes, bones, joints, meninges, and the urogenital tract as common sites of extrapulmonary TB involvement. Out of a total of 6433 patients, only 44 had genitourinary tuberculosis, which underlines the rarity of this anatomical site. HIV is cited as a cause of extrapulmonary TB in the study [12], underscoring the necessity for personalized treatment due to NTMs' resistance to certain anti-TB medications [13], potentially resulting in misdiagnosis [14].

TB diagnosis relies on Z-N staining, but it has limited specificity, especially in MTB-NTM co-existence. Thus, positive microscopy but a negative GeneXpert MTB/RIF result prompted suspicion of NTM. After 45 days, the sputum culture revealed a bacterial growth of 10 colonies on L-J medium, but immunochromatographic tests for qualitative culture identification were negative for MTB. For validation of the results and identification of the NTM species, the obtained culture was sent to a reference laboratory. The Genotype AS kit differentiating species belonging to the MTB Complex from different species of NTM [15], excluded *Mycobacterium* spp. DNA, diagnosing *Mycobacterium avium* infection. This species, together with intracellular *Mycobacterium*, is part of the *Mycobacterium avium complex* (MAC). MAC species are particularly implicated in pulmonary pathology [16]. Also, Gary W. Procop's study notes these species as frequently involved in HIV infections [17]. Knowing the exact species of NTM is important because more than 175 species of NTM have been described in the literature, of those, not all of them have clinical significance [18]. The species show different degrees of virulence, thus influencing the clinical features: MAC together with *Mycobacterium abcessus* are particularly implicated in pulmonary infections [19], while *Mycobacterium marinum* and *ulcerans* are associated with skin and soft tissue pathologies [20]. The diagnostic process highlights the necessity of specialized laboratories capable of conducting intricate tests to identify NTM infections, as these bacteria microscopically resemble MTB [21].

The urine sample's antibiogram revealed MDR-TB (multidrug-resistant) which is resistant to Rifampicin and Isoniazid, posing treatment challenges, unravelling a new side of our case. MDR-TB strains do not respond favourably to the use of regular anti-TB drugs [22]. These species pose a challenge to clinicians, as they narrow the range of possible applicable treatments. Suchindran S.'s study links HIV to MDR-TB development [23]. The chances of HIV-positive patients contracting MDR-TB are 1.42 times higher than for seronegative patients [24], emphasizing early identification of multidrug-resistant MTB strains,

together with the prompt initiation of antiretroviral treatment, improves the chances of survival in patients with HIV-MDR-TB co-infection [25].

Conclusion

In conclusion, the case presented highlights the complexities associated with co-infection of MTB and NTM in HIV-positive patients. Multidisciplinary management of co-infections requires close collaboration between clinical and laboratory personnel, with a focus on personalized treatment interventions tailored to the individual patient's needs.

Authors' Contribution

AAR (Writing - original draft, Data Curation, Resources, Formal Analysis)
BT (Conceptualization, Project Administration, Supervision, Validation)
IT (Writing- review & editing, Data Curation, Investigation)

Conflict of interest

None to declare.

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