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CASE REPORT
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Paradoxical Immune Reconstitution Inflammatory Syndrome Complicating HIV/AIDS with Disseminated Tuberculosis: A Case Report

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Abstract

Tuberculosis (TB) remains a leading cause of global mortality and is the most common opportunistic infection in individuals with Human Immunodeficiency Virus (HIV). Among its severe manifestations, Tuberculosis Meningitis (TBM) presents a significant clinical challenge due to its high mortality rate and the complexities of treatment. This case report presents a 33-year-old Middle Eastern male diagnosed simultaneously with human immunodeficiency virus/acquired immune deficiency syndrome and disseminated tuberculosis including tuberculosis meningitis. Initial management included anti-tuberculosis treatment and prophylactic steroid, followed by the initiation of antiretroviral therapy five weeks later. Despite these interventions, the patient developed Immune Reconstitution Inflammatory Syndrome (IRIS). The case highlights the challenges in managing opportunistic infections in advanced human immunodeficiency virus cases, emphasizing the need for new strategies to reduce the incidence of immune reconstitution inflammatory syndrome and its complications while identifying the most effective approach in managing such cases.

Keywords: Tuberculosis; Human Immunodeficiency Virus; Antiretroviral Therapy; CNS Immune Reconstitution Inflammatory Syndrome (CNS IRIS); Tuberculous Meningitis

Introduction

Tuberculosis (TB) ranks among the top ten causes of mortality worldwide, leading as the primary cause of death from a single infectious agent and making it the most prevalent opportunistic infection among individuals infected with Human Immunodeficiency Virus (HIV) [1]. The World Health Organization (WHO) reported that approximately 10.0 million people were diagnosed with TB in 2022, of these new cases, 6.3 million occurred in individuals living with HIV [2].

Tuberculosis Meningitis (TBM), a severe form of extrapulmonary TB, contributes notably to the disease lethality, representing a substantial proportion of extrapulmonary cases. This form is critical due to its high mortality rate and the complex clinical management it requires [3]. Globally, 164,000 adults are estimated to have developed TBM in 2019, 23% were among people living with HIV [4]. Moreover, in 2019, an estimated 78,200 adults died from Tuberculous Meningitis (TBM), representing 48% of all reported TBM cases that year [4]. However, receiving the treatment decreases the mortality of TBM to an average of 27% [4]. In the Kingdom of Saudi Arabia, the TB scenario remains a concern, with 3,004 new and relapsed cases reported in recent data, reflecting an incidence rate of 8.7 per 100,000 populations with lack of data regarding TBM [5].

People living with HIV are at heightened risk of developing TB meningitis and other opportunistic infections [6]. As a result, early initiation Antiretroviral Therapy (ART) is crucial for reducing mortality and enhancing quality of life in HIV patients; however, there are possible side effects associated with treatment initiation [7]. Immune Reconstitution Inflammatory Syndrome (IRIS), which affects 20% of HIV-positive individuals after ART initiation, is one of the most frequent complications that can arise [7]. IRIS was initially identified in patients undergoing treatment for leprosy and TB in the 1980s [7]. At that time, clinicians observed a paradoxical worsening of fever, weight loss, and dyspnea in pulmonary TB patients [7].

At the time, it was unclear how this worked. However, it was later linked to a change in the immune system's status. With the emergence of the HIV/AIDS epidemic and the introduction of Highly Active Antiretroviral Therapy (HAART) in the late 1980s and early 1990s, IRIS became recognized as a condition most commonly linked to HIV treatment [7]. It can, however, happen in situations or circumstances unrelated to HIV [7].

Clinical manifestations of IRIS can be divided into two categories: unmasked IRIS and paradoxic IRIS. Paradoxic IRIS is a clinical situation in which an opportunistic infection is known to be present before immune reconstitution and where the patient experiences both a strong inflammatory response and an aggravation of the known opportunistic infection upon reversal. Unmasked IRIS describes clinical situations in which the presence of an opportunistic infection was unknown [8].

This case report describes a paradoxical IRIS occurring in a Middle Eastern male with advanced HIV and disseminated TB.

Case Presentation

A 33-year-old Middle Eastern male with no prior medical or surgical history presented to the emergency department with a three-month history of fever, productive cough, and unintentional weight loss of approximately 10 kg. The patient, who has a 32-pack-year smoking history, reported heterosexual unprotected sexual activity with multiple partners, and a history of substance abuse, primarily cannabis. His family history was unremarkable for any chronic or infectious diseases.

On examination, the patient appeared cachectic but was not in acute distress. Vital signs were normal. Physical examination of the chest revealed bilateral crackles, more pronounced in the right upper lung field, while the rest of his examinations including a neurological assessment revealed no focal deficit.

Initial laboratory tests, including complete blood count, renal and liver function tests, were within normal limits. Imaging studies raised significant concerns. The chest X-ray showed bilateral prominent hilar and bronchovascular markings with patchy opacification in the right upper lobe. A subsequent chest CT scan revealed bilateral miliary nodules with consolidative nodularity and cavitations, particularly in the upper lobes. An echocardiogram showed normal systolic function without valvular dysfunction.

Given the patient's presentation, an HIV test was conducted, which returned positive. His viral load was 6,38,000 copies/mL, and his CD4 T-cell count was just 18 cells/µL, indicating severe immunosuppression. With these findings, the likelihood of a disseminated infection, including TB was high.

The patient was promptly isolated in a negative pressure room, and a TB workup was initiated. Although initial sputum samples were negative for Acid-Fast Bacilli (AFB) and MTB PCR, the Quantiferon-TB Gold test returned positive. Further diagnostic step including bronchoscopy with Bronchoalveolar Lavage (BAL) was performed, MTB PCR from BAL was detected and PCR for Pneumocystis Jirovecii Pneumonia (PCP) was also positive. Consequently, the patient was started on therapeutic Bactrim (Trimethoprim/ Sulfamethaxazole) 960 mg three times a day for 21 days.

In the following day of hospitalization, the patient developed sudden onset of confusion. A new symptom that was not there at presentation. A brain CT scan showed no acute abnormalities. Given the new neurological symptom, a lumbar puncture was conducted. The Cerebrospinal Fluid (CSF) analysis revealed low glucose level, elevated protein and a predominance of lymphocytes, findings consistent with tuberculous meningitis. CSF culture confirmed drug-susceptible Mycobacterium tuberculosis. The TB infection was now considered disseminated, involving the central nervous system, necessitating more aggressive treatment.

The patient was diagnosed with disseminated TB, including miliary pulmonary TB and TBM, and started on a regimen of Rifinah (Rifampicin and Isoniazid) 900 mg orally daily, Pyrazinamide 1000 mg orally daily, and Levofloxacin 1000 mg IV daily. Dexamethasone was administered and tapered over eight weeks to manage the potential CNS involvement. The patient initially responded well to the treatment with his episodic confusion subsiding, though intermittent fever persisted.

Five weeks into anti-TB therapy, ART was initiated with Dolutegravir 50 mg twice daily and Emtricitabine / Tenofovir alfenamide once daily. The patient showed signs of improvement, becoming fully oriented without residual neurological deficits. His fever resolved, and he was discharged home in a stable condition on anti-TB and ART medications, including prophylactic Bactrim after completion of Pneumocystis Jirovecii Pneumonia (PCP) treatment.

One month after discharge, the patient returned to the emergency department with sudden right-sided weakness and motor aphasia. The family attendant denied any associated fever, changes in consciousness, or new substance use. His vital signs were within normal limits, the patient maintained good eye contact and responded to sounds by turning his eyes. His extra-ocular movements and visual fields were intact. Power was 3/5 on the right side and 5/5 on the left side. Laboratory results were within his baseline. However, viral load was suppressed with 51,200copies/mL, and the CD4 T-cell was 173 cells/µL.

A brain CT revealed a left pontine hypo-density, subsequent CT angiography showed significant stenosis in the left Middle Cerebral Artery (MCA) and Internal Carotid Artery. An MRI and MRA (Figure 1) further revealed that localized tuberculous meningitis was encasing and narrowing the cerebral arteries at the circle of Willis and the proximal MCA, leading to multiple embolic infarcts in the left frontal and parietal regions, with mass effect in the left midbrain.

Paradoxical IRIS diagnosis was made, and the patient was started on Prednisone at a dose of 1.5 mg/kg per day for two weeks with tapering, and Atorvastatin 40 mg daily. After consulting with a neurologist, a decision was made to add Aspirin to his regimen one week later, despite the risk of bleeding. Follow-up neurological examination showed resolution of expressive motor function.

The patient had made significant strides in his recovery and was discharged home to continue ART, Anti TB, and tapering steroids. IV levofloxacin switched to oral. With plans for continued outpatient follow-up to manage both his TB and HIV conditions.

Discussion

This case report highlights the challenges in managing HIV/AIDS in a patient co-infected with disseminated TB. Emphasizing the significant risk of IRIS as acomplication following ART initiation. People living with HIV are at an elevated risk of developing extra-pulmonary TB, especially with decreased CD4 T-cell count [9]. A modeling study estimated that, in 2019, 164,000 adults worldwide developed TBM, with 23% of cases occurring in people living with HIV [6]. Among HIV-infected individuals, TBM often presents with an altered level of consciousness, or progressive dementia characterized by social withdrawal and personality changes, although presentation can vary across populations [9].

IRIS is a serious complication in the management of HIV/TB co-infection. Observational studies have found that in HIV patients on ART, key risk factors for developing IRIS include male gender,

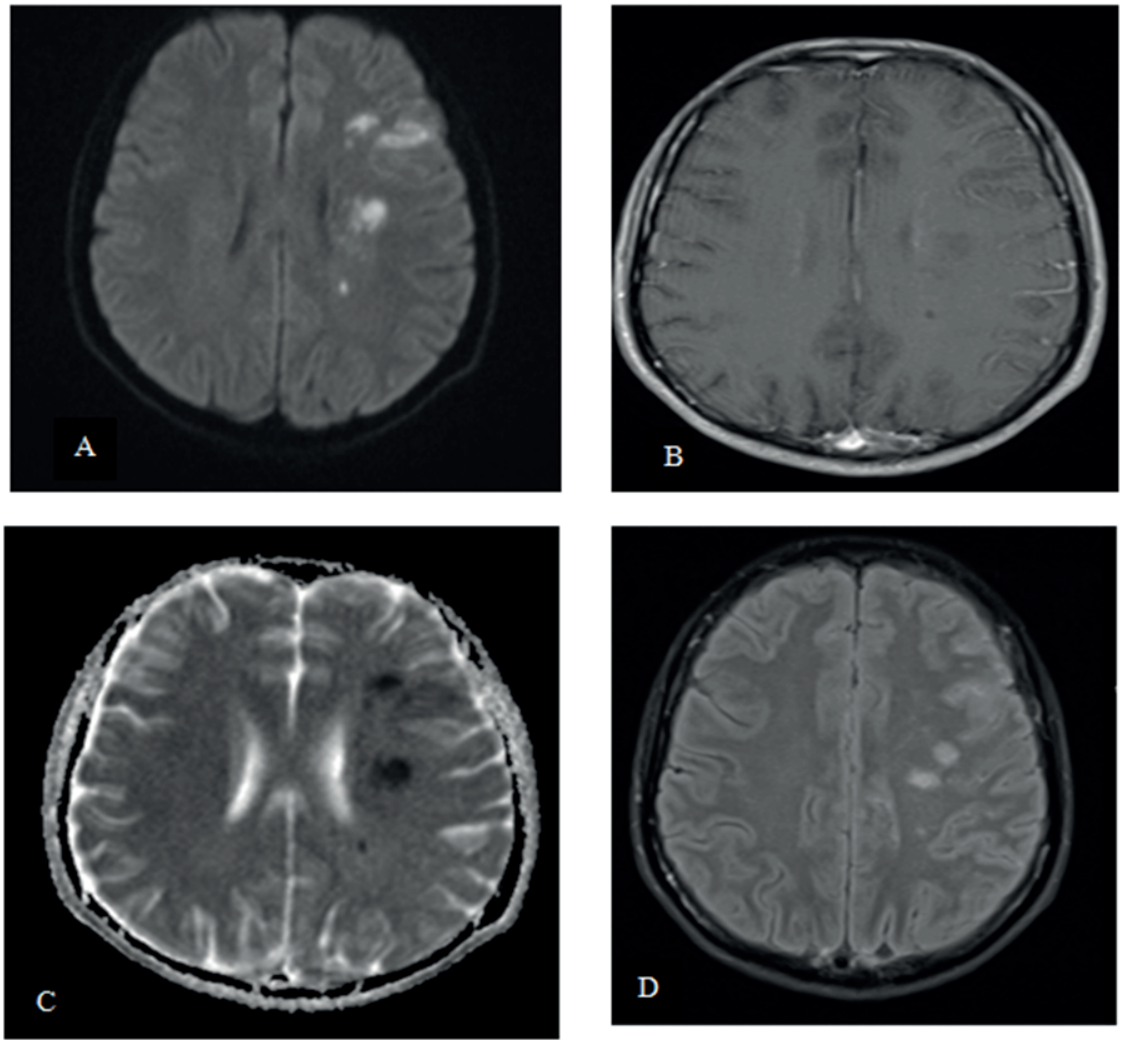

Figure 1: MRI performed at presentation of neurological deficit.
A: Diffusion-weighted imaging.
B: T1-weighted contrast.
C: Apparent diffusion coefficient.
D: Fluid-attenuated inversion recovery.

younger age, low baseline CD4 T-cell counts, rapid increases in CD4 counts, rapid virological suppression, and concurrent treatment of opportunistic infections with high antigenic loud [4]. In HIV/TB co-infection, IRIS is happening in up to 18% of cases, with 25% requiring hospitalization due to sever morbidity [10].

The patient in this report had advanced HIV and simultaneous diagnoses of disseminated TB and TBM, both of which are AIDS-defining conditions. Given that he had not received prior Anti-Tuberculosis Treatment (ATT) or ART, he was at a considerable risk for developing IRIS. Due to the risk of CNS IRIS, starting ART was delayed for five weeks following the initiation of ATT, and prophylactic prednisolone was administered concurrently with ATT. Despite these measures, the patient still developed IRIS which led to worsened TBM as evidenced by both clinical deterioration and radiological findings as the initial brain MRI at the time of TBM diagnosis demonstrated a more generalized meningoencephalitis associated with a disseminated infection, while a follow-up MRI post-ART initiation revealed a more localized tuberculous meningitis affecting the basal cisterns and cerebral arteries, along with the new development of stroke characterized by significant vascular involvement leading to embolic strokes. Management included a Prednisone at a dose of 1.5 mg per kg over two weeks, alongside supportive measures such as hydration, physiotherapy, and speech therapy.

The timing of ART initiation in TBM remains critical and yet unresolved question. Randomized controlled trials, including SAPIT, CAMELIA, and STRIDE, have demonstrated mortality benefits from initiating ART as early as two weeks after starting ATT in HIV/AIDS patients co-infected with TB. However, these trials excluded

TBM cases, where CNS IRIS poses a life-threatening risk [11]. A randomized, double-blind, placebo-controlled trial investigating the timing of ART initiation in TBM found no survival benefits with immediate ART initiation and reported more severe adverse events, suggesting that delaying ART may be more beneficial [12].

This case underscores the importance of a personalized approach to balance the risks of IRIS against the benefits of early ART initiation. The patient's clinical deterioration, despite delayed ART initiation and the use of prophylactic corticosteroids, indicates the persistent risk of CNS IRIS under current management strategies. Future research should aim to prevent CNS IRIS by finding the ideal timing for ART initiation and deciding the most effective steroid dosing as prophylactic.

Conclusion

In patients infected with advanced HIV, thorough investigations to rule out concurrent opportunistic or latent infections, such as tuberculosis (TB), are essential before initiating ART, particularly given the risk of IRIS as a serious complication. Managing HIV/AIDS co-infected with TB requires a personalized approach and the involvement of a multidisciplinary team to address the complexities of treatment. While delaying ART initiation in cases of TB is currently the recommended strategy, the optimal timing for initiating ART remains uncertain in cases with TBM. Further research is needed to refine treatment protocols and improve outcomes in this high-risk population.

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