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TUBERCULOUS MENINGITIS AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A PATIENT ON ADALIMUMAB: DIAGNOSTIC CHALLENGES IN THE SETTING OF SUSPECTED NON-TUBERCULOUS MYCOBACTERIA CO-INFECTION

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ABSTRACT

Background: Tumour necrosis factor-alpha (TNF-alpha) inhibitors increase susceptibility to granulomatous infections, including both *Mycobacterium tuberculosis* (MTB) and nontuberculous mycobacteria. We describe a complex case of sequential disseminated *Mycobacterium avium complex* (MAC) and central nervous system MTB infection in a patient treated with adalimumab, complicated by hemophagocytic lymphohistiocytosis (HLH).

Case report: A 65-year-old man on long-term adalimumab for psoriasis presented with prolonged fever, hepatosplenomegaly, cytopenia and elevated inflammatory markers. Bone marrow aspiration revealed hemophagocytosis and liver and bone marrow biopsy revealed granulomatous inflammation. Polymerase chain reaction (PCR) testing of bronchoalveolar lavage (BAL) fluid identified MAC, supporting a diagnosis of disseminated MAC-associated HLH. The patient responded to triple MAC therapy (azithromycin, ethambutol, rifampicin), intravenous immunoglobulin and low-dose corticosteroids, with rapid clinical improvement. Three months later, he was readmitted with fever and altered mental status. Brain magnetic resonance imaging showed meningeal thickening. Lumbar puncture revealed cerebrospinal fluid pleocytosis, hypoglycorrhachia and elevated protein. PCR detected MTB complex deoxyribonucleic acid and a rifampicin resistance gene, prompting the initiation of a four-drug antituberculosis regimen (isoniazid, pyrazinamide, levofloxacin, ethambutol) and high-dose dexamethasone. The patient improved and was discharged after a month of hospitalization, remaining clinically stable at 1-year follow-up.

Conclusion: This case highlights the risk of sequential or overlapping MAC and MTB infections in patients receiving TNF-alpha inhibitors, the potential for HLH as a serious complication, and the diagnostic value and limitations of BAL PCR testing. Vigilant screening and multidisciplinary management are essential in such high-risk populations.

KEYWORDS

Hemophagocytic lymphohistiocytosis, *Mycobacterium avium complex*, *Mycobacterium tuberculosis*, immunocompromised host infections, tumour necrosis factor-alpha (TNF-alpha) inhibitors

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LEARNING POINTS

- The increased risk of opportunistic infections associated with long-term tumour necrosis factor-alpha inhibitor use necessitates ongoing infection screening.
- Hemophagocytic lymphohistiocytosis triggered by mycobacterial infections requires prompt recognition and targeted treatment.
- Polymerase chain reaction results should be interpreted with caution in complex clinical scenarios, as deoxyribonucleic acid detection may indicate colonization rather than active infection.

INTRODUCTION

Tumour necrosis factor-alpha (TNF-alpha) inhibitors, such as adalimumab, have significantly advanced the treatment of immune-mediated diseases. However, their use is associated with an increased risk of opportunistic infections, particularly those caused by mycobacteria, as TNF-alpha plays a critical role in host defence against intracellular pathogens, especially in the formation and maintenance of granulomas[1,2].

We report a rare case of a patient with psoriatic arthritis receiving adalimumab who presented with fever of unknown origin. The initial workup revealed disseminated *Mycobacterium avium* complex (MAC) infection diagnosed via polymerase chain reaction (PCR) from bronchoalveolar lavage (BAL), complicated by hemophagocytic lymphohistiocytosis (HLH). The patient subsequently developed central nervous system tuberculosis (TB), underscoring the diagnostic complexity, and the need for sustained clinical vigilance in immunosuppressed individuals receiving TNF-alpha inhibitors.

CASE DESCRIPTION

A 65-year-old man presented with a 2-week history of high-grade fever (peaking at 39.5°C), generalized malaise, and profuse sweating. His past medical history was significant for chronic plaque psoriasis, managed with long-term immunosuppressive therapy using adalimumab for the past ten years. On admission, his vital signs were stable apart from a fever. Physical examination, including cardiopulmonary and lymph node assessment, was unremarkable. Initial laboratory evaluation revealed mild leukopenia (3,650/µl), normocytic anaemia (haematocrit 30%), and abnormal liver function tests, with elevated levels of alkaline phosphatase (582 U/l), gamma-glutamyl transferase (813 U/l), aspartate aminotransferase (94 U/l), and alanine aminotransferase (92 U/l). Inflammatory markers were raised, as evidenced by an elevated C-reactive protein (6 mg/dl), while procalcitonin remained within normal range (0.4 ng/ml).

A comprehensive infectious workup was performed. Tuberculin skin testing, peripheral blood smears for *Plasmodium spp.*, serum galactomannan, and screening

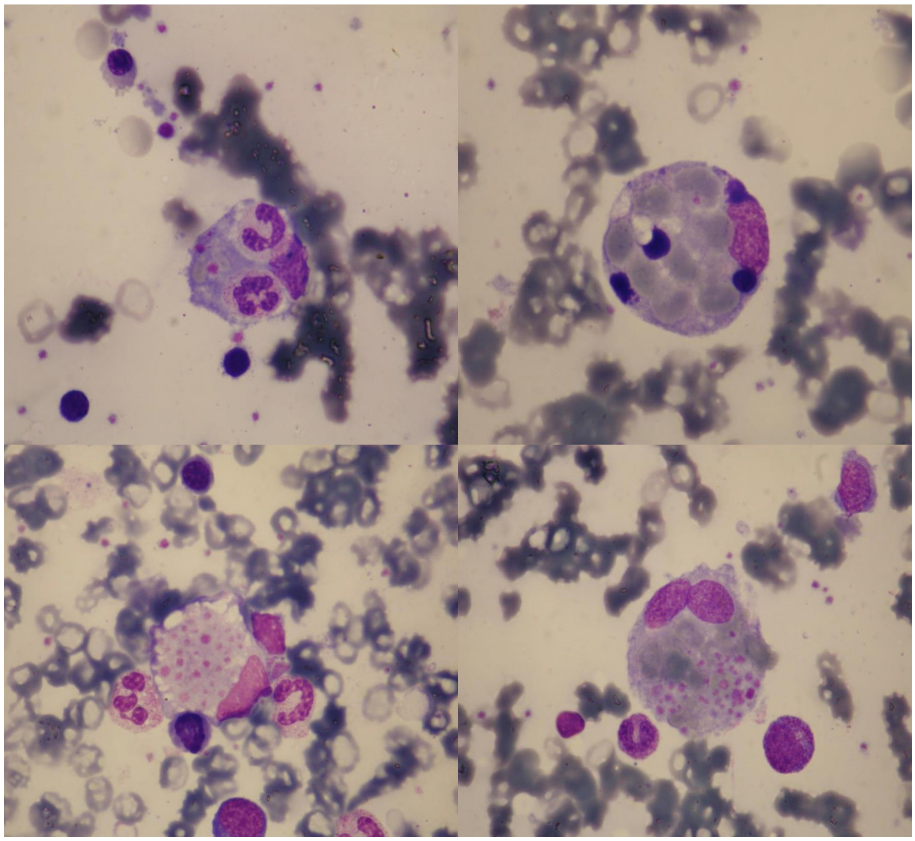


Figure 1. Images of hemophagocytosis from the bone marrow aspirate.

for human immunodeficiency virus and hepatitis C virus were all negative. Serological testing suggested previous exposure to hepatitis B virus (HBcAb positive), and the Wright test for *Brucella* was negative. Additional serologies for herpes simplex virus-1, herpes simplex virus-2, human herpes virus-6, human herpes virus-8, parvovirus B19, *Anaplasma*, *Ehrlichia*, *Coxiella*, *Bartonella*, *Rickettsia*, *Cryptococcus*, *Toxoplasma*, West Nile virus, *Leptospira*, and *Leishmania* were all negative. Polymerase chain reaction (PCR) testing for cytomegalovirus and Epstein-Barr virus showed no detectable viral deoxyribonucleic acid (DNA). Immunological studies were unremarkable, and cultures for bacterial, fungal, and mycobacterial pathogens from blood samples yielded no growth. Whole-body computed tomography scan revealed moderate hepatosplenomegaly, mild ascites, para-aortic lymphadenopathy, and pulmonary fibrosis with superimposed ground-glass opacities. In light of mild haematuria, cystoscopy was performed, which revealed no suspicious lesions, and urine cytology was negative for malignancy. Given the progressive pancytopenia, a bone marrow aspiration was performed, revealing prominent hemophagocytosis *(Fig. 1)*.

A subsequent bone marrow biopsy confirmed these findings and demonstrated non-necrotizing granulomatous inflammation. PCR testing for *Mycobacterium tuberculosis* complex on the bone marrow was negative. Liver biopsy showed extensive granulomatous inflammation with negative Ziehl-Neelsen and periodic acid-Schiff stains. Bronchoscopy was later performed and revealed no endoscopic abnormalities. Cytological analysis of the BAL fluid showed a few squamous and inflammatory cells without evidence of malignancy. However, PCR testing of the BAL fluid detected MAC, confirming disseminated MAC infection.

The patient met six out of eight HLH-2004 diagnostic criteria for hemophagocytic lymphohistiocytosis HLH: persistent fever, splenomegaly, cytopenia, hypertriglyceridemia, markedly elevated serum ferritin, and hemophagocytosis on bone marrow examination[3]. Based on these findings and the detection of disseminated MAC, a diagnosis of secondary HLH was established. Management included intravenous immunoglobulin and low-dose corticosteroids. Once the underlying infection was identified, a triple antimicrobial regimen was initiated, consisting of azithromycin (600 mg/daily), ethambutol (1000 mg/daily), and rifampicin (600 mg/day). This treatment led to defervescence, and normalization of liver enzymes and blood counts within 1 week. Corticosteroid tapering was gradually initiated, and the patient was discharged in a stable and clinically improved condition.

Three months after discharge, the patient was readmitted due to recurrence of fever and altered mental status. Emergency brain magnetic resonance imaging revealed meningeal thickening without evidence of hydrocephalus or other acute abnormalities *(Fig. 2)*.

A central nervous system infection was suspected and

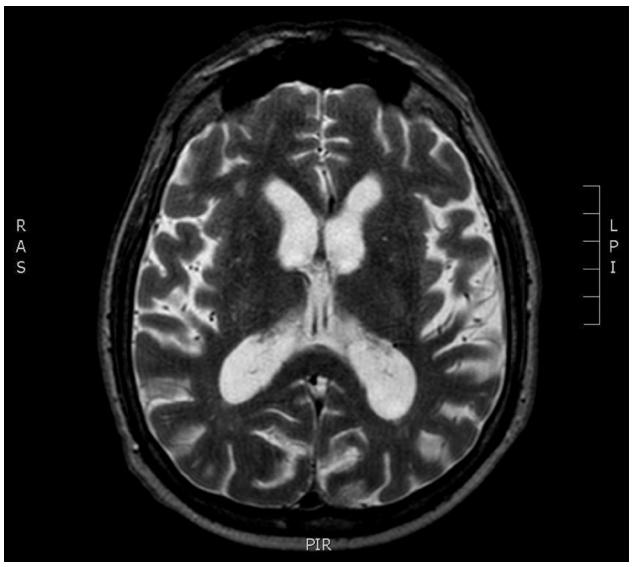


Figure 2. Brain magnetic resonance imaging (T2W_TSE sequence) performed during the patient's second hospitalization for altered mental status, showing marked meningeal thickening.

confirmed by lumbar puncture, which showed low lymphocytic pleocytosis (10 cells/µl), hypoglycorrhachia (cerebrospinal fluid, CSF glucose 30 mg/dl, with CSF:serum glucose ratio < 0.5), elevated protein levels (231 mg/dl), and a negative cryptococcal antigen test. PCR analysis of the CSF detected *M. tuberculosis* complex DNA along with a rifampicin resistance gene.

These findings prompted a reassessment of the initial diagnosis of nontuberculous mycobacterial infection. The patient was initiated on a four-drug antituberculosis regimen comprising isoniazid (300 mg/day), pyrazinamide (500 mg three times daily), levofloxacin (750 mg/day), and ethambutol (1000 mg/day), along with high-dose dexamethasone (0.4 mg/kg/day), which was tapered gradually over 6 to 8 weeks. Clinical improvement was rapid, and the patient was discharged after 1 month of hospitalization. He subsequently completed an 18-month course of isoniazid, pyrazinamide, and levofloxacin, with ethambutol administered for the initial 2 months. At one-year follow-up, the patient remained clinically stable on acitretin for psoriatic arthritis, with only mild residual neurological deficits.

DISCUSSION

This case highlights the diagnostic and therapeutic complexity of granulomatous infections in an immunocompromised patient undergoing long-term adalimumab therapy. The patient initially presented with systemic inflammatory features and was ultimately diagnosed with HLH, a rare hyperinflammatory syndrome typically triggered by infections, malignancies, or autoimmune conditions. While viral pathogens are the most common triggers, both *M. tuberculosis* (MTB) and nontuberculous mycobacteria (NTM) have been documented as causes of secondary HLH[4,5].

In this case, disseminated MAC infection—identified by PCR in BAL fluid—was initially considered the primary aetiology. PCR-based testing of BAL has proven valuable

for the early detection of MAC, particularly in smear-negative or sputum-scarce patients[6]. Licata et al. reported a sensitivity of 73% for MAC PCR in BAL specimens in culture-confirmed NTM cases, highlighting its diagnostic value[7]. On the other hand, official international guidelines for the treatment of NTM pulmonary infections caution that NTM can be isolated from respiratory specimens due to environmental contamination, which may not always indicate true infection[8]. In our patient, PCR enabled the early initiation of targeted antimicrobial therapy, resulting in initial clinical improvement. Nevertheless, the subsequent onset of neurological deterioration, along with the detection of *M. tuberculosis* complex DNA in the CSF and rifampicin resistance, required a reassessment of the initial diagnosis.

Co-infection or sequential infection with MTB and NTM is rare but clinically significant. Hwang et al. identified such coinfection in 85 respiratory specimens from 69 patients, with MTB predominating in 63.8% and NTM isolated in 10.1%[9]. These cases present diagnostic and therapeutic challenges, as MTB and NTM share overlapping clinical and radiologic features. NTM may be overlooked if microbiologic evaluation is focused solely on TB, and coinfection may complicate treatment, particularly in the context of antimicrobial resistance. In our case, it remains uncertain whether the patient experienced true co-infection or whether the initial MAC detection represented colonization rather than invasive disease. The subsequent development of central nervous system TB supports the possibility of latent TB reactivation under anti-TNF therapy and emphasizes the importance of pre-treatment screening and ongoing monitoring in immunosuppressed individuals. Notably, the initial MAC diagnosis was based solely on a positive PCR result from BAL fluid and did not fulfil the official international microbiological criteria for confirmed NTM pulmonary disease[8]. In contrast, World Health Organization guidelines recommend nucleic acid amplification tests (NAATs) as the first-line diagnostic tool for TB in CSF, due to their high sensitivity and capacity for rapid rifampicin resistance detection[10].

Collectively, this case underscores the heightened vulnerability of patients receiving TNF-alpha inhibitors to both MTB and MAC infections, the diagnostic complexities posed by overlapping clinical syndromes, and the importance of careful interpretation of molecular results, particularly PCR. Management of such infections requires a multidisciplinary approach integrating clinical, radiological, and microbiological data, with a high index of suspicion for evolving or atypical presentations. These cases demand coordinated, specialist-led care to ensure accurate diagnosis and optimal therapeutic outcomes.

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