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CASE REPORT

Disseminated Tuberculosis Driving Secondary Haemophagocytic Lymphohistiocytosis Following Adalimumab and Treatment for Latent Tuberculosis

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Abstract

We describe the case of a 63-year-old man presenting with fevers, hyperferrintinaemia and pancytopaenia. He was known to have psoriatic arthritis, managed with adalimumab and methotrexate. Haemophagocytic lymphohistiocytosis (HLH) was diagnosed, and he was treated with intravenous anakinra whilst searching for an aetiology. Despite previous treatment for latent tuberculosis, he developed changes typical for miliary tuberculosis and was started on antituberculosis therapy; whole genome sequencing later demonstrated isoniazid monoresistance. This case demonstrates both the importance of recognising *Mycobacterium tuberculosis* as a trigger of HLH, and also the risk of latent tuberculosis treatment failure in the setting of monoresistance.

Key words: haemophagocytic lymphohistiocytosis; tuberculosis; adalimumab; isoniazid monoresistance; case report

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Introduction

Haemophagocytic lymphohistiocytosis (HLH) is an hyperinflammatory syndrome characterised by persistent activation of macrophages and cytotoxic T lymphocytes which results in hypercytokinaemia and hyperinflammation. Whilst HLH is an underrecognized condition, the crude incidence is at least 2 per million person years, with an overall 1-year survival of 56% (Cox et al, 2024). The incidence of HLH is increasing over time, likely as a result of increased ascertainment and the increasingly frequent use of immunosuppression and cell-based therapies such as Chimeric antigen receptor T-cells (Abdelhay et al, 2023; West et al, 2022). Secondary HLH (sHLH) can be triggered by multiple conditions including infections, malignancies and inflammatory diseases.

Disseminated *Mycobacterium tuberculosis (M. tuberculosis)* infection is a rare cause of sHLH and reactivation of tuberculosis is a well-recognized complication of treatment with Tumour-Necrosis Factor (TNF) inhibitors in individuals with latent

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infection (Solovic et al, 2010). An extreme presentation of disseminated tuberculosis infection is secondary haemophagocytic lymphohistiocytosis (HLH). Whilst screening and treatment for latent tuberculosis infection (LTBI) prior to commencing Tumour-Necrosis Factor inhibitors is standard of care, treatment for LTBI may fail in unrecognised isoniazid monoresistance—exposing patients to the risk of disseminated disease. This case highlights the importance of prompt recognition of HLH, a comprehensive search for an underlying driver and giving early pathogen-, and inflammation-directed treatment.

Case Report

Initial Presentation

A 63-year-old man arrived at his neighborhood hospital after experiencing mild nausea and vomiting along with a fever (38.4 °C) for five days. On admission, he had a mild lymphopenia (0.8×10^9/L), a C-reactive protein of 73 mg/L, alanine aminotransferase 272 IU/L, alkaline phosphatase of 351 IU/L and a ferritin of 3595 µg/L. A computed tomography scan of the liver at presentation showed trace pericholecystic free fluid and he was treated initially for presumed cholecystitis with intravenous co-amoxiclav. He remained febrile and became progressively pancytopaenic with a haemoglobin of 104 g/L, lymphocytes of 0.3×10^9/L and platelets of 132×10^9/L.

His background was significant for psoriatic arthritis diagnosed in 2014. He had commenced the Tumour-Necrosis Factor inhibitor, adalimumab (Hyrimoz™), in addition to his regular methotrexate, in April 2019. He was born in Ecuador, where he lived prior to moving to Europe 20 years previously. Prior to starting adalimumab, he had a positive interferon gamma release assay (Quantiferon TB-Gold Plus) and was treated for LTBI with 24 weeks of isoniazid 300 mg once daily (with pyridoxine), completing treatment 40 months prior to this presentation.

Diagnostic Work-Up

Following the acute admission, initial bacterial cultures of blood, sputum and urine were all negative. He had a negative respiratory viral panel, malaria film, *Histoplasma* urinary antigen, and serum Beta-D-glucan and galactomannan. He had negative serology for HIV, Hepatitis A–E viruses, *Toxoplasma sp.*, syphilis, *Leishmania spp.* infection. There was evidence of previous Epstein-Barr Virus and Cytomegalovirus infection.

He subsequently underwent whole body ^{18}F-fluorodeoxyglucose positron emission tomography magnetic resonance imaging which demonstrated diffusely increased hepatic, splenic and bone marrow activity, with small volume avid lymph nodes and diffusely increased activity in the lungs (Fig. 1A). Magnetic resonance imaging of his liver was unremarkable. A bone marrow biopsy was performed which demonstrated increased histiocytes and evidence of haemophagocytosis, it also contained occasional small non-necrotizing granulomas as well as a prominent plasma cell population.

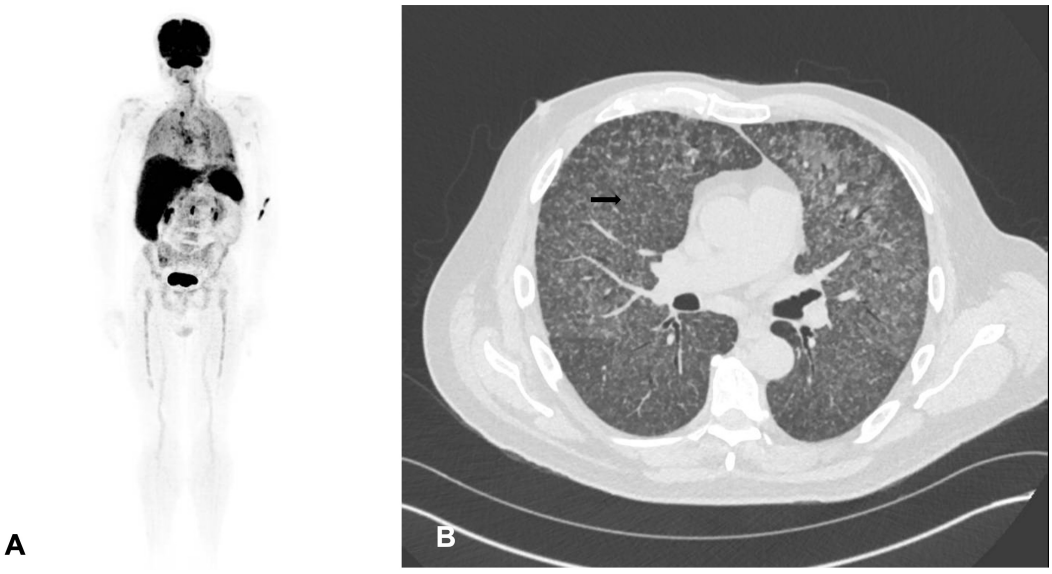

Fig. 1. Imaging findings suggestive of disseminated tuberculosis. ^{18}F-fluorodeoxyglucose (FDG) uptake scan demonstrating avid hepatic, splenic, pulmonary, and bone marrow uptake (A); subsequent high-resolution computed tomography of the chest demonstrating miliary pattern bilaterally (B-arrow).

He commenced treatment for secondary haemophagocytic lymphohistiocytosis with anakinra (2 mg/Kg intravenously twice a day) and three days later received 1000 mg intravenous methylprednisolone while he underwent investigations for the HLH driver (HScore at commencement of anakinra was 197, 80–88% probability HLH). On the fourth day of HLH treatment he developed a new oxygen requirement with bilateral crepitations on auscultation. High-resolution computed tomography of the chest demonstrated widespread diffuse micronodular infiltrates and ground-glass opacification with mediastinal and upper abdominal lymph nodes (Fig. 1B).

This was considered typical for disseminated *Mycobacterium tuberculosis* infection and he was started on a standard four drug regimen (rifampicin, isoniazid, pyrazinamide and ethambutol). He later underwent a bronchial alveolar lavage, which was positive by GeneXpert PCR for *Mtb.* complex (no mutation of *rpoB* detected). Later GeneXpert PCR performed on his original bone marrow aspirate sample was also found to be positive for *Mtb.* complex.

Magnetic resonance imaging of his brain was performed to determine if there had been any disseminated spread to his central nervous system. This demonstrated four small contrast enhancing lesions in the right cerebellum and right middle superior frontal gyrus (Fig. 2). There was no leptomeningeal enhancement or neurological symptoms. These changes were felt to be potentially compatible with *M. tuberculosis* central nervous system infection, and his regimen was subsequently changed to replace ethambutol with moxifloxacin for its greater central nervous system penetration.

He clinically improved following the first week of anti-tuberculosis therapy in conjunction with treatment for HLH, with down-trending ferritin and inflammatory markers and was subsequently discharged.

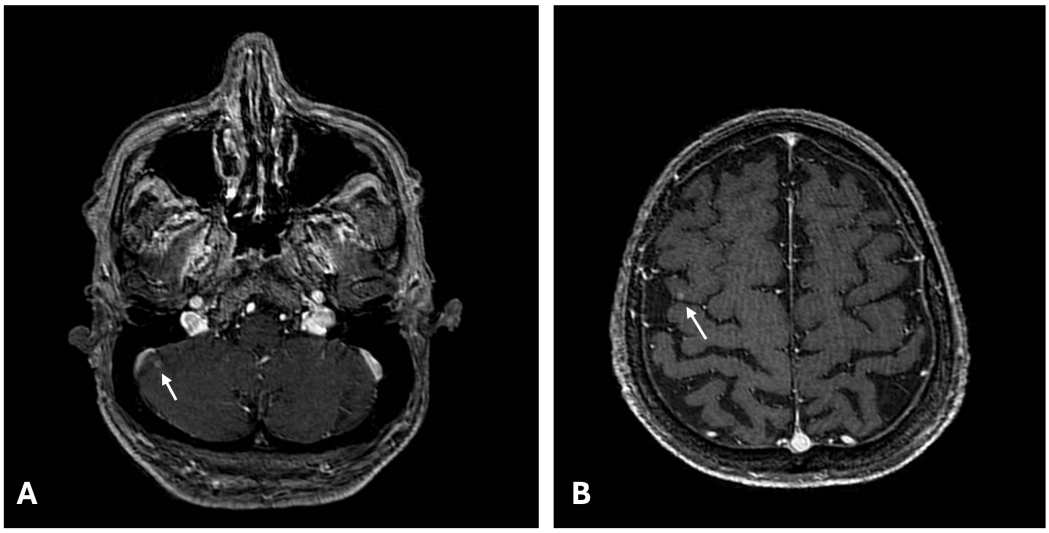

Fig. 2. Magnetic resonance imaging. (A) Enhancing right cerebellar nodule (T1 post-GAD) (arrow). (B) Enhancing right middle frontal gyrus nodule (T1 post-GAD) (arrow).

M. tuberculosis was later cultured from the bone marrow and bronchial washings samples. Whole genome sequencing (WGS) of this isolate (performed routinely in the UK) revealed a *European-American* lineage and isoniazid monoresistance. At seven months from his initial presentation, he remains well continuing rifampicin, pyrazinamide, moxifloxacin with no specific HLH treatment ongoing and no evidence of HLH recurrence.

Discussion and Review of the Literature

We report a case of HLH caused by disseminated *M. tuberculosis* infection as a result of reactivation of latent tuberculosis on combination methotrexate and adalimumab. *M. tuberculosis* is a well-recognised trigger of secondary haemophagocytosis (Padhi et al, 2015), however is less common than other infectious triggers (Lerolle et al, 2016). Whilst disseminated tuberculosis is relatively common in individuals with advanced immunocompromise, especially advanced HIV infection (Barr et al, 2020), the development of secondary HLH following disseminated infection is rare. Use of TNF inhibitors may disproportionally increase the risk of disseminated or extra-pulmonary tuberculosis in cases associated with reactivation following treatment initiation (Dixon et al, 2010). Two recent systematic reviews have highlighted the role of *Mtb*. in driving secondary HLH, and the relatively high-yield of bone marrow samples in disseminated infection (Fauchald et al, 2023; Kurver et al, 2024).

Six-months of daily isoniazid has 60–90% efficacy in the prevention of the progression of latent infection to active disease (Getahun et al, 2015), but is ineffective in the approximately 8% of patients with isoniazid monoresistance (Hr-TB)—which is associated with worse outcomes and the development of further resistance (World Health Organization, 2018). Failure of LTBI treatment with six-month of isoniazid monotherapy was most likely a result of preexisting Hr-TB. Alternate reg-

imens such as three-month of daily rifampicin and isoniazid have the potential to be used in situations where Hr-TB is a concern (World Health Organization, 2018).

The clinical challenges presented by this case were prompt recognition of HLH and starting inflammation directed treatment early. All diagnoses of HLH warrant an exhaustive search for a driving pathology. In this case, until miliary changes developed, tuberculosis had been considered somewhat less likely as he had been previously treated for LTBI.

Conclusion

Clinicians should be aware of the risk of tuberculosis reactivation with varying immunosuppression and that tuberculosis is a rare, but well described, driver of secondary HLH. Additionally, Hr-TB may be associated with the failure of treatment for latent tuberculosis infection and that the high prevalence of this infection in many regions means clinicians in all specialties should be aware of the possibility of Hr-TB and its association with worse outcomes.

Learning Points

- *M. tuberculosis* is an underrecognized and important driver of HLH.
- Treatment for LTBI may be unsuccessful in the setting of isoniazid monoresistance.
- Prompt recognition and treatment of disseminated tuberculosis is required in HLH.

Availability of Data and Materials

Not applicable.

Author Contributions

TS and JM wrote the first draft of the manuscript. TS, HQ, DL, MN, MB, DM and JM cared for the patient, acquired data and contributed significant changes to the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Informed consent was obtained from all study participants.

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Conflict of Interest

The authors declare no conflict of interest. Mahdad Noursadeghi is serving as one of the Editorial Board members of this journal. We declare that Mahdad Noursadeghi had no involvement in the review of this article and has no access to information regarding its review.

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