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Macrophage Activation Syndrome Revealing Tuberculous Lymphadenitis in an Adolescent: A Case Report and Review of Literature

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Abstract

Background: Macrophage activation syndrome (MAS), considered within the spectrum of secondary hemophagocytic lymphohistiocytosis (HLH), is a fulminant hyperinflammatory syndrome caused by uncontrolled activation of macrophages, T lymphocytes, and cytokine pathways. Infection-triggered MAS is well recognized, but tuberculosis remains an uncommon and underdiagnosed precipitant in children, particularly when the underlying focus is extrapulmonary. **Case presentation:** We report on the case of a 14-year-old adolescent admitted for prolonged fever, marked weight loss, cervical lymphadenopathy, and splenomegaly. The biological work-up disclosed bicytopenia, hyperferritinemia, and hypertriglyceridemia, raising suspicion of MAS/secondary HLH. Bone marrow aspiration demonstrated hemophagocytosis. Etiological investigations subsequently identified tuberculous lymphadenitis, confirmed by histopathology showing caseating granulomatous inflammation and molecular detection of Mycobacterium tuberculosis. **Management and outcome:** The patient received corticosteroid therapy to control the hyperinflammatory state together with antituberculous treatment, with favorable clinical and laboratory evolution. **Conclusion:** Tuberculosis-associated MAS should be considered in any child from a tuberculosis-endemic setting who presents with persistent fever, cytopenias, hyperferritinemia, organomegaly, and unexplained inflammatory syndrome. Early recognition of HLH features, rapid etiological investigation, and prompt initiation of both antituberculous therapy and appropriate immunomodulation are essential to improve outcome.

Keywords

Macrophage Activation Syndrome, Hemophagocytic Lymphohistiocytosis,

Tuberculosis, Tuberculous Lymphadenitis, Child, Hyperferritinemia

1. Introduction

Macrophage activation syndrome (MAS) is a life-threatening hyperinflammatory disorder that overlaps biologically and clinically with secondary hemophagocytic lymphohistiocytosis (HLH). It is characterized by ineffective cytotoxic control of immune activation, sustained stimulation of macrophages and T cells, massive cytokine release, and progressive tissue damage [1]-[4].

In children, MAS is classically discussed in the setting of rheumatic disease, particularly systemic juvenile idiopathic arthritis, but it may also be triggered by infection, malignancy, or less commonly by tuberculosis [2]-[4]. Tuberculosis-associated HLH is rare; however, the true incidence is likely underestimated because clinical features often mimic sepsis, severe systemic infection, malignancy, or advanced inflammatory disease [5]-[7].

The diagnostic challenge is particularly marked when tuberculosis is extrapulmonary and paucibacillary, as in peripheral lymph node disease, where microbiological confirmation may be delayed or initially absent. In endemic settings, this overlap may postpone both antituberculous treatment and immunomodulatory therapy, thereby worsening prognosis [5]-[9].

We report on a pediatric case of MAS revealing tuberculous lymphadenitis. Beyond the case itself, this report aims to highlight the practical diagnostic clues, the pathophysiological links between Mycobacterium tuberculosis infection and HLH/MAS, and the therapeutic principles relevant to clinicians managing children in tuberculosis-endemic regions.

2. Case Presentation

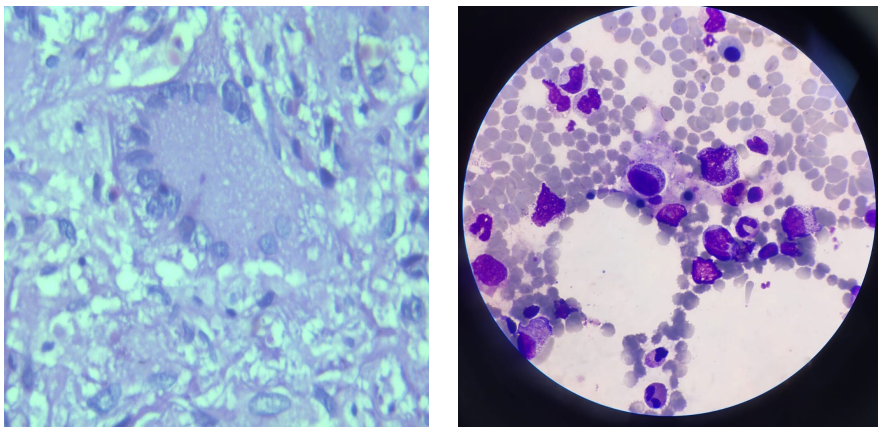
A 14-year-old adolescent with no significant personal medical history was admitted for prolonged fever evolving over approximately two months, associated with marked weight loss (10 kg) and deterioration of general condition. A remote family history of pulmonary tuberculosis was noted.

On examination, the patient was hemodynamically and respiratory stable. Moderate splenomegaly was noted, without hepatomegaly. Multiple cervical lymph nodes were present, firm, mobile, and non-tender. No other major abnormalities were documented in the initial clinical assessment.

The laboratory work-up revealed bicytopenia, consisting of normocytic anemia with hemoglobin at 9.4 g/dL and thrombocytopenia with a platelet count of 100,000/μL. There was also marked hyperferritinemia (3511 ng/mL) and hypertriglyceridemia (2.15 g/L). Liver function tests were within normal limits. In the context of persistent fever, splenomegaly, cytopenias, and elevated inflammatory markers, these findings raised strong suspicion of macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis (HLH).

The infectious work-up was negative, including cytomegalovirus (CMV), toxoplasmosis, rubella, Epstein-Barr virus (EBV), hepatitis B, hepatitis C, and HIV serologies. Immunological investigations were also performed and were unremarkable.

Bone marrow aspiration was subsequently performed and demonstrated hemophagocytosis (**Figure 1(a)** and **Figure 1(b)**), increasing the total to 6/8 HLH-2004 criteria and confirming the diagnosis of a hyperinflammatory hemophagocytic syndrome.



(a) (b)

Figure 1. Microscopic image demonstrating hemophagocytosis (Provided by Prof. H. Yahiaoui).

The lymph node biopsy was performed on a cervical lymph node due its accessible superficial location. Histopathological examination revealed caseating granulomas consistent with tuberculous infection. In addition, molecular testing using the Genexpert MTB/RIF assay detected Mycobacterium tuberculosis, confirming the diagnosis and excluding Rifampicine resistance.

Prior to lymph node excision, initial investigations for tuberculosis included clinical evaluation and routine infections work-up, however, no microbiological confirmation was obtained at that stage. Chest imaging did not show evidence of pulmonary involvement, suggesting isolated tuberculous lymphadenitis.

Regarding treatment, the patient received systemic corticosteroid therapy in combination with standard antituberculous treatment. Corticosteroids were initiated with high-dose intravenous methylprednisolone (pulse therapy), followed by a gradual tapering regimen of oral corticosteroids guided by clinical and biological response. Antituberculous therapy consisted of a standard first-line regimen including isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE), in accordance with current guidelines, with a planned total duration of six months. Clinical improvement was rapidly observed after treatment initiation, with prompt defervescence and progressive normalization of laboratory abnormalities.

Regarding follow-up, the patient was monitored on a monthly basis after discharge. The clinical course remained favorable, with sustained resolution of fever,

progressive improvement in general condition, and normalization of biological parameters. No relapse of macrophage activation syndrome/secondary HLH or tuberculosis was observed during the follow-up period. The treatment was well tolerated, with no reported adverse effects.

3. Discussion

MAS/secondary HLH represents a syndrome of immune dysregulation rather than a single disease entity. Defective cytotoxic activity of natural killer cells and cytotoxic T lymphocytes impairs elimination of activated antigen-presenting cells, perpetuating macrophage activation and cytokine amplification. Interferon-gamma, interleukin-1, interleukin-6, interleukin-18, tumor necrosis factor-alpha, and soluble interleukin-2 receptor pathways all contribute to the clinical phenotype of fever, cytopenias, hepatic dysfunction, coagulopathy, hypertriglyceridemia, and extreme hyperferritinemia [1]-[4].

The HLH-2004 criteria remain the most widely used diagnostic framework, especially in pediatrics, although they were originally developed for study enrollment rather than bedside diagnosis [1]. In real-world settings, clinicians often have to act before all eight variables are available, because tests such as NK-cell activity and soluble interleukin-2 receptor are not universally accessible. Contemporary consensus guidance therefore emphasizes that diagnosis should be syndromic and dynamic, integrating clinical deterioration, ferritin kinetics, cytopenias, organomegaly, coagulopathy, and evidence of immune activation rather than relying on a rigid checklist alone [2] [3].

Our patient fulfilled a highly suggestive clinicobiological profile, including prolonged fever, splenomegaly, bicytopenia, hypertriglyceridemia, hyperferritinemia, and bone marrow hemophagocytosis. Importantly, hemophagocytosis is neither fully sensitive nor specific for HLH, but in an appropriate context it remains a valuable supportive finding [1]-[3].

Tuberculosis is an uncommon but increasingly recognized trigger of secondary HLH. Earlier reviews had identified only a limited number of published cases, whereas more recent systematic reviews have substantially expanded the literature, underscoring both the rarity of the condition and its high associated mortality [5]-[7]. The largest recent review found an overall mortality approaching 40%, with improved survival when antituberculous therapy was combined with HLH-directed treatment rather than delayed or omitted [7].

Several mechanisms may explain TB-associated HLH. Persistent antigenic stimulation by Mycobacterium tuberculosis may drive uncontrolled macrophage and T-cell activation; disseminated or occult disease may provide a large inflammatory burden; and delayed diagnosis may allow a sustained cytokine storm to evolve. Although disseminated and miliary forms are classically overrepresented, extrapulmonary tuberculosis, including tuberculous lymphadenitis, may also serve as the initiating focus, as shown in the present case [5]-[7] [10].

Tuberculous lymphadenitis is one of the most common forms of extrapulmo-

nary tuberculosis in children, usually involving cervical nodes. Diagnosis is often difficult because presentation may be subacute, microbiological yield can be limited, and differential diagnoses include reactive adenitis, bacterial adenitis, lymphoma, atypical mycobacterial infection, and other granulomatous disorders [8] [9] [11]. Histopathology showing necrotizing granulomatous inflammation remains highly informative, and WHO guidance supports the use of Xpert MTB/RIF or Xpert Ultra on lymph node aspirates or biopsy specimens as an initial diagnostic test in patients with suspected extrapulmonary TB [8] [9] [12]-[14].

The therapeutic challenge in TB-associated MAS lies in treating two apparently opposing processes simultaneously: an uncontrolled inflammatory syndrome and an active infection. In practice, these are not competing priorities but parallel imperatives. Antituberculous treatment is the cornerstone because eradication of the trigger is essential; however, in severe HLH physiology, delaying immunomodulation may be fatal [3] [5]-[7]. Corticosteroids are commonly used, particularly in patients with organ dysfunction, progressive cytopenias, central nervous system involvement, or marked systemic inflammation. IVIG and, in selected severe cases, etoposide-based regimens have also been reported, although evidence remains largely observational in TB-associated HLH [2] [3] [6] [7].

In the present case, the combination of corticosteroids and antituberculous treatment was followed by favorable clinical and biological recovery. This outcome aligns with the practical principle that early control of hyperinflammation, together with prompt treatment of tuberculosis, can be lifesaving. The exact duration and intensity of immunomodulation should be individualized according to severity, organ dysfunction, and response to treatment.

From a pediatric tuberculosis perspective, current WHO guidance indicates that children aged 3 months to 16 years with peripheral lymph node tuberculosis limited to lymph nodes may be eligible for a shorter regimen, whereas other forms of extrapulmonary disease generally require a standard 6-month course [8]. In complex presentations such as TB-associated HLH, treatment duration should ultimately reflect disease extent, microbiological data, imaging findings, local programmatic recommendations, and specialist input.

This case also emphasizes an important practical message for clinicians working in endemic settings: prolonged fever plus cytopenias plus ferritin elevation should prompt active consideration of HLH/MAS, but the search for an infectious trigger must proceed in parallel. In a child with lymphadenopathy, weight loss, and constitutional symptoms, tuberculosis should remain high on the differential diagnosis even when the initial presentation is dominated by inflammatory or hematologic abnormalities.

4. Conclusions

Tuberculous lymphadenitis may rarely be revealed by macrophage activation syndrome/secondary HLH in children. Because the presentation overlaps with sepsis, malignancy, and systemic inflammatory disorders, diagnosis may be delayed un-

less clinicians actively integrate persistent fever, splenomegaly, cytopenias, hyperferritinemia, and suggestive epidemiologic or clinical clues for tuberculosis.

Rapid etiological investigation, including tissue pathology and molecular testing when available, is essential. Early combined treatment directed both at the triggering tuberculosis and the hyperinflammatory syndrome appears crucial for survival. This diagnosis deserves particular attention in high TB-burden regions, where earlier suspicion may shorten time to treatment and improve outcome.

5. Key Learning Points

- Persistent fever, splenomegaly, cytopenias, hypertriglyceridemia, and hyperferritinemia in a child should immediately raise suspicion of MAS/secondary HLH.
- Tuberculosis is an uncommon but important infectious trigger of HLH, particularly in endemic settings.
- Tuberculous lymphadenitis can present with limited local findings while driving major systemic inflammation.
- Histopathology and rapid molecular testing on lymph node material are central to diagnosis.
- Successful management often requires simultaneous treatment of the trigger (tuberculosis) and the hyperinflammatory response.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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