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Case Report

Beyond Occam's Razor: Diffuse Large B-Cell Lymphoma With Concurrent Acid-Fast Bacilli Positivity–A Case Report

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Abstract: In tuberculosis-endemic regions, necrotizing lymphadenitis with Acid-Fast Bacilli (AFB) is often presumed to indicate tuberculous etiology, but this assumption may lead to misdiagnosis when immunophenotypic evaluation is not performed. In this report, we present the case of an immunocompetent elderly man who presented with prolonged high-grade fever, progressive abdominal distension, and stable cervical and submandibular lymphadenopathy. He had been empirically started on antitubercular therapy (ATT) following fine-needle aspiration cytology findings of granulomatous lymphadenitis with AFB positivity, but failed to improve. On re-evaluation, he was found to have hepatosplenomegaly and generalized lymphadenopathy, and he fulfilled criteria for hemophagocytic lymphohistiocytosis (HLH). Imaging suggested a lymphoproliferative disorder, and repeat lymph node biopsy with immunohistochemistry confirmed Diffuse Large B-Cell Lymphoma (DLBCL). Despite therapy for both, prognosis was suboptimal. This case highlights the role of timely tissue diagnosis and immunohistochemistry in preventing delays in appropriate treatment and argues against the Ockham's Razor principle.

Keywords: Diffuse Large B-Cell Lymphoma, Necrotizing Lymphadenitis, Acid-Fast Bacilli, Hemophagocytic Lymphohistiocytosis, Case Report

Introduction

In tuberculosis (TB)-endemic regions, necrotizing lymphadenitis with Acid-Fast Bacilli (AFB) is commonly regarded as confirmatory for TB. Although this reflects Ockham's Razor by favoring the simplest explanation, it may conceal serious alternative diagnoses, including hematolymphoid malignancies such as diffuse large B-cell lymphoma (DLBCL). McFadden (2023); Puvaneswaran and Shoba (2012) DLBCL, an aggressive non-Hodgkin lymphoma, often presents with prolonged fever, weight loss, hepatosplenomegaly, and generalized lymphadenopathy, closely resembling disseminated TB (Miyake et al., 1997; Bottineau et al., 2019).

In resource-limited settings, empirical antitubercular therapy (ATT) is frequently initiated based on AFB positivity and/or granulomatous inflammation without immunophenotypic confirmation. Fine-Needle Aspiration Cytology (FNAC) can detect AFB but cannot reliably distinguish TB from lymphoma with necrotizing or reactive changes. This delays accurate diagnosis until clinical deterioration prompts a repeat biopsy (Banerjee et al., 2021; Centkowski et al., 2005).

Secondary hemophagocytic lymphohistiocytosis (HLH), a hyperinflammatory syndrome triggered by infections, autoimmune diseases, or malignancies, may further obscure diagnosis. (Henter et al., 2007) Characterized by persistent fever, cytopenias, hepatosplenomegaly, hyperferritinemia, and coagulopathy, HLH can be associated with an infectious/malignant diagnosis. Yildiz et al. (2022) There are few reports that describe patients treated empirically for TB based on AFB positivity who later prove to have lymphoma; few associated with HLH (Centkowski et al., 2005; Costa et al., 2004; Dres et al., 2012).

This case emphasizes cautious interpretation of AFB positivity and the need for early immunohistochemistry and reconsideration of differential diagnoses in TB-endemic settings.

Patient Information

A 62-year-old-man, with no known comorbidities or high-risk behaviors, presented with history of high-grade fever up to 103°F, associated with profuse sweating and no chills, rigors, or diurnal variation for eight months. He noted reduced appetite and a dragging sensation in the left

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hypochondrium over four months. He also noticed multiple, non-tender, non-progressive swellings in the cervical and submandibular regions. There was no past history of TB, TB contact, or family history of malignancy or similar illnesses.

Clinical Findings

On presentation, he looked ill and pale, with generalized lymphadenopathy involving cervical, submandibular, axillary, and inguinal nodes. The nodes were firm, non-tender, and non-matted with non-tethered skin. Abdominal examination revealed splenomegaly, palpable 5-6 cm below the costal margin, non-tender, firm consistency, with mild hepatomegaly. There were no signs of chronic liver disease. Other systemic examinations were unremarkable.

Timeline

The patient initially presented to a local hospital, where FNAC of a cervical lymph node demonstrated granulomatous lymphadenitis with acid-fast bacilli positivity. That time, the FNAC sample didn't undergo TB culture or PCR-based molecular testing (CBNAAT). Based on these findings, a presumptive diagnosis of TB was considered, and ATT was started. Due to persistent symptoms after 2-months of ATT, further evaluation was undertaken in our hospital (Fig 1).

Diagnostic Assessment

Vital signs confirmed persistent fever; rest within normal limits. The differential diagnosis was extrapulmonary TB, hematolymphoid malignancies such as Hodgkin and non-Hodgkin lymphoma, secondary HLH triggered by infection or malignancy, other tropical infections including brucellosis and visceral leishmaniasis, and autoimmune conditions such as adult-onset Still's disease or systemic lupus erythematosus.

Laboratory investigations revealed pancytopenia (Table 1). Liver function tests showed mildly elevated AST (45 U/L), with normal renal parameters. Serum triglycerides were 526 mg/dL, ferritin was markedly elevated at 4,983 ng/mL, and fibrinogen was borderline at 200 mg/dL. In the context of persistent high-grade fever and splenomegaly, these findings generated an H-score estimating a 93–95% probability of secondary HLH.

Chest X-ray was unremarkable. Contrast-enhanced CT of the chest and abdomen demonstrated multiple enlarged, conglomerated mesenteric and retroperitoneal lymph nodes with hepatosplenomegaly (Fig 2A).

An excisional lymph node biopsy was subsequently performed, which revealed necrotizing lymphadenitis with Langerhans-type giant cells. Ziehl–Neelsen staining showed AFB negativity, and CBNAAT was negative. In view of atypical clinical progression, immunohistochemistry was conducted, which ultimately established the diagnosis of diffuse large B-cell lymphoma (DLBCL) (Fig 2B–F).

Therapeutic Intervention

The patient received ATT, corticosteroids for HLH, supportive care (transfusions, antipyretics, nutritional support), and subsequent chemotherapy after diagnosis of lymphoma. ATT (Weight-based regimen) was restarted as per the National Tuberculosis Elimination Program daily regimen for drug-sensitive TB.

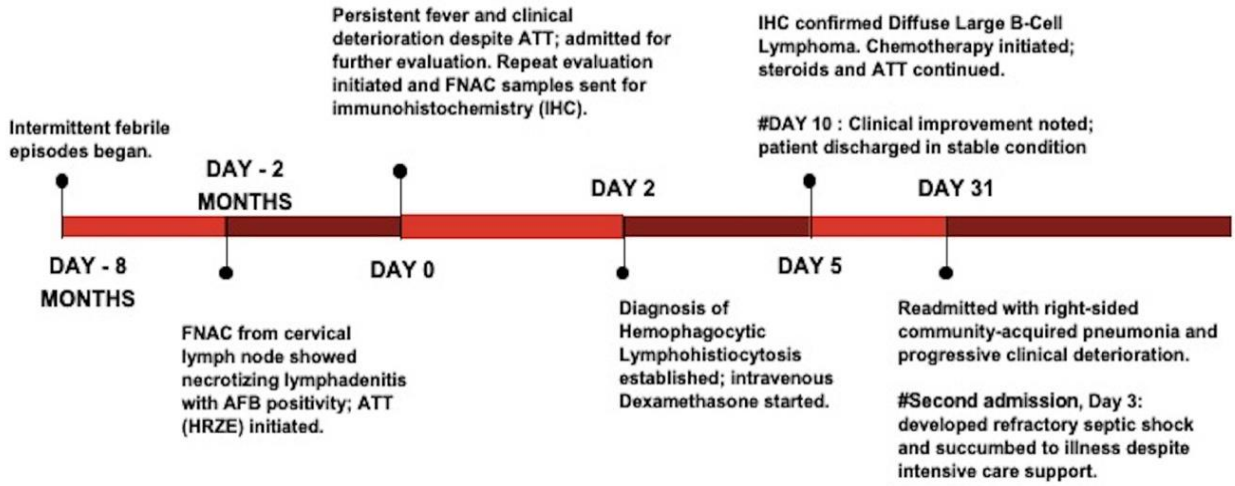

Fig. 1: Timeline of the patient from the day of illness till final outcome

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Table 1: Basic investigations, performed during evaluation of the case

Investigation	Reference range with SI unit	Day 1	Day 7
Hemoglobin	13-17 g/dL	4.2	5.8
Total Leukocyte Count	4-11×10³ cells/mm³	3.72	2.38
Differential Leukocyte Count (Neutrophils/Lymphocytes/Monocytes)	40-70/20-40/2-8%	45/26/8	62/22/8
Platelet	150-400×10³ cells/mm³	101	53
Total Bilirubin/Direct Bilirubin	0.3–1.2/0–0.2 mg/dL mg/dL	1.10/0.76	0.96/0.29
Alanine Transaminases/Aspartate Transaminases	0-50/0-50 U/L	49/45	184/45
Alkaline Phosphatase	30-120 U/L	110	108
Gamma Glutamyl Transferase	0-55 U/L	46	55
Total Protein/Albumin/Globulin	6.6-8.3/3.5-5.2/2.5-3.2 g/dL	6.4/2.8/3.6	6.3/2.9/3.4
Urea/Creatinine	17-43/0.72-1.18 mg/dL	46/1.1	21/0.78
Sodium/Potassium/Calcium	135–145/3.5–5.0/8.5–10.5 mg/dL	136/4.1/8.2	134/4.4/8.3
Uric Acid	3.5–7.2 mg/dL	7.6	7.9

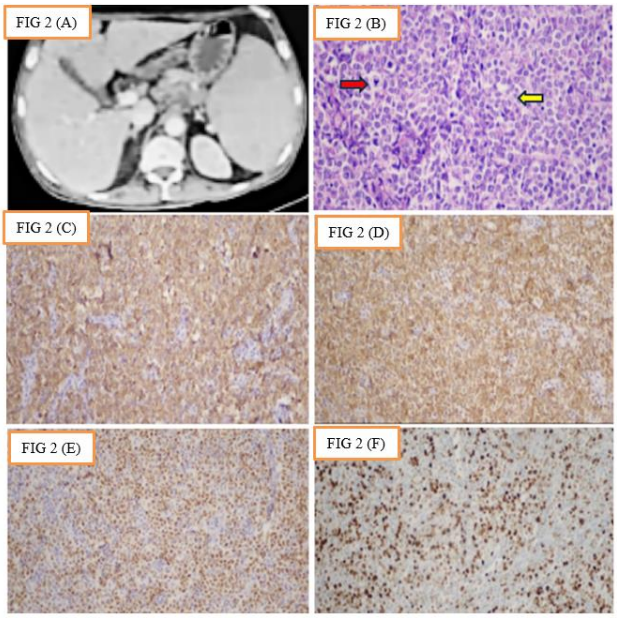

Fig. 2: Radiological and histopathological lymph node images. Contrast-enhanced CT scan of the abdomen (axial view) demonstrating hepatosplenomegaly with multiple enlarged abdominal lymph nodes (A); Hematoxylin and eosin (H&E, ×400) showing diffuse proliferation of medium to large atypical lymphoid cells (yellow arrow) with high nuclear-to-cytoplasmic ratio, irregular nuclear contours, coarse chromatin, prominent nucleoli, and brisk mitoses (red arrow) (B); Immunohistochemistry (IHC) for CD20 showing strong membranous positivity confirming B-cell lineage (C); IHC for CD10 showing diffuse membranous positivity, consistent with germinal center derivation (D); IHC for BCL6 demonstrating nuclear positivity, supporting a germinal center B-cell (GCB) phenotype (E); IHC for Ki-67 showing a proliferative index of approximately 90%, indicating high-grade activity (F). All these features confirmed diffuse Large B-Cell Lymphoma, GCB subtype

For a 70 kg adult male, the intensive phase consisted of 4 fixed-dose combination tablets daily containing rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol 275 mg per tablet, given for 2 months, and planned to be followed by a continuation phase with 4 tablets daily containing isoniazid 75 mg, rifampicin 150 mg, and ethambutol 275 mg per tablet for 4 months. Pyridoxine 20 mg once daily was advised throughout the treatment duration. The patient was managed as a case of HLH and was started on intravenous dexamethasone at a dose of 17 mg /day (10 mg/m²/day). Supportive transfusions were given as required. Chemotherapy was started using a standard regimen for DLBCL. The patient was started for chemotherapy with the R-CHOP regimen for DLBCL, comprising Rituximab 375 mg/m² IV on Day 1, Cyclophosphamide 750 mg/m² IV on Day 1, Doxorubicin 50 mg/m² IV on Day 1, Vincristine 1.4 mg/m² IV on Day 1, and Prednisolone 100 mg orally on Days 1–5, to be administered every 21 days with appropriate supportive care and monitoring for treatment-related toxicities. The patient's clinical condition improved on the ATT, Chemotherapy, and Steroids, and the patient became afebrile for more than 48 hours. The patient was later discharged on Follow-up in the Infectious Medicine and Clinical Hematology Departments.

Follow Up and Outcome

Despite the initiation of appropriate, guideline-directed intensive therapy and an initial transient clinical response, the patient subsequently exhibited progressive clinical deterioration. This was characterized by worsening asthenia, persistent high-grade pyrexia, productive cough, and a marked decline in functional status. Approximately 21 days following discharge, he developed right-sided community-acquired pneumonia, necessitating readmission to the intensive care unit.

During the second hospitalization, the patient demonstrated features of escalating systemic decompensation, including hemodynamic instability and evolving multiorgan dysfunction. Despite aggressive

supportive management, including broad-spectrum intravenous antimicrobial therapy, vasopressor support, and invasive mechanical ventilation, his condition continued to deteriorate. He ultimately succumbed on the third day of his second hospitalization due to refractory septic shock.

This clinical course led to the fulminant and aggressive nature of the underlying disease process, highlighting the complexity of management and the difficulty in achieving a favourable outcome despite timely and evidence-based therapeutic interventions.

Discussion

This case describes the diagnostic complexity and mortality associated with delayed recognition of lymphoma in a patient with AFB-positive lymphadenitis and secondary HLH. The co-existence of TB and non-Hodgkin lymphoma, particularly DLBCL, is uncommon but clinically significant and poses substantial diagnostic and therapeutic challenges. Both disorders share constitutional symptoms such as fever, night sweats, weight loss, and lymphadenopathy, thereby increasing the risk of misdiagnosis or delayed recognition. In TB-endemic settings, clinicians often initiate ATT following identification of AFB, reflecting Ockham's Razor, which may obscure an underlying malignancy(Puvaneswaran and Shoba, 2012; Dres et al., 2012).

In this case, constitutional symptoms, generalized lymphadenopathy, splenomegaly, and the initial demonstration of AFB in lymph node tissue favored a diagnosis of tuberculous lymphadenitis. However, failure to respond to ATT and persistent systemic inflammation prompted further reassessment. Retrospective IHC performed on stored tissue subsequently confirmed DLBCL as the coexisting pathology. This clinical course highlights the limitation of rigidly applying Ockham's Razor, as AFB positivity alone did not adequately explain the progressive disease (McFadden, 2023; Miyake et al., 1997).

Secondary HLH further complicated the presentation. HLH is a hyperinflammatory syndrome caused by uncontrolled immune activation and is associated with infections such as TB, autoimmune diseases like lupus, and hematologic malignancies, particularly B-cell lymphomas. The case fulfilled HLH-2004 criteria with a high H-score, demonstrating hyperferritinemia, hypertriglyceridemia, elevated liver enzymes, and bicytopenia. Henter et al. (2007); Yildiz et al. (2022) HLH secondary to lymphoma carries a poor prognosis and requires prompt recognition and treatment.

Clinically, a lack of improvement despite microbiological confirmation of TB should prompt re-evaluation for coexisting pathology. Persistent constitutional symptoms, cytopenias, organomegaly, or features suggestive of HLH warrant excisional biopsy and comprehensive histopathological assessment. Similar reports describing DLBCL masquerading as extrapulmonary TB or coexisting within tuberculous lymph nodes have been documented in the literature (Miyake et al., 1997; Costa et al., 2004; Dres et al., 2012; Chandra et al., 2025; Tadar et al., 2022).

The pathophysiological association between TB and lymphoma remains uncertain. Chronic immune stimulation in TB may contribute to lymphomagenesis, whereas lymphoma-associated immune dysregulation may predispose patients to opportunistic infections such as TB. Chandra et al. (2025) Concurrent HLH further reflects a profound immune imbalance.

An important limitation in this case is that concomitant TB was not definitively microbiologically confirmed. The discrepancy between the initial AFB-positive result and subsequent negative microbiological studies warrants consideration. Such discordance may occur because mycobacterial burden in lymph node tuberculosis is often low and unevenly distributed, leading to variable detection across different tissue samples. In addition, prior initiation of anti-tubercular therapy may reduce bacillary load and decrease the sensitivity of subsequent microbiological testing. Technical factors related to specimen quality, tissue processing, or sampling from different nodal areas may also contribute to discordant findings. This diagnostic uncertainty further emphasizes the need for comprehensive clinicopathological correlation and repeat evaluation when the clinical course is inconsistent with the presumed diagnosis.

Conclusion

AFB positivity alone should not be considered definitive evidence of active tuberculosis, particularly when the subsequent clinical course, microbiological investigations, or treatment response are discordant. Persistent or atypical lymphadenopathy should raise suspicion for coexisting hematolymphoid malignancies. Presence of lymphoma-related symptoms or lack of response to ATT necessitates biopsy with immunohistochemistry. Secondary HLH may complicate underlying infection or malignancy and requires early immunosuppressive therapy. Ockham's Razor has limitations in the presence of coexisting pathologies and should not preclude comprehensive clinical reassessment.

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Author's Contributions

Om Sharma: Did literature search, collected data, drafted the manuscript and approved.

Shaurya Gupta and Prasan Kumar Panda: Gave concept and design, did literature search, analyzed data, reviewed the manuscript and approved.

Ethics and Consent to Participate

The study was conducted according to accepted ethical guidelines for the conduct of research on HUMANS. No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008. Considering the retrospective observational single case study and de-identified nature of the case, ethical approval by AIIMS Rishikesh ethics committee/IRB was not required, however, individual Written informed consent was obtained.

Informed Consent

Individual written informed consent was obtained.

Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. However, any further requirements, it is available with corresponding author, and on request can be provided.

Conflict of Interest

The author or authors declare that they have no conflict of interest with respect to the author or publication of this article.

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