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Hematological Manifestations of Undiagnosed Tuberculosis: A Report of Two Rare Cases

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ABSTRACT

Background. Tuberculosis (TB) is a prevalent infectious disease with diverse clinical manifestations. Hematological abnormalities, though uncommon, can present as primary features of TB, complicating its diagnosis and management. These atypical presentations often mimic hematological malignancies, posing diagnostic challenges, particularly in endemic regions.

Case Report. This report discusses two rare cases of disseminated TB with distinct hematological presentations. The first case involved a 57-year-old male with autoimmune hemolytic anemia (AIHA), characterized by intravascular hemolysis confirmed by a positive Coombs test, elevated LDH, and hyperbilirubinemia. The second case featured a 42-year-old female with hypersplenism due to massive splenic involvement in miliary TB, leading to extravascular hemolysis and

pancytopenia. Both patients responded well to anti-tubercular therapy (ATT), with adjunctive corticosteroids required in the first case.

Conclusions. These cases highlight the protean hematological manifestations of disseminated TB and emphasize the importance of considering TB in the differential diagnosis of unexplained hematological abnormalities. Early recognition, comprehensive evaluation, and timely initiation of ATT are critical for favorable outcomes.

Keywords: Tuberculosis; Pancytopenia; Hypersplenism; Hemolytic anemia; Miliary tuberculosis; Disseminated tuberculosis

Abbreviations:

- **TB:** Tuberculosis
- **AIHA:** Autoimmune hemolytic anemia
- **ATT:** Anti-tubercular therapy
- **CBNAAT:** Cartridge-based nucleic acid amplification test
- **LDH:** Lactate dehydrogenase
- **IGRA:** Interferon-gamma release assay

INTRODUCTION

Tuberculosis (TB) continues to be one of the most significant global health challenges, remaining a leading cause of infectious disease-related morbidity and mortality. It disproportionately impacts populations in resource-limited settings, where access to healthcare services, early diagnostic tools, and effective treatment options can be scarce [1,2]. Despite advancements in TB diagnostics and therapeutic strategies, the burden of the disease persists, with more than 10 million new cases and

approximately 1.4 million deaths reported annually. TB is caused by *Mycobacterium tuberculosis*, a highly adaptive intracellular pathogen that primarily targets the lungs, resulting in pulmonary TB. However, this bacterium has the capacity to disseminate to almost any organ system, leading to extrapulmonary TB, which accounts for a substantial proportion of TB cases in both endemic and non-endemic areas

Pulmonary TB is the most widely recognized form of the disease due to its characteristic respiratory symptoms and associated transmission dynamics. However, extrapulmonary TB presents unique diagnostic challenges, particularly when it manifests in less typical ways, such as through hematological abnormalities. These extrapulmonary presentations are often underdiagnosed or misdiagnosed due to their nonspecific clinical features, which can overlap with other systemic diseases. Common hematological abnormalities observed in TB patients include anemia, leukocytosis, thrombocytopenia, and, in some cases, pancytopenia. Such abnormalities are particularly prominent in disseminated TB, a severe form of the disease characterized by the widespread dissemination of *M. tuberculosis* through the bloodstream and lymphatic systems. The systemic nature of disseminated TB allows it to affect the bone marrow and hematopoietic systems, resulting in a spectrum of hematological complications [3,4].

The overlap of hematological abnormalities associated with TB and those seen in hematological malignancies, such as leukemia or lymphoma, adds further complexity to the diagnostic process. Pancytopenia, for example, can be indicative of bone marrow infiltration by *M. tuberculosis*, yet it is often mistaken for more sinister conditions, leading to diagnostic delays. Similarly, autoimmune phenomena triggered by the immune response to *M. tuberculosis*, such as hemolytic anemia, contribute to the diagnostic ambiguity in affected patients. These atypical presentations necessitate a multidisciplinary approach to diagnosis, involving clinical evaluation, laboratory investigations, and imaging studies to avoid misdiagnosis and ensure timely intervention [5].

This report presents two cases of disseminated TB with atypical hematological manifestations. These cases underscore the diagnostic and therapeutic challenges posed by such presentations, highlighting the importance of maintaining a high index of suspicion for TB, particularly in endemic regions and among patients with unexplained hematological abnormalities. The cases also

emphasize the critical role of integrating clinical, laboratory, and radiological findings to achieve an accurate diagnosis and implement effective management strategies.

TB's systemic nature and its ability to mimic other diseases reinforce the need for vigilance among clinicians, especially when confronted with unexplained clinical and laboratory findings. Understanding the diverse ways in which TB can present is crucial for reducing diagnostic delays, preventing complications, and improving patient outcomes. Disseminated TB remains a vivid reminder of the complexities associated with this ancient disease and the need for ongoing research, education, and awareness to combat its global impact effectively.

CASE REPORT

Case 1: Intravascular Hemolysis due to Autoimmune Mechanisms

A 57-year-old male, occasional alcohol consumer, presented with a one-month history of fever, anorexia, and significant weight loss. There was no history of cough, loose stools, or other systemic complaints. Examination revealed malnutrition, jaundice, and minimal splenomegaly, with clear lungs and no lymphadenopathy.

Investigations

- Pancytopenia: Hemoglobin (Hb) 8.6 g/dL, TLC 1100/μL, Platelets 1.1 × 10^5/µL.
- Biochemical abnormalities: LDH 1080 IU/L, total bilirubin 2.6 mg/dL, hypoalbuminemia 2.6 g/dL, ALP 972 IU/L.
- Peripheral smear: Normocytic normochromic anemia.
- Imaging: CECT thorax and abdomen showed hepatomegaly with a 3.3 × 3.3 cm cystic lesion and randomly distributed nodular changes in the lungs.

Despite broad-spectrum antibiotics and antihelminthics, pancytopenia worsened (Hb 6.0 g/dL, TLC <1000/μL, platelets 23,000/μL). Bone marrow biopsy revealed granulomatous inflammation suggestive of TB, confirmed by a positive IGRA. Initial ATT led to fever resolution, but anemia persisted (Hb 5.8 g/dL), with rising bilirubin (4.6 mg/dL). A direct Coombs test confirmed AIHA. The patient was started on prednisolone (1 mg/kg/day) alongside ATT, leading to a dramatic recovery and resolution of pancytopenia.

Figure 1: Bone marrow biopsy showing granulomatous inflammation. **Figure 2:** CT image demonstrating hepatomegaly with cystic lesions.

Case 2: Extravascular Hemolysis due to Hypersplenism

A 42-year-old female presented with fever, anorexia, weight loss, and left upper abdominal discomfort. A similar febrile episode a year earlier had required blood transfusions for anemia and jaundice. Examination revealed malnutrition, icterus, anemia, fever, and massive hepatosplenomegaly without lymphadenopathy.

Investigations

- Pancytopenia: Hb 6 g/dL, TLC 3100/µL, Platelets 1.2 × 10^5/µL.
- Biochemical abnormalities: Total bilirubin 4.6 mg/dL (indirect 3.2 mg/dL), ALP 786 IU/L.
- Imaging: CECT thorax and abdomen revealed massive splenomegaly with multiple hypodense lesions.
- Further studies: MRI and PET-CT identified metabolically active lesions in the spleen, liver, and pelvic bones, with suspected infective emboli causing infarcts in the kidneys and long bones.

Sputum CBNAAT confirmed miliary TB, and fundoscopy revealed choroidal tubercles. ATT was initiated, resulting in resolution of pancytopenia and anemia within two weeks. The pathology was attributed to hypersplenism causing extravascular hemolysis.

Figure 3: CT thorax showing splenomegaly. **Figure 4:** PET-CT demonstrating miliary TB involvement.

DISCUSSION

Tuberculosis (TB), a complex infectious disease, exhibits a wide array of hematological abnormalities, particularly in its disseminated forms. These atypical presentations, though rare, add layers of complexity to the diagnosis and management of TB, as illustrated by the two cases discussed.

Case 1: Autoimmune Hemolytic Anemia (AIHA)

Autoimmune hemolytic anemia is an immune-mediated condition in which autoantibodies target red blood cells, leading to their premature destruction. In the context of TB, AIHA is believed to result from immune dysregulation triggered by *Mycobacterium tuberculosis*. In this case, intravascular hemolysis was evident through hallmark indicators, including a positive direct Coombs test, elevated lactate dehydrogenase (LDH), and hyperbilirubinemia [6,7].

Management required a dual approach to address both the immune-mediated hemolysis and the underlying infection. Corticosteroids played a vital role in suppressing the immune response, while anti-tubercular therapy (ATT) targeted the mycobacterial infection. This combined strategy was effective in resolving symptoms and normalizing hematological parameters, underscoring the importance of an integrated treatment approach. AIHA in TB, while rare, is a serious complication that demands prompt recognition to prevent severe anemia and associated morbidity.

Case 2: Hypersplenism and Extravascular Hemolysis

Hypersplenism, characterized by heightened sequestration and destruction of blood cells within the spleen, is a recognized complication of massive splenic involvement in disseminated TB. In this case, extravascular hemolysis occurred in the absence of direct immune-mediated mechanisms, distinguishing it from AIHA. Imaging studies confirmed massive splenomegaly with hypodense lesions, consistent with splenic TB.

Treatment focused on ATT, which effectively reduced the splenic burden and resolved anemia and pancytopenia. Unlike AIHA, corticosteroids were unnecessary, as the pathology was non-immune-mediated. This case highlights the importance of differentiating hypersplenism from immune-mediated hemolysis to guide appropriate therapeutic interventions [8,9].

Pathophysiological Insights

The hematological manifestations in TB stem from multiple mechanisms:

1. **Bone Marrow Involvement:** Granulomatous infiltration disrupts hematopoiesis, leading to pancytopenia.
2. **Immune Dysregulation:** AIHA results from autoantibody formation, causing complement-mediated intravascular hemolysis.
3. **Hypersplenism:** Splenic enlargement enhances the sequestration and destruction of blood cells, resulting in extravascular hemolysis.

TB-associated immune dysregulation involves a complex interplay between innate and adaptive immunity. Regulatory T cells, which suppress excessive immune activation, are often upregulated in TB, potentially contributing to autoimmunity and conditions such as AIHA.

Diagnostic Challenges

Hematological presentations of TB frequently mimic hematological malignancies and autoimmune disorders, complicating timely diagnosis. In both cases, thorough evaluation—including bone marrow biopsy, advanced imaging, and microbiological confirmation (e.g., IGRA, CBNAAT)—was crucial in identifying TB as the root cause. These diagnostic modalities remain pivotal in distinguishing TB from other conditions with similar clinical features.

Management Strategies

Effective management of TB-associated hematological abnormalities hinges on:

1. **Timely Anti-Tubercular Therapy (ATT):** The cornerstone of treatment, addressing the underlying infection and reversing systemic manifestations.
2. **Adjunctive Corticosteroids:** Critical in immune-mediated complications like AIHA to suppress hemolysis.
3. **Supportive Care:** Includes blood transfusions and monitoring for severe anemia or pancytopenia, as needed.

Broader Implications

These cases underscore the diverse hematological presentations of TB and the importance of maintaining high clinical suspicion, particularly in endemic regions. Distinguishing between intravascular and extravascular hemolysis is crucial, as it directly influences therapeutic decisions. A multidisciplinary approach involving infectious disease specialists, hematologists, and radiologists is essential to optimize outcomes.

By highlighting these rare presentations, this report aims to enhance clinical awareness and encourage early diagnosis, which is paramount in reducing the morbidity and mortality associated with TB.

Conclusion

Tuberculosis (TB) exemplifies the complexity of infectious diseases, with its ability to present a wide array of clinical and hematological manifestations. The cases discussed in this report highlight the importance of considering TB in the differential diagnosis of unexplained hematological abnormalities, particularly in endemic regions. These atypical presentations, including autoimmune hemolytic anemia (AIHA) and hypersplenism-induced pancytopenia, demonstrate the disease's capacity to mimic other conditions such as hematological malignancies, posing significant diagnostic and therapeutic challenges.

The timely diagnosis and effective management of TB-associated hematological complications hinge on an integrated, multidisciplinary approach. This involves recognizing clinical patterns, leveraging advanced diagnostic tools, and tailoring therapeutic strategies to address both the underlying infection and its systemic manifestations. Anti-tubercular therapy (ATT) remains the cornerstone of treatment, while adjunctive therapies like corticosteroids play a critical role in managing immune-mediated complications such as AIHA. Differentiating between immune-mediated and non-immune-mediated mechanisms, as seen in these cases, is essential to guide appropriate interventions and avoid unnecessary treatments.

These cases underscore the broader importance of clinical vigilance and adaptability, particularly in TB-endemic regions. Healthcare professionals must maintain a high index of suspicion for TB in patients with unexplained hematological findings, even when the presentation is atypical. Enhanced awareness, continued education, and access to robust diagnostic infrastructure are critical to improving early recognition and reducing the burden of TB-associated complications.

Beyond the clinical implications, these cases highlight the need for global health initiatives to address TB as a public health priority. Strengthening diagnostic capacities, promoting research on

TB's varied presentations, and fostering collaboration among healthcare professionals are essential steps toward better outcomes. TB is diverse presentations require clinicians to think beyond its pulmonary manifestations and adopt a holistic diagnostic approach. By emphasizing early diagnosis, appropriate management, and interdisciplinary collaboration, healthcare systems can improve outcomes for patients with complex and atypical presentations of TB. These efforts are vital in reducing the morbidity and mortality associated with this ancient yet persistent disease.

PATIENT CONSENT

Consent for the publication of these case reports was obtained from the patients, ensuring adherence to ethical standards for medical reporting. All identifying details have been omitted to maintain patient anonymity.

CONFLICT OF INTEREST The authors declare no conflict of interest related to this study or its publication.

AUTHOR'S CONTRIBUTIONS:

Anamitra Hait: Conceptualization, data curation, investigation, writing—original draft preparation, and visualization.

Arbind Kumar Chaudhary: Methodology, formal analysis, validation, supervision, and writing—review and editing.

All authors have read and approved the final manuscript.

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FIGURES, TABLES AND SCHEMES

Figure 1: **Figure 1:** Bone marrow biopsy of Case 1 showing granulomatous inflammation.

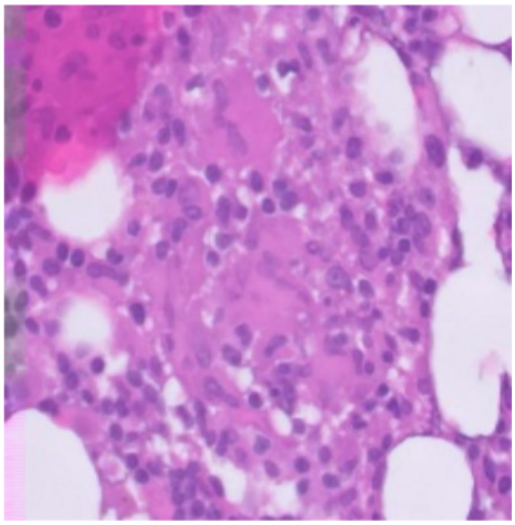

Fig no 1:Bone marrow biopsy of the patient showing granulomatous lesion

Figure 2: Imaging of Case 1 showing nodular changes in the lung.

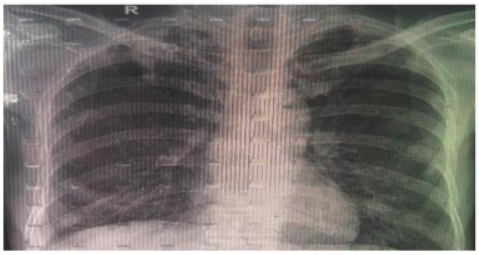

fig no 2 :Chest X ray showing nodular changes in lung

Figure 3: CT of Case 2 demonstrating metabolically **CT thorax showing miliary tuberculosis**

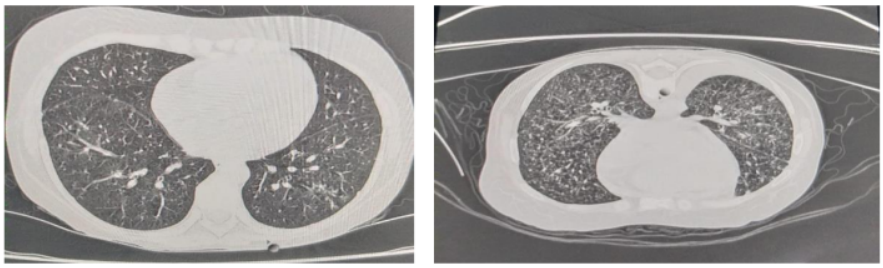

FIG NO 3: CT thorax showing miliary tuberculosis

Figure 4: Pet Ct Scan Showing Miliary Distribution Of Tuberculosis

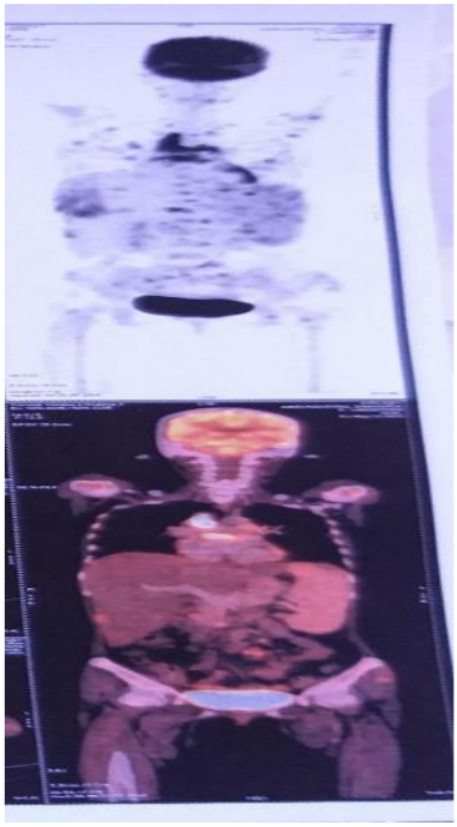

FIG NO 4: PET CT SCAN SHOWING MILIARY DISTRIBUTION OF TUBERCULOSIS