Unusual pattern of Hodgkin Lymphoma presented as Hemophagocytic Lymphohistiocytosis with combined heterogeneous LRBA gene mutation

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition of overstimulated immune activation. Although neoplastic conditions often trigger HLH, Hodgkin's lymphoma (HL) is uncommon. LPS-responsive, beige-like anchor protein (LRBA) deficiency results in altered recycling of cytotoxic T-lymphocyte associated protein 4 (CTLA4) on the regulatory T cells membrane. Several studies have reported the association of HLH and HL with LRBA deficiencies.

Aim

To report a case of HLH triggered by Hodgkin's lymphoma with unusual presentations that may have led to a delay in diagnosis, accompanied by an incidentally found, unreported LRBA mutation.

Objectives

- To describe the clinical course of a rare case of HL presenting as HLH.
- To highlight the diagnostic challenges in HL without lymphadenopathy.
- To explore the possible contribution of LRBA mutation to atypical presentation.

Methods

A 23-year-old man presented with symptoms of HLH associated with EBV reactivation.

- Lab tests: pancytopenia, elevated CRP, LDH, and sIL2r.
- Peripheral blood smear: 6% atypical morphologic lymphocytes.
- Imaging: Contrast-enhanced CT revealed only hepatosplenomegaly; no lymphadenopathy.
- Bone marrow biopsy: showed hypercellularity with diffuse histiocytic infiltration.
- Bone marrow immunohistochemistry: positive for Hodgkin's lymphoma markers *(Fig. 1)*.
- FDG PET/CT scan: detected a lymph node in the left groin region with increased FDG uptake *(Fig. 2)*.
- Lymph node biopsy and immunohistochemistry: confirmed HL diagnosis *(Fig. 3)*.
- Genetic testing: revealed a heterozygous LRBA mutation.

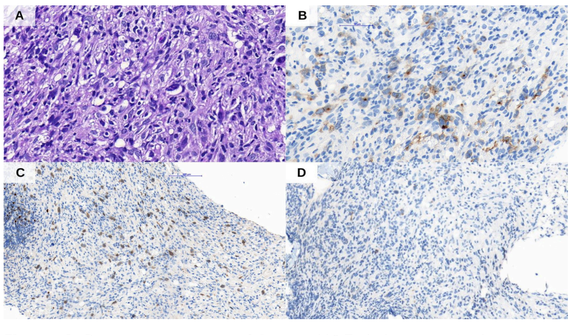


Figure 1. Bone marow core biopsy: H&E stain revealed increased histiocytes and architectural effacement (A). Scattered, large cells stained positive for CD30 (B) and PAX5(C) consistent with Hodgkin's Lymphoma. A few EBVpositive cells are found (D)

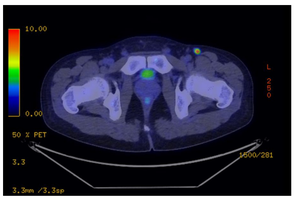


Figure 2. FDG PET/CT scan showed diffused bone marrow enhancement. There is only one lymph node with the diameter of 12 mm in the left groin region with increased FDG uptake was found.

Results

- Initial diagnosis delayed due to atypical HLH-like presentation.
- PET/CT imaging enabled detection of hidden lymphadenopathy not seen on CT.
- Lymph node biopsy revealed Reed-Sternberg cells positive for CD30, CD15, PAX5, and EBV-encoded RNA; negative for CD20, CD3, and CD5.
- Patient received antineoplastic therapy (4 cycles), resulting in complete remission of HL and HLH.
- Incidental LRBA mutation was discovered; its role in the presentation remains unclear.

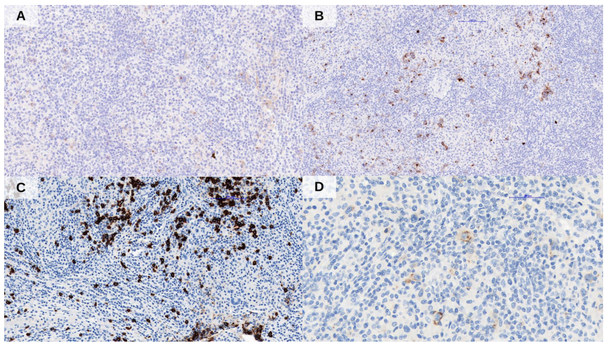


Figure 3. Lymph node biopsy: There were Reed-Sternberg cells that stained positive for CD30 (A) and CD15 (B) with the absence of CD20 (C), CD3, CD5 and PAX5 (not shown). Epstein-Barr virus-encoded RNA immunoreactivity was recognized (D)

Summary

This is a rare case of Hodgkin's lymphoma presenting initially as HLH without classic lymph node enlargement, leading to diagnostic confusion and delayed treatment. Diagnosis was confirmed via PET/CT and biopsy. The patient responded well to therapy. A heterozygous LRBA gene mutation was incidentally found, which may have contributed to the unusual clinical presentation.

Discussion

The absence of lymphadenopathy—typically seen in HL—contributed to the diagnostic delay. Viral infections (EBV, CMV) further obscured the diagnosis due to overlapping symptoms with HLH. PET/CT proved critical in detecting atypical presentations of HL. The LRBA gene, located on chromosome 4q31.3, is known to be associated with CTLA4 recycling disruption. LRBA mutations can lead to a wide range of immunological issues: cytopenias, hypogammaglobulinemia, autoimmunity, and lymphocytic infiltration of various organs. While LRBA mutations have been observed in both HL and HLH independently, the interplay between LRBA deficiency, HLH, and HL in this case is not yet clearly understood and warrants further investigation.

References

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