Case Report

Granulomatous Inflammation Masking Nodular Lymphocyte Predominant Hodgkin Lymphoma: A Diagnostic Pitfall

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Abstract

Extensive granulomatous inflammation in a lymph node is a significant diagnostic pitfall that can mask underlying malignancies, including Nodular Lymphocyte-Predominant Hodgkin lymphoma (NLPHL). Hodgkin lymphomas are lymphoid neoplasms with characteristic Reed-Sternberg cells (RS cells) and variants of RS cells in the mixed reactive background of neutrophils, eosinophils, plasma cells, and polymorphic lymphoid cell population. Granulomatous inflammation occasionally may accompany the polymorphic mixed reactive population but is sometimes so extensive that it masks the primary underlying pathology. This can lead to delayed and missed diagnosis. We report a rare case of Nodular Lymphocyte-Predominant Hodgkin lymphoma (NLPHL) masked by exuberant granulomatous lymphadenitis.

Introduction

Hodgkin lymphomas (HL) are lymphoid neoplasms with characteristic Reed-Sternberg cells (RS cells), which may be large mononuclear or multinucleated neoplastic cells, in a mixed reactive background. They are classified into classical Hodgkin Lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin Lymphoma (NLPHL), each having different cytomorphologic and immunophenotypic characteristics [1]. NLPHL is a rare form of HL, accounting for approximately 5% of all HL cases, and association with extensive granulomatous inflammation is even rarer [2]. Sometimes, granulomatous inflammation is so extensive that it may mask the main pathology. We report a rare case of NLPHL masked by extensive granulomatous inflammation.

Case Report

A 34-year-old adult male presented with an axillary mass of 4×4×3 cm for one year, from December 2023 to November 2024. The patient gave a history of a recent rapid increase in the size of the mass for the past 2 months. The patient was

physically well with no history of fever, weight loss, pain, or any other constitutional symptom. Complete blood count and renal and liver function tests were within normal limits. The Erythrocyte Sedimentation Rate (ESR) was 6 mm in the first hour. Fine needle aspiration (FNA) was performed twice, which, on microscopic examination, showed multiple small noncaseating epithelioid cell granulomas, multinucleate giant cells, and a polymorphous lymphoid cell population. No characteristic RS cell was appreciable. The Ziehl-Neelsen (ZN) stain for acid-fast bacilli and periodic acid-schiff reagent stain for fungal profile were non-contributory, cartridge-based nucleic acid amplification technique (CBNAAT) findings for tuberculosis (TB) were negative, and Bactec culture was negative for tubercular growth. Because no definitive diagnosis could be reached despite repeating fine needle aspiration cytology (FNAC) twice, the patient was scheduled for a trucut biopsy (excision could not be done because the mass was adherent to underlying blood vessels). Multiple core biopsies were taken and stained with hematoxylin and eosin stain. Microscopic examination of biopsies showed multiple small discrete noncaseating sarcoid-like epithelioid cell granulomas and a polymorphous lymphoid cell population. However, the number of macrophages with inconspicuous to small nucleoli was slightly increased. ZN stain was again non-contributory. In addition, there were a few scattered cells with a large lobulated nucleus and prominent nucleolus (lymphocyte-predominant, LP/atypical RS cells). There were no eosinophils, neutrophils, or plasma cell infiltration. Focal areas of fibrosis and fibrotic bands were seen. Considering a few scattered suspicious LP cells, an Immunohistochemistry (IHC) panel for Hodgkin lymphoma was advised. Identification of LP cells followed by IHC played a pivotal role in reaching the diagnosis. The IHC was negative for CD15 and CD30 and positive for CD20, OCT2, and PAX5, making the diagnosis of NLPHL. The patient responded to treatment very well.

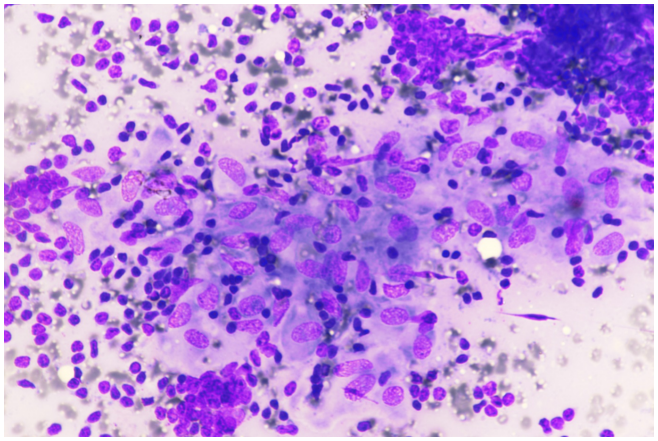

Figure 1: Fine needle aspiration cytology showing granulomatous inflammation (Giemsa stain, original magnification x 400).

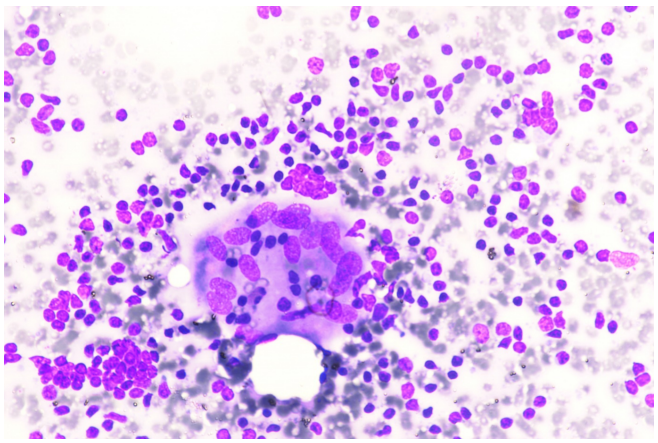

Figure 2: Fine needle aspiration cytology showing multinucleate giant cell (Giemsa stain, original magnification x 400).

Discussion

Granulomatous inflammation in CHL has been reported by many authors [3, 4], but to the best of our knowledge, there are only a few reports documenting association with NLPHL [5, 6]. Granulomas are characterized histologically as discrete nodules composed of epithelioid histiocytes and multinucleated giant cells surrounded by small lymphocytes and fibroblasts at the periphery. They generally represent a body's immune response trying to fight off the tumor vigorously. This showcases a strong immunity and should have a more favorable prognosis. However, some studies have suggested that HL with the formation of necrotizing granulomas may indicate a poor prognosis [4]. Granulomas associated with HL should be

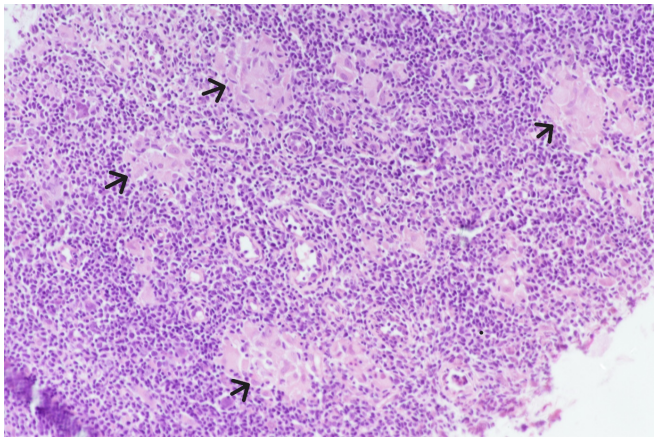

Figure 3: Trucut biopsy showing multiple small discrete noncaseating epithelioid cell granulomas (Hematoxylin and Eosin stain, original magnification x 200).

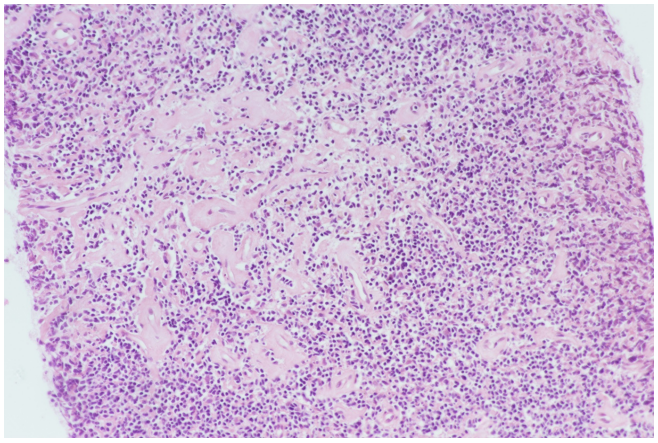

Figure 4: Trucut biopsy showing fibrotic band (Hematoxylin and Eosin stain, original magnification x 200).

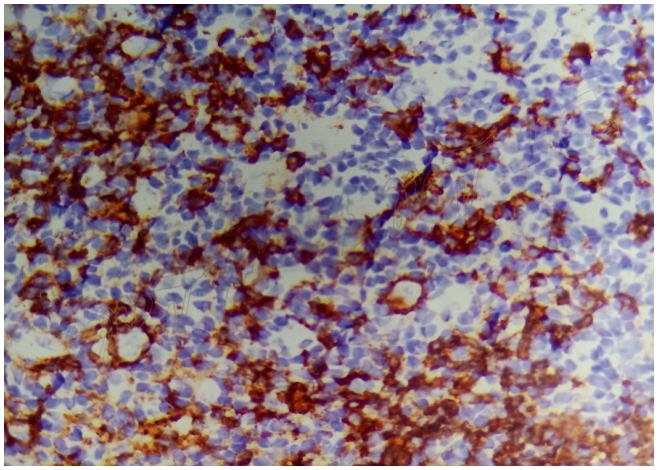

Figure 5: IHC showing positive membranous and cytoplasmic staining for CD20 in LP cells and reactive B cells (CD20 immunostain, original magnification x 200).

differentiated from other common causes of granulomatous lymphadenitis. Sometimes granulomatous inflammation is so extensive that it leads to diagnostic dilemmas, especially in FNAC (fine needle aspiration cytology). Khurana et al. (1998) also pointed out that malignancies associated with granulomas are difficult to diagnose accurately on FNAC [7]. This dilemma becomes even more profound in NLPHL, which lacks plasma cells and mixed leucocytic infiltrate (characteristic background in CHL). Moreover, TB is the most common cause of granulomatous lymphadenitis in developing countries like India. In that case, a diligent search for RS cells/LP cells, the morphology of lymph nodes on biopsy, IHC, and clinical suspicion help in reaching the diagnosis. Further, TB can be confirmed with the help of a modified ZN stain, culture, and CBNAAT. In most cases, granulomas in tuberculosis are bigger, irregular, and associated with caseous necrosis. Besides TB, many other common causes of granulomatous inflammation add to the diagnostic dilemma. Granulomas in sarcoidosis are

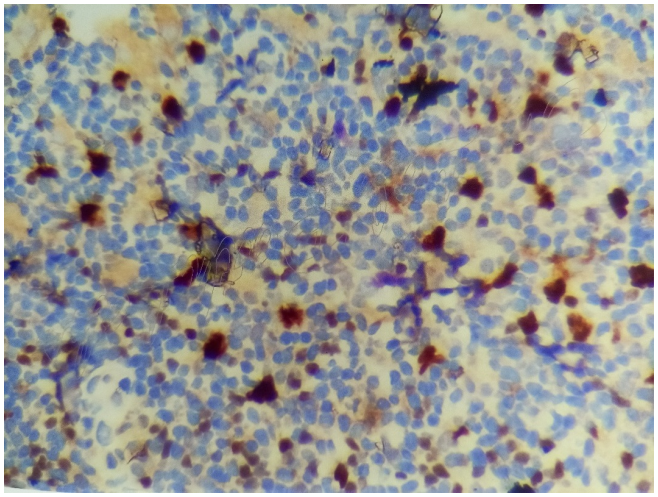

Figure 6: IHC showing positive nuclear staining for OCT2 in LP cells (OCT2 immunostain, original magnification x 200).

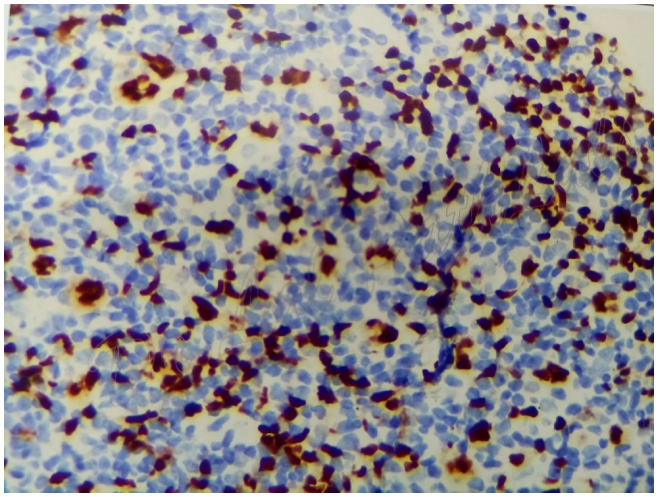

Figure 7: IHC showing positive nuclear staining for PAX5 in LP cells (PAX5 immunostain, original magnification x 200).

small, compact, discrete, and non-caseating, exactly like the ones found in HL. In our case also, granulomas were multiple, small, and sarcoid-like. However, because sarcoidosis is a diagnosis of exclusion, all causes of granulomatous inflammation must be ruled out before making a diagnosis of sarcoidosis. Fungal infections can also cause granulomatous lymphadenitis which can be confirmed with the help of special stains and culture. Many authors have reported the association of epithelioid cell granuloma with Non-Hodgkin Lymphoma and other malignancies also [8, 9, 10]. It is also crucial to differentiate NLPHL with extensive granulomatous inflammation, not only from other granulomatous causes but also from CHL, as treatment modalities and prognostic implications are different for each disease. This requires IHC for a definitive diagnosis because NLPHL has a distinctive immunophenotypic profile, a B-cell immunophenotype that differs from that of the CHL and other non-Hodgkin lymphomas. The LP cells are monoclonal B cells that express CD20, BCL6, CD79a, PAX5, OCT2 and are CD45 positive and are CD15 and CD30 negative. Whereas RS cells in CHL are positive for CD15, CD30, Pax5 and negative for other B cell markers. Another clinical clue in NLPHL is a typical axillary mass (peripheral lymph nodes) which is increasing in size rapidly with cytology and histopathology showing multiple small noncaseating granulomas. The final diagnosis is made on histopathologic examination and IHC findings.

Conclusion

In summary, extensive granulomatous inflammation in NLPHL is a rare association leading to delayed and sometimes incorrect diagnosis. Therefore, in cases of granulomatous lymphadenitis where TB and other infectious causes are excluded, a high index of suspicion for an underlying lymphoma must be maintained in axillary swellings, warranting a diligent search for rare LP cells and a low threshold for confirmatory immunohistochemistry. Although TB is the most common cause of granulomatous lymphadenitis, careful cytologic, histological examination, and specific tissue diagnosis are essential for every granulomatous inflammation. Rapidly enlarging, painless masses (especially axillary mass) with non-caseating granulomatous inflammation should be investigated thoroughly to prevent incorrect or delayed diagnosis.

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