

Recurrent Nodular Lymphocyte Predominant Hodgkin Lymphoma with Diagnostic Evolution Over Two Decades

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ABSTRACT

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare subtype of Hodgkin lymphoma with distinct pathologic and clinical characteristics. We present the case of a 51-year-old man with a nearly 20-year history of NLPHL characterized by multiple relapses, diagnostic reclassification, and treatment de-escalation. This case illustrates the diagnostic challenges in distinguishing NLPHL from lymphocyte-rich classical Hodgkin lymphoma (LRCHL), the indolent natural history of NLPHL with prolonged remissions, and the role of active surveillance in managing asymptomatic relapsed disease.

KEYWORDS: Nodular Lymphocyte Predominant Hodgkin Lymphoma; Lymphocyte-Rich Classical Hodgkin Lymphoma; Relapsed Hodgkin Lymphoma

INTRODUCTION

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) accounts for approximately 5% of all Hodgkin lymphoma cases and is distinguished from classical Hodgkin lymphoma (CHL) by the absence of classic Hodgkin/Reed-Sternberg cells and the presence of characteristic lymphocyte-predominant (LP) cells. Unlike CHL, the LP cells in NLPHL consistently express CD20 and lack CD30 expression. The clinical course of NLPHL is typically indolent, with most patients presenting with early-stage disease and experiencing excellent long-term survival.¹⁻³ However, late relapses are common, and transformation to diffuse large B-cell lymphoma (DLBCL) occurs in 8–14% of patients.⁴

The distinction between NLPHL and lymphocyte-rich classical Hodgkin lymphoma (LRCHL) can be challenging, as LRCHL shares morphologic features with NLPHL but has an immunophenotype consistent with CHL.^{5,6} This diagnostic overlap has significant therapeutic implications, as NLPHL may be managed with observation alone or rituximab, while CHL typically requires chemotherapy.

We present a case that highlights these diagnostic and therapeutic challenges over a nearly 20-year disease course.

CASE PRESENTATION

Initial Presentation (2006)

A 31-year-old man presented with an eight-month history of progressive left axillary swelling. He had a history of multiple angioliipomas and initially attributed the mass to another lipoma. Physical examination revealed a golf ball-sized left axillary mass. He denied fevers, night sweats, weight loss, or other B symptoms. His medical history was notable only for a right inguinal hernia repair upon initial presentation.

Excisional biopsy of the left axillary lymph node (May 25, 2006) revealed a 6.0 × 4.0 × 3.0 cm node with histopathology consistent with nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). Immunohistochemistry demonstrated LP cells that were CD20+, CD30+, CD79+ (weak), CD45RB+, EMA+, CD15–, CD3–, and EBV–. Flow cytometry showed a polytypic B-cell population (17%) with a kappa:lambda ratio of 1.2:1 and a T-cell population (79%) with a CD4:CD8 ratio of 4.4:1.

Staging workup included CT of the neck, chest, abdomen, and pelvis, which showed moderate left axillary adenopathy without other pathologic lymphadenopathy. Laboratory studies were unremarkable (WBC 6,300/μL, hemoglobin 16.5 g/dL, platelets 252,000/μL, LDH normal). Bone marrow biopsy (June 21, 2006) was negative for Hodgkin lymphoma, with 45% cellularity and small nondiagnostic lymphoid nodules occupying 3% of the intertrabecular space.

The patient was diagnosed with stage IA NLPHL and treated with involved-site radiation therapy (ISRT) to the left axilla and neck with a left axillary boost. He tolerated treatment well with only mild fatigue and transient erythema, achieving complete remission.

First Relapse (2007)

Fourteen months after completing radiation therapy, surveillance PET/CT (July 2007) demonstrated new areas of increased FDG uptake in the right axillary lymph node, subcutaneous nodules in the right axilla and shoulder, bilateral inguinal lymph nodes, and a left subpectoral lymph node. The prior left axillary uptake had resolved. Physical examination was unremarkable, with no palpable lymphadenopathy; the patient's multiple angioliipomas complicated clinical assessment.

Repeat PET/CT (August 2007) confirmed persistent findings. Excisional biopsy of a left upper chest wall lymph node

(October 2, 2007) revealed a $3.1 \times 1.8 \times 1.2$ cm node with histopathology initially interpreted as NLPHL. Immunohistochemistry showed LP cells that were CD20+, CD30+, CD45RB+, CD15-, CD3-, CD57-, and EMA-.

Expert pathology reclassified the lymphoma as lymphocyte-rich classical Hodgkin lymphoma (LRCHL) rather than NLPHL in February 2008. This reclassification was based on immunophenotypic features more consistent with CHL.

Pre-chemotherapy evaluation included MUGA scan (LVEF 62%, RVEF 57%) and pulmonary function tests, both normal. The patient began ABVD chemotherapy in November 2007. However, bleomycin was discontinued after the first cycle due to pulmonary toxicity.

The patient completed six cycles of ABVD and achieved complete remission. He remained in remission for approximately 15 years.

Surveillance Period (2008–2022)

During the prolonged remission, the patient developed hypothyroidism, likely radiation-induced given the cervical radiation field, and was maintained on levothyroxine (175 mcg daily, with 350 mcg on Mondays and Fridays). His multiple angioliopomas remained stable.

In October 2021, surveillance PET/CT demonstrated FDG-avid right axillary lymphadenopathy. Fine-needle aspiration (October 25, 2021) showed very rare atypical lymphocytes. Flow cytometry demonstrated a reactive/polytypic lymphoid population (64% T-cells, 34% polytypic B-cells). Immunohistochemistry showed CD30- and rare CD15+ cells. Core biopsy was recommended.

Excisional biopsy of the right axillary lymph node (November 5, 2021) revealed a benign lymph node with mild paracortical hyperplasia and no evidence of malignancy. Immunohistochemistry and flow cytometry were consistent with a reactive process. The patient continued observation.

Second Relapse (2023)

In July 2023, the patient (now 48 years old) noticed right axillary lymphadenopathy in the setting of a rash from a new deodorant. He remained asymptomatic without B symptoms.

PET/CT (September 2023) demonstrated Deauville 5 disease with increased size and number of right axillary and subpectoral lymph nodes (largest 2.9×1.7 cm). Intense uptake was also noted in the right thyroid lobe, likely consistent with thyroiditis. Laboratory studies were unremarkable (WBC 5.5, hemoglobin 16.9 g/dL, platelets 181,000/ μ L, CMP and LFTs normal).

Excisional biopsy of the right axillary lymph node (October 2, 2023) revealed a node with histopathology consistent with NLPHL. The sections showed largely effaced lymph node parenchyma with enlarged irregular lymphoid aggregates in a nodular pattern. Atypical large LP cells with irregularly shaped lobulated nuclei, conspicuous nucleoli, open

chromatin, and pale cytoplasm were identified. Immunohistochemistry demonstrated LP cells that were CD19+, PAX-5+, OCT2+, BOB1+, with CD30 highlighting scattered cells (a mix of immunoblasts and a subset of lesional cells). The LP cells were surrounded/rosetted by CD3+ T-cells, and CD21 highlighted variably expanded and disrupted follicular dendritic meshworks. Flow cytometry showed 63% T-cells (CD4:CD8 ratio 3.5) with polytypic TRBC1 expression and 34% polytypic B-cells.

Given the diagnostic discrepancy between the 2007 LRCHL diagnosis and the 2023 NLPHL diagnosis, the case was presented at a multidisciplinary tumor board, and slides were sent for repeat expert review. The consensus diagnosis was NLPHL.

His physicians discussed management options:

- If NLPHL: Observation alone or single-agent rituximab, given asymptomatic status and indolent biology;
- If LRCHL: Chemotherapy (pembrolizumab-GVD)

Given the confirmed NLPHL diagnosis and asymptomatic status, active surveillance was chosen.

Follow-Up (2024–2026)

At follow-up in January 2024, the patient remained asymptomatic with no palpable lymphadenopathy. Angioliopomas were stable. Surveillance continued.

PET/CT (November 2024) showed increased size of right axillary, subpectoral, and supraclavicular lymphadenopathy with a new enlarged portacaval lymph node, raising concern for stage III disease if the portacaval node was involved.

PET/CT (May 2025) demonstrated stable disease at the above sites with questionable uptake in the portacaval node.

PET/CT (October 2025) remained stable compared with prior studies, compatible with stable biopsy-proven Hodgkin lymphoma.

At the most recent evaluation (2026), the patient, now a 51-year-old man, remains asymptomatic, aside from a mobile mass on the chest consistent with an angioliopoma, which was not FDG-avid. Current management is observation alone, with options for single-agent rituximab and/or involved-site radiation therapy if progression occurs. [Figure 1]

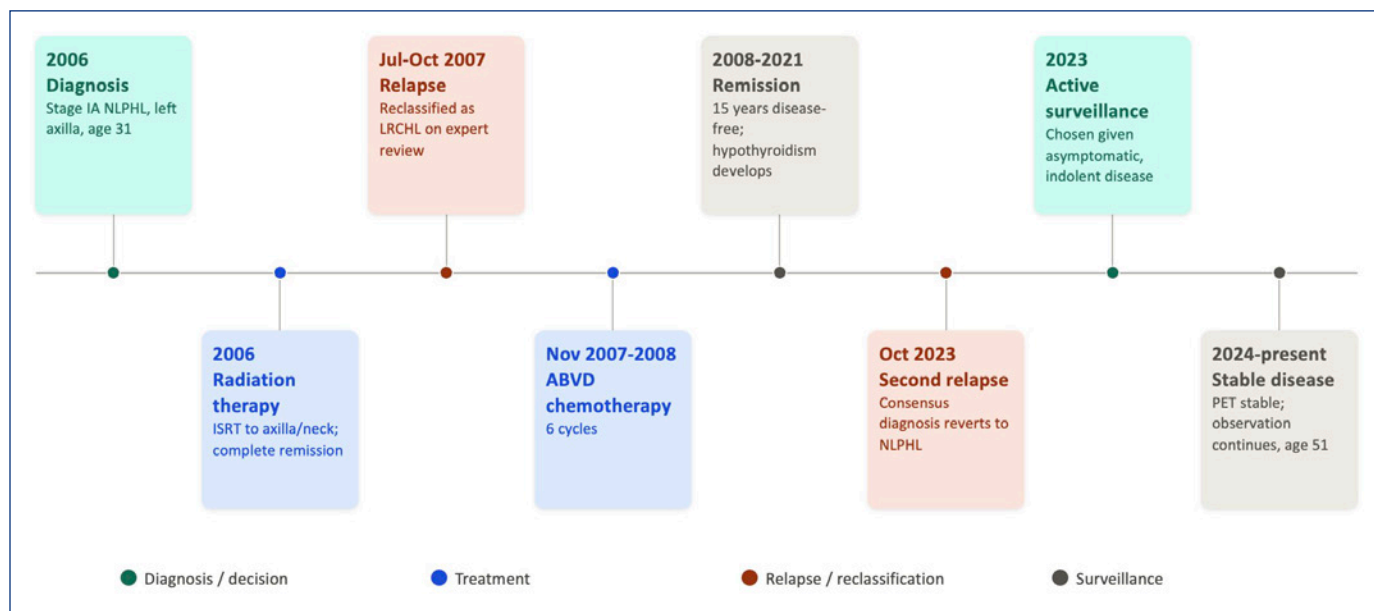
DISCUSSION

This case illustrates several interesting aspects of NLPHL biology, diagnosis, and management.

Diagnostic Challenges: NLPHL vs. LRCHL

The distinction between NLPHL and LRCHL is critical for treatment planning but can be challenging. Both entities share morphologic features, including a lymphocyte-rich background and nodular architecture. However, they differ in immunophenotype: NLPHL LP cells are CD20+, CD45+,

Figure 1. Clinical timeline of a recurrent NLPHL case spanning two decades



CD79a+, BCL6+, PAX-5+, CD15-, and typically CD30-, while LRCHL Hodgkin/Reed-Sternberg cells are CD30+, CD15+, PAX-5+ (weak), CD20- (majority), and CD45-.^{3,4}

In this case, the 2007 relapse specimen was initially diagnosed as NLPHL locally but reclassified as LRCHL upon expert review. The 2023 relapse specimen was diagnosed as NLPHL by both local and expert pathologists. This apparent “reversion” from LRCHL to NLPHL raises several possibilities:

1. Misclassification at one time point: LRCHL occupies an intermediate position between CHL and NLPHL, with overlapping features. The 2007 specimen may have had borderline features that were interpreted differently by different pathologists.⁷

2. Clonal evolution: Although rare, it is theoretically possible for the tumor to evolve between subtypes, though this has not been well-documented in the literature.

3. Two distinct lymphomas: The patient may have had sequential, unrelated lymphomas, though this is unlikely given the clinical continuity.

This case underscores the importance of expert hematopathology review, particularly for cases with atypical features or discordant diagnoses.

Indolent Natural History and Active Surveillance

NLPHL has an excellent prognosis, with five-year overall survival exceeding 90%.^{1,3} However, late relapses are common, occurring in up to 30% of patients.^{1,4} In a Memorial Sloan Kettering study of 163 NLPHL patients, five-year progression-free survival (PFS), second PFS (PFS2), and overall survival (OS) were 85%, 97%, and 99%, respectively.¹ Only one of seven deaths was lymphoma-related.

Active surveillance is a viable initial management strategy for selected NLPHL patients, particularly those with asymptomatic, non-bulky disease. In the MSK study, patients managed with active surveillance had slightly shorter PFS than those receiving active treatment (5-year PFS 77% vs. 87%, $p=0.017$), but this did not translate into differences in PFS2 or OS.¹ Only 27% of patients managed with active surveillance eventually required treatment, after a median of 61 months, and there were no deaths.

This patient's disease course exemplifies the indolent biology of NLPHL: a 15-year disease-free interval after ABVD, followed by stable disease on observation for over two years at the second relapse. The NCCN Guidelines recommend observation as an option for asymptomatic patients with stage III–IV NLPHL and for asymptomatic, non-bulky relapsed NLPHL.

Surveillance Challenges: Angiolipomas

This patient's multiple angiolipomas complicated clinical and imaging surveillance. Angiolipomas can be FDG-avid and may mimic lymphomatous involvement on PET/CT. This highlights the importance of integrating clinical, pathologic, and imaging data in NLPHL surveillance.

CONCLUSION

This case of recurrent NLPHL over nearly 20 years illustrates the diagnostic challenges in distinguishing NLPHL from LRCHL, the indolent natural history of NLPHL with prolonged remissions, and the role of active surveillance in managing asymptomatic relapsed disease. Expert pathology review is essential for accurate diagnosis, and treatment

should be individualized based on disease biology, symptoms, and patient preferences. For asymptomatic patients with indolent relapsed NLPHL, observation alone is a reasonable strategy, with rituximab and/or radiation therapy reserved for symptomatic or progressive disease.

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Disclosures

The authors have no conflicts of interest to disclose.

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