TPM Vol. 32, No. S3, 2025
ISSN: 1972-6325
https://www.tpmap.org/

NON-HODGKIN'S LYMPHOMA: A DIAGNOSTIC CONUNDRUM

JEYARAMAN SAI PRITAM
POST GRADUATE STUDENT, DEPARTMENT OF GENERAL MEDICINE, SAVEETHA MEDICAL COLLEGE AND HOSPITAL. ORCHID ID -0009-0007-2460-2582

D. KANIMOZHI
ASSISTANT PROFESSOR DEPARTMENT OF GENERAL MEDICINE, SAVEETHA MEDICAL COLLEGE AND HOSPITAL ORCHID ID -0009-0004-441-0709

DR SARANYA PALANISWAMY
ASSISTANT PROFESSOR, DEPARTMENT OF GENERAL MEDICINE, SAVEETHA MEDICAL COLLEGE AND HOSPITAL ORCHID ID -0009-0007-7337-7828

R KANNAN
PROFESSOR DEPARTMENT OF GENERAL MEDICINE, SAVEETHA MEDICAL COLLEGE AND HOSPITAL ORCHID ID -0000-0003-3536-6515

Abstract:
Non-Hodgkin's Lymphoma (NHL) encompasses a broad spectrum of lymphoid malignancies, with varied presentations depending on the histological subtype and extent of disease. Diffuse Large B-Cell Lymphoma (DLBCL), the most common and aggressive form of NHL, often presents with rapidly enlarging lymphadenopathy, but may also mimic chronic infections or inflammatory conditions, leading to delayed diagnosis. We report the case of a 41-year-old female with no known comorbidities who presented with intermittent fever and progressive left axillary and inguinal lymphadenopathy over a six-month period. Despite initial symptomatic improvement with antibiotics and a non-diagnostic lymph node biopsy, the patient continued to experience worsening symptoms, including lower limb swelling and newly developed cervical swelling with dysphagia. On examination, right tonsillar hypertrophy was noted. CT imaging revealed a well-defined mass involving the oropharynx and tonsil, with extensive cervical lymphadenopathy and compression of adjacent vascular structures. CT venogram of the lower limbs showed significant lymphadenopathy in the iliac and inguinal regions, causing compression of the left iliac vein, but no evidence of thrombosis. Histopathological analysis of a right tonsillectomy specimen demonstrated features consistent with high-grade lymphoma. Immunohistochemistry confirmed Diffuse Large B-Cell Lymphoma (DLBCL), non-germinal center subtype. The patient was staged as Ann Arbor Stage 3B and initiated on R-CHOP chemotherapy, completing five cycles with ongoing follow-up.
This case shows the diagnostic complexity of NHL, particularly when early symptoms overlap with more common infectious or inflammatory conditions. Persistent lymphadenopathy, non-responsiveness to empirical treatment, and evolving systemic features warrant thorough re-evaluation with appropriate imaging and biopsy. Extranodal involvement, especially of the tonsils, should raise suspicion for lymphoma in the right clinical context. Prompt diagnosis and immunophenotyping are crucial for timely initiation of therapy, especially in aggressive subtypes like DLBCL.

Keywords: Non-Hodgkin's Lymphoma, Diffuse Large B-Cell Lymphoma, DLBCL, Tonsillar lymphoma, Lymphadenopathy, R-CHOP, Immunohistochemistry, Lymphoproliferative disorder, Deep vein thrombosis mimic, Extranodal NHL

INTRODUCTION:

Non-Hodgkin's Lymphoma (NHL) represents a diverse group of lymphoid malignancies originating from B, T, or natural killer (NK) cells. It accounts for approximately 4% of all cancers globally and is the seventh most common cancer in both men and women in the United States [1]. NHL encompasses a spectrum ranging from indolent forms like follicular lymphoma to aggressive subtypes such as Diffuse Large B-Cell Lymphoma (DLBCL), which is the most common subtype and constitutes nearly 30–40% of all cases worldwide [2].
The clinical presentation of NHL is highly variable, often depending on the subtype, the anatomical site involved, and the stage of the disease. Common features include painless lymphadenopathy, constitutional B symptoms (fever, night sweats, weight loss), and, in advanced stages, extranodal involvement [3]. However, many patients, especially those with early-stage or atypical forms, may lack classical features, leading to diagnostic uncertainty.

The presence of generalized lymphadenopathy with systemic symptoms, as in this case, often raises differential diagnoses such as chronic infections, autoimmune conditions, or tuberculosis, particularly in regions where infectious diseases are endemic [4].

Delayed diagnosis is frequently reported in literature due to reliance on initial symptomatic improvement, false-negative biopsies, or partial imaging studies. In many patients, especially when initial histopathology is inconclusive or performed on small or poorly preserved samples, repeat biopsies and comprehensive imaging become necessary [5]. Tonsillar involvement, although uncommon as an initial site, has been documented in NHL, particularly DLBCL, and may present with dysphagia, odynophagia, or upper airway symptoms [6]. Immunohistochemistry plays a critical role in confirming the diagnosis and subtyping of lymphoma, aiding therapeutic decisions and prognostic evaluation.

Given the heterogeneity of presentation and diagnostic challenges, this case explains the importance of maintaining a high index of suspicion in patients with persistent or progressive lymphadenopathy. Early use of advanced imaging and repeat tissue sampling, guided by clinical evolution, can improve diagnostic yield and outcomes.

Case Presentation

Initial Symptoms and Early Management

A 41-year-old woman with no prior medical comorbidities presented with a six-month history of intermittent fever. Alongside the fever, she developed persistent left axillary and bilateral inguinal lymphadenopathy. At an outside hospital, she was started empirically on intravenous antibiotics and discharged following symptomatic relief. However, there was no reduction in lymph node size over time.

Subsequent biopsy of the axillary lymph node performed at another center did not yield a definitive diagnosis. With no improvement, she continued to be managed conservatively with symptomatic treatment.

Progression of Symptoms

Over the following weeks, the patient noticed a worsening of lymphadenopathy, particularly in the inguinal region. She also developed swelling of the left lower limb. Despite a normal Doppler ultrasound, she was empirically started on oral anticoagulation (Apixaban) under the suspicion of deep vein thrombosis.

Later, the patient presented to our hospital with new complaints of aggravated lower limb swelling, progressive swelling in the cervical region, and increasing difficulty swallowing both solids and liquids. Clinical examination revealed prominent swelling in the cervical region and right tonsillar hypertrophy with congestion on its surface.

Laboratory Investigations

Baseline blood investigations showed normocytic normochromic anemia (Hemoglobin – 9.4 g/dL), with mild anisopoikilocytosis and occasional polychromatophilic macrocytes. Total leukocyte count was 6760/mm³ with a differential of neutrophils 66%, lymphocytes 22.9%, monocytes 8%, eosinophils 2.7%, and basophils 0.4%. The iron profile was within normal limits (Iron – 72 µg/dL, TIBC – 296 µg/dL, Serum Ferritin – 159 ng/mL).

Table 1: Hematological and Iron Profile Results

Parameter	Value	Normal Range	Interpretation
Hemoglobin (Hb)	9.4 g/dL	12–15.5 g/dL	Low – Anemia
RBC count	3.55 M/µL	4.2–5.4 M/µL	Low
PCV	30.1 %	36–46 %	Low
MCV	84.8 fL	80–96 fL	Normal
MCH	26.5 pg	27–33 pg	Slightly Low
MCHC	31.2 g/dL	32–36 g/dL	Slightly Low
RDW	31.2 %	11.5–14.5 %	High Anisopoikilocytosis
Platelet Count	1.95 Lakh/µL	1.5–4.5 Lakh/µL	Normal
TLC	6760 /µL	4000–11000 /µL	Normal
Differential Count	N 66%, L 22.9%, M 8%, E 2.7%, B 0.4%	–	Within acceptable range
Iron	72 µg/dL	60–170 µg/dL	Normal
TIBC	296 µg/dL	250–450 µg/dL	Normal
Serum Ferritin	159 ng/mL	30–400 ng/mL	Normal

Radiological Assessment

A contrast-enhanced CT (CECT) of the neck showed a well-defined lobulated lesion in the oropharynx involving the lateral pharyngeal mucosa and the right palatine tonsil. The lesion measured 27 x 24 x 35 mm and extended across the midline, significantly narrowing the oropharyngeal airway. It also involved adjacent spaces including the pharyngomucosal, parapharyngeal, and retropharyngeal regions, with compression of the right internal jugular vein and associated extensive cervical lymphadenopathy.

To evaluate the lower limb swelling, a CT venogram was done. It revealed multiple enlarged conglomerate lymph nodes along the left external iliac and inguinal regions causing severe compression of the left external iliac vein. Collateral circulation was noted with reformation of the femoral vein. Additionally, splenomegaly with multiple well-defined nodular lesions and extensive retroperitoneal lymphadenopathy were identified. No thrombus was detected in any segment of the deep venous system.

Table 2: Imaging Summary

Imaging Modality	Key Findings
CECT Neck	Lobulated enhancing oropharyngeal mass involving right tonsil (27 x 24 x 35 mm), crossing midline, narrowing airway; extensive cervical lymphadenopathy; IJV compression
CT Venogram – Lower Limbs	Enlarged nodal masses compressing left external iliac vein (6.3 x 6.8 cm), multiple collaterals seen; splenomegaly with nodular lesions; no evidence of DVT

Histopathological Diagnosis

Given the right tonsillar enlargement and systemic findings, the patient underwent a right tonsillectomy. Histopathological examination revealed complete architectural effacement of lymphoid tissue, sheets of atypical medium- to large-sized lymphoid cells with scant cytoplasm, tingible body macrophages, and increased mitotic figures—findings consistent with a high-grade lymphoproliferative disorder.

Immunohistochemistry confirmed strong membranous positivity for CD20 and Bcl2, consistent with Diffuse Large B-Cell Lymphoma (DLBCL), non-germinal center subtype.

Staging and Treatment

Based on imaging and systemic involvement including cervical, axillary, inguinal, retroperitoneal lymph nodes, and splenic lesions, the patient was staged as Stage 3B Non-Hodgkin's Lymphoma. She was started on the standard R-CHOP chemotherapy regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone), and had successfully completed five cycles at the time of this report.

Table 3: Histopathological and Immunohistochemical Profile

Feature	Observation
Histopathology	Sheets of medium to large atypical lymphoid cells, tingible body macrophages, high mitotic activity, diffuse effacement
Granulomas	Not seen
CD20	Strong membranous positivity
Bcl2	Positive
Diagnosis	Diffuse Large B-Cell Lymphoma (Non-Germinal Center Subtype)

DISCUSSION

Non-Hodgkin's Lymphoma (NHL) is a diverse group of lymphoid neoplasms with varied clinical behaviors and outcomes. Among the subtypes, Diffuse Large B-Cell Lymphoma (DLBCL) is the most prevalent, accounting for nearly 30% of NHL cases worldwide [6]. It is typically aggressive in nature and can present either with localized disease or with widespread nodal and extranodal involvement.

Our case is a classic example of how DLBCL can masquerade as a chronic inflammatory condition, especially in regions where infections such as tuberculosis are common mimickers. The patient presented with prolonged fever and lymphadenopathy, which initially responded partially to antibiotics. However, the absence of resolution in lymph node size, progression of lymphadenopathy, and evolving systemic symptoms were critical red flags.

A study by Küppers et al. emphasizes that extranodal involvement, including tonsillar masses as in our case, is a well-recognized feature of DLBCL and may present with airway symptoms, odynophagia, or obstructive complaints [7]. The oropharyngeal region, particularly the Waldeyer's ring, is a known site for extranodal lymphomas and can be the primary presentation [8]. In our patient, oropharyngeal mass with tonsillar hypertrophy was the diagnostic turning point, leading to a confirmatory biopsy.

Delayed diagnosis, as seen here, is unfortunately not uncommon. As shown in a study by Cheson et al., many patients with DLBCL are misdiagnosed initially due to overlapping symptoms with infections or autoimmune disorders, especially when early biopsies are non-representative or when imaging does not fully capture the disease burden [9]. Repeat biopsies and comprehensive imaging studies are often warranted in such situations to reach a definitive diagnosis.

Radiologically, CT venogram in our patient showed significant nodal mass compressing the left external iliac vein, mimicking a deep vein thrombosis. However, no thrombus was seen, and the lower limb swelling was secondary to venous compression by nodal masses—a phenomenon described in prior literature [10]. Moreover, splenic involvement and retroperitoneal lymphadenopathy pointed to advanced disease, fulfilling criteria for Ann Arbor Stage III classification with systemic B symptoms (Stage IIIB) [11].

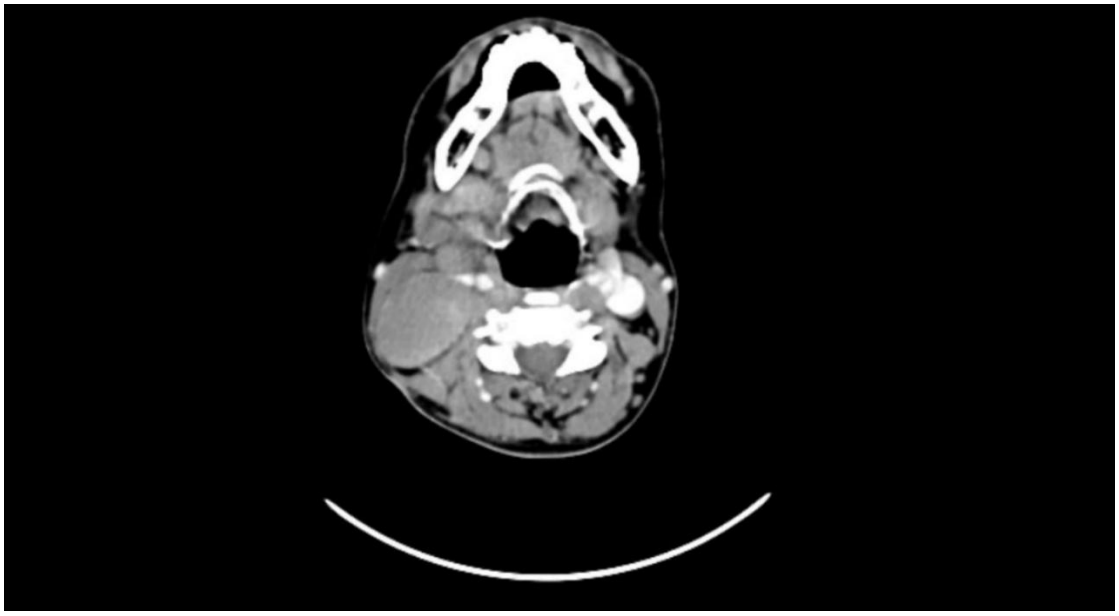
Immunohistochemistry plays a crucial role in NHL subtyping. CD20 and Bcl2 positivity, as found in our patient, confirmed the diagnosis of DLBCL of the non-germinal center B-cell subtype. This subtype is typically associated with a poorer prognosis compared to its germinal center counterpart, as noted in the pivotal study by Hans et al., where cell-of-origin classification had significant prognostic implications [12].

The R-CHOP regimen remains the standard first-line therapy for DLBCL and has shown good response rates even in advanced-stage disease. As supported by the landmark GELA study, the addition of Rituximab to the CHOP regimen significantly improved overall survival in elderly patients and remains widely adopted across age groups [13].

This case shows the need for high clinical suspicion and timely escalation of investigations when lymphadenopathy does not follow a benign or infectious course. It also demonstrates the diagnostic complexity of NHL and the importance of a multidisciplinary approach involving clinicians, radiologists, and pathologists.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73(1):17–48.
2. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press; 2017.
3. Zelenetz AD, Gordon LI, Wierda WG, et al. NCCN Guidelines Insights: Non-Hodgkin's Lymphomas, Version 3.2016. *J Natl Compr Canc Netw.* 2016;14(9):1067–1079.
4. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. *Blood.* 2006;107(1):265–276.
5. Ansell SM. Non-Hodgkin Lymphoma: Diagnosis and Treatment. *Mayo Clin Proc.* 2015;90(8):1152–1163.
6. Guo R, Sun J, Li Y, et al. Tonsillar lymphoma: Clinical features and diagnostic pitfalls. *Medicine (Baltimore).* 2018;97(48):e13369.
7. Campo E, Swerdlow SH, Harris NL, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*. 2011;117(19):5019-5032. doi:10.1182/blood-2011-01-293050
8. Küppers R, Dalla-Favera R. Mechanisms of chromosomal translocations in B cell lymphomas. *Oncogene*. 2001;20(40):5580–5594. doi:10.1038/sj.onc.1204602
9. Ioachim HL, Medeiros LJ. Lymphomas of the head and neck region. *Am J Surg Pathol*. 1987;11(Suppl 1):60-75.
10. Cheson BD. Diagnosis and management of lymphoma. *Semin Hematol*. 2016;53(4):221–232. doi:10.1053/j.seminhematol.2016.10.001
11. Murphey MD, Smith WS, Smith SE, Kransdorf MJ, Temple HT. Imaging of musculoskeletal lymphoma with radiologic-pathologic correlation. *Radiographics*. 1995;15(2):349-370. doi:10.1148/radiographics.15.2.7761640
12. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res*. 1971;31(11):1860–1861.
13. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103(1):275–282. doi:10.1182/blood-2003-05-1545
14. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346(4):235–242. doi:10.1056/NEJMoa011795



TPM Vol. 32, No. S3, 2025
ISSN: 1972-6325
https://www.tpmap.org/

Open Access