A DIAGNOSTIC ODYSSEY THROUGH FOUR LYMPHOMA ENTITIES: THE IMPORTANCE OF REPEATED HISTOPATHOLOGICAL ASSESSMENT

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INTRODUCTION

Lymphoma classification is an integrated process combining tissue architecture, morphology, immunophenotype and, when indicated, molecular genetics. Accurate classification is essential because histological subtype directly informs prognosis, treatment selection and eligibility for disease-specific and cellular therapies. Contemporary WHO and International Consensus classifications increasingly recognize biologically heterogeneous entities and emphasize multidisciplinary hematopathology expertise.

At relapse or progression, clinicoradiological findings may not necessarily represent recurrence of the previously diagnosed lymphoma. Histological transformation, phenotypic evolution, sampling limitations, treatment-related changes and alternative diagnoses may produce substantial diagnostic uncertainty. PET/CT is central to response assessment in FDG-avid lymphomas, but metabolically active lesions may require tissue confirmation when the result will alter management.

We present a challenging seven-year diagnostic course characterized by sequential pathological diagnoses, repeated non-diagnostic biopsies and persistent Hodgkin/B-cell phenotypic overlap, illustrating the importance of longitudinal tissue reassessment and expert hematopathology review.

RESULTS

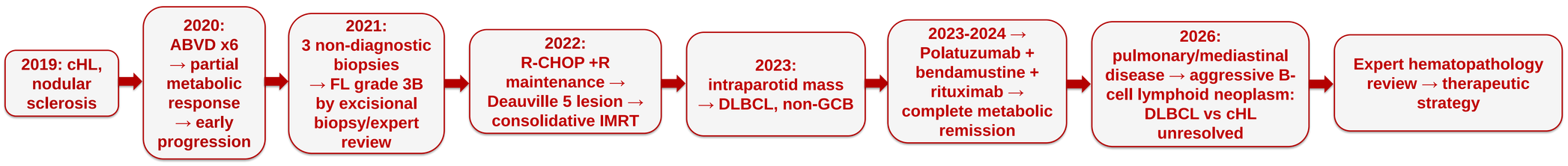
A 71-year-old woman presented in 2019 with a right axillary mass and subsequently demonstrated disseminated nodal, splenic and pulmonary involvement. An initial core needle biopsy was inconclusive. Excisional right axillary lymph-node biopsy established classical Hodgkin lymphoma (cHL), nodular sclerosis subtype. Hodgkin/Reed–Sternberg cells were CD30+, weak PAX5+, weak CD20+, CD45-, CD15 weak/negative and EBER-negative.

The patient received six cycles of ABVD (January-June 2020). CT demonstrated marked tumour reduction; however, PET/CT in September 2020 showed persistent metabolically active disease (Deauville score 5), followed by unequivocal metabolic progression in December 2020. Three subsequent biopsies in 2021 were non-diagnostic or demonstrated atypical lymphoid proliferation. A retroperitoneal biopsy confirmed lymphoma but showed overlapping Hodgkin/B-cell features, precluding definitive classification.

HISTOPATHOLOGICAL RECLASSIFICATION: An excisional cervical lymph-node biopsy in September 2021 demonstrated a predominantly follicular (>75%) B-cell proliferation expressing CD20, CD79a, PAX5, CD10, BCL2 and BCL6, supporting follicular lymphoma (FL) grade 3B. Expert review confirmed this diagnosis in January 2022. Given the clinical context and residual diagnostic uncertainty, the patient received R-CHOP, followed by rituximab maintenance. CT demonstrated marked radiological response; however, PET/CT identified residual metabolically active disease at the L3 latero-aortic node (Deauville score 5), for which IMRT (40 Gy in 20 fractions) was administered.

SECOND HISTOLOGICAL EVOLUTION: In 2023, a right intraparotid mass developed. An initial biopsy was non-diagnostic; repeat biopsy demonstrated diffuse large B-cell lymphoma (DLBCL), non-germinal-centre B-cell subtype, with a CD45+, PAX5+, MUM1+, BCL2+, CD30+, CD10- phenotype. The patient received local radiotherapy followed by six cycles of polatuzumab vedotin, bendamustine and rituximab, achieving a complete metabolic response on PET/CT in 2024.

CURRENT DISEASE: In 2026, after approximately two years of documented remission, the patient developed persistent cough and anorexia. CT revealed multiple bilateral pulmonary nodules, pulmonary consolidation and mediastinal/hilar lymphadenopathy. Image-guided lung biopsy demonstrated malignant lymphoid infiltration with marked crush artefact and a high proliferation index (Ki-67 80%).The neoplastic cells expressed CD20+, PAX5+, CD10-, CD3-, BCL2+, BCL6+ (50%) and MUM1+ (20%), with variable CD30/CD15 expression. The biopsy demonstrated pulmonary involvement by an aggressive B-cell lymphoid neoplasm with a high proliferation index (Ki-67 80%); however, definitive classification was precluded by limited morphology and marked crush artefact, with DLBCL and classical Hodgkin lymphoma remaining in the differential diagnosis. Importantly, the morphology and immunophenotype were considered comparable with those of the February 2021 retroperitoneal biopsy, which had also shown overlapping Hodgkin/B-cell features without definitive classification. Given the persistent diagnostic overlap, expert hematopathology reassessment is required to clarify the diagnosis and guide subsequent therapeutic strategy.



CONCLUSION

This case highlights the diagnostic complexity of lymphoma in the setting of evolving disease biology, limited tissue sampling and substantial phenotypic overlap.

Sequential pathological diagnoses of classical Hodgkin lymphoma, follicular lymphoma grade 3B and DLBCL, followed by a 2026 pulmonary biopsy showing an aggressive B-cell lymphoid neoplasm with unresolved DLBCL/cHL differential, underscore the limitations of interpreting relapse solely through imaging or historical diagnosis. The current WHO-HAEM5 and ICC frameworks underscore the importance of integrating morphology, immunophenotype and molecular findings when classifying aggressive B-cell lymphomas.

The case also illustrates a critical clinical principle: radiological or metabolic progression should not automatically be interpreted as relapse or transformation of the previously established lymphoma subtype. When disease behaviour is discordant with previous pathology, repeat tissue acquisition, preservation of tissue architecture and expert hematopathology review should be prioritized before major therapeutic decisions.

Adequate tissue architecture is particularly important when differentiating follicular lymphoma from transformed large B-cell lymphoma and when evaluating large B-cell lymphomas with overlapping phenotypes. Current guidance emphasizes specialized hematopathology assessment for LBCL diagnosis.

The current case further emphasizes that accurate classification is not merely diagnostic it determines the therapeutic pathway,

KEY MESSAGE: When lymphoma behaves unexpectedly, re-biopsy before re-treatment.

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