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Case Report

Gray Zone Lymphoma Presenting as a Thigh Mass: A Diagnostic Challenge and 10-Year Follow-Up

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Abstract

Background: Gray zone lymphoma (GZL) is a rare neoplasm that has overlapping characteristics of classical Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL). It is difficult to diagnose, with no standardized protocol, resulting in therapeutic challenges.

Case Description: We report a 60-year-old man with an asymptomatic soft-tissue thigh mass, initially misdiagnosed as a cyst. After MRI and excision, it was diagnosed as nodular sclerosis Hodgkin lymphoma, with an initial treatment protocol of ABVD. Histopathological re-evaluation led to a GZL diagnosis and prompted a change in chemotherapy protocols, with no tumor recurrence after 10 years of follow-up.

Conclusions: Comprehensive immunohistochemical profiling and expert pathology re-evaluation are critical to diagnosing GZL. In our patient, B-cell-targeted immunochemotherapy with R-EPOCH was followed by durable long-term remission.

Keywords: *Gray zone lymphoma, Hodgkin lymphoma, Non-Hodgkin lymphoma, R-EPOCH.*

Introduction

Lymphomas comprise a group of malignant neoplasms of lymphocytes as a result of pathological clonal proliferation. They are broadly categorized as Hodgkin or non-Hodgkin, the latter being the most frequent. Classical Hodgkin lymphoma (cHL) is characterized by the presence of large and multinucleated transformed B cells called Reed-Sternberg cells. Non-Hodgkin lymphomas have a large variety of histological appearances; the most common is diffuse large B-cell lymphoma (DLBCL), characterized by a diffuse malignant proliferation of B cells. [1-3]

Gray zone lymphoma (GZL) is a term used for neoplasms that have characteristics of classical Hodgkin lymphoma and diffuse large B-cell lymphoma, making it difficult to classify them as one or the other. They are rare, resulting in diagnostic challenges and affecting therapeutic protocol selection, which justifies their description. Clinically, GZL is associated with B symptoms (fever, diaphoresis, weight loss) or asymptomatic adenopathies. There is no standard treatment for GZL because of how uncommon it is; however, DA-EPOCH-R protocols are the most commonly used. [1-3]

Case Presentation

A 60-year-old male, with a past medical history of obesity and hypertension, presented with several years' evolution of a left thigh mass. In a previous consultation, it was diagnosed as a ganglion cyst based solely on physical examination. The patient reported no pain, B symptoms, or other manifestations associated with the mass. However, years later, he noticed an increase in the size of the lesion.

A study with magnetic resonance imaging (MRI) scan of the left thigh showed an 88 x 59 x 79 mm lesion, isointense on T1-weighted images and hyperintense on STIR sequences, with heterogeneous signal intensity on T2-weighted images that decreased on gradient-echo sequences. It showed no contrast enhancement. The lesion was located in the soft tissues anterior to the left sartorius muscle, displacing the great saphenous vein in the mid-thigh region and displacing the proximal left femoral vein and artery inferiorly.

A month later, the mass was surgically excised (Figure 1). Study of the pathological sample reported distorted architecture with diffuse and dense proliferation of polymorphic cells, separated in some areas by fibroconnective bands, composed of small lymphocytes, plasma cells, histiocytes, and scattered eosinophils. Within this background, scattered mononucleated cells with prominent nucleoli were observed, alongside binucleated cells and sporadic multilobated forms (Figure 2).

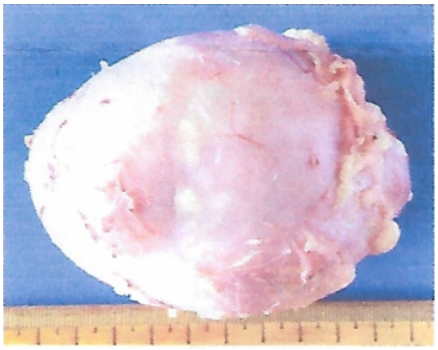


Figure 1. Excised mass.

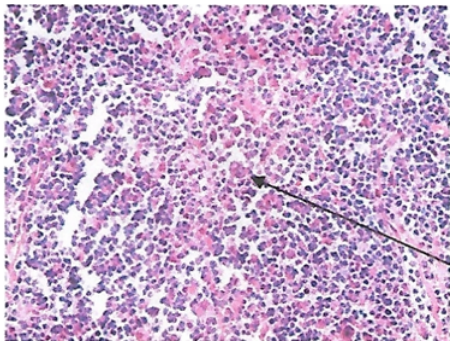


Figure 2. Histopathological Examination.

Immunohistochemical analysis demonstrated Reed–Sternberg cells with positivity for CD15, CD20, and CD30. The background T-cell infiltrate was positive for CD3, and the Ki-67 proliferation index was moderate. Based on these immunophenotypic findings, an initial diagnosis of nodular sclerosis Hodgkin lymphoma was established.

A complementary PET/CT from the brain to the proximal third of the thigh reported metabolically active nodal tumor disease below the diaphragm.

Chemotherapy was initiated with the ABVD protocol (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine). Concurrently, a second revision of the histopathological sample with other staining showed an overlap between Hodgkin lymphoma and diffuse large B-cell lymphoma, with atypical cells positive for CD30, CD15, CD20, CD45, and strongly positive for PAX5. Additionally, a study for EBER by in situ hybridization was performed, which turned out negative.

Based on these results, the diagnosis was revised to Gray Zone Lymphoma (B-cell lymphoma with features intermediate between DLBCL and cHL). Consequently, a month after ABVD was initiated, treatment was modified to the R-EPOCH fixed-dose protocol (Rituximab, Doxorubicin, Etoposide, Vincristine, Prednisone, Cyclophosphamide) every 21 days for 6 cycles. Follow-up PET/CT performed three and six months after the last cycle demonstrated no evidence of active tumor disease with 18 FDG affinity.

Subsequently, the patient remained under regular oncological follow-ups, remaining asymptomatic and with no evidence of tumor recurrence during 10 years of follow-up. He was then discharged from oncological follow-up.

Discussion

Gray zone lymphoma (GZL) represents an uncommon malignant neoplasm situated between classical Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL) in its clinical, morphological, and immunophenotypic characteristics. Historically, it has been described as a mediastinal entity related to primary mediastinal B-cell lymphoma; however, non-mediastinal presentations have been reported, more frequently observed in older patients, which constitute a diagnostic and therapeutic challenge. [4-7]

GZL diagnosis is complex due to phenotypic pleomorphism and transitional features. Its morphology shows cells similar to Reed-Sternberg cells alongside large B cells. Immunophenotypically, it shows a transitional profile where neoplastic cells co-express markers typical of cHL (CD30, CD15) alongside strong B-cell lineage drivers (CD20, PAX5, CD45), as demonstrated in our patient's immunohistochemical panel. [4-7]

Diagnostic misclassification between GZL and classical Hodgkin lymphoma of the nodular sclerosis subtype (cHL-NS) represents a frequent clinical challenge. This diagnostic overlap stems from shared histopathological characteristics, such as sclerotic fibrous bands and a rich inflammatory microenvironment. Recognizing this distinction is critical, as misdiagnosing GZL as cHL-NS can lead to suboptimal disease control under traditional cHL regimens like ABVD, whereas prompt pathological revision allows an appropriate transition to intensive B-cell-targeted immunochemotherapy. [3,5]

Furthermore, ruling out Epstein-Barr virus (EBV) association is a helpful step in this differential diagnosis; in non-mediastinal GZL, EBER testing is characteristically negative, whereas cHL can express EBV-encoded RNAs (EBER). [5]

From a clinical management perspective, an adequate physical examination and comprehensive histopathological evaluation, even in asymptomatic patients, are important to avoid misdiagnosis and reduce the risk of tumor progression. Similarly, a timely diagnosis is critical to selecting appropriate treatment. For GZL, data suggest that cHL-directed regimens (such as ABVD) are associated with inferior progression-free survival. Studies suggest that DLBCL-directed regimens that include rituximab are associated with better progression-free survival. [5-7] A retrospective analysis by Evens et al. found frontline DLBCL-directed regimens (CHOP ± R or DA-EPOCH-R) were associated with better 2-year progression-free survival than ABVD ± R (52% vs. 23%, P = 0.03). [8] Additionally, a prospective study by Wilson et al. showed that 62% of 24 patients with mediastinal GZL achieved continuous complete remissions with DA-EPOCH-R. [9] Ahluwalia et al. reported two HIV-positive patients who also achieved complete response with DA-EPOCH-R followed by rituximab maintenance. [10]

In our patient, re-evaluation of the histopathological specimen, including additional immunohistochemical staining, helped establish the final diagnosis of gray zone lymphoma. Following diagnostic clarification, treatment was switched from ABVD to R-EPOCH. Post-treatment PET/CT demonstrated a sustained complete metabolic response at the 3- and 6-month evaluations, with no evidence of active disease. The patient subsequently remained free of documented recurrence throughout 10 years of follow-up until discharge. It is worth noting that, in this patient, treatment was changed after the first ABVD cycle, so response to this regimen could not be assessed.

Conclusion

Gray zone lymphoma is a challenging clinicopathological neoplasm. Its diagnosis requires a high index of suspicion, comprehensive immunohistochemical profiling, and expert pathology re-evaluation. Early recognition is important to select appropriate treatment; in our patient, revision of the diagnosis and a change to R-EPOCH immunochemotherapy were followed by sustained remission, with no documented recurrence after 10 years of follow-up. Further case reports and prospective studies are needed to help establish a standard treatment.

Conflict of Interest

The author declares no financial or competing interests. The author is a first-degree relative of the patient. Clinical data were obtained retrospectively from the patient’s medical records; the author was not involved in the patient’s clinical care or follow-up.

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