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Grey Zone Lymphoma: A Diagnostic and Therapeutic Challenge – A Case Report

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Abstract **Case Report**

Grey zone lymphoma (GZL) is a rare and aggressive B-cell lymphoma with features intermediate between primary mediastinal B-cell lymphoma (PMBL) and classical Hodgkin lymphoma (cHL). Its diagnostic complexity stems from significant morphological, immunophenotypic, and molecular overlaps with other lymphoma subtypes, often leading to misdiagnosis and suboptimal treatment. This case report describes a 34-year-old woman presenting with superior vena cava syndrome due to a large mediastinal mass, initially misdiagnosed as primary mediastinal B-cell lymphoma (PMBL) and later revised to GZL after comprehensive immunohistochemical analysis. Despite treatment with dose-adjusted EPOCH-R chemotherapy and salvage therapy, the disease progressed, highlighting the refractory nature of GZL. The introduction of pembrolizumab, an anti-PD-1 monoclonal antibody, marked a turning point, demonstrating significant clinical and metabolic response. This case underscores the diagnostic challenges of GZL, the limitations of conventional therapies, and the potential of immune checkpoint inhibitors in managing refractory disease. It emphasizes the need for a multidisciplinary approach, advanced diagnostic techniques, and personalized therapeutic strategies to improve outcomes in this complex and poorly defined lymphoma subtype. Further research is essential to refine treatment algorithms and identify predictive biomarkers for GZL.

Keywords: Grey Zone Lymphoma, Primary Mediastinal B-Cell Lymphoma, Hodgkin Lymphoma, Checkpoint Inhibitors.

INTRODUCTION

Grey zone lymphoma (GZL), also referred to as B-cell lymphoma with characteristics intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL), is a rare condition that poses significant diagnostic challenges, despite advancements in our understanding of GZL, its diagnosis and treatment remain challenging due to the significant overlap in morphological, immunophenotypic, and molecular features with other lymphoma subtypes [1]. It was first recognized as a distinct entity in the World Health Organization (WHO) classification in 2008 and further refined in the 2016 revision of the WHO classification.

This case report describes a patient with GZL who was initially misdiagnosed with primary mediastinal B-cell lymphoma (PMBCL), highlighting the critical importance of a comprehensive diagnostic evaluation. The case underscores the necessity of accurate diagnosis to optimize patient management and improve outcomes.

CASE REPORT

A 34-year-old woman with no significant past medical history presented with a two-month history of progressive facial edema and erythema. Physical examination revealed swelling of the face and neck, conjunctival suffusion, and distended chest vein collaterals, raising suspicion for superior vena cava (SVC) syndrome.

A contrast-enhanced computed tomography (CT) scan of the neck and chest revealed a large anterior mediastinal mass (77 × 62 × 84 mm) compressing the SVC, along with a pericardial effusion. A mediastinal core needle biopsy was performed.

The biopsy initially suggested a diagnosis of classical Hodgkin lymphoma (cHL), with immunohistochemical staining identifying large atypical binucleated cells that were CD30+, CD15+ in a subset of cells, indicating heterogeneous expression, CD20-, and PAX5+ (weak).

However, As per hospital protocol, the slides were reviewed by a second pathologist, who identified additional immunohistochemical features: CD30+, CD15-, CD20+ (strong and diffuse), BCL2+, MUM1+, EBV-, CD23+, and CD68-. These findings, along with the mediastinal location and clinical presentation, supported a revised diagnosis of primary mediastinal B-cell lymphoma (PMBL).

Laboratory investigations revealed hemoglobin of 10.6 g/dL, leukocytes 14 G/L, absolute neutrophil count 12 G/L, absolute lymphocyte count 1 G/L, platelets 377 G/L, and lactate dehydrogenase (LDH) at 176 U/L (reference upper limit: 243 U/L). The remaining metabolic panel was within normal limits, and serologic testing for hepatitis B, hepatitis C, and HIV was negative.

A baseline 18F-FDG PET/CT scan demonstrated a bulky hypermetabolic mediastinal mass, with SUVmax values of 28.5 in the right hilar region and 22.2 in the left prevascular region. Based on the initial staging assessment, the patient was classified as Ann Arbor stage II.

She was started on dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) chemotherapy. After four cycles, an interim PET/CT scan showed persistent mediastinal uptake (SUVmax 7, residual mass 18 × 9 mm) with a Deauville score of 4. The patient completed six cycles of dose-adjusted EPOCH-R, followed by involved-field radiation therapy.

A post-treatment PET/CT scan revealed persistent metabolic activity with increasing SUVmax (15 vs. 7 previously) and progression in mass size (20.5 mm vs. 18 mm). These findings were consistent with disease progression (Deauville score 5). Consequently, the patient was switched to salvage chemotherapy with RDHAOx (rituximab, dexamethasone, high-dose cytarabine, oxaliplatin). However, after two cycles, further mediastinal progression was noted, precluding an autologous hematopoietic cell transplantation.

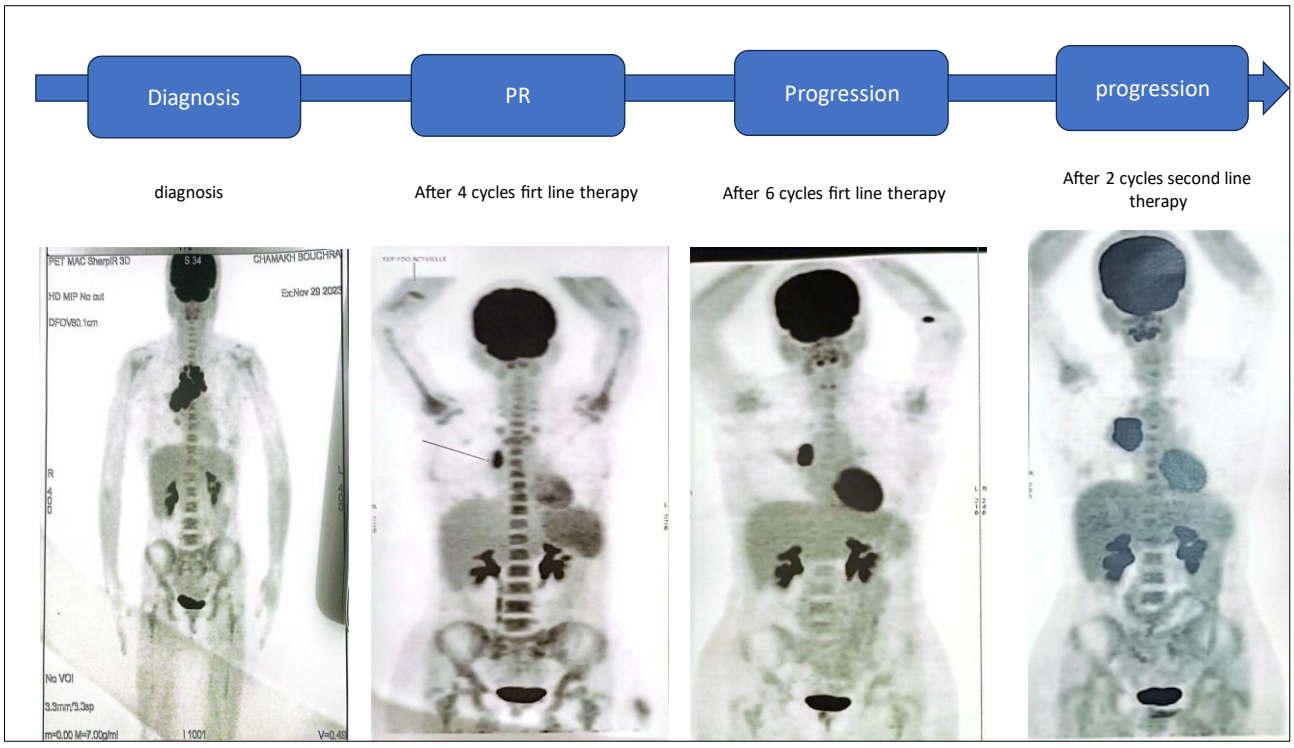

Figure 1: Disease Progression and Treatment Response Timeline in Grey Zone Lymphoma (GZL) Management

Given the refractory nature of the disease and the failure of multiple lines of chemotherapy, pembrolizumab, an anti-PD-1 monoclonal antibody recently approved for the treatment of Hodgkin and non-Hodgkin lymphomas, was initiated. At this stage, the clinical presentation, characterized by overlapping histopathological and immunophenotypic features, was highly suggestive of grey zone lymphoma (GZL).

The decision to introduce pembrolizumab was based on emerging evidence supporting the efficacy of immune checkpoint inhibitors in heavily pretreated lymphomas, particularly in cases exhibiting primary refractory behavior. Pembrolizumab was administered at a standard dosage, targeting the PD-1 pathway, which is frequently exploited by tumor cells to evade immune surveillance.

A PET/CT scan performed three months after treatment initiation demonstrated a complete metabolic response, with a significant reduction in tumor burden. Given the patient's clinical improvement, she is currently

scheduled for autologous hematopoietic cell transplantation (auto-HCT) as part of the consolidation strategy.

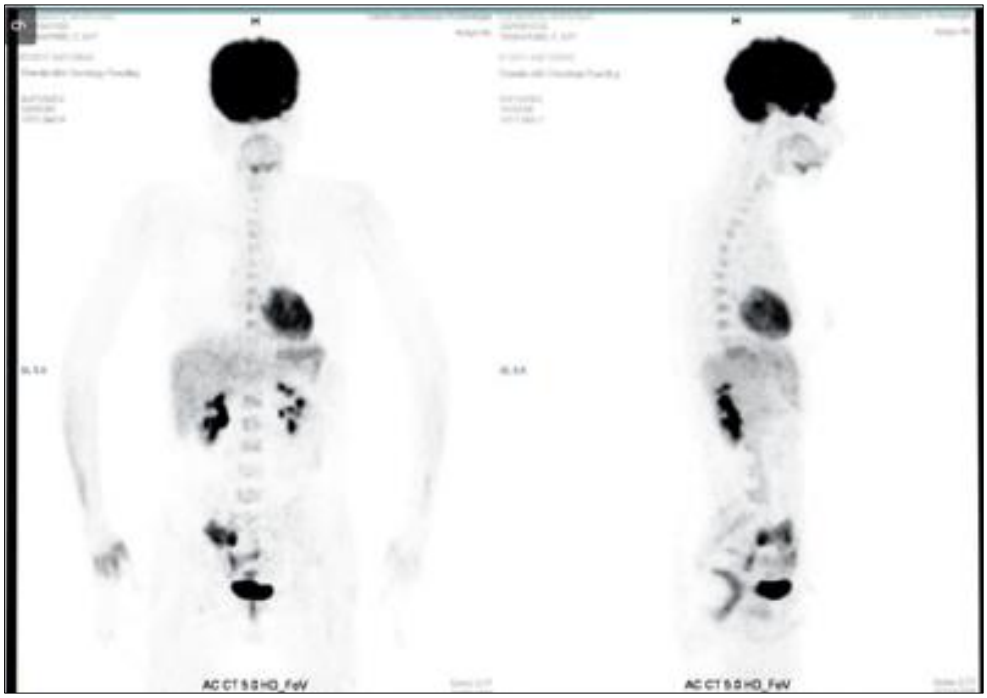

Figure 2: PET scan showing a complete metabolic response Deauville 1 after 3 cures pembrolizumab

This case highlights the diagnostic complexity of grey zone lymphoma (GZL) and underscores the necessity of a comprehensive immunophenotypic evaluation. Additionally, it illustrates the therapeutic challenges associated with refractory disease and the potential efficacy of immune checkpoint inhibitors in this setting.

DISCUSSION

Grey zone lymphoma (GZL) is a rare and diagnostically challenging entity at the intersection of classical Hodgkin lymphoma (cHL) and a primary mediastinal B-cell lymphoma (PMBL), requiring meticulous pathological assessment and innovative therapeutic strategies. This case underscores the significant diagnostic and therapeutic challenges associated with GZL, particularly in refractory disease progression. The patient's clinical course highlights the critical importance of a comprehensive diagnostic approach, incorporating advanced immunohistochemical and molecular techniques, as well as the potential role of novel therapeutic strategies in managing this aggressive and poorly defined lymphoma subtype.

The initial biopsy suggested cHL based on CD30+ and CD15+ staining, but a second review identified CD20+, BCL2+, and MUM1+, leading to a revised diagnosis to a PMBL. This highlights the diagnostic challenge of mediastinal lymphomas, particularly GZL, which shares features of both cHL and PMBL. Given its rarity and aggressiveness, GZL requires thorough immunohistochemical evaluation and expert pathological review to prevent misclassification, as accurate diagnosis is crucial for appropriate treatment and prognosis.

Despite its recognition as a provisional entity by the WHO in 2008, the absence of well-defined markers complicates its identification [2]. This diagnostic uncertainty underscores the need for a multidisciplinary approach, integrating comprehensive immunohistochemical analysis and expert pathological review to guide accurate classification and optimize therapeutic strategies [3].

GZL is known for its resistance to conventional chemotherapy. In this case, the patient exhibited primary refractory disease despite receiving both dose-adjusted EPOCH-R and RDHAOx, emphasizing the need for alternative therapeutic approaches.

Current treatment strategies can be categorized as follows:

- Dose-adjusted EPOCH-R is the most commonly recommended first-line regimen. It has demonstrated high response rates, but resistance remains a major concern in GZL [4].
- High-dose chemotherapy followed by autologous hematopoietic cell transplantation (auto-HCT) has shown improved progression-free and overall survival in selected patients, particularly those with limited prior therapy [5].

- Radiotherapy may be beneficial for bulky or localized disease, although its impact on overall survival remains controversial [6].

The failure of standard chemotherapy underscores the need for novel therapeutic strategies, the effectiveness of checkpoint inhibitors in PMBL and cHL, both characterized by 9p24.1-driven PD-L1 overexpression, suggests its potential relevance in GZL. Given the shared biological features, especially in mediastinal cases, PD-1 blockade may offer a targeted therapeutic approach [7].

Pembrolizumab, an anti-PD-1 monoclonal antibody, was introduced in this case, marking a turning point in disease management. By targeting the PD-1 pathway, pembrolizumab restores immune surveillance, offering a potential therapeutic breakthrough for refractory GZL. It contributes to the growing evidence supporting immune checkpoint inhibitors as a viable option when conventional therapies fail.

The management of GZL remains a significant clinical challenge due to its rarity, diagnostic ambiguity, and aggressive nature. While dose-adjusted EPOCH-R is a standard frontline therapy, its efficacy is limited in refractory cases. This case highlights the potential of immune checkpoint inhibitors as a viable treatment option when conventional approaches fail. However, further clinical studies are needed to refine treatment algorithms, identify predictive biomarkers, and establish the long-term efficacy of novel agents in GZL.

Ultimately, a personalized approach integrating comprehensive molecular profiling and targeted therapies may be key to improving outcomes in this rare and complex lymphoma subtype.

CONCLUSION

Grey zone lymphoma (GZL) is a rare, aggressive lymphoma with overlapping features of cHL and PMBL, posing significant diagnostic and therapeutic challenges. This case highlights the importance of the pathologist to ensure accurate diagnosis and the potential of immune checkpoint inhibitors, like pembrolizumab, in refractory disease. A multidisciplinary approach and personalized therapies are crucial for improving outcomes in GZL. Further research is needed to refine treatment strategies for this complex subtype.

REFERENCES

1. Agić, D., Lakic, T., & Nikin, Z. (2022). Grey zone lymphoma - diagnostic and therapeutic challenge. *Medical review*. DOI: http://dx.doi.org/10.2298/MPNS22S1101A
2. Sarkozy, C., Copie-Bergman, C., Damotte, D., Ben-Neriah, S., Burroni, B., Cornillon, J., ... & Traverse-Glehen, A. (2019). Gray-zone lymphoma between cHL and large B-cell lymphoma: a histopathologic series from the LYSA. *The American journal of surgical pathology*, *43*(3), 341-351.
3. Bosch-Schips, J., Granai, M., Quintanilla-Martinez, L., & Fend, F. (2022). The grey zones of classic Hodgkin lymphoma. *Cancers*, *14*(3), 742.
4. Dunleavy, K., Pittaluga, S., Grant, N., Steinberg, S., Shovlin, M., Tay, K., ... & Wilson, W. H. (2008). Gray Zone Lymphomas: Clinical and Histological Characteristics and Treatment with Dose-Adjusted-EPOCH-R.
5. Kharfan-Dabaja, M., & Raj, R. (2017). Efficacy of High-Dose Therapy and Autologous Hematopoietic Cell Transplantation in Gray Zone Lymphoma: A US Multicenter Collaborative Study. Biology of blood and marrow transplantation: *journal of the American Society for Blood and Marrow Transplantation*, *24*(3), 486-493. DOI : 10.1016/j.bbmt.2017.11.033
6. Kritharis, A., Pilichowska, M., & Evens, A. (2016). How I manage patients with grey zone lymphoma. *British Journal of Haematology*, *174*. DOI : https://doi.org/10.1111/bjh.14174
7. Camus, V., Bigenwald, C., Ribrag, V., Lazarovici, J., Jardin, F., & Sarkozy, C. (2021). Pembrolizumab in the treatment of refractory primary mediastinal large B-cell lymphoma: safety and efficacy. *Expert review of anticancer therapy*, *21*(9), 941-956.