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Rare Aggressive B-Cell Lymphomas: Challenge for a Pathologist, Challenge for a Clinician 2. Mediastinal gray zone lymphoma

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Abstract

Mediastinal gray zone lymphoma (MGZL) is a distinct type of lymphoma. Given its rarity, heterogeneity, and diagnostic challenges, MGZL demands heightened awareness, refined diagnostic strategies, and collaborative research to optimize patient outcomes.

Keywords: Mediastinal; Grey Zone Lymphoma; CD30; ASCT; Checkpoint Inhibitor

Abbreviations: MGZL: Mediastinal Gray Zone Lymphoma; PMBL: Primary Mediastinal B-Cell Lymphoma; CHL: Classical Hodgkin Lymphoma; NSCHL: Nodular Sclerosis CHL; PEMGZL: Primary Extramediastinal GZL; DLBCL: Diffuse Large B Cell Lymphoma; R/R: Relapsed/Refractory Cases; HRS: Hodgkin/Reed–Sternberg.

Introduction

MGZL is a rare disease [1]. It affects mainly young adult males. Patients typically present with large anterior mediastinal mass. Involvement of extranodal sites is uncommon [2]. Non-mediastinal GZL (PEMGZL) are older (median 51 vs. 35 years), have less early-stage disease (46% stage I/II vs. 89%), and less bulky disease (0% vs. 44%) [2].

Diagnosis of GZL

Its diagnosis is challenging [1].

Morphological Features

MGZL is not uniform. It varies between different areas. The main feature is the presence of mixture of HRS–like cells, large pleomorphic B cells, and background infiltrate. This infiltrate contains eosinophils, histiocytes and small lymphocytes. These lymphocytes express CD3 and CD4 positive. Neutrophilic infiltrates are not typically present. Neoplastic cells are relatively sparse. They are bigger and more pleomorphic than DLBCL/PMBL. HRS–like cells express strong uniform CD20 and CD79a. A significant fibrosis is frequent. Necrosis can be present and extensive [3].

Cytogenetic Studies

Often reveal 9p24.1 amplification (PD-L1/PD-L2/JAK2), supporting immune evasion mechanisms. Typical Immunophenotyping of GZL tumor cells are: i. CD45 positive. ii. CD20, CD79a and PAX5 positive, B-cell markers. iii. OCT2 and BOB1 positive, B cell-specific transcription factors iv. CD30 is usually positive (diffuse and strong). v. variable expressions of CD15. vi. IRF4/MUM1 is usually positive. This positivity reflects activated B-cell phenotype. vii. Lack of surface immunoglobulin expression. viii. CD68 and BCL-6 positive. Both are germinal center transcription factors. They are positive in 68% of patients. ix. MGZL is usually EBV-negative. Isolated EBV-positive cases are rare [3]. The recommended immunostains panel for diagnosis is CD45, CD20, PAX5, CD79a, MUM1, CD15, CD30, OCT-2, BOB.1, and EBV/EBER [1]. Most studies focus on CD20. It is often essential parameter in diagnosis [3].

Genetic and Molecular Profiles of MGZL

GZL has intermediate features between CHL and PMBL. MGZL shows distinct pattern that set it unique. Common hyper- and hypomethylated targets are shared by MGZL (and PMBL). Further

analysis of MGZL also revealed hypomethylated CpG on 7 genes (ACVR1C, ERN1, HOXA5, ISL1, PTGS2, TMEFF2, and ZNF215). MGZL cases exhibited a mutation profile closely resembling cHL and PMBCL, with most recurrent mutations in SOCS1 (45%), B2M (45%), TNFAIP3 (35%), GNA13 (35%), LRRN3 (32%), and NFKBIA (29%). GZL without thymic involvement had distinct pattern enriched in TP53, BCL2, and BIRC6 mutations (apoptosis related defects) and depleted in GNA13, XPO1, or NF-κB signaling pathway mutations (TNFAIP3, NFKBIE, IKBKB, and NFKBIA) [1].

Differential diagnosis

• **CHL:** its differentiation from MGZL is difficult. CD30 commonly shows diffuse strong expression pattern, similar to that seen in MGZL. CD15 may be expressed in CHL. Diffuse strong expression of CD15 favors MGZL [3]. IRF4/MUM1 is positive in most CHL [3].

• **PMBL:** neoplastic cells occur in sheets. Cell morphology is previously discussed. CD15 and CD30 are strongly positive. PMBL frequently has variable positivity of CD30.

• PMBL and CHL are biologically related. PMBL has a striking molecular similarity to CHL (a distinctive cytokine pathway, BCR signaling pathway components expression, and NF-κB and JAK-STAT pathway activation) [1].

Treatment Approaches

MGZL is rare and has aggressive behavior. Age, performance status of the patient, stage of disease and CD20 and CD30 expression can influence response to treatment [4,5].

Frontline Therapy

- Chemotherapy ± radiation

o DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin + rituximab) are commonly used. Standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) shows variable effectiveness.

- Radiotherapy is often used for localized disease or large mediastinal masses bulky masses and typically administered after chemotherapy to consolidate the treatment [4,5].

Relapsed/refractory cases (R/R)

- Autologous stem cell transplant (ASCT)

o Primarily for R/R patients who achieve remission after salvage chemotherapy

o In checkpoint inhibitors or chemotherapy responders for consolidation [4,5].

- Brentuximab Vedotin (anti-CD30 antibody) + Nivolumab (PD-1 inhibitor)

o ~70% overall response rate in R/R MGZL (CheckMate 436).

- Checkpoint Inhibitors (Nivolumab, Pembrolizumab)

May be used in R/R MGZL patients [4,5].

Prognosis

Poor prognosis compared to related lymphomas with lower survival rates and higher relapse risk [1]. BCL-6 and CD68 are biomarkers of poor survival. Intensity of CD15 and CD209 (also known as DC-SIGN, dendritic cell-specific ICAM-grabbing non-integrin positive cells) staining may be indicative of poor prognosis 4 [3].

Conclusion

Future directions should focus on refining diagnostic criteria, exploring novel therapeutic strategies, and developing collaborative clinical trials to better define evidence-based management for this challenging lymphoma subtype.

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