Gray Zone Lymphoma

Current Diagnosis and Treatment Options

Monika Pilichowska, MD[a], Athena Kritharis, MD[b], Andrew M. Evens, DO, MSc[b,*]

KEYWORDS

- Gray zone lymphoma • B-cell • Classical Hodgkin lymphoma
- Diffuse large B-cell lymphoma • Biology • Prognosis • Treatment

KEY POINTS

- The WHO recognizes a distinct category of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL), also known as gray zone lymphoma (GZL).
- The immunophenotype of GZL is frequently discordant with tumor cells morphologically resembling DLBCL, but immunophenotypically being more consistent with cHL, and vice versa.
- Clinically, the initial case descriptions of GZL were primarily with mediastinal presentation; however, a nonmediastinal (systemic) clinical subtype is now fully recognized.
- Regardless of clinical presentation, patients with GZL have relatively high relapse rates, especially compared with primary mediastinal DLBCL and cHL.
- Off of a clinical trial, we advocate treating GZL with a DLBCL-directed regimen (eg, R-CHOP or DA-EPOCH-R) with consideration for consolidative radiotherapy for bulk disease.

INTRODUCTION

Gray zone lymphoma (GZL) is a rare neoplasm initially described in 2005 based on the recognition of an aggressive subset of primary mediastinal B-cell lymphoma (PMBCL) with poor prognosis.[1] GZL was officially first recognized in the World Health Organization classification as a distinct entity in 2008 as a B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL).[2] Since this time, there has been more insight into the

[a] Department of Pathology and Laboratory Medicine, Tufts Medical Center, 800 Washington Street, Boston, MA 02111, USA; [b] Division of Hematology/Oncology, Tufts Medical Center, 800 Washington Street, Boston, MA 02111, USA
* Corresponding author.
E-mail address: AEvens@tuftsmedicalcenter.org

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pathologic diagnosis, biology, and clinical outcomes for patients with GZL. Although initially clinically described as primarily involving the mediastinum,[1,3,4] further analyses have elucidated primary mediastinal and nonmediastinal (systemic) clinical disease presentations.[5,6] Notably, this article does not include discussion of the gray zone entity of lymphoma with features of intermediate DLBCL and Burkitt lymphoma.

GZL with mediastinal presentation (MGZL) is similar in presentation to cHL in part as it typically occurs in young adults in the third and fourth decade. Conversely, patients with GZL without mediastinal presentation (NMGZL) are typically older and more often present with advanced-stage disease. Furthermore, unlike cHL and PMBCL, both MGZL and NMGZL have a more aggressive clinical course with comparatively inferior outcomes. Given its newer recognition and relative paucity of associated clinical data, continued description of this unique disease entity is warranted. The following is a detailed review of the current literature and descriptions of the diagnosis, biology, prognosis, and treatment of GZL.

CASE STUDY

A 26-year-old Middle Eastern man was seen for second opinion of a new diagnosis of stage IIBXE cHL. On initial presentation, he experienced several weeks of nonproductive cough and drenching night sweats. A chest radiograph showed left upper lobe consolidation and he was started on antibiotics for a presumed pneumonia. His symptoms did not abate. Computerized tomography of the chest indicated multiple soft tissue masses that filled the upper mediastinum including an 11 cm $\times$ 14 cm anterior mediastinal mass with hilar adenopathy. Bronchoscopy at outside hospital with left anterior mediastinoscopy was performed. Based on morphology and positivity for CD15 and CD30, an initial diagnosis of nodular sclerosis Hodgkin lymphoma was made. The laboratory data were notable for a mild anemia, with hemoglobin 12 g/dL and hematocrit of 36% without further abnormalities. There was no evidence of bone marrow involvement on staging biopsy.

Additional pathologic review conducted at our institution and the National Institutes of Health (NIH) noted unusual morphology and immunophenotype. In addition to areas of cHL, the tumor exhibited extensive syncytial sheets of large cells, Reed-Sternberg cells, and variants. The neoplastic cells showed strong positivity for CD20 and CD15 with strong to variable positivity for CD30 (**Fig. 1**). The final diagnosis was B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL (ie, GZL). The patient was treated with cyclophosphamide, doxorubicin, oncovin, and prednisone and rituximab (CHOP-R) for six cycles. The patient had a Deauville score of 3 after two cycles and was Deauville score 2 at end of chemotherapy; he subsequently received mediastinal involved-node radiation therapy (3000 cGy). The patient currently remains disease-free 34 months following initial diagnosis.

BIOLOGY

GZL is known to arise from an altered B cell. In GZL, the putative cell of origin is thymic B cell, which is also a common precursor for cHL and PMBCL. This common precursor hypothesis explains why cHL, PMBCL, or GZL may relapse as the other related entity and why they are found as synchronous neoplasms.[7] The notion of a common cell of origin is supported by data examining gene expression signatures of GZL, PMBCL, and cHL being similar as were numerous genetic abnormalities, such as gains in chromosome 9p and 2p.[8] However, because GZL may differentiate in either direction (eg, Reed-Sternberg cell/variant or DLBCL), epigenetic changes as opposed