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Educational Case: Gastric High-Grade B-Cell Lymphoma With *MYC* and *BCL2* Gene Rearrangement (Double-Hit Lymphoma)

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289517715040>.¹

Keywords

pathology competencies, organ system pathology, hematopathology, white cell disorder, high-grade lymphoma, gastric ulcer, C-MYC, BCL2

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Primary Objective

HWC 3.3: Categories of Lymphoma. Compare and contrast low-grade or indolent lymphomas and high-grade or aggressive lymphomas with respect to underlying pathophysiology that yields specific morphologic features and clinical behavior.

Competency 2: Organ System Pathology. Topic: Hematopathology: White Cell Disorder (HWC); Learning Goal 3: Classification of Leukemia and Lymphomas.

Secondary Objective

Objective N1.1: Genetic Mechanisms of Neoplasia. Discuss and provide examples of molecular genetic mechanisms that underlie cancers, including germline mutations (including point mutations, deletions, amplifications, and translocations) and epigenetic changes.

Competency 1: Disease Mechanism and Processes; Topic: Neoplasia (N); Learning Goal 1: Genetic Basis of Neoplasia.

Patient Presentation

A 64-year-old man with no prior significant history presents to his primary care provider for vomiting bright red blood intermittently in the past few weeks before presentation along with dark black stool, decreased appetite, abdominal pain, and night sweats. He reports experiencing a sharp pain in his right leg emanating from his gluteal region for which he was prescribed daily ibuprofen 2 weeks ago at an outside hospital. The pain improves somewhat with ibuprofen but not completely. On physical examination, he has a left upper quadrant abdominal tenderness and bilateral inguinal lymphadenopathy. He does not appear to be in distress and vital signs are within normal limits.

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Table 1. Complete Blood Count and Iron Studies.

Complete Blood Count and Iron Studies	Patient Value (Reference Range)
WBC	5.7 K/mm ³ (4.5-11.0 K/mm ³)
RBC	3.16 million/mm ³ (4.50-5.90 million/mm ³)
Hemoglobin	7.7 g/dL (13.5-17.5 g/dL)
Hematocrit	23.8% (41.0%-53.0%)
MCV	72.5 fL (80.0-100.0 fL)
MCH	23.8 pg (27.0-33.0 pg)
MCHC	31.6% (32.0%-36.0%)
RDW	13.9% (11.5%-14.7%)
Platelet	221 K/ μ L (130-400 K/mm ³)
Transferrin	184 mg/dL (192-382 mg/dL)
Total iron binding capacity	256 μ g/dL (280-400 μ g/dL)
Iron percent saturation	9.4% (20%-50%)

Abbreviations: MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell.

Diagnostic Findings, Part 1

On further workup, a complete blood count (CBC) was performed (Table 1). A follow-up gastroenteroscopy shows numerous gastric ulcers with heaped up borders ranging from 8 to 15 mm throughout the stomach. An X-ray showed non-displaced fractures of the right obturator ring with mixed lytic/sclerotic lesions.

Questions/Discussion Points, Part 1

What Are the Histologic Findings in This Case?

Biopsy of the gastric ulcer shows a denuded surface epithelium. The architecture of the underlying submucosa is disrupted by a diffuse proliferation of large atypical lymphoid cells. Residual gastric glands are still noted in the background of the neoplastic cells with no evidence of a low-grade lymphoma (Figure 1A).

What Does the Complete Blood Count Show and What Is the Differential Diagnosis?

The CBC shows low mean corpuscular volume (72.5 fL) and decreased hemoglobin (7.7 g/dL) with a normal red cell distribution width consistent with a microcytic anemia. The differential diagnosis for microcytic anemia includes iron deficiency anemia, anemia of inflammation and chronic disease, thalassemia, and sideroblastic anemia. Further laboratory testing showed decreased transferrin and iron percentage saturation (Table 1) consistent with iron deficiency anemia in this patient.

What Is the Differential Diagnosis of Gastric Endoscopic Findings?

The differential diagnosis at this point for the gastric ulcers includes nonsteroidal anti-inflammatory drugs, *Helicobacter*

pylori infection, and malignancy such as gastric adenocarcinoma. Nonsteroidal anti-inflammatory drugs can cause gastric ulcer through multiple mechanisms such as disrupting the mucosa barrier, creating irritation to the epithelium, and preventing the production of prostaglandins.² *Helicobacter pylori* infection results in inflammation with lymphocytes, neutrophils, plasma cells, and macrophages to the site, which results in damage to the epithelium.³

Diagnostic Findings, Part 2

Sections of the gastric ulcer biopsy show proliferation of large atypical cells (Figure 1A). An immunohistochemical staining shows these cells to be negative for pan-cytokeratin (Figure 1B), T-cell markers and CD30, while expressing B-cell markers (Figure 1C) along with BCL2, BCL6, CD10, and c-MYC. The neoplastic cells also show an increased proliferation rate with a Ki-67 of approximately 80% (Figure 1D). The neoplastic cells are negative for MUM1 and BCL1. The large size of the cells and expression of B-cell markers by immunohistochemistry findings were initially consistent with a de novo diffuse large B-cell lymphoma (DLBCL), germinal center immunophenotype with a high Ki-67, and coexpression of BCL2 and c-MYC by immunohistochemistry. Follow-up fluorescence in situ hybridization (FISH) studies displayed c-MYC and BCL2 gene rearrangement, with no BCL6 gene rearrangement by a break apart probe. In light of the FISH findings, per World Health Organization (WHO) 2017 criteria, this is reclassified as a high-grade B-cell lymphoma (HGBCL) with MYC and BCL2 rearrangement, also known as double-hit lymphoma.

Questions/Discussion Points, Part 2

What Other Lymphomas Are Most Commonly Seen in Gastrointestinal Tract?

Primary gastrointestinal (GI) lymphoma is rare and usually GI tract involvement is due to the spread of the disease from another site. Stomach accounts for the most common site followed by small intestine and ileocecal area. Most common lymphomas are B lineage followed by T lineage and Hodgkin lymphoma. Among the B-lineage lymphomas, the most common lymphomas include follicular lymphoma, mantle cell lymphoma, mucosa-associated tissue (MALT) lymphoma, and DLBCL. Diffuse large B-cell lymphoma can be primary or arise from a low-grade lymphoma.⁴ Low-grade B-cell lymphomas are mainly composed of small to medium cells with low proliferation rate, while DLBCL and HGBCLs commonly have large cells with higher proliferation rate (higher Ki67). Mantle cell lymphoma, which is a mature B-cell neoplasm, is usually composed of small- to medium-sized lymphocytes with irregular nuclear contour and can involve the GI tract. The neoplastic cells in mantle cell lymphoma in addition to the B-cell markers (CD20, PAX5, CD19, CD79a) also express CD5 and BCL1 (cyclin-D1). The proliferation rate can vary in mantle cell

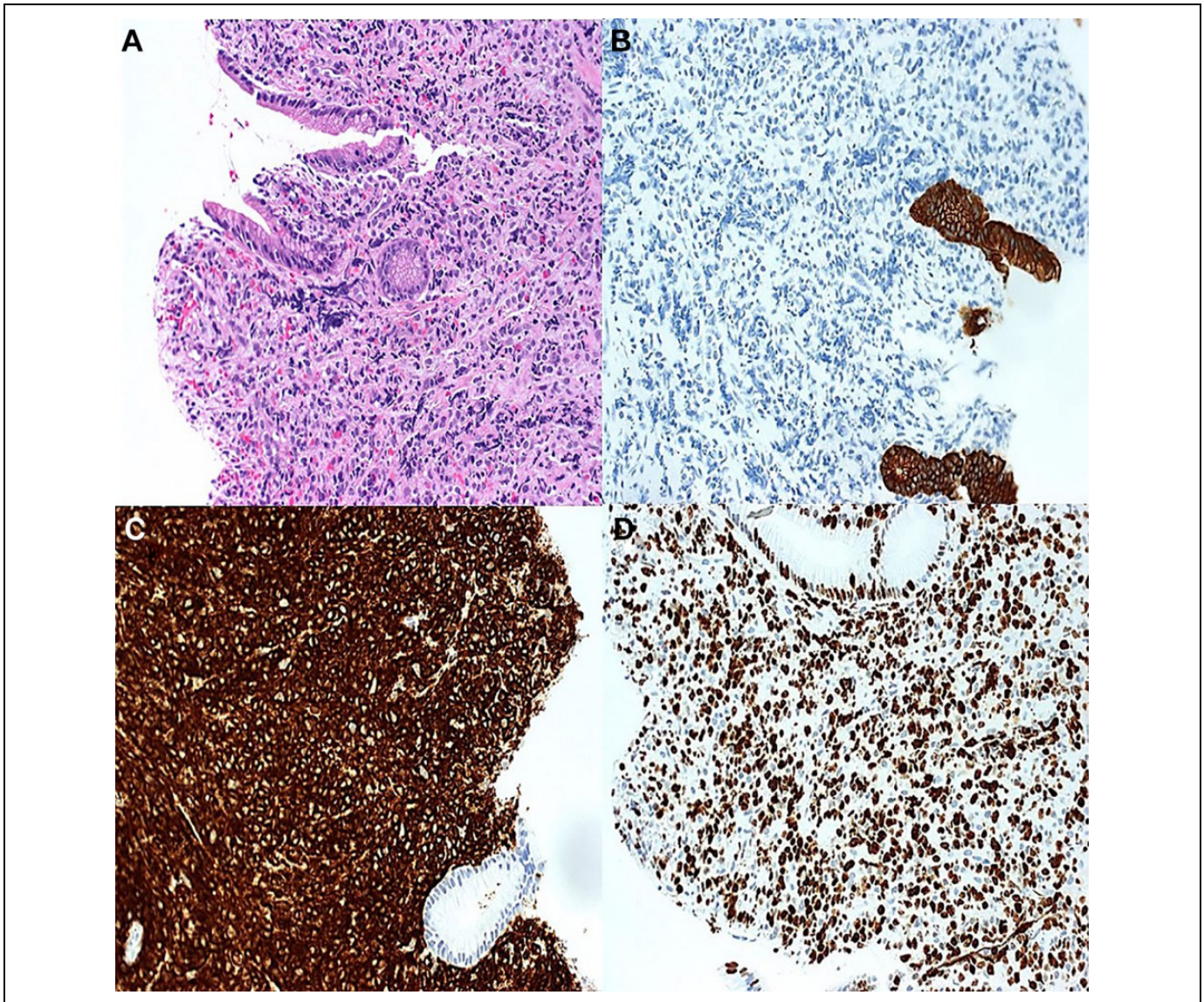


Figure 1. A, Hematoxylin and eosin stain showing denuded surface epithelium with proliferation of large atypical lymphoid cells ($\times 20$). B, AE1/AE3 showing the neoplastic cells in the subepithelium are negative and highlights the remaining non-neoplastic epithelial cells ($\times 20$). C, CD20 immunostain showing diffuse positivity in the neoplastic cells ($\times 20$). D, Ki-67 immunostain showing approximately 80% proliferation rate in the neoplastic B cells ($\times 20$).

lymphoma; however, high proliferation rate (Ki67 $> 30\%$) is considered to be associated with adverse prognosis.⁵ Follicular lymphoma is a neoplasm that is composed of germinal center B cells including centrocytes and centroblasts and usually shows a follicular growth pattern. The neoplastic cells in the follicles express B-cell markers with coexpression of BCL6, CD10, and BCL2. The histologic grade of follicular lymphoma is based on the number of centroblasts present in the follicles. Grade 1-2 cases have few centroblasts (0-15 per high-power field [HPF]) and grade 3 cases have >15 centroblasts per HPF.⁶ Mucosa-associated lymphoid tissue lymphoma is mainly composed of small mature B lymphocytes which express B-cell markers with coexpression of BCL2 and low proliferation rate. The

neoplastic cells are negative for CD10, BCL6, and CD5. In GI tract, MALT lymphoma is associated with *H pylori* infection, which this organism is thought to have a direct oncogenic effect on the B cells.⁷ Diffuse large B-cell lymphoma, not otherwise specified (NOS) in contrast to the MALT lymphoma, follicular lymphoma, and mantle cell lymphoma is composed of large neoplastic mature B cells which show a diffuse growth pattern. The proliferation rate is high in DLBCL in the neoplastic cells. Morphologically and immunophenotypically DLBCL, NOS and HGBCL DLBCL, NOS are not distinguishable; however, DLBCL, NOS does not harbor MYC along with BCL2 and/or BCL6 rearrangement, which are observed in HGBCL.

What Is High-Grade B-Cell Lymphoma With MYC and BCL2 and/or BCL6 Rearrangement and How Is It Different From Diffuse Large B-Cell Lymphoma, Not Otherwise Specified?

In DLBCL, the neoplastic cells are typically large and the nuclei of the cells are the same size or larger than a macrophage or more than twice the size of a normal lymphocyte. Additionally, as the name implies, the neoplastic cells show a diffuse proliferative pattern. Diffuse large B-cell lymphoma has been divided into different subcategories based on its morphologic and molecular findings and clinical outcomes. Diffuse large B-cell lymphoma, NOS, is a subcategory that includes the neoplasms that would not fit any other category.^{2,8,9} Diffuse large B-cell lymphoma is an aggressive B-cell neoplasm that can arise in a nodal or extranodal site in which GI tract is the most common location.^{8,10} Diffuse large B-cell lymphoma, NOS lacks the rearrangements of MYC along with BCL2 and/or BCL6 that are observed in HGBCL.⁸

In contrast, HGBCL is an aggressive mature B-cell neoplasm that morphologically and biologically is different from DLBCL, NOS. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement so called double-/triple-hit lymphoma is a subcategory of HGBCL.¹⁰ By definition, double-/triple-hit HGCLs harbor c-MYC translocation along with BCL2 and/or BCL6 rearrangement (Figure 2). The diagnostic criteria for HGBCL is relatively strict and cases which show BCL2 and/or BCL6 translocation without c-MYC translocation or those with c-MYC translocation along with other genes other than *BCL2* and *BCL6* or case with extra copies of these genes are not considered in this category. Per WHO, cases of large B-cell lymphoma with c-MYC rearrangement without rearrangement of BCL2 and/or BCL6 but rather gain of BCL2 or BCL6 (absence of rearrangement) are still categorized as DLBCL, NOS.

What Is the Epidemiology of High-Grade B-Cell Lymphoma?

These lymphomas are most commonly seen in elderly individuals in their 60s and 70s with slight male predominance.^{9,11-13}

What Is the Immunophenotype of High-Grade B-Cell Lymphoma?

The neoplastic cells in HGBCL express pan-B-cell markers such as CD19, CD20, CD22, PAX5, and CD79a while lacking immature markers such as CD34 and TdT. Other markers that could be positive in the neoplastic cells are BCL2, BCL6, CD10, MUM1, and c-MYC.¹⁴ The Ki-67 may have variable expression ranging from 80% to 95% in cases resembling Burkitt lymphoma to <30% in cases resembling DLBCL.^{15,16} Therefore, Ki67 does not serve as prognostic marker for the presence of double- or triple-hit lymphoma. Most double-hit HGBCLs express BCL2 and c-MYC by immunohistochemistry and have a germinal center phenotype. The expression of these

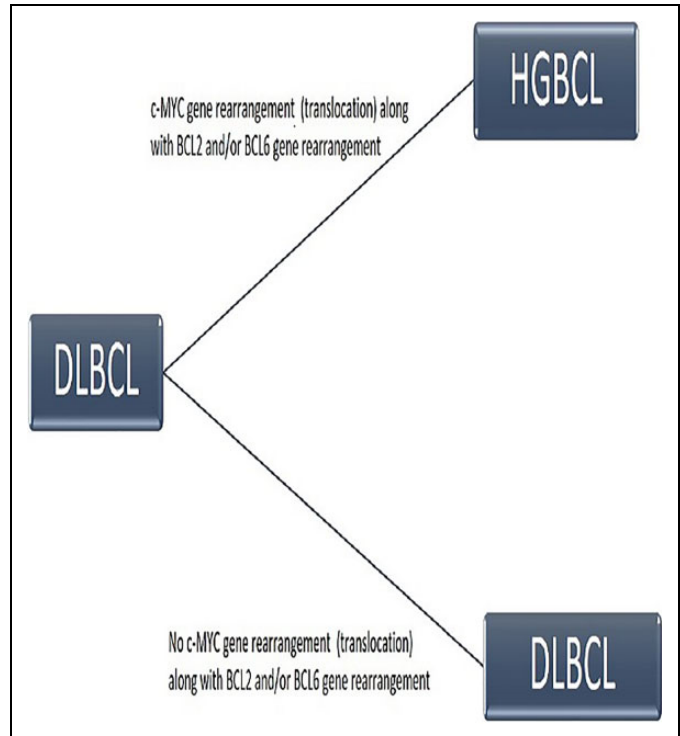


Figure 2. Diagnostic algorithm showing large B-cell lymphomas which harbor c-MYC translocation along with BCL2 and/or BCL6 rearrangement are diagnosed as HGBCL, and if the neoplasm doesn't harbor the aforementioned translocations, it will be categorized as DLBCL. DLBCL indicates diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma.

2 markers may also be seen in DLBCL. Ultimately, the diagnosis of HGBCL is based on the presence of c-MYC with BCL2 and/or BCL6 gene rearrangement by molecular studies and not based on histology and immunohistochemical profile alone.

What Are the Molecular Findings in High-Grade B-Cell Lymphoma?

Chromosomal translocations observed in HGBCL with MYC and BCL2 and/or BCL6 rearrangement include c-MYC which is located at chromosome 8q24 and plays a role in cellular proliferation, growth, and apoptosis. BCL2 is located at 18q21 which has an antiapoptotic role, and BCL6 located at 3q27 mediates lymphogenesis.¹⁷ Complex karyotype is also commonly observed in double-hit HGBCLs. Patients with double- or triple-hit lymphomas have worse prognosis compare to ones not harboring these translocations and usually require more aggressive treatment.

What Is the Treatment and Prognosis of High-Grade B-Cell Lymphoma?

Patients with double- or triple-hit lymphomas have worse prognosis compare to ones not harboring these translocations.

Patients with HGBCL commonly present with high-risk clinical features and advanced-stage disease, which may result in worse prognosis and lower rate of response to therapy.¹⁸ Rituximab (anti-CD20 monoclonal antibody), cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), which is the mainstay of therapy for DLBCL, does not usually confer a good response in patients with double-/triple-hit HGBCL and will likely show a low complete response rate. In these patients, treatment with rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) has been shown to lead to better event-free survival compared to R-CHOP.¹⁹

What Is the Prevalence of Double-Hit/Triple-Hit High-Grade B-Cell Lymphoma in the Gastrointestinal Tract?

Stomach accounts for the most common site of lymphoma in the GI tract. Most common lymphomas of the stomach are DLBCL and MALT lymphoma. Large B-cell lymphomas can be primary or arise from a low-grade lymphoma.^{4,20} A study performed by Cox et al showed no cases of double-/triple-hit lymphoma in the GI tract.²¹ Another study by Choi et al showed 2 cases with MYC and BCL6 rearrangement in stomach among 101 cases of B-cell lymphoma in the GI tract.²² He et al evaluated 188 cases of primary gastric B-cell lymphoma, which showed no cases with double-hit lymphoma; however, cases with multiple gene amplification and gains of MYC, BCL2, and BCL5 were noted.²³

Teaching Points

- High-grade B-cell lymphoma is an aggressive mature B-cell neoplasm that morphologically and biologically is different from DLBCL, NOS.
- High-grade B-cell lymphomas compared to low-grade B-cell lymphomas have a high proliferation rate (increased Ki67), and morphologically, the cells are large (twice or more the size of a lymphocyte or size of a histiocyte nucleus).
- High-grade B-cell lymphoma with c-MYC and BCL2 and/or BCL6 rearrangement, so-called double-/triple-hit lymphoma, is a subcategory of HGBCL.
- Rearrangements of c-MYC, BCL2, and/or BCL6 that are seen in HGBCL are not present in DLBCL, NOS.
- High-grade B-cell lymphoma by immunohistochemistry is positive for B-cell markers (CD19, CD20, CD79a, PAX5) and may express BCL2, BCL6, CD10, MUM1, and c-MYC. The neoplastic cells lack expression of CD34 and TdT.
- An HGBCL which has c-MYC and BCL2 gene rearrangement without BCL6 rearrangement is called a double-hit lymphoma and an HGBCL which has rearrangement of all 3 genes (c-MYC, BCL2, and BCL6) is called a triple-hit lymphoma.
- Patients with double- or triple-hit lymphomas have worse prognosis compared to ones not harboring these translocations and don't respond to R-CHOP therapy as well as patients with DLBCL, NOS.
- Patients with double-/triple-hit HGBCL have been shown to have a better event-free survival with R-EPOCH therapy.


Declaration of Conflicting Interests

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