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Gastrointestinal Tract Lymphomas

A Review of the Most Commonly Encountered Lymphomas

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• ***Context.***—**The gastrointestinal (GI) tract is the most common site of extranodal non-Hodgkin lymphoma, accounting for 20% to 40% of all extranodal lymphomas. The majority of these are systemic processes secondarily involving the GI tract. Primary GI lymphomas are less common, accounting for approximately 10% to 15% of all non-Hodgkin lymphoma. Most non-Hodgkin lymphoma involving the GI tract are of B-cell lineage, of which diffuse large B-cell lymphoma is the most common subtype, irrespective of location.**

Objective.—**To review the lymphoproliferative neoplasms of B-cell and T-cell lineage involving the luminal GI tract according to the most prevalent subtypes at each anatomic site.**

Data Source.—**Systematic search of the PubMed database for updated literature on GI lymphomas epidemiology, subtypes, clinical, endoscopic, and genetic findings. Histologic images are derived from our collection of clinical cases.**

Conclusions.—**The GI tract is the most common site of extranodal lymphoproliferative neoplasms. Recognition of the most frequently encountered GI lymphomas is imperative for patient management and treatment.**

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Although gastrointestinal (GI) tract lymphomas comprise only 1% to 4% of all malignant neoplasms of the GI tract, the GI tract is the most common site of extranodal lymphomas worldwide, accounting for up to 40% of all extranodal non-Hodgkin lymphomas. In order of frequency, the most common sites involved are the stomach (65%), small intestine (20%–30%), colon (10%–20%), and esophagus (<1%).[1–6] Lymphomas of the hepatobiliary system and pancreas are uncommon, comprising less than 1% of cases. Similar to their nodal counterparts, the majority of GI lymphomas are non-Hodgkin lymphomas of B-cell lineage with diffuse large B-cell lymphoma (DLBCL) and marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) comprising the majority of cases.[3,4] Conversely, T-cell lymphomas are uncommon, estimated to account for 4% to 6% of GI tract lymphomas.[7] The prevalence of the particular lineage (B cell or T cell) and subtype vary according to the site within the luminal GI tract (Figure 1). Examples of this include a high frequency of MALT lymphoma and DLBCL in the stomach, mantle cell lymphoma (MCL) in the terminal ileum, jejunum, and colon and enteropathy-associated T-cell lymphoma (EATL) and follicular lymphoma (FL) in the small intestine.[3,8] GI lymphomas commonly present as localized tumors; however, multifocal disease, including multiple polypoid lesions ("lymphomatous polyposis") as well as intraabdominal sites and regional lymph node involvement, are also common.

The GI tract is also one of the most common sites of involvement by iatrogenic immunodeficiency-associated lymphoproliferative disorders, defined as a heterogeneous group of lymphoid or plasmacytic proliferation in the context of solid organ, stem cell, or bone marrow transplantation (posttransplant lymphoproliferative disorders). Posttransplant lymphoproliferative disorder may present as localized or multifocal lesions and is further classified into 4 major categories, including non-destructive, polymorphic, monomorphic, and classical Hodgkin's lymphoma posttransplant lymphoproliferative disorder. This classification is based on a combination of cellular composition, phenotypic features, degree of architectural distortion, and cytogenetic findings. For the sake of this review, we will focus on commonly encountered non–posttransplant lymphoproliferative disorder neoplasms. However, it is important to consider posttransplant lymphoproliferative disorder in the setting of immunosuppression for solid organ or stem cell transplant recipients. Other hematopoietic neoplasms, including Hodgkin lym-

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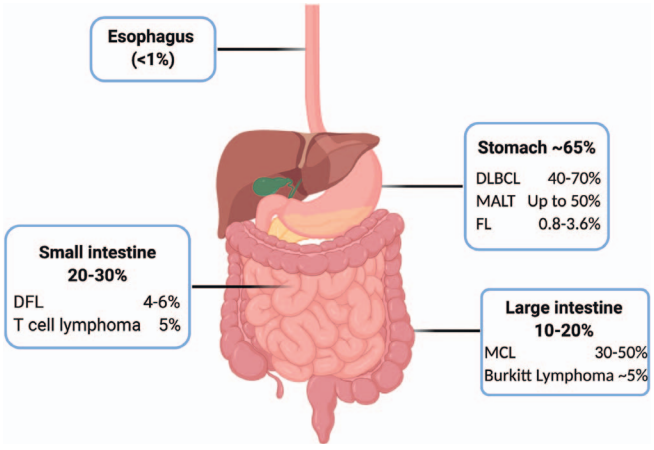

Figure 1. *Prevalence of lymphoma and subtypes within the luminal gastrointestinal tract. Abbreviations: DFL, duodenal-type follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MALT, marginal zone lymphoma of mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma. Figure 1 created with Biorender.com.*

phomas, extramedullary plasmacytoma, myeloid sarcoma, and histiocytic/dendritic cell neoplasms, seldom involve the GI tract.

In contrast to their nodal counterparts, various primary GI lymphomas are associated with well-recognized risk factors implicated in lymphomageneses, such as *Helicobacter pylori* infection, celiac disease, immunodeficiency syndromes (ie, common variable immunodeficiency), solid organ transplantation, and idiopathic inflammatory bowel disease.

The 2017 World Health Organization (WHO) classification of hematopoietic neoplasms revised criteria for several classic entities and recognized a few novel ones, including Epstein-Barr virus-positive mucocutaneous ulcer (EBV-MCU), duodenal-type follicular lymphoma (DFL), monomorphic epitheliotropic intestinal T-cell lymphoma, and intestinal T-cell lymphoma, not otherwise specified.[9] These entities appear to harbor distinct histopathologic, clinical, and biologic features that are further discussed herein.

This review discusses the most commonly encounter lymphoid neoplasms based on their prevalent location within the luminal GI tract.

MALIGNANT LYMPHOMAS OF THE ESOPHAGUS

Esophageal lymphomas are exceedingly uncommon, accounting for less than 1% of all GI lymphomas and 0.2% of extranodal non-Hodgkin lymphomas.[10,11] Esophageal lymphomas are most commonly the result of secondary involvement by a systemic process, usually through direct extension from adjacent anatomic sites.

The most common subtypes described are DLBCL and MALT lymphomas, which show similar morphologic and immunophenotypic findings to lymphomas found elsewhere in the GI tract; few cases of primary T-cell lymphomas have been reported. In addition, EBV-MCU, a newly recognized entity in 2017 WHO,[9] usually presents in the oropharynx and GI tract, including esophageal mucosa.

Clinically, patients present with dysphagia and hematochezia. Endoscopic findings are attributed to submucosal-based infiltrates, which may lead to mucosal protrusion, producing polypoid lesions and mucosal nodularity.

EBV-Positive Mucocutaneous Ulcer

EBV-MCU is a distinct clinicopathologic entity first described by Dojcinov et al[12] in 2010 and defined as an indolent lymphoproliferative disorder commonly occurring in elderly patients, typically in the context of immunosuppression.[9] The incidence of this entity is not well established. It is mostly described in the oropharyngeal mucosa (52%), skin (29%), and GI tract (19%; 40% colon, 30% esophagus, 20% rectum, and 10% terminal ileum).[13,14] Clinical features are related to the site of involvement, and these tumors present with well-circumscribed mucosal ulceration(s). These lesions are typically localized; systemic symptoms are rarely present.

Microscopic examination demonstrates mucosal ulceration with sharply demarcated borders. The underlying inflammatory infiltrate is composed of a polymorphic hematolymphoid population consisting of plasma cells, histiocytes, lymphocytes, eosinophils, scattered neutrophils, and a variable number of large atypical lymphoid cells. The large atypical lymphoid cells show a variable degree of cytologic atypia, often showing Hodgkin-like features (Figure 2, A and B). In addition, background increased apoptotic bodies, necrosis, and angioinvasion may be present.[15]

Immunophenotyping shows the large atypical lymphoid cells are composed of PAX5/CD20/CD79a positive B cells, which variably express CD30 (Figure 2, C). Other B-cell markers, including OCT2 and BOB1, are also positive. By definition, EBV by in situ hybridization is consistently positive in the large lymphoid cells (Figure 2, D). EBV by in situ hybridization positivity may also be seen in the background small mature lymphocytes. The background polymorphic lymphoid population is predominantly composed of T cells, namely cytotoxic CD8+ T cells. Gene rearrangements in *IgH* and *TCR* have been reported in 38.9% and 37.6% of cases, respectively.[9,12]

In general, the clinical course is self-limited and indolent, with the majority of reported cases showing complete regression with discontinuation of any immunosuppressive agents. In patients for whom withdraw of immunosuppression is not possible or who do not achieve a complete response, treatments with numerous modalities including rituximab therapy, localized radiation, and surgical excision have been reported with favorable outcomes.[9,13,14,16,17] A review of the medical literature reports one fatal case occurring in a young patient with a history of primary immunodeficiency and CHARGE syndrome, which includes coloboma, heart defects, choanal atresia, growth retardation, and genital and ear abnormalities.[16]

MALIGNANT LYMPHOMAS OF THE STOMACH

The stomach is the most common extranodal site involved by non-Hodgkin lymphomas. Gastric lymphomas represent up to 65% of all GI lymphomas, between 30% and 40% of all extranodal lymphomas, and 1% to 7% of all gastric malignancies The gastric antrum and fundus are the most frequent sites involved. Approximately 90% of gastric lymphomas are of B-cell lineage, while the remaining 10% are T-cell lymphomas and Hodgkin's lymphoma.[18]

A variety of gastric lymphoma subtypes has been described, including DLBCL, MALT lymphoma, MCL, FL, Burkitt lymphoma, and rarely T-cell lymphomas. DLBCL is the most common subtype, followed by MALT lymphoma. Primary gastric T-cell lymphomas are rare and are mostly

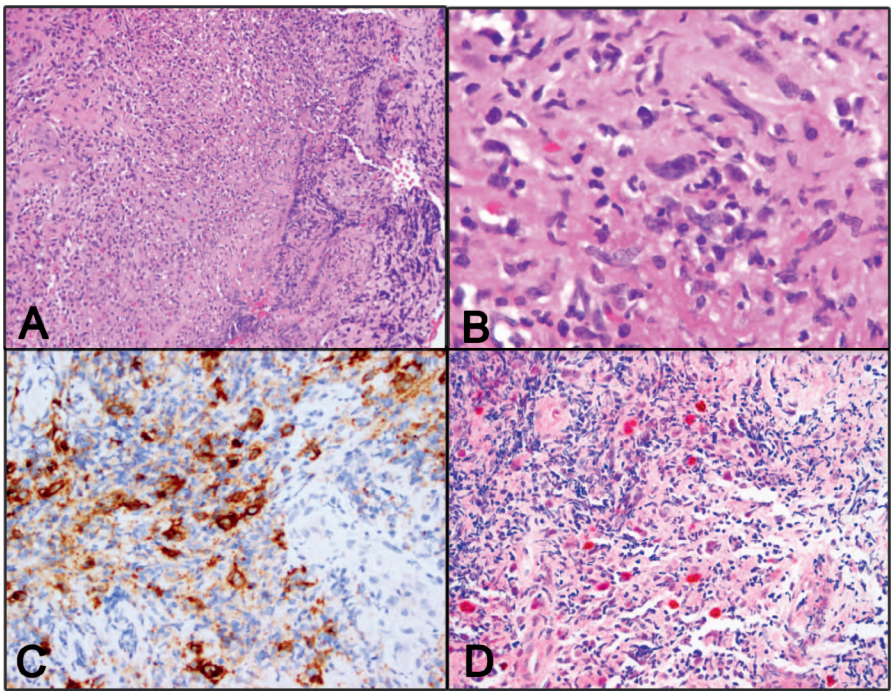

Figure 2. *Epstein Barr–positive mucocutaneous ulcer. A, Ulcerated esophageal squamous mucosa with prominent band-like polymorphic inflammatory infiltrate with numerous scattered large cells. B, Large atypical cells demonstrate Hodgkin-like features. C, Large atypical cells are positive for CD30, and (D) EBV by in situ hybridization (original magnifications ×100 [A], ×400 [B], ×200 [C and D]).*

encountered in the setting of human T-cell leukemia virus type 1 infections (adult T-cell leukemia/lymphoma).[19]

Clinically, patients with gastric lymphomas present with nonspecific symptoms, including dyspepsia, nausea, and vomiting. Patients may present with a palpable mass. Endoscopic findings vary from unremarkable to erythematous mucosa, enlarged and thickened gastric folds, erosions, and ulceration, which may mimic inflammatory conditions, including reactive gastropathy and gastritis or epithelial malignancies, including conventional gastric adenocarcinoma (Figure 3, A through C). The majority of lymphomas present as localized lesions; the multifocal disease is less common.[18,20]

Mucosa-Associated Lymphoid Tissue Lymphomas

Gastric MALT lymphomas are extranodal low-grade lymphomas accounting for up to 50% of all gastric lymphomas.[9] As with the majority of MALT lymphomas, a preceding history of chronic antigenic stimulation leads to the formation of extranodal lymphoid tissue (acquired MALT), leading to clonal evolution and malignant transformation. Gastric MALT lymphoma is highly associated with chronic gastritis secondary to *H pylori*, which induces the formation of acquired MALT over time. It has been reported that *H pylori* can be identified in more than 90% of gastric MALT lymphomas, suggesting a direct link between the infection and lymphoma development. Intriguingly, patients with *H pylori* infection are also at increased risk for the development of gastric adenocarcinoma.

Microscopic features include a diffuse and/or nodular lymphoid infiltrate predominantly present within the lamina propria and superficial submucosa. The neoplastic lymphoid cells are small and mature and show mild nuclear atypia with irregular nuclear borders. Lymphoma cells frequently have abundant clear cytoplasm, oftentimes imparting a monocytoid appearance. Rare and scattered background large lymphoid cells may be seen; however, their presence does not warrant a designation of large cell transformation. In addition, background small mature plasma cells, particularly at the periphery of lymphoid aggregates and in submucosal foci, are often present. Dutcher bodies may also be identified. Indeed, plasmacytic differentiation is seen in approximately one third of all gastric MALT lymphomas.[9] Although not diagnostically specific, another histologic feature is the presence of lymphoepithelial lesions, defined as intraepithelial invasion by groups of lymphocytes, which may or may not result in glandular destruction (Figure 4). Lymphoepithelial lesions may be occasionally encountered in inflammatory or reactive processes.

Immunophenotyping shows neoplastic lymphoid cells are composed of CD20-positive B cells that are negative for CD5, CD10, CD23, BCL-6, LMO2, HGAL, and cyclin-D1.[1] Approximately half of all cases aberrantly coexpress CD43. In situ hybridization studies for kappa and lambda light chains are used to assess the presence of a clonal plasma cell component. The lymphoma cells harbor immunoglobulin gene mutations. Transformation to DLBCL is reported in 2% to 8% cases.[21,22]

Cytogenetic findings in MALT lymphoma are variable and are dependent on the site of involvement. The most common translocation in all MALT lymphomas is t(11;18)(q21;q21), which is also the most common translocation in gastric and pulmonary MALT lymphomas, followed by t(1;14)(p22;q31) and rarely t(3;14)(p14.1;q32). These translocations involve the *API2*, *MALT1*, *BCL10*, *IGH*, and *FOXP1* genes. The presence of either t(11;18) or t(1;14) is associated with poor response to *H pylori* eradication therapy.[23–26] As in the case of gastric DLBCL, trisomy 3 is the most common aberration in GI MALT lymphomas, identified in 40% to 60% of cases.[11,24] These translocations and numerical chromosomal abnormalities lead to activation of transcription factors, including nuclear factor kappa-B, that consequently promote cell survival and proliferation.[23]

Gastric MALT lymphoma follows an indolent clinical course; the 5-year survival rate is approximately 90%.[27,28] *H*

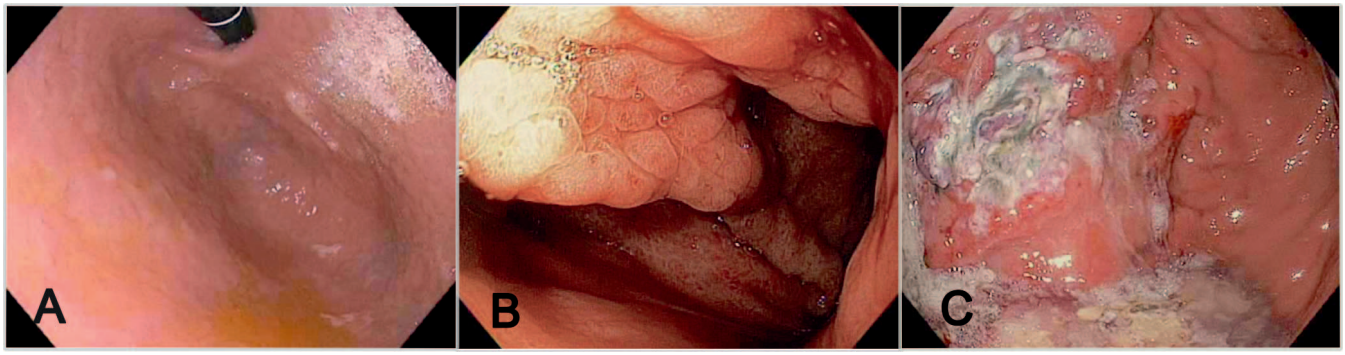

Figure 3. *Endoscopic presentation of gastric lymphoma, showing a spectrum of endoscopic findings, including (A) patchy irregular mucosa, (B) enlarged and thickened gastric folds, and (C) ulceration and lesions mimicking gastric adenocarcinoma.*

pylori eradication is the first treatment of choice in *H pylori*–positive cases, which commonly results in complete disease regression.

Diffuse Large B-Cell Lymphoma

DLBCL is defined as a neoplasm of medium to large B-lymphoid cells with nuclear size greater than or equal to that of a macrophage or more than twice the size of normal lymphocytes arranged in a diffuse growth pattern.[9] DLBCL constitutes up to 70% of all gastric lymphomas.[8] Primary gastric DLBCL may arise de novo or represent transformation from antecedent low-grade B-cell lymphoma, usually MALT lymphoma.[8] In the latter scenario, evidence of transformation from MALT lymphoma includes numerous small cytologically atypical lymphocytes with or without plasma cell component. In addition, evidence of a monotypic plasma cell component, when present and determined by in situ hybridization assays, is another diagnostic clue. It is important to note that clusters of large cells encountered on a background of MALT lymphoma may pose a diagnostic pitfall as they may represent remnants of reactive germinal centers, which may be confluent. Thus, it is important to differentiate this from large cell transformation. Designation of large cell transformation requires the presence of definitive sheets of large neoplastic lymphoid cells.

Microscopic examination shows diffuse proliferation of lymphoid cells forming sheets that intersect between gastric glands and abnormally expand the lamina propria. The lymphoma cells typically range in size from medium to large with round to irregular and vesicular nuclei, variably prominent nucleoli, and scant pale or eosinophilic cytoplasm (Figure 5, A).

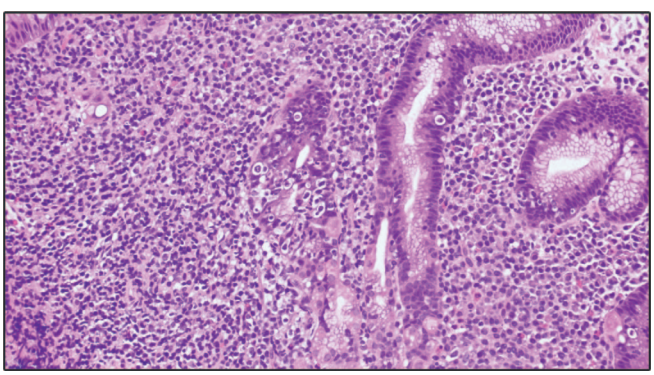

Figure 4. *Gastric mucosa-associated lymphoid tissue (MALT). Gastric mucosa showing a diffuse lymphoplasmacytic infiltrate, which is composed of small and mature lymphocytes with mild cytologic atypia and numerous background small plasma cells. Note the prominent lymphoepithelial lesions leading to glandular destruction (original magnification ×200).*

Immunophenotypically, the large CD20/CD79a/PAX-5–positive B cells often display an activated B-cell phenotype (either CD10–/BCL-6– or CD10–/BCL-6+/MUM-1+)[29] (Figure 5, B through D). Approximately half of all cases express BCL-2, BCL-6, and CD43.[29,30]

Cytogenetic studies frequently identify complex abnormalities, including loss of chromosome 6 and gain in chromosome 3. Complete or partial trisomy 3 is one of the most common aberrations in gastric DLBCL, similar to those of other extranodal DLBCL.[31] Amplification of *MYC* and *BCL6* are more commonly present than in nodal DLBCL. Translocations involving *FOXP1* have been associated with DLBCL arising from MALT lymphoma.[32,33]

Studies have shown that survival from de novo gastric DLBCL is less favorable than that of transformed large cell lymphoma from an antecedent low-grade lymphoma.[34–36] Some studies have shown no significant difference in survival between germinal center B cell and activated B-cell immunophenotypes in the context of gastric DLBCL.[29,34,37] Chemotherapeutic drugs including rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (also known as R-CHOP), with or without radiation therapy, is currently used to manage gastric DLBCL; the overall survival rate is between 84% and 100%, and complete remission is achieved in 92% to 100% patients.[38,39]

Follicular Lymphoma

Gastric FL is rare, with a reported incidence of 0.8% to 3.6% of gastric lymphomas.[40,41] Thus, owing to the low incidence of primary gastric FL, emphasis should be placed on clinical staging to exclude secondary involvement by a systemic process. FL of the GI tract is discussed in detail in the small intestine section.

T-Cell Lymphomas

Gastric T-cell lymphomas are rare, accounting for 1.5% of all the GI tract lymphomas, and are commonly associated with human T-cell leukemia virus type 1 infection. Other associated factors, such as *H pylori* and EBV infection, have also been identified.[42]

Microscopic examination of gastric T-cell lymphomas shows neoplastic lymphoid cells that are most frequently medium to large in size and display mild-to-moderate

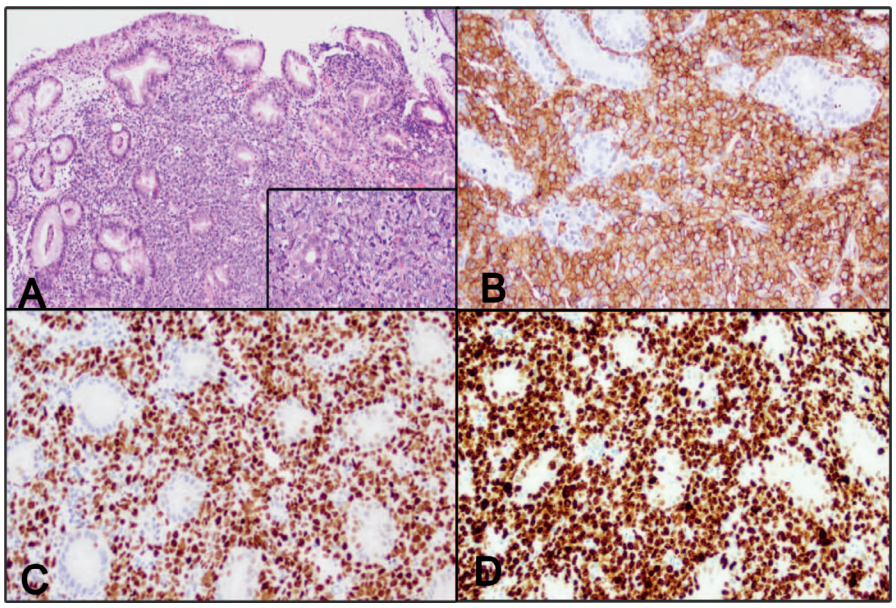

Figure 5. *Gastric diffuse large B-cell lymphoma (DLBCL). A, Gastric mucosa showing a diffuse infiltrate of large neoplastic lymphoid cells with open vesicular nuclei and prominent nucleoli (inset). B, Lymphoma cells are positive for CD20 and (C) BCL-6. D, Ki-67 proliferation index is high (>90%) (original magnifications ×100 [A], ×400 [A inset], ×200 [B through D]).*

variation in size and shape. Gastric T-cell lymphomas can be classified into helper/inducer T-cell subtype, which is the most common, and cytotoxic suppressor T-cell subtype. The classification is based on immunophenotype of tumor cells as follows: CD4+/CD8– and CD103, in gastric T-cell lymphomas helper/inducer subtype and CD4–/CD8+ or CD4–/CD8– and CD103+ and/or CD56+ in gastric T-cell lymphomas cytotoxic suppressor T-cell subtype.[43] T-cell lymphomas are discussed in detail in the small intestine section.

MALIGNANT LYMPHOMAS OF THE SMALL INTESTINE

Small intestinal lymphomas account for 20% to 30% of all GI lymphomas and 15% to 20% of all small intestinal neoplasms.[11] The most common small intestinal lymphomas are DLBCL and MALT lymphoma, which subsumes immunoproliferative small intestinal disease. The revised 2017 WHO classification of hematolymphoid tumors[9] includes 2 major primary small intestinal lymphomas; duodenal-type follicular lymphoma and intestinal T-cell lymphomas. In this section, we primarily focus the discussion on these 2 entities.

Follicular Lymphoma

DFL is relatively uncommon, accounting for approximately 4% to 6% of primary GI lymphomas.[44,45] DFL is defined as a primary GI low-grade B-cell lymphoma of germinal center phenotype and is considered a variant of follicular lymphoma with distinct features. The second portion of the duodenum is the most common site of involvement, followed by the jejunum and ileum. Lesions are usually incidentally detected during endoscopy and include mucosal polyp(s) or irregular mucosal nodules (Figure 6). Multifocal disease has also been described. It is important to correlate with clinical staging to exclude secondary small intestinal involvement by systemic FL before the designation of DFL.

Microscopically, DFL shares many morphologic and immunophenotypic features with nodal FL. Neoplastic follicles expand intestinal villi and/or the lamina propria and are typically restricted to the mucosa but may extend into the submucosa. These follicles are predominantly composed of small mature cleaved lymphoid cells (centrocytes) with rare to infrequent centroblasts, consistent with low-grade morphology (grade 1-2). Tingible body macrophages and mantle zones are usually absent (Figure 7, A and B). High-grade features including more than 15 centroblasts per high power field, infiltration into muscularis propria and/or peri-intestinal adipose tissue, and involvement of nearby mesenteric lymph nodes are not characteristic features of DFL and when present should prompt one to consider secondary involvement by systemic FL.

Immunophenotyping shows CD20-positive lymphoma cells that express germinal center markers, including CD10, BCL-6, HGAL, and LMO2 and, similar to nodal FL, aberrantly coexpress BCL-2 (Figure 7, C and D).[46] Lymphoma cells are negative for CD5, CD43, and cyclin-D1. CD21 immunohistochemistry highlights follicular dendritic cells within follicles, which are arranged in a peripheral pattern imparting a characteristic "hollowed out" appearance.[44] The Ki-67 proliferative index is low (<20%). Histologic transformation to large-cell lymphoma has been reported, but this phenomenon is far less likely than in nodal FL.[47,48]

Similar to its nodal counterpart, DFL harbors t(14;18)(q32;q21)(IGH/BCL2). However, Takata et al,[49] in a large study analyzing gene expression, noted that the pattern of gene expression in DFL more closely resembles that of gastric MALT lymphomas rather than nodal FL. This study showed frequent upregulation of *CCL20*, *CCR6*, and *MAdCAM-1* in DFL and gastric MALT, which were downregulated in nodal FL.

DFL is associated with an excellent prognosis, showing a 5-year overall survival of 100%.[50–52] Tari et al[52] suggested that a "watch and wait" approach is appropriate for the treatment of DFL; the overall survival rate approaches 100%.[48,51] In our institution, we frequently use endoscopic clips as fiducials for radiotherapy of localized disease.[53]

T-Cell Lymphoma

Intestinal T-cell lymphomas account for 5% of all GI lymphomas.[7] The revised 2017 WHO classification of hematolymphoid tumors[9] has recognized the following 4

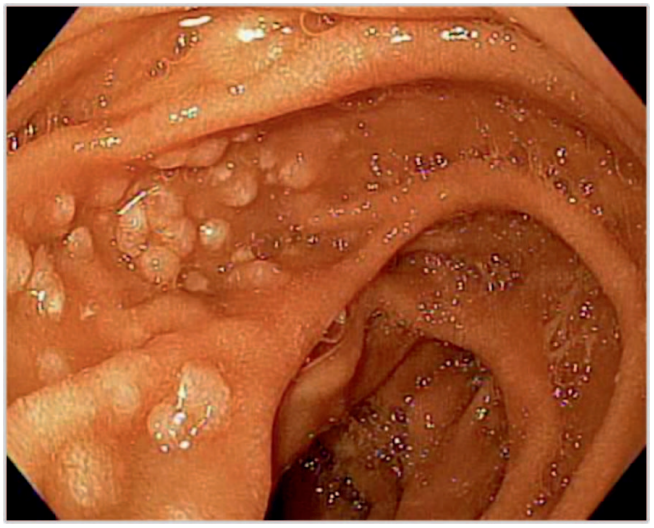

Figure 6. *Duodenal-type follicular lymphoma (DFL). Endoscopic presentation of DFL demonstrating multiple small mucosal polyps within the distal duodenum.*

distinct entities: (1) enteropathy-associated T-cell lymphoma, (2) monomorphic epitheliotropic intestinal T-cell lymphoma, (3) indolent T-cell lymphoproliferative disorder of the GI tract, and (4) intestinal T-cell lymphoma, not otherwise specified.

Enteropathy-Associated T-Cell Lymphoma.—EATL is defined as a neoplasm derived from intraepithelial T cells that manifest in individuals with celiac disease. Most patients harbor the human leukocyte antigen–DQ2 or human leukocyte antigen–DQ8 genotype, which are strongly associated with celiac disease. Symptomatology is nonspecific and similar to that of celiac disease, including weight loss, diarrhea, and abdominal discomfort. Lack of response to a gluten-free diet (refractory celiac disease) is also seen.[54]

Microscopically, EATL is seen in a diffuse distribution with associated surface mucosal ulceration. The neoplastic lymphoid cells are composed of medium to large atypical lymphocytes displaying significant cytologic atypia and varying degrees of nuclear membrane irregularities and prominent nucleoli with pale-to-clear cytoplasm. Numerous large cells with pleomorphic and anaplastic features are also commonly encountered. The background nonneoplastic lymphoid population is heterogenous and polymorphic, including numerous small lymphocytes, eosinophils, plasma cells, and histiocytes (Figure 8, A). Background spotty necrosis is usually present. Epithelial invasion by neoplastic lymphocytes may be prominent. The adjacent uninvolved intestinal mucosa may show histologic features characteristic of celiac disease, including intraepithelial lymphocytosis, villous blunting, crypt hyperplasia, and increased lymphoplasmacytic infiltration of the lamina propria.

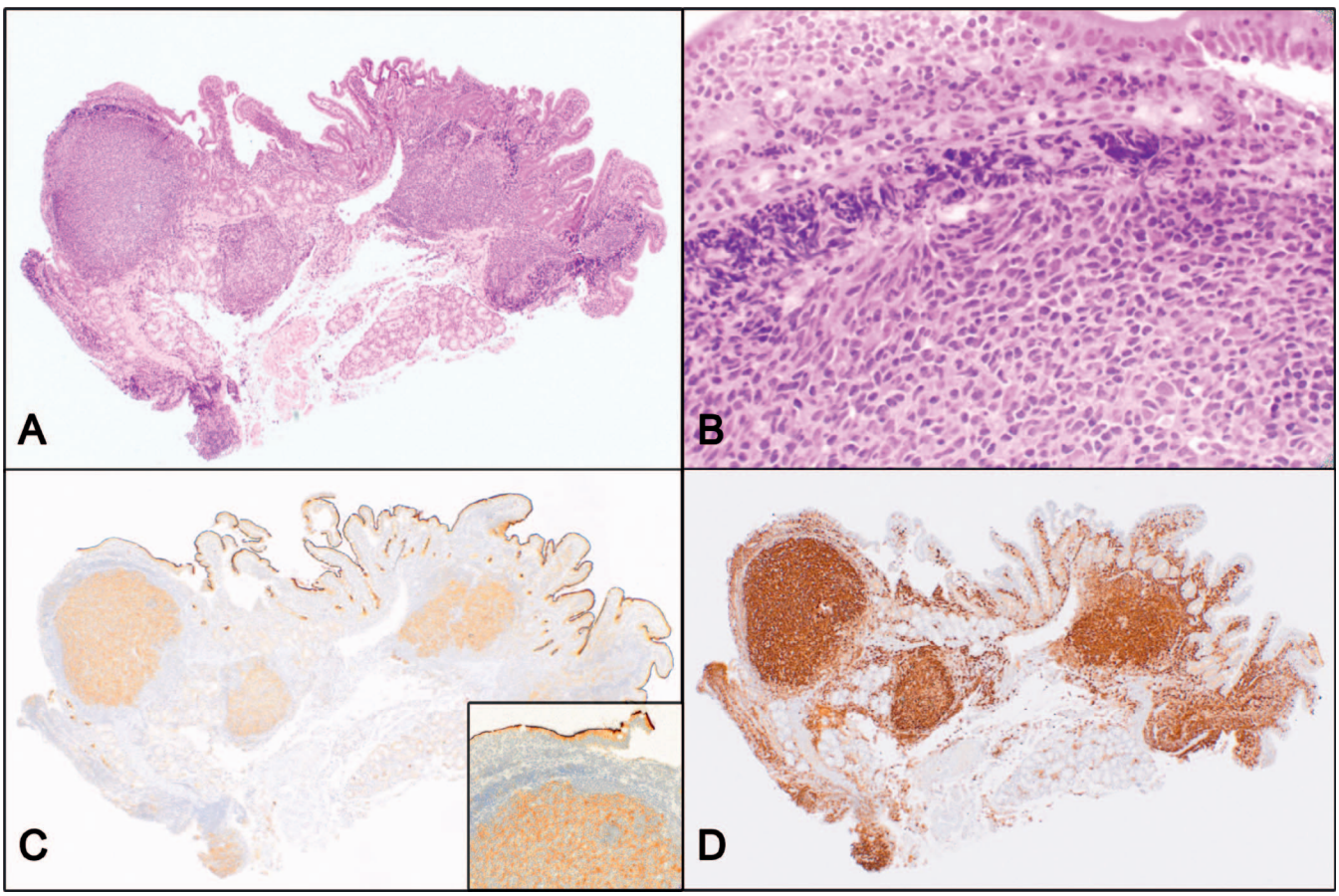

Figure 7. *Duodenal follicular lymphoma. A, The lamina propria is expanded by neoplastic follicles. B, Follicles are predominantly composed of centrocytes and rare background centroblasts. C, The neoplastic follicles are positive for CD10 membrane stain (inset) and (D) BCL-2 (original magnifications ×20 [A, C, and D] and ×200 [B and C inset]).*

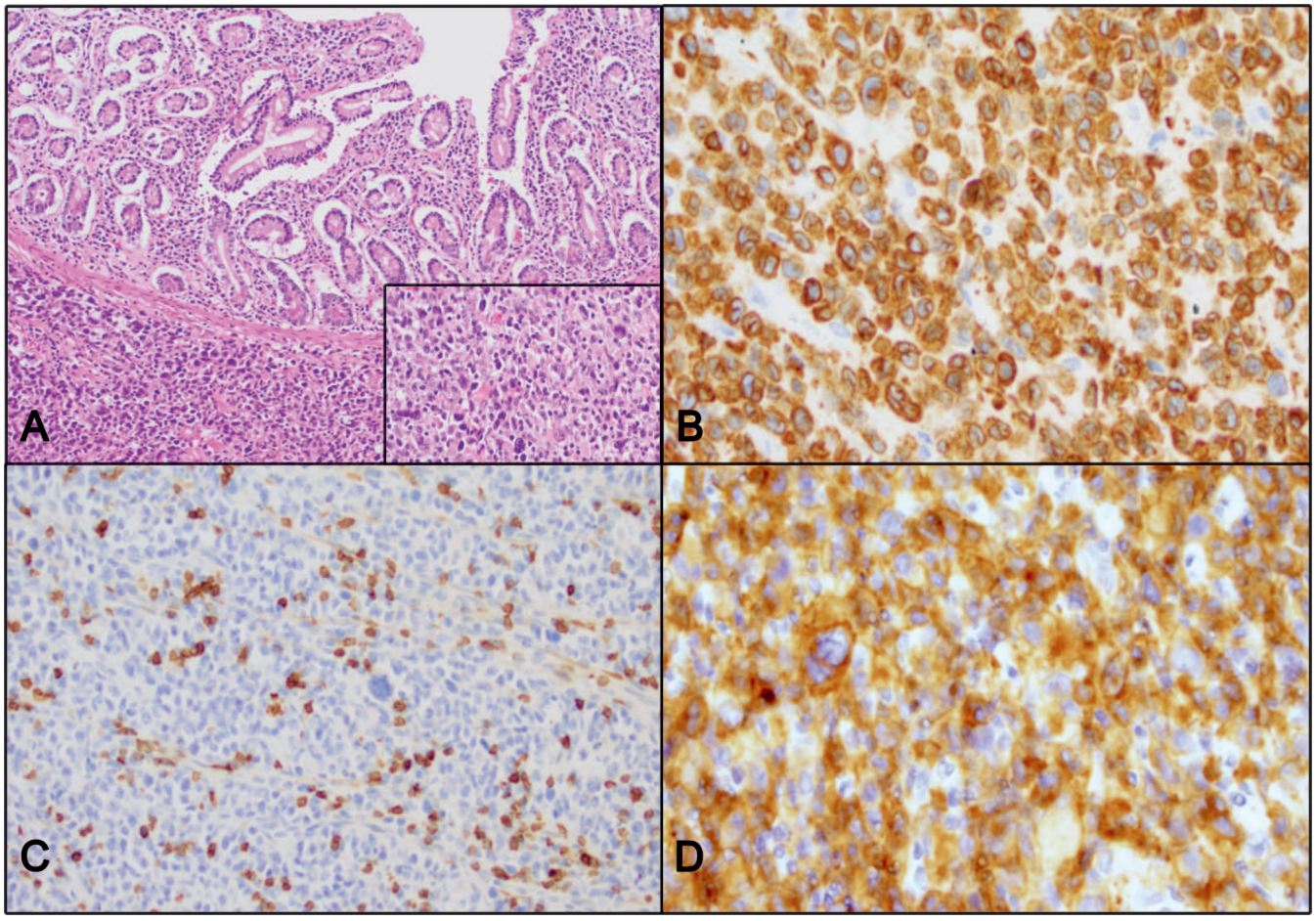

Figure 8. *Enteropathy-associated T-cell lymphoma. A, Sheets of large cells with numerous scattered pleomorphic and anaplastic forms (inset). B, Lymphoma cells are CD3 positive, and (C) CD5 negative. D, CD30 is positive in large anaplastic cells (original magnifications ×100 [A], ×200 [B and C], and ×400 [A inset and D]).*

Immunophenotyping shows neoplastic lymphoid cells express CD3, CD7, CD103, and cytotoxic granule proteins, including TIA-1, perforin, and granzyme-B. Lymphoma cells are typically negative for CD5, CD4, CD8, and CD56 (Figure 8, B through D). Alpha/beta T-cell receptor (TCR) expression is more common, suggesting alpha/beta phenotype. The Ki-67 proliferative index is high (>50%).

Genetic abnormalities identified in EATL include gain of 9q34 and deletion of 16q12.1.[55] Prognostic factors are not well established, and the clinical outcomes are unfavorable.

Monomorphic Epitheliotropic T-Cell Lymphoma.—Monomorphic epitheliotropic intestinal T-cell lymphoma, formerly designated EATL type II, is also derived from intraepithelial T cells. In contrast to EATL, there is no clear association with celiac disease or human leukocyte antigen haplotypes.[55] The disease shows a higher prevalence among Asian and Hispanic populations. The small intestine is the most common site of involvement with jejunum (73%) predominating, followed by ileum (27%).[56] Clinical manifestations are nonspecific and include weight loss, abdominal pain, diarrhea, perforation, and obstruction.

Microscopic examination shows a diffuse transmural lymphoid infiltrate with accompanying mucosal ulceration. Epitheliotropism by neoplastic lymphoid cells is often striking. The lymphoma cells are small to medium in size with dark to finely dispersed chromatin, inconspicuous nucleoli, and moderate amounts of clear cytoplasm, imparting a monotonous (monomorphic) appearance (Figure 9, A and B). In contrast to EATL, pleomorphic or anaplastic morphologic features, as well as a polymorphic nonneoplastic inflammatory background, are not characteristic.

Immunophenotypically, the neoplastic lymphoid cells are positive for CD3, CD8, CD56, and TIA-1, and negative for CD5 (Figure 9, C through E). Gamma/delta TCR expression predominates, suggesting gamma/delta TCR origin.[57] A subset of cases (9%) may coexpress CD4 and CD8.[58] The Ki-67 proliferative index is variable but typically greater than 50%.

Clonal *TCR* rearrangements are detected in more than 90% of the cases.[1,9,58] Activating mutations in *STAT5B* are the most common genetic aberrations found, followed by *JAK3* and *GNAI2*.[59] In addition, Roberti et al,[60] through whole-exome sequencing studies, demonstrated frequent alterations in *SETD2* tumor suppressor genes.

Indolent T-Cell Lymphoproliferative Disorder of the GI Tract.—The WHO classification defines indolent T-cell lymphoproliferative disorder as an indolent, nonepitheliotropic, clonal T-cell lymphoproliferative disorder that involves the mucosa of any portion of the GI tract but is most commonly encountered in the small and large intestine. Clinically, patients may present with chronic,

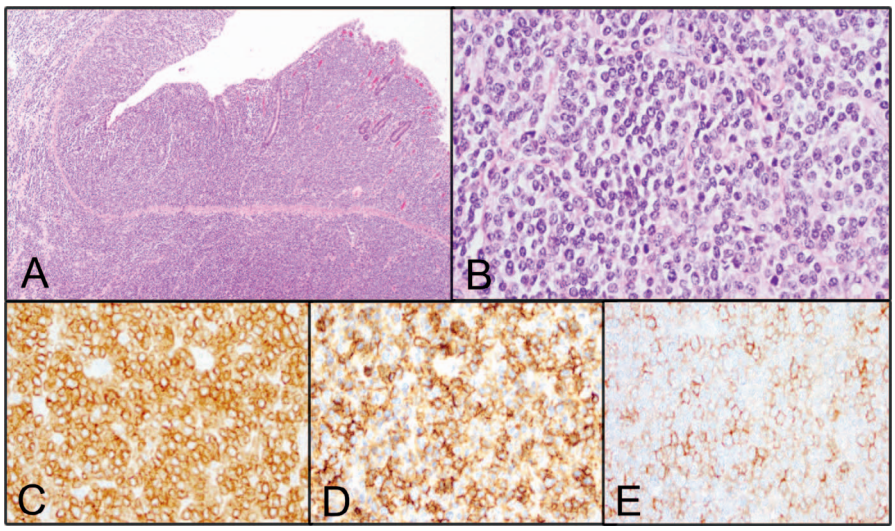

Figure 9. *Monomorphic epitheliotropic T-cell lymphoma. A, Diffuse transmural infiltrate composed of small mature lymphoid cells. B, Monotonous cells with clear cytoplasm. C, By immunohistochemistry, neoplastic lymphoid cells are diffusely positive for CD3, (D) CD8, and (E) CD56 (original magnifications ×50 [A] and ×200 [B through E]).*

nonspecific symptoms, such as weight loss, abdominal pain, vomiting, and diarrhea. Endoscopic findings include mucosal thickness, hyperemia, polypoid lesions, and superficial erosion.[61,62]

Microscopically, the lamina propria is expanded by small lymphocytes with a monotonous appearance causing crypt displacement without overt architectural destruction. The infiltrate is composed of small lymphocytes with round or slightly irregular nuclei, inconspicuous nucleoli, and scant, pale cytoplasm. Nonnecrotizing granulomas may also be seen. Intraepithelial lymphocytes are not increased but may be focally seen within crypts.

On immunophenotyping, the neoplastic lymphoid cells are positive for mature T-cell markers, including CD3, CD2, CD5, and CD7, but negative for CD56 and CD103. The neoplastic lymphoid cells may express CD4 or CD8 and coexpress TIA-1. Of note, a subset of cases with double negativity (CD4– and CD8–) has been reported that exhibits a more aggressive clinical course.[9,63] Ki-67 proliferation rate is low (<10%).

Although all cases have clonal rearrangements of the *TCR* gene, additional genetic abnormalities are not well defined. Sharma et al.[64] identified 4 of 5 cases of CD4 positive phenotype indolent T-cell lymphoproliferative disorder with a *STAT3-JAK2* fusion, which is described as the first recurrent genetic abnormality in indolent T-cell lymphoproliferative disorder.

Intestinal T-Cell Lymphoma, Not Otherwise Specified.—As the name implies, intestinal T-cell lymphoma, not otherwise specified is a diagnosis of exclusion and refers to a heterogeneous group of T-cell lymphomas that lack the morphologic and phenotypic criteria of the above entities. Thus, owing to its heterogeneity, it is believed that nodal and extranodal peripheral T-cell lymphomas, some of which represent primary GI lymphomas, are best classified within this group, including aggressive primary intestinal T/NK-cell lymphomas[9]. These neoplasms typically follow an aggressive clinical course, including widespread disease at presentation.[65]

MALIGNANT LYMPHOMAS OF THE LARGE INTESTINE

Lymphomas involving the large intestine are uncommon, accounting for 10% to 20% of all GI tract lymphomas and 0.2% of all colorectal malignancy.[5,11,66] The majority of cases are of B-cell lineage; colorectal T-cell lymphomas are rare. Prevalence of involvement includes cecum (57%), ascending colon (18%), transverse colon (10%), descending colon (5%), and rectosigmoid colon (10%). Distal colonic, rectal, and anal involvement are more commonly encountered in patients with HIV-related immunodeficiency.[11,67] The most common lymphoma subtypes present in the large intestine are MALT lymphoma, MCL, DLBCL, Burkitt lymphoma, and EBV-MCU; the latter is previously discussed in the lymphomas of the esophagus section.

The clinical presentation of colorectal lymphomas is variable and nonspecific and includes abdominal pain, rectal bleeding, diarrhea, and the presence of abdominal mass forming lesion(s). Lymphoma associated with inflammatory bowel disease is controversial; some studies describe a small but significant increase in the risk of lymphoma related to therapy with immunomodulators and anti–tumor necrosis factor agents. However, inflammatory bowel disease, independent of therapeutical agents, does not appear to be a significant risk factor for the development of lymphoma.[68]

Endoscopically, neoplasms may present as solid lesions with ulceration, mimicking colorectal carcinoma, or with polyposis (lymphomatous polyposis).

Mantle Cell Lymphoma

MCL is defined as a mature B-cell neoplasm with overall aggressive biologic features. MCL is estimated to represent less than 4% of primary GI lymphomas.[69] Overall, GI involvement by MCL is variable, with large studies reporting 30% to 50% incidence in MCL patients.[70–72] In keeping with the high prevalence of secondary GI involvement by MCL, some studies have demonstrated a positive correlation between homing receptor expression on neoplastic lymphoid cells and GI involvement.[73]

MCL in the GI tract may characteristically present as multiple mucosal polyps involving segments of the luminal intestine, also known as multiple lymphomatous polyposis, a term describing the unique endoscopic and clinical appearance[74] (Figure 10). These findings are because of expanded or enlarged mucosal lymphoid mantle zones, which take the form of polypoid mucosal lesions that may

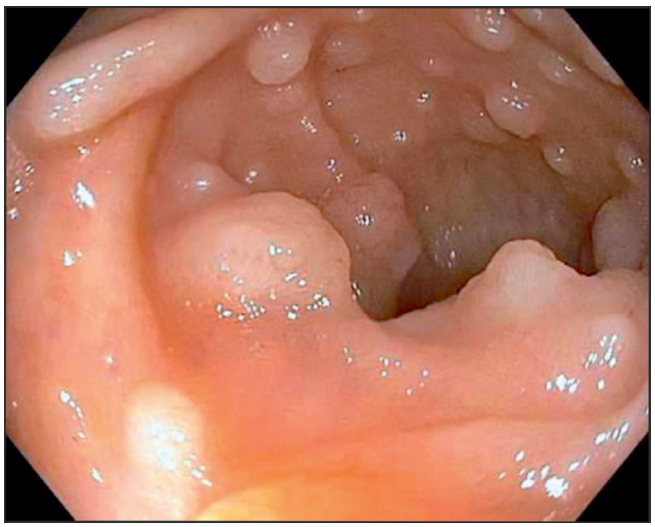

Figure 10. *Endoscopic imaging showing multiple intestinal polyps and nodules, which were biopsy-proven mantle cell lymphoma.*

mimic adenomatous polyposis. Multiple lymphomatous polyposis may be multifocal or diffuse. Nevertheless, it is important to note that multiple lymphomatous polyposis is not specific for MCL and may be seen in other lymphoproliferative neoplasms, including FL and MALT lymphoma.[70,75] Other endoscopic patterns include ulcerated mucosa, solitary lesions, and mucosal protrusion.[70] However, random biopsies of the macroscopically normal colon may also uncover the presence of MCL involvement on microscopic examination.

Microscopic features include diffuse infiltration of monotonous lymphoid cells with irregular nuclear borders, inconspicuous nucleoli, and scant cytoplasm (Figure 11, A). The small-to-medium size neoplastic cells may be arranged in a nodular and/or mantle-zone pattern, similar to their nodal counterparts. Surrounding crypts may be affected by lymphocytic infiltration; however, lymphoepithelial lesions are not characteristic.

Immunophenotyping shows that the neoplastic lymphoid cells are B cells expressing CD20, CD43, and cyclin-D1 with aberrant coexpression of CD5 in most cases; neoplastic cells are negative for CD10, BCL-6, HGAL, LMO2, and CD23 (Figure 11, B through D). SOX-11 is also a sensitive marker, particularly in cyclin-D1–negative cases and aggressive variants, including pleomorphic and blastoid variants, which may show aberrant phenotypes.[9] Similar to nodal MCL, genetic studies have shown the characteristic t(11;14)(q13;q32) translocation involving the *IgH* and *CCND1* gene is present in all cases, except cyclin-D1–negative cases.

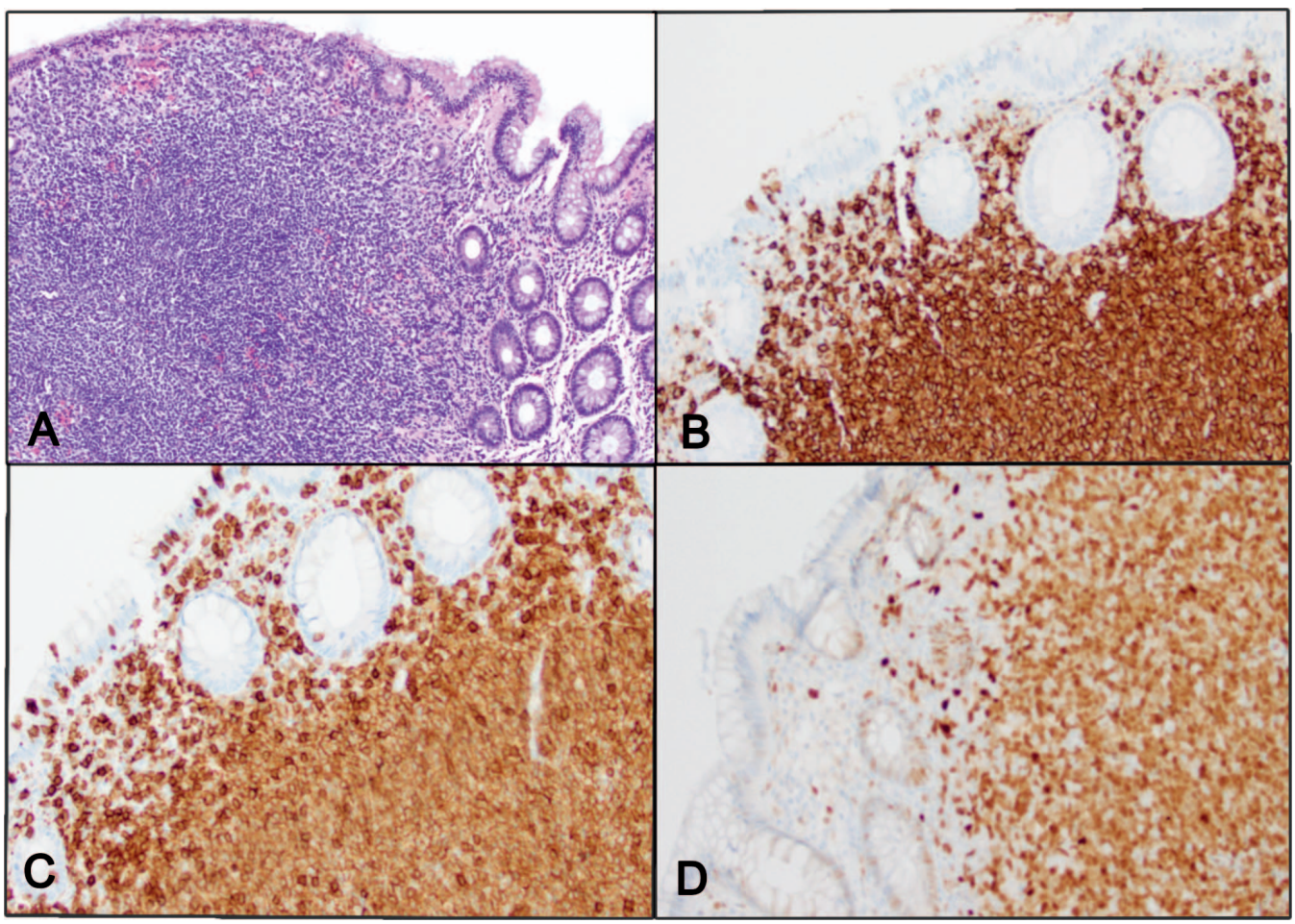

Figure 11. *Mantle cell lymphoma. A, Colonic mucosa showing a diffuse infiltrate of small mature atypical lymphoid cells. Lymphoma cells are positive for (B) CD20, (C) CD5, and (D) Cyclin-D1 (original magnifications ×100 [A] and ×200 [B through D]).*

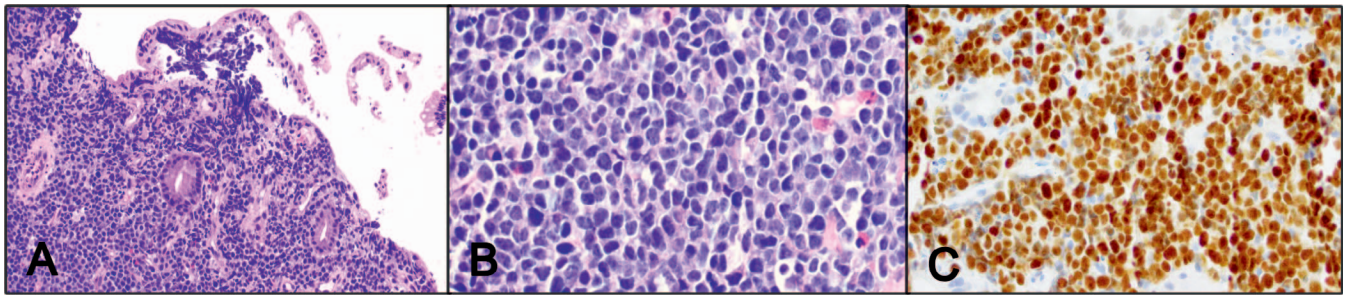

Figure 12. *Burkitt lymphoma. A, Colonic mucosa showing a diffuse lymphoid infiltrate comprised of medium sized neoplastic lymphocytes with blastoid-appearing nuclei and characteristic "squared-off" nuclear borders (B). C, Lymphoma cells are strongly positive for MYC (original magnifications ×200 [A] and ×400 [B and C]).*

Burkitt Lymphoma

Burkitt lymphoma is a predominantly extranodal aggressive high-grade B-cell lymphoma harboring *MYC* translocations.[9] Three distinct epidemiologic clinical variants are recognized as follows: endemic, sporadic, and immunodeficiency-associated. Association with EBV and HIV infection is well recognized. The most common extranodal site involved by nonendemic Burkitt lymphoma is the GI tract, followed by the peritoneum, kidney, ovary, and testicle. The sporadic variant commonly presents within the abdomen (60%–80%), particularly in the ileocecal region; the endemic and immunodeficiency-associated types less commonly involve the GI tract. Burkitt lymphoma accounts for only 5% of all primary GI tract non-Hodgkin lymphoma.[1,76]

Microscopic examination demonstrates a diffuse lymphoid infiltrate composed of medium-sized neoplastic lymphocytes with vesicular chromatin and scant amphophilic cytoplasm with frequently squared-off borders. Neoplastic cells are characteristically monotonous in appearance, and background reactive lymphoid cells are few. Scattered and admixed histiocytes engulfing cellular debris, imparting the characteristic "starry-sky" appearance, may be prominent, and mitotic figures and apoptotic bodies are easily identified (Figure 12, A and B).

Immunophenotyping shows neoplastic CD20-positive lymphoid cells with diffuse and strong expression of germinal center markers, including CD10 and BCL-6. BCL-2 is characteristically negative. The Ki-67 proliferation index is essentially 100%. High MYC protein expression by immunohistochemistry is common[77] (Figure 12, C). The paucity of reactive CD3+ T cells in the background is also a hallmark feature. EBV is seen in approximately one-third of all HIV-associated cases as detected by in situ hybridization.

Genetic studies classically demonstrate *MYC* translocation involving band 8q24.2 translocated to the *IGH* region on chromosome 14q32, t(8;14)(q24;q32); a subset of cases involve the *IGK* locus on 2p12 [t(2;8)], or *IGL* locus on 22q11 [t(8;22)].[9] Cases that lack detectable *MYC* rearrangements, comprising approximately 10% of cases, may show chromosome 11q alteration, which is now recognized as a provisional entity in the recently revised 2017 WHO and has an association with immunosuppression.[9]

SUMMARY

Herein, we have emphasized the high prevalence of extranodal GI lymphomas and reviewed selected lymphoproliferative neoplasms based on their most commonly encountered locations within the luminal GI tract. It is essential to recognize the various lymphoid neoplasms within the GI tract in conjunction with the clinical and endoscopic features as GI biopsies are among the most common specimens in academic and private pathology practices. Recognition of these lymphomas' morphology, immunophenotype, and genetic/molecular features provides appropriate clinical management and treatment.

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