Update on Gastrointestinal Lymphomas

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Herein we review the following selection of gastrointestinal lymphomas: monomorphic epitheliotropic intestinal T-cell lymphoma; indolent T-cell lymphoproliferative disorder of the gastrointestinal tract; intestinal T-cell lymphoma, not otherwise specified; duodenal-type follicular lymphoma; and Epstein-Barr virus–positive mucocutaneous ulcer. Definitions reflect the 2016 revision of the World Health Organization classification of lymphoid neoplasms. Clinical, morphologic, and immunophenotypic characteristics of each entity are emphasized.

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The gastrointestinal (GI) tract is the most common extranodal site of involvement for non-Hodgkin lymphomas, and atypical lymphoid infiltrates in GI biopsies are a common challenge for pathologists who see such biopsies in routine practice. In addition, there are numerous inflammatory and reactive conditions in the GI tract that can give rise to, mimic, or mask lymphomas. As elsewhere, the GI tract is home to a diverse group of lymphoid neoplasms, most of which are of B-cell lineage, with diffuse large B-cell lymphoma being the most common. Important T-cell lineage lymphomas also occur in GI locations, however, and some are related to underlying GI diseases or treatment. Many of these lymphomas have an aggressive clinical course, but others are indolent and may not always require treatment. For the practicing pathologist, knowledge of these entities can facilitate appropriate treatment and, equally importantly, avoid overtreatment of those patients who do not need aggressive therapy. The most recent iteration of the World Health Organization (WHO) classification of hematolymphoid neoplasms has introduced some important changes to the schema used to categorize lymphomas that affect the GI tract, and several T-cell and natural killer cell lymphomas have been reclassified and/or introduced. Below we describe a selection of GI lymphomas and lymphoproliferations whose proper diagnosis has important clinical ramifications. An emphasis is placed on less common, but often more diagnostically challenging, T-cell entities and their diagnostic criteria and classification as outlined by the updated WHO classification scheme. In addition, 2 B-cell entities with relatively indolent behavior are covered, one an Epstein-Barr virus (EBV)–related proliferation and the other a form of follicular lymphoma (FL) restricted to the GI tract with indolent behavior.

MONOMORPHIC EPITHELIOTROPIC INTESTINAL T-CELL LYMPHOMA

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) was formerly known as “type II” enteropathy-associated T-cell lymphoma (EATL). Even in this older classification, it was recognized that the “type II” form of the disease was rarely (if ever) associated with underlying celiac disease/gluten-sensitivity enteropathy. It also was known to have important morphologic and immunophenotypic differences from the “classic” form of EATL. Recognizing these distinctions, the 2016 WHO classification formally separated these 2 entities and now defines MEITL as a primary intestinal T-cell lymphoma that is not associated with celiac disease, and which has characteristic morphology and immunohistochemical features.

Monomorphic epitheliotropic intestinal T-cell lymphoma is the most common primary intestinal T-cell lymphoma occurring in Asia and is more common in people of Hispanic origin. The male to female ratio is approximately 2:1. Patients typically present with nonspecific symptoms, such as abdominal pain, weight loss, nonmalabsorptive diarrhea, GI obstruction, perforation, and bleeding. The disease often spreads diffusely within the intestinal mucosa, with or without tumefactive lesions, in a pattern that contrasts with EATL, which is often associated with large and ulcerative tumors that may perforate the intestine. Ulceration may be present in MEITL, and involvement of the mesenteric lymph nodes is common. The small intestine is most often affected, with occasional cases involving the stomach and colon.

Monomorphic epitheliotropic intestinal T-cell lymphoma is a clinically aggressive disease, with frequent early dissemination and a median survival of 7 months.

Morphologically, the small intestine has abnormal villous architecture with broad villi expanded by the tumor cells in the lamina propria. Of note, background inflammation, including lamina propria lymphoplasmacytosis and, notably, intraepithelial lymphocytes in nonepithelial areas of the type seen in celiac disease, is conspicuously absent. In the diseased areas of the intestine and adjacent mucosa, however, the neoplastic lymphocytes have prominent and often sheetlike epitheliotropism, leading to disruption of the crypt and surface epithelium (Figure 1, A and B). Cytologically, they are intermediate in size, with a uniform,
monotonous appearance; the nuclei are round, typically with regular contours and scant cytoplasm. As opposed to EATL, pleomorphism is not typical.

The lymphoma cells are positive for CD3, CD8, CD56 (Figure 1, C and D), and MATK in most cases, but negative for CD4, CD30, and often CD5. Approximately 20% of cases show aberrant expression of CD20, a feature that can potentially lead to diagnostic confusion with B-cell entities, such as diffuse large B-cell lymphoma or Burkitt lymphoma. By contrast, classic EATL is usually negative for CD4, CD8, CD56, and MATK, with variable CD30 positivity. The lymphoma cells in MEITL are often γ-δ type, whereas those in classic EATL are α-β T cells. Some cases of MEITL, however, are T-cell receptor null/silent. Mutations in STAT5B and SETD2 have been described in the MEITL cases of γ-δ derivation.

Clinically, this disease presents in adulthood and tends to occur more commonly in men, and it can involve any part of the GI tract. It occurs in children occasionally. No cases have been reported in association with celiac disease. In a recent study in which the disease was described, patients in 4 of 10 cases carried a diagnosis of inflammatory bowel disease (IBD; ie, Crohn disease or ulcerative colitis), with variable treatments, including 5-aminosalicylic acid, infliximab, 6-mercaptopurine, mycophenolate mofetil, methotrexate, and anti–tumor necrosis factor inhibitors (adalimumab and certolizumab). However, because many of the histologic features may overlap with IBD and the study authors were not able to review the original material, it is uncertain whether these patients truly had preceding IBD, or whether the lymphoproliferative disorder itself had been initially misdiagnosed as IBD.

Presenting signs and symptoms are nonspecific and include abdominal pain, weight loss, dyspepsia, vomiting, and diarrhea. The clinical course is chronic and relapsing, with rarely reported disseminated disease, including bone marrow and peripheral blood involvement, usually after many years.

The disease most often localizes in the small bowel and colon; however, all sites in the GI tract may be affected.
including the esophagus and oral cavity. By endoscopy, the affected GI mucosa is thickened with prominent folds, nodularity, and/or polyps. The surface can be hyperemic with superficial erosions. Some patients may have regional (eg, mesenteric) lymphadenopathy.

Microscopically, the lamina propria is expanded by a dense and monotonous lymphoid infiltrate. The mucosal crypts or glands are displaced and often distorted, but not destroyed. Although focal epitheliotropism may be seen, it is not a prominent feature. Cryptitis and crypt abscesses are absent, but granulomas may be focally present, potentially mimicking those seen in Crohn disease. The lymphoid infiltrate is composed of small, mature lymphocytes with round nuclei and regular nuclear contours (Figure 2).

The lymphoma cells are mature T cells with expression of CD2, CD3, CD5, CD4, or CD8, and variable expression of CD7. CD56 expression is notably absent, distinguishing this entity from MEITL. All reported cases have shown expression of TCRβ, with no cases showing TCRγ. The Ki-67 proliferative rate is extremely low (<10%). Clonal rearrangements of TCR (either γ or β) have been observed in all cases, and all have been negative for EBV by in situ hybridization (EBER), distinguishing this entity from extranodal natural killer/T-cell lymphoma of nasal type, which can involve the GI tract.

**INTESTINAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED**

Intestinal T-cell lymphoma, not otherwise specified, is not a specific disease entity but a term used to denote a heterogeneous group of T-cell lymphomas occurring in the GI tract with insufficient evidence to diagnose EATL or MEITL, because of incomplete clinical information, inadequate biopsy, or insufficient immunophenotypic data. Additionally, a portion of cases may actually be peripheral T-cell lymphoma, not otherwise specified, with GI involvement. This entity has an aggressive clinical course, with several reported cases showing widespread disease at presentation. In one small collection of cases, most involved the colon. No reported cases have a history of celiac disease at presentation.

The morphologic and immunohistochemical characteristics are heterogeneous, because this term likely encompasses multiple disease entities.

**DUODENAL-TYPE FL**

Follicular lymphoma is a common type of B-cell lymphoma composed of cells with follicle center (germinal center) immunophenotype. In its systemic form, it can involve any tissue and be nodal and/or extranodal, although purely extranodal presentations are rare. The GI tract is a common site of involvement in the systemic form of the disease, particularly when retroperitoneal and/or mesenteric disease is not strictly graded in the same manner as nodal FL, they do not express activation-induced cytidine deaminase. The indolent behavior of duodenal-type FL may raise the question as to whether it is neoplastic at all, but the disease harbors the same t(14;18)(q32;q21) translocation between the IGH and BCL2 genes seen in conventional FL. The duodenal type, however, seems to have fewer additional genetic aberrations than conventional FL, and some evidence suggests that its gene expression profile overlaps with that of extranodal marginal

undergoing upper endoscopy for other unrelated reasons, such as dyspepsia or suspected gastroesophageal reflux. The disease is usually found in the small intestine, most often with duodenal involvement in the second portion (D2), and also affects the more distal small intestine in many cases. The clinical course is indolent, with excellent long-term survival, even when disease recurs in the intestine. A small subset of patients (<10%) progress to nodal disease. A variety of therapies have been used, but for most patients treatment is not likely to be necessary and a watch-and-wait approach is reasonable.

The only way to be absolutely certain of the diagnosis of duodenal-type FL (versus GI involvement by conventional FL) is to perform clinical staging (eg, imaging, bone marrow biopsy), to rule out systemic disease and/or intestinal involvement by mesenteric or retroperitoneal disease.

Morphologically, well-circumscribed round neoplastic follicles are present in the mucosa and submucosa, creating small nodules and mucosal polyps corresponding to the endoscopic appearance. The neoplastic follicles are similar to those seen in nodal disease and are composed of a uniform population of centrocytes, often with nuclear clefts, and only rare centroblasts (Figure 3, A). Although the disease is not strictly graded in the same manner as nodal FL, it corresponds to low-grade (grades 1–2) disease in that scheme. The lymphoma cells often infiltrate outside of the neoplastic follicles into the surrounding lamina propria, although this is usually most easily appreciated using immunohistochemistry.

The lymphoma cells show an immunophenotype similar to that of nodal FL, with expression of CD20, CD10 (Figure 3, B), Bcl-2, and BCL6. The Ki-67 proliferative rate is low. As opposed to systemic FL, they do not express activation-induced cytidine deaminase. The indolent behavior of duodenal-type FL may raise the question as to whether it is neoplastic at all, but the disease harbors the same t(14;18)(q32;q21) translocation between the IGH and BCL2 genes seen in conventional FL. The duodenal type, however, seems to have fewer additional genetic aberrations than conventional FL, and some evidence suggests that its gene expression profile overlaps with that of extranodal marginal

**Figure 2. Nondestructive lymphoid infiltrates in the gastrointestinal (GI) tract in a case of indolent T-cell lymphoproliferative disorder of the GI tract (hematoxylin-eosin, original magnification ×40). Photomicrograph courtesy of Serhan Alkan, MD.**

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zone lymphomas of mucosa-associated lymphoid tissues (MALT lymphomas).

EBV-POSITIVE MUCOCUTANEOUS ULCER

An entity recognized only recently, EBV-positive mucocutaneous ulcer is an immunosuppression or age-related proliferation of EBV-positive atypical large B cells affecting skin or mucous sites, possibly related to local trauma or inflammation. It has an indolent clinical course and may spontaneously regress in some cases. The disease occurs in the setting of immunosuppression that leads to inadequate immune surveillance for EBV, including that caused by advanced age (median age >70 years), human immunodeficiency virus infection, or iatrogenic origins, such as in patients with autoimmune or inflammatory conditions and solid organ transplant recipients. Most patients have a favorable clinical course, with nearly all reported cases showing resolution following a reduction of immunosuppressive therapy. Other interventions, such as local radiation or chemotherapy, may be necessary for those patients in whom the immunosuppression cannot be reversed, such as in the elderly.

Involved mucosal surfaces are ulcerated with underlying dense, bandlike infiltrate of atypical cells, necrotic debris, and underlying small T cells (Figure 4, A). Plasma cells are present to a varying degree; they may be prominent and may be light chain-restricted. A substantial number of large atypical lymphocytes are present within the necrosis, sometimes in dense sheets. The large cells resemble those

Figure 3. Atypical follicle in the duodenum (hematoxylin-eosin, original magnification ×200 [A]; CD10, original magnification ×200 [B]).

Figure 4. Epstein-Barr virus–positive mucocutaneous ulcer with ulceration and prominent lymphoid infiltrate including Reed-Sternberg–like cells (hematoxylin-eosin, original magnifications ×20 [A]; and ×400 [B]).
seen in diffuse large B-cell lymphoma or Hodgkin lymphoma, with large pleomorphic nuclei and prominent nucleoli (Figure 4, B). In the setting of iatrogenic immunosuppression for a solid organ transplant, this is a type of posttransplantation lymphoproliferative disorder.30 The distinction between diffuse large B-cell lymphoma and EBV-positive mucocutaneous ulcer is important in the posttransplantation setting because EBV-positive mucocutaneous ulcer has an indolent course. The lesions are typically well circumscribed at the base and surrounded by a rim of reactive lymphocytes, which are mainly T cells.

The large, atypical lymphocytes are positive for PAX5, OCT2, MUM1, CD30, and EBER, and negative for CD10 and BCL-6. CD79a and BOB1 are often positive with variable expression of CD15 and CD20.23 Surrounding T cells are EBER negative and express normal pan–T-cell markers, including CD3. It is especially important to distinguish these cases from classical Hodgkin lymphoma, which is exceedingly rare in the tubular GI tract.

**SUMMARY**

Above we have described a selection of lymphoid neoplasms arising in the GI tract with diverse clinical, morphological, and immunophenotypic features. Some are aggressive, requiring equally aggressive chemotherapeutic regimens, whereas others do not require treatment at all. To make these diagnoses accurately, one needs complete access to and understanding of all clinical, morphologic, and immunophenotypic data.

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