Lymphoproliferative Disorders of the Gastrointestinal Tract

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The gastrointestinal (GI) tract is a site of continual exposure to foreign antigens. As a result, it contains prominent organized lymphoid tissue that has the potential to give rise to a wide variety of lymphoproliferative disorders. Physiologic lymphoid tissue is present in the upper aerodigestive tract in the Waldeyer ring region, as well as in the small and large intestines, especially prominent in the terminal ileum and appendix. Although the esophagus and stomach are not associated with prominent lymphoid tissue under normal conditions, the stomach can develop acquired mucosa-associated lymphoid tissue (MALT) under pathologic conditions, the prototypical example being the development of lymphoid follicles in response to Helicobacter pylori infection. Lymphoid tissue of the GI tract, whether physiologic or acquired, includes mucosal lymphoid aggregates, intraepithelial lymphocytes, and lamina propria lymphoid cells. Together, these contain a spectrum of cell types, including B cells, plasma cells, and a wide variety of T-cell subsets, including helper T cells, cytotoxic T cells, and γδ T cells. This diversity of normal lymphoid elements is reflected in the wide spectrum of lymphoproliferative disorders than can involve the GI tract.

The most common specimen encountered by anatomic pathologists for the diagnosis of GI lymphoproliferative disorders is the endoscopic biopsy. These have the potential to lead to difficulty in diagnosis because of limited sampling as well as the crush artifact often encountered in small biopsies because of the fragility of lymphoid cells. This difficulty can be compounded by the wide variety of clinicopathologic entities that can show overlapping morphologic and immunophenotypic features. When dealing with these biopsies, it is important to obtain as much clinical information as possible, including the endoscopic appearance and distribution of the lesions. Molecular genetic analysis for clonality can be very helpful in the diagnosis of lymphoproliferative disorders, but these results must always be interpreted in the context of morphologic and clinical features.

MALT LYMPHOMA

A variety of small B-cell lymphomas can involve the GI tract, the most common being extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). These can involve the entire length of the GI tract, the stomach being the most common site of involvement.

MALT lymphomas can show a wide morphologic spectrum. Similar to other lymphomas involving the GI tract, they are characterized by a diffuse infiltration of the lamina propria. MALT lymphomas start as expansion of the marginal zone around secondary lymphoid follicles, typically expanding the interfollicular area and replacing normal glandular tissue (Figure 1, A). Residual reactive secondary follicles are often present, surrounded by the lymphomatous infiltrate. These follicles may be intact, but they are often infiltrated and overrun by the lymphoma, in a process known as follicular colonization. The areas of residual disrupted germinal center cells may be appreciated on morphologic examination based on the presence of tingible body macrophages and centroblasts, or may only be appreciated by immunohistochemistry. A CD21 stain often highlights disrupted follicular dendritic cell meshworks, and disrupted collections of germinal center B cells may be highlighted on stains for BCL6 or CD10. MALT lymphomas

Conclusions.—Interpretation of lymphoid infiltrates in gastrointestinal biopsies requires synthesis of morphologic, immunophenotypic, molecular genetic, and clinical information. Knowledge of indolent lymphoproliferative disorders that may mimic aggressive lymphomas will help in preventing misdiagnoses.

often show invasion into the gastric glands, forming lymphoepithelial lesions (Figure 1, B), defined as groups of 3 or more small lymphocytes that invade and destroy part of the gland. However, these are not completely specific for MALT lymphoma and have been described in other lymphomas and reactive infiltrates. Within the stomach, most MALT lymphomas are associated with H. pylori infection, and many cases will regress with H. pylori eradication. Organisms are sometimes detected on hematoxylin-eosin examination, or may require special histochemical stains or immunohistochemistry.

MALT lymphomas can show a wide cytologic spectrum (Figure 1, C and D). The cells are predominantly small, often with irregular nuclei resembling small lymphocytes of the germinal center (centrocyte-like). They often have abundant pale cytoplasm, giving them a monocytoid appearance. Plasmacytic differentiation is common, and tumors can show a range of plasmacytoid small lymphocytes as well as mature plasma cells. The plasmacytoid cells may also contain Dutcher bodies. Scattered large cells resembling centroblasts may also be present.

Several features are useful in the morphologic distinction between MALT lymphoma and reactive lymphoid aggregates, with a spectrum of changes described in the Wotherspoon system for scoring gastric lymphoid infiltrates. This is a 5-tier system based on morphologic features divided into: (1) chronic active gastritis, (2) chronic active gastritis with florid lymphoid follicle formation, (3) suspicious lymphoid infiltrate, probably reactive, (4) suspicious lymphoid infiltrate, probably lymphoma, and (5) MALT lymphoma. The level of suspicion on morphologic examination alone depends on the degree of the small lymphocytic infiltration expanding the lamina propria, and the presence or absence of lymphoepithelial lesions. In morphologically suspicious cases, immunohistochemistry and molecular genetic studies will resolve the diagnosis in most instances.

Immunohistochemistry can be instrumental in distinguishing MALT lymphoma from benign reactive lymphoid infiltrates and from other small B-cell lymphomas. A CD20 stain is commonly helpful in demonstrating the diffuse nature of the B-cell infiltration, distinguishing it from a prominent reactive lymphoid infiltrate in which B cells are predominantly localized to follicles. In cases with plasmacytic differentiation, light chain restriction by κ and λ immunohistochemistry will be very useful in supporting a
diagnosis of lymphoma. However, residual polyclonal plasma cells may be retained in the superficial mucosa, and their presence does not exclude a diagnosis of lymphoma in the underlying lamina propria. A keratin stain may highlight lymphoepithelial lesions. As discussed above, stains for CD21, BCL6, and CD10 often highlight evidence of follicular colonization. Stains for CD20 and light chain restriction can establish a diagnosis of B-cell lymphoma, but MALT lymphoma does not have a specific immunohistochemical marker. It must be distinguished from other small B-cell lymphomas based on negative staining for CD10, BCL6, CD5, cyclin D1, and SOX11 (see below).

Molecular genetic testing for B-cell clonality is useful in cases with borderline morphologic and immunohistochemical features. Using common polymerase chain reaction (PCR) techniques for B-cell clonality, up to 90% of MALT lymphomas will demonstrate a clonal B-cell population. However, molecular genetic findings cannot be used in isolation, because occasional cases of follicular gastritis can show clonal PCR results. Fluorescent in situ hybridization studies for the t(11;18)(q21;q21) translocation can be useful in the diagnosis of MALT lymphoma, but this translocation is only present in approximately 25% of gastric lymphomas. The presence of the t(11;18) strongly predicts for failure of regression following Helicobacter pylori eradication.

Rectal tonsil is a reactive proliferation that can mimic MALT lymphoma because of the formation of endoscopically visible polypoid or nodular lesions. These are expansile lesions that often extend into the submucosa. They typically show a prominent component of reactive lymphoid follicles, often with germinal centers. The predominant localization of B cells to the follicles and a monomorphic medium-sized morphology of Burkitt lymphoma is characterized by a diffuse monomorphic infiltrate of medium-sized cells, often with a prominent component of tingible body macrophages imparting a starry sky appearance on low-power microscopic examination. The nuclei have finely clumped chromatin with multiple small nucleoli, and often show squared-off borders with surrounding cells. However, all of these morphologic features may not be readily appreciated on small endoscopic biopsies with areas of crush artifact. Careful attention to morphologic, immunophenotypic, and molecular genetic features is needed to differentiate between these lymphomas.

**AGGRESSIVE B-CELL LYMPHOMAS**

A variety of aggressive B-cell lymphomas can involve the GI tract, including diffuse large B-cell lymphoma, Burkitt lymphoma, and high-grade B-cell lymphomas with MYC and BCL2 or BCL6 translocations (so-called double-hit lymphomas). Determination of cell size is an essential starting point in this differential diagnosis, which may be difficult on small endoscopic biopsies with areas of crush artifact. Careful attention to morphologic, immunophenotypic, and molecular genetic features is needed to differentiate between these lymphomas.

Burkitt lymphoma is characterized by a diffuse monomorphic infiltrate of medium-sized cells, often with a prominent component of tingible body macrophages. The nuclei have finely clumped chromatin with multiple small nucleoli, and often show squared-off borders with surrounding cells. However, all of these morphologic features may not be readily appreciated on small endoscopic biopsies (Figure 3, A). By immunohistochemistry, Burkitt lymphoma is positive for CD20, and it demonstrates a germinal center phenotype, expressing CD10 and BCL6. They characteristically demonstrate a proliferation rate on Ki-67 staining of close to 100%. They are usually negative for BCL2 but may show weak staining. Most cases show MYC translocation, usually involvingIGH, IKG, or IGL genes, and lack rearrangements involving BCL2 and BCL6 genes. However, some cases of Burkitt lymphoma may lack MYC translocation.

In well-preserved material, the distinction between Burkitt lymphoma and diffuse large B-cell lymphoma is usually straightforward, based on cell size. Unlike the monomorphic medium-sized morphology of Burkitt lymphoma, diffuse large B-cell lymphoma contains at least a component of large cells and is typically more pleomorphic.
than Burkitt lymphoma (Figure 3, B). However, this morphologic distinction may be difficult in small biopsies with variable morphologic preservation. Immunohistochemical stains may be helpful. Although some diffuse large B-cell lymphomas may show an immunophenotype identical to Burkitt lymphoma, lack of CD10, strong staining for BCL2, or a proliferation rate significantly less than 100% should make one consider a diagnosis of diffuse large B-cell lymphoma or other high-grade B-cell lymphoma. It is important to note that MYC rearrangements are not specific for Burkitt lymphoma and are present in approximately 10% of diffuse large B-cell lymphomas.15

The 2016 update of the WHO classification now includes 2 high-grade B-cell lymphoma categories: (1) high-grade B-cell lymphoma with MYC and BCL2 or BCL6 translocations (double-hit lymphomas), and (2) high-grade B-cell lymphoma, not otherwise specified.10 Double-hit lymphomas may show a diffuse large B-cell lymphoma morphology or show a morphologic appearance more closely resembling Burkitt lymphoma. Cases previously diagnosed as B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma that lack MYC translocation are now diagnosed as high-grade B-cell lymphoma, not otherwise specified. A detailed discussion of double-hit lymphomas and related lymphomas is beyond the scope of this review and can be found elsewhere.16

T-CELL LYMPHOMAS

The GI tract can be involved by a variety of T-cell and NK-cell lymphoproliferative disorders. The most common are derived from intraepithelial T cells, often associated with celiac disease.

The 2008 WHO classification identified 2 types of enteropathy-associated T-cell lymphoma (EATL).9 Type 1 EATL (80%–90% of cases) was typically associated with celiac disease, whereas type 2 EATL (10%–20% of cases) was less often associated with celiac disease and showed distinct morphologic and immunophenotypic features. Based on distinct clinical and pathologic features, the 2016
A revision of the WHO classification has distinguished these 2 entities with different names. Cases previously diagnosed as type 1 EATL will now be designated as enteropathy-associated T-cell lymphoma (EATL), whereas cases previously described as type 2 EATL will be now designated as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).

Enteropathy-associated T-cell lymphoma is closely associated with celiac disease, and as such is seen more often in populations with a high prevalence of celiac disease (in patients of northern European origin, and less common in Asian populations). Patients may have a previous history of celiac disease, but in many patients histologic features of celiac disease may only be apparent in adjacent mucosa at the time of lymphoma diagnosis. Histologically, EATL may show a wide morphologic spectrum, but it usually shows a range of medium and large lymphoid cells, often admixed with a mixed inflammatory infiltrate (Figure 4, A). The most common immunophenotype is a cytotoxic T-cell phenotype (positive for CD3, T-cell receptor β [TCR-β], CD7, and cytotoxic molecules granzyme B, perforin, and TIA-1). They are typically negative for CD56. CD30 may be expressed, and may be associated with large cell morphology, raising the differential diagnosis of anaplastic large cell lymphoma. Adjacent mucosa typically shows features of celiac disease, with villous blunting and increased intraepithelial lymphocytes.

Refractory celiac disease may precede a diagnosis of EATL. Refractory celiac disease is defined as resistance or unresponsiveness to at least 12 months of treatment with a strict gluten-free diet. As such, it is a clinical diagnosis rather than a histologic diagnosis. Once a clinical diagnosis of refractory celiac disease is made, it can be divided into 2 groups based on the immunophenotype of the intraepithelial lymphocytes and the presence or absence of T-cell clonality. The intraepithelial lymphocytes of type 1 refractory celiac disease have a normal immunophenotype and are polyclonal. Type 2 cases typically show an abnormal immunophenotype, including down-regulation of CD8, and often show a clonal T-cell rearrangement. Patients with type 2 refractory celiac disease are more likely to develop overt EATL compared with patients with type 1 disease. Although type 2 refractory celiac disease has been described as “cryptic” EATL or EATL in situ, it must be distinguished from overt EATL, which typically shows a mass lesion with extensive lymphoid infiltration of the mucosa and submucosa.

Monomorphic epitheliotropic intestinal T-cell lymphoma does not show a significant association with celiac disease, and it is most common in Asian populations. Unlike EATL, MEITL typically shows a monomorphic morphology consisting of small and medium cells (Figure 4, B). A mixed inflammatory infiltrate is typically absent. The adjacent mucosa often shows increased intraepithelial lymphocytes (Figure 4, C and D), but complete features of celiac disease are usually absent. By immunohistochemistry, the cells are usually positive for CD3, CD8, and CD56. They can express either the γδ TCR or the αβ TCR. Monomorphic epitheliotropic intestinal T-cell lymphoma shows genetic features different from those of EATL, more commonly showing MYC amplification. STAT5B mutations have been reported in 7 of 19 MEITL cases (36.8%). All cases with STAT5B mutations had a γδ phenotype.

Other T- and NK-cell lymphomas may be encountered in the GI tract. Although some cases of EATL may show anaplastic morphology and strong CD30 expression, a diagnosis of anaplastic large cell lymphoma should only be made in the absence of celiac disease based on both histologic features in the adjacent mucosa and serologic testing. The expression of ALK1 in such a case would be diagnostic of an ALK+ anaplastic large cell lymphoma and would exclude a diagnosis of EATL. Extranodal NK/T-cell lymphoma, nasal type, may also involve the GI tract. This can be distinguished from EATL and MEITL by the expression of Epstein-Barr virus–encoded small RNA and an NK-cell phenotype.

**INDOLENT T- AND NK-CELL LYMPHOPROLIFERATIVE DISORDERS**

The GI tract can be involved by indolent NK- and T-cell lymphoproliferative disorders that may be misdiagnosed as aggressive lymphomas. Such NK-cell lymphoproliferative disorders of the GI tract have been reported as lymphomatoid gastropathy and NK-cell enteropathy, representing the...
same disease.\textsuperscript{22,23} Patients may be asymptomatic or present with vague GI symptoms. Endoscopic evaluation typically reveals multiple lesions measuring less than 2 cm that may be raised lesions, mucosal hemorrhage, target lesions, or superficial ulcers. These can be limited to a single site or can involve the entire GI tract. Histologically, these lesions are characterized by expansion of the lamina propria by medium and large cells with irregular nuclei and abundant cytoplasm (Figure 5, A and B). Cases involving the stomach occasionally show infiltration into the glandular epithelium, resembling lymphoepithelial lesions of MALT lymphoma. By immunohistochemistry, the infiltrate shows an NK-cell phenotype, typically positive for CD3 (cytoplasmic), CD56, CD7, and cytotoxic molecules granzyme B, perforin, and TIA-1 (Figure 5, C and D). They do not express T-cell markers CD5, CD4, and CD8, and are negative for Epstein-Barr virus by Epstein-Barr virus-encoded small RNA in situ hybridization (Figure 5, E). Upon follow-up, patients often had persistent lesions with no evidence of progression, and several cases showed regression. Observation without treatment is recommended in these patients.

The morphology and immunophenotype of these cases may be readily misdiagnosed as extranodal NK/T-cell lymphoma, nasal type. These would typically present as a mass lesion, show angioinvasion, and be associated with Epstein-Barr virus, features that have not been described in NK-cell enteropathy. Based on the CD56 expression, the differential diagnosis may also include MEITL. However, MEITL typically presents as a mass lesion, shows epitheliotropism in adjacent mucosa, expresses CD8, and demonstrates clonal T-cell rearrangements by PCR.

Indolent T-cell lymphoproliferative disorder of the GI tract may show clinical features similar to those of NK-cell enteropathy, and can be readily misdiagnosed as an aggressive peripheral T-cell lymphoma.\textsuperscript{24} Patients may present with symptoms that mimic inflammatory bowel disease, including diarrhea, abdominal pain, vomiting, food intolerance, and dyspepsia. Similar to NK-cell enteropathy, these can involve 1 site or multiple sites of the GI tract, most commonly involving the small and large intestines. Endoscopically, lesions were variably described as thickened intestinal folds, as having an “irregular” appearance, or as

Figure 4. Enteropathy-associated T cell lymphoma (EATL) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). A, EATL showing a pleomorphic lymphoid infiltrate with an inflammatory infiltrate including eosinophils. B, MEITL showing a monomorphic population of medium cells lacking an inflammatory infiltrate. C and D, Adjacent mucosa in MEITL shows prominent intraepithelial lymphocytes (C) that are positive for CD3 by immunohistochemistry (D) (hematoxylin-eosin, original magnifications $\times$400 [A and B], $\times$100 [C] and $\times$40 [D]).

Arch Pathol Lab Med—Vol 142, January 2018

Lymphoproliferative Disorders of the GI Tract—Skinnider

49
multiple small polyps. Histologically, the biopsies showed nondestructive expansion of the lamina propria by a dense infiltrate of small lymphocytes with slightly irregular nuclei (Figure 6, A and B). In most cases, the cells were positive for CD2, CD3, CD5, CD8, TIA-1, and TCR-β (Figure 6, C through F). Other cases were positive for CD4, or negative for both CD4 and CD8. They uniformly showed a low proliferation rate on Ki-67 staining (less than 10%). Polymerase chain reaction demonstrated a clonal T-cell population. All patients demonstrated a protracted clinical course with persistence of disease, but showed no evidence of progression to aggressive lymphoma. Optimal treatment of these patients is not clear. Several patients were treated with chemotherapy based on a diagnosis of peripheral T-cell lymphoma, including EATL or MEITL. Both of these typically present as mass lesions. EATL typically shows medium and large atypical cells, distinct from the small lymphocytic morphology of indolent T-cell lymphoproliferative disorder. Although MEITL can show a monomorphous small lymphocytic morphology, the presence of a mass lesion and expression of CD56 would argue against a diagnosis of indolent T-cell lymphoproliferative disorder.

CONCLUSIONS

The GI tract can be involved by a wide variety of B-cell and T/NK-cell lymphoproliferative disorders. Making such diagnoses on endoscopic biopsies may be difficult because of limited material, and awareness of the full spectrum of lymphoproliferative disorders of the GI tract will help to prevent misdiagnosis. Knowledge of all available clinical information, including endoscopic findings, is important in working up lymphoid lesions on small biopsies. Judicious
use of PCR for clonality has its place, but awareness of clonal indolent disorders is needed.

References


Figure 6. Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract. A and B. The lamina propria is expanded (A) by a population of small lymphocytes with slight nuclear irregularity (B). C through F. By immunohistochemistry, the infiltrate is positive for CD3 (C) and CD8 (D), negative for granzyme B (E), and positive for TIA-1 (F) (hematoxylin-eosin, original magnifications ×20 [A], ×400 [B], and ×40 [C through F]).


