Gastrointestinal Lymphomas

Entities and Mimics

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- The gastrointestinal tract is the most common extra-nodal site of lymphoma involvement. Although B-cell lymphomas are by far the most frequent type found in this location, gastrointestinal lymphomas are a diverse group of neoplasms, many of which are characterized by distinctive clinicopathologic settings. Diffuse large B-cell lymphoma and marginal-zone lymphoma of mucosa-associated lymphoid tissue are commonly encountered, but other less-common entities can pose diagnostic challenges, mimicking both benign, reactive conditions and each other. We describe several different lymphoma subtypes, with a focus on frequently encountered challenges in differential diagnosis.


Gastrointestinal lymphomas can pose diagnostic challenges based solely on hematoxylin-eosin–stained morphology. However, an understanding of benign, inflammatory entities, along with careful clinicopathologic correlation and judicious use of immunohistochemistry, is very helpful in confirming histologic impressions. Both common and rare entities will be discussed in this article, including the diagnostic approaches and important clinical features.

REPORTS OF CASES AND PATHOLOGIC FINDINGS

Case 1

A 61-year-old man presented with dyspepsia and was found, on endoscopic examination, to have nodular mucosa in the jejunum, which was biopsied. The examination was otherwise normal. Hematoxylin-eosin–stained sections showed a prominent, nodular lymphoid infiltrate in the mucosa of the small intestine, composed of small lymphocytes arranged in back-to-back follicles (Figure 1, A). The differential diagnosis in this type of biopsy should include benign/reactive follicular hyperplasia and lymphoid neoplasm. Gastrointestinal involvement by mantle cell lymphoma is often characterized by “lymphomatous polyposis,” which can present with multiple polypoid or nodular mucosal projections, sometimes mimicking an inherited polyposis syndrome; however, other less-common entities should also be considered. The differential diagnosis should include follicular hyperplasia, follicular lymphoma, and mantle cell lymphoma. Extranaural marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma) does not typically have a nodular appearance unless the neoplastic cells colonize reactive follicles. In evaluating these possibilities, the morphologic features can guide the immunohistochemical workup. At high magnification, the cells in this case were monotonous, cleaved centrocytes (Figure 1, B). A reactive, germinal center would have greater heterogeneity and would typically include occasional tingible-body macrophages. Mantle cell lymphoma often has hyalinized vessels or epithelioid histiocytes admixed with small-to-intermediate lymphoid cells and angulated (but not usually cleaved) nuclear contours. A useful panel of immunohistochemical stains would include CD20, CD3, CD5, CD10, and bcl-2. The bcl-2 is only necessary if follicular hyperplasia is a consideration because nearly all B-cell lymphomas of small cells express bcl-2. In this case, the follicles results were positive for CD20, CD10 (Figure 1, C), and bcl2 (Figure 1, D). The CD5 and CD3 marked background T cells, and the cyclin D1 immunohistochemical studies were negative. Therefore, the best diagnosis in this case was follicular lymphoma. Clinical staging showed that the lymphoma was limited to the gastrointestinal tract, making this a good example of primary intestinal follicular lymphoma.

Primary intestinal follicular lymphoma is a rare subtype of follicular lymphoma. It typically presents in the second portion of the duodenum, and less-frequently, in the jejunum and appears endoscopically as one or more small polyps. Although typically asymptomatic, it may present with bowel obstruction. Staging must be performed to exclude gastrointestinal involvement by a more widespread follicular lymphoma, such as one involving retroperitoneal lymph nodes. Patients with confirmed primary intestinal follicular lymphoma seem to have excellent survival and may not require treatment.

Case 2

A 50-year-old man presented with diarrhea. An esophagogastrduodenoscopy showed no evidence of disease. His diarrhea persisted and he developed weight loss. Subsequently, he returned to the emergency room with an acute abdomen and was found to have a jejunal perforation (Figure 2, A). Hematoxylin-eosin–stained sections showed a transmural infiltrate of intermediate to large, atypical cells, some with a horseshoe- or wreath-shaped nuclei (see Figure 2, B and C). Numerous eosinophils were admixed with the neoplastic cells. In the uninvolved areas, the enteric villi were blunted and the surface epithelium contained numerous intraepithelial lymphocytes, a pattern consistent with celiac disease (see Figure 2, D). The differential diagnosis in this case included diffuse large B-cell lymphoma (DLBCL) as well as T-cell lymphomas, with...
enteropathy-associated T-cell lymphoma (EATL) at the top of the differential diagnostic list. A useful immunohistochemical panel would include pan–T-cell markers, including CD2, CD3, CD4, CD5, CD7, CD8, and TCR-βF1 (a marker of naïve T cells). In this case, the neoplastic cells expressed CD2, CD4, CD7, and TCR-βF1. CD5 was not expressed. CD30 was also performed and showed focal expression. The overall histologic and immunophenotypic appearance was, therefore, consistent with EATL. Such cases can be composed of very pleomorphic cells and can be mistaken for anaplastic large cell lymphoma (ALCL) when “Hallmark-type” nuclear morphology is present. The cells of ALCL, however, should have strong and uniform expression of CD30. The EATL is a rare, mature T-cell lymphoma associated with celiac disease (celiac sprue; gluten-sensitive enteropathy), which has increased in incidence in the United States during the past 25 years. There is considerable overlap between an inflammatory condition known as ulcerative jejunitis, which occurs in patients with refractory celiac sprue, and early EATL. Identical T-cell clones have been found in patients with refractory sprue, ulcerative jejunitis, and subsequent EATL, suggesting that these represent a spectrum of the same neoplastic process.

Most often, EATL occurs in the jejunum and may present with intestinal perforation. In cases where celiac disease has been documented before the development of lymphoma, patients typically present with the classic type of EATL. In other cases, however, patients may present with intestinal perforation without a documented history of celiac disease. In these cases, patients may have classic-type EATL, arising in previously undiagnosed celiac disease, or they may have type-II EATL. Monomorphic EATL (type II) tends to have homogeneous, intermediate-sized cells rather than the pleomorphic cells seen in the classic cases. Many of these cells express CD8, CD56, and the γδ T-cell receptor. Because these cases lack the clinicopathologic features of classic EATL and have a distinct morphology and immunophenotype, their inclusion within the diagnostic category of EATL has recently been questioned. The differential diagnosis in both the classic and monomorphic types includes peripheral T-cell lymphoma, not otherwise specified. Case 3

A 16-year-old adolescent girl presented with rectal bleeding. A flexible sigmoidoscopy revealed a 2-cm “mass” in the distal rectum, very near the anorectal junction. This was excised during the same procedure and hematoxylin–eosin–stained sections contained a diffuse infiltrate of mature-appearing plasma cells that disrupted the normal mucosal architecture (Figure 3, A and B). A reactive condition with extensive chronic inflammation was considered, but the plasma cells were found to be restricted to κ light chain expression on immunohistochemistry. The patient had no evidence of disease elsewhere and the initial, working diagnosis was a plasmacytoma. Additional immunostains revealed scattered, small B lymphocytes positive for CD20, some in small clusters, and a population of small, CD3+ T lymphocytes predominantly

Figure 1. Primary intestinal follicular lymphoma. A follicular pattern of infiltration with back-to-back follicles (A) is composed of small lymphocytes with cleaved nuclei (B). The follicles express CD10 (C) and bcl-2 (D) (hematoxylin–eosin, original magnifications ×40 [A], ×400 [B], and ×100 [C and D]).
surrounding the plasma cells at the periphery of the lesion. In a few areas, the B cells infiltrated and damaged the crypt epithelium, creating destructive lymphoepithelial lesions. Based on these histologic findings and the patient’s young age, a diagnosis was made of extranodal marginal-zone lymphoma of mucosa-associated lymphoid tissue (MALT) with extensive plasmacytic differentiation. Serum protein electrophoresis results showed no evidence of a monoclonal serum protein.

Plasmacytic differentiation in MALT lymphoma is fairly common, seen to some extent in about one-third of MALT lymphoma cases. Occasionally, as in this case, plasma cells are the predominant cell type, potentially leading to confusion with other hematolymphoid neoplasms, such as plasmacytoma and lymphoplasmacytic lymphoma. Thus, MALT lymphoma with plasmacytic differentiation should be considered in the differential diagnosis of any plasmacytic lesion, particularly in the setting of a disease site or clinical scenario that would be unusual for a plasmacytoma, such as a very young patient. Although the gastrointestinal tract is the most common location for MALT lymphomas to occur, the colon is an uncommon site. About 85% of gastrointestinal examples occur in the stomach, most in association with Helicobacter pylori infection. In the colon, however, the rectum and cecum are the leading sites of involvement.

In addition to differentiation from other plasmacytic neoplasms, the differential diagnosis with reactive conditions can be challenging. In the stomach, the dividing line between severe H pylori gastritis and MALT lymphoma is often indistinct. The so-called rectal tonsil, a benign lymphoplasmacytic collection occurring in the distal rectum near the anorectal junction, is another potential mimic of lymphoma. Based on hematoxylin-eosin histology alone, the most helpful feature is a truly destructive appearance to the process, leading to disruption of normal mucosal architecture through the formation of destructive, lymphoepithelial lesions created by the neoplastic B cells (and/or the plasma cells, as in this case). In cases with prominent (or predominant) plasmacytic differentiation, a low threshold for ordering immunoglobulin (Ig) light chain immunostains and/or in situ hybridization studies that demonstrate a clonal light chain restriction can aid the diagnosis and differentiation from a chronic inflammatory process. Additionally, even when plasma cells seem to be the predominant population, a CD20 immunostain will often reveal more neoplastic B cells than first seen, including cells within destructive, lymphoepithelial lesions. Finally, serum protein electrophoresis will sometimes reveal a monoclonal protein (usually IgG) in patients with plasmacytic MALT lymphoma.

Therapy for patients such as this is controversial and poorly studied. The use of H pylori eradication treatment for gastric MALT lymphomas is well established, and there have been a few reports of this therapy being effective in MALT lymphomas in other parts of the gastrointestinal tract, although it is not clear whether this is...
due to eradication of *H pylori* specifically or whether it simply results in the eradication of some other organism(s) responsible for an inflammatory precursor to lymphoma. The patient in this case ultimately received low-dose radiation therapy after a follow-up biopsy revealed residual disease.

**Case 4**

A 28-year-old Middle Eastern man presented with severe diarrhea. As part of the evaluation of this condition, an upper endoscopy was performed, showing some subtle, duodenal mucosal changes, including scattered erosions. Duodenal biopsies were obtained during the endoscopy. The mucosa contained a dense infiltrate of plasma cells that expanded the mucosa and disrupted the mucosal architecture, pushing the crypts apart and blunting the overlying villi (Figure 4). Although the blunted villi created an appearance reminiscent of the mucosal changes seen in celiac disease, there was no increase in intraepithelial lymphocytes. Furthermore, apart from surface erosions, there was no evidence of active (neutrophilic) inflammation, such as active cryptitis, arguing against upper-tract involvement by inflammatory bowel disease. The plasma cells were immunohistochemically positive for CD138, but negative for \(\kappa\) and \(\lambda\) light chains (on both immunohistochemistry and in situ hybridization). Those findings prompted immunostains for IgA, IgG, and IgM heavy chains, which revealed overwhelming IgA expression on the plasma cells without light chain expression, resulting in the diagnosis of immunoproliferative small intestinal disease (IPSID).

Considered a variant of MALT lymphoma with nearly complete plasmacytic differentiation, IPSID is a rare disorder. Its name results from its preferential involvement of the small intestine, but it is also known by an alternative moniker—IgA heavy chain disease—because the neoplastic cells in about one-half of cases produce an abnormal, truncated IgA heavy chain that is missing the variable (\(V_H\)) and the first constant (\(C_H1\)) regions and that can be found in the serum. The disease occurs most commonly in young men (median age of 25), has an association with low

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**Figure 3.** Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue with plasmacytic differentiation. A, The rectal mucosa contains a dense infiltrate of plasma cells that disrupts the normal mucosal architecture. B, Higher magnification shows sheets of mature-appearing plasma cells that were light chain–restricted (hematoxylin-eosin, original magnifications \(\times200\) [A] and \(\times400\) [B]).

**Figure 4.** Immunoproliferative small intestinal disease. Duodenal biopsy shows flattened mucosa diffusely infiltrated by mature-appearing plasma cells that expressed immunoglobulin-A heavy chain without light chain expression (hematoxylin-eosin, original magnification \(\times400\)).

**Figure 5.** Diffuse, aggressive B-cell lymphoma. A, The patient’s colon was involved by a lymphoma with a “starry-sky” pattern. B, Ki-67 immunostain shows a high proliferative fraction (hematoxylin-eosin, original magnification \(\times400\) [A]; original magnification \(\times600\) [B]).

**Figure 6.** Mantle cell lymphoma. A, The patient had lymphomatous polyposis throughout the gastrointestinal tract, composed of small lymphocytes with angulated nuclear contours (inset). B, Cyclin D1 immunostain shows nuclear expression (hematoxylin-eosin, original magnifications \(\times20\) [A] and \(\times40\) [inset]; original magnification \(\times200\) [B]).
socioeconomic status, and a geographic distribution that includes the Middle East, the Mediterranean region, and the cape region of South Africa, although occasional cases have been reported in other locales, including the Far East, Europe, the United States, and elsewhere. The condition presents with abdominal pain, diarrhea, malabsorption, and resultant weight loss occurring during the course of several months to years. Patients may also manifest clubbing of the digits. The neoplastic infiltrate produces one or more masses in the small intestine, often with enlarged mesenteric lymph nodes. As in other MALT lymphomas with extensive plasmacytic differentiation, a neoplastic, small B-cell population can often be found using CD20 immunohistochemistry, which can serve to highlight destructive lymphopelithelial lesions. As just as gastric MALT lymphomas are known to be related to infection with H. pylori, IPSID is suspected to result from Campylobacter infection, and early cases have a relatively high rate of response to broad-spectrum antibiotics. Unfortunately, the disease may be at an advanced stage at diagnosis and tends to behave aggressively. In addition, it is relatively common for IPSID to progress to a high-grade lymphoma indistinguishable from DLBCL. Although it has since been confirmed as a clonal process, the lamina propria plasmacytosis and villous blunting seen in the mucosa, coupled with the response to antibiotics, led observers in the past to believe that IPSID was entirely an inflammatory process, and it can resemble upper-tract involvement by inflammatory bowel disease as well as celiac disease, although it lacks the intraepithelial lymphocytes and total villous flattening typical of celiac disease.

A histologic staging system for IPSID has been proposed, based on the hematoxylin-eosin appearance. Stage A disease is restricted to the intestinal mucosa and regional nodes, stage B involves infiltration beyond the muscularis mucosae, and stage C is characterized by high-grade lymphoma (equivalent to DLBCL), which may have an immunoblastic or plasmablastic appearance. Therapy for IPSID centers on surgical resection of masses as well as systemic chemotherapy for unresectable disease.

Case 5

A 59-year-old man presented with gastrointestinal bleeding. A portion of the sigmoid colon was resected and showed transmural, diffuse architectural effacement by an infiltrate with a “starry sky” pattern (Figure 5, A). High-power examination revealed large cells with moderate pleomorphism and a high mitotic rate. Apoptotic bodies and tingible body macrophages were present in the background, imparting the “starry sky” appearance. Immunohistochemical studies were performed. The neoplastic cells expressed CD20, CD10, and bcl2. Ki-67 showed a proliferative fraction of greater than 80% (Figure 5, B). Based on morphology and immunophenotype, the differential diagnosis included DLBCL and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma. Classic Burkitt lymphoma was excluded based on the bcl-2 expression and the morphology of the cells. In cases with a high proliferative rate, a germinal-center immunophenotype, and bcl-2 expression, fluorescence in situ hybridization studies for MYC rearrangement, BCL2/IgH translocation, and BCL6 rearrangements are helpful in identifying cases that may behave aggressively clinically. The most recent edition of the WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues (4th ed, 2008) includes a new provisional entity, entitled B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma. This category is intended to include highly proliferative B-cell lymphomas with an immunophenotype or morphologic features suggestive of Burkitt lymphoma; however, it can be difficult to determine which cases to include in this category. In prior classification schemes, many of these cases were classified as Burkitt-like or simply called DLBCL.

Many of these cases have an MYC rearrangement in the context of a complex karyotype, with or without juxtaposition of MYC to one of the Ig genes. Burkitt lymphoma, on the other hand, typically has a simple karyotype involving the Ig loci. Studies have shown that some of these “unclassifiable” cases have additional BCL2 to IgH translocations or, less-frequently, BCL6 rearrangements. Many hematopathologists have begun to refer to cases as double-hit if it has a MYC rearrangement and either a BCL2 to IgH translocation or a BCL6 rearrangement. If all 3 are present, the term triple-hit is used, although those cases are rare.

Although there has been no definite national or international consensus to date on which cases should be included in the new B-cell lymphoma, unclassifiable, category, it may be most important to identify cases that have MYC rearrangement and BCL2/IgH or BCL6 rearrangements. Those cases indicate an aggressive lymphoma with a poor prognosis. Although current treatment approaches differ depending on the institution, identifying those cases may allow clinical trials that will ultimately determine the optimal treatment approach.

In a search for double-hit lymphoma cases, immunohistochemistry can also be used to help determine which cases would benefit from fluorescence in situ hybridization studies. Ki-67 expression can vary widely, but one large study found a median proliferative fraction of 80% to 90%. Most cases are positive for CD10, 17,23,24 Most, but not all, of these double-hit cases are BCL2-".

Case 6

A 50-year-old man presented with abdominal pain and was found to have massive splenomegaly on physical examination. Laboratory studies revealed microcytic anemia. As part of the workup for blood loss, a colonoscopy was performed, revealing innumerable polyps throughout the colon. Additional polyps were seen on upper endoscopy, particularly in the duodenum. The clinical diagnosis initially included an inherited polyposis syndrome, such as familial adenomatous polyposis, and biopsies were obtained at the time of endoscopy, with a request to “rule out adenomas” on the requisition sheet that accompanied the specimens to the pathology department.

The histologic examination revealed no epithelial dysplasia. Instead, the submucosa was filled with a nodular infiltrate of small lymphocytes, which infiltrated between the Brunner glands and extended focally into the overlying mucosa (Figure 6, A). These monotonous lymphocytes had dense chromatin and somewhat angulated nuclear contours (Figure 6, A and inset) and were admixed with rarer histiocytes having abundant, eosinophilic cytoplasm. The histologic differential diagnosis included prominent benign lymphoid aggregates, follicular lymphoma, MALT lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and mantle cell lymphoma. The diffuse nature of the process argued against a benign condition, and the lack of well-developed follicular structures (despite a nodular appearance) was felt to make follicular lymphoma less likely. Immunohistochemical stains confirmed that the lymphocytes were overwhelmingly CD20+B cells. A CD5 stain was negative, revealing only admixed, small T cells in a pattern identical to that seen with a CD3 stain, and arguing against chronic lymphocytic leukemia/small lymphocytic lymphoma, because the literature contains numerous reports of other lymphomatous processes, including DLBCL, follicular lymphoma, and MALT lymphoma, producing similar clinical appearances. A cyclin D1 immunostain was performed, however, and revealed nuclear positivity, confirming the ultimate diagnosis of mantle cell lymphoma (Figure 6, B).

The clinical and endoscopic appearance in this case is a classic picture of so-called lymphomatous polyposis, which is most commonly attributable to mantle cell lymphoma. The term is not synonymous with a diagnosis of mantle cell lymphoma, however, because the literature contains numerous reports of other lymphomatous processes, including DLBCL, follicular lymphoma, and MALT lymphoma, producing similar clinical appearances. Lymphomatous polyposis can strongly mimic an inherited polyposis syndrome clinically, and biopsy is required to confirm the diagnosis. The histologic appearance of monotonous, small lymphocytes with angulated nuclei is suggestive of mantle cell lymphoma, as are the admixed, hyalinized vessels and eosinophilic histiocytes (“pink histiocytes”) that are found among the lymphoma cells. Further, the nodular infiltration pattern is the most commonly seen in mantle cell lymphoma involving the gastrointestinal tract.
Absence of CD5 expression is unusual in mantle cell lymphoma, and can prove confusing in making the diagnosis. Cyclin D1-negative cases have been reported but are extremely rare and somewhat controversial. Happily, cyclin D1 positivity is typically present even in the absence of CD5 staining, as in this case, although care is needed to avoid misdiagnosis of such cases as some other type of CD5-negative lymphoma, such as MALT lymphoma. Correlation with the histologic features described should raise the suspicion of mantle cell lymphoma, prompting the performance of cyclin D1 testing. Most mantle cell lymphomas harbor the characteristic t(11;14)(q13;q32) translocation involving IGH and CCND1 genes, although the immunopositivity for cyclin D1 usually obviates the need for cyogenetic or molecular studies in making the diagnosis. The prognosis for mantle cell lymphoma is relatively poor, and the disease has the distinction of being similarly incurable but, clinically, more aggressive than other lymphomas composed of small lymphocytes. The proliferation fraction, as measured by Ki-67 immunostaining, is clinically significant, with a high (40–60%) proliferation fraction being an adverse prognostic indicator.

**SUMMARY**

The gastrointestinal tract is a common extranodal site of involvement by lymphomas, which can prove diagnostically confusing because of their ability to mimic a variety of benign conditions, as well as each other. Nonetheless, a systematic approach, applying clinical and morphologic clues, along with judicious use of immunohistochemistry, can typically lead to an accurate diagnosis. A diagnostic approach that combines an expectation of common entities, such as reactive lymphoid aggregates, DLBCL, and MALT lymphoma, with maintenance of a “weather eye” for more unusual entities or appearances, such as double-hit lymphomas, EATL, and complete plasmacytic differentiation, is crucial to successful navigation of the sea of lymphoid infiltrates arising in the gastrointestinal tract.

**References**


