Lymphoproliferative Disorders of the Gastrointestinal Tract
A Review and Pragmatic Guide to Diagnosis

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Context.—The gastrointestinal tract is the most common location of extranodal lymphomas, with the stomach as the most frequent site of involvement and with the small intestine second in frequency.1 Large intestinal and rectal lymphomas are far less common but are discovered in patients with AIDS and sporadically in patients with ulcerative colitis and Crohn disease.2–4 In a study of 371 patients with primary gastrointestinal lymphomas registered in a German multicenter study, stomach accounted for 277 of cases (74.8%), whereas small intestine and ileocecal region represented 61 cases (16.4%).5 Only 9 cases (2.4%) in that series were restricted to the colorectal area, with the remaining cases involving multiple gastrointestinal sites. The incidence of primary gastric lymphomas, specifically extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) type, has vacillated, with a peak reached in the 1990s subsequent to the increasing recognition of MALT lymphoma as a specific diagnostic entity, followed by a persistent decline in the past decade; this decline may be related to the improved clinical management and reduction in Helicobacter pylori infection.6

The concept of extranodal marginal zone lymphoma of MALT type has revolutionized the criteria for the morphologic diagnosis of an extranodal lymphoma, specifically those lymphomas dominated by small lymphocytes. Since the initial descriptions of lymphomas of MALT in 1983 and 1984, the morphologic criteria have evolved and expanded to encompass the following: a more precise definition of various cell types in MALT lymphoma, proposals for "lymphoepithelial lesions" and "follicular colonization," the relationship between MALT lymphomas and marginal zone B cells, and a scoring system for diagnosis of gastric MALT lymphoma.7–10 Moreover, the morphologic criteria have expanded to embrace immunophenotypic, biologic, molecular genetic, and clinical discoveries.10–18 Developments, such as the association of gastric MALT lymphoma with H pylori infection, the notion of acquired MALT, the biology of autoantigen activation and continuous somatic mutations, the documentation of genetic aberrations, for example, the discovery of the t(11;18)(q21;q21) chromosomal translocation in lymphomas of MALT, and the clinical implications of the documentation of genetic aberrations, for example, the discovery of the t(11;18)(q21;q21) chromosomal translocation in lymphomas of MALT, and the clinical implications...
The goal of this review is to critique the salient lymphoid and associated with lymphoid Arch Pathol Lab Med—Vol 135, October 2011 application of immunologic and
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The major criteria for a solid foundation for diagnosis, especially with respect to small gastrointestinal biopsy specimens.

**FLORID LYMPHOID HYPERPLASIA (“PSEUDOLYMPHOMA”) VERSUS MALIGNANT LYMPHOMA**

In establishing a histologic diagnosis of an extranodal lymphoma, pathologists are aware that various forms of reactive lymphoid hyperplasia clinically and pathologically mimic gastrointestinal lymphomas, such as gastric lymphoid hyperplasia and chronic lymphocytic gastritis.

To confuse the issue, malignant lymphoma of extranodal marginal zone (MALT) type may develop in association with these reactive lymphoid infiltrates, including those in stomach. 22

In the 1960s and 1970s, the morphologic criteria to distinguish extranodal lymphoma from extranodal lymphoid hyperplasia were derived from those used traditionally to distinguish malignant lymphoma from lymphoid hyperplasia in lymph nodes. 23 The major criteria for this distinction included monomorphic lymphocytic infiltrates, cellular atypia, germinal centers, and architectural disruption. 24

Since most gastrointestinal lymphomas are large B-cell lymphomas with associated monomorphism, cellular atypia, and architectural destruction (eg, eradication of glands), these conventional criteria generally have proved germane. At the converse end of the continuum, obvious reactive lymphoid conditions similarly do not usually present diagnostic difficulties. Lymphocytic infiltrates that display polymorphism, that contain a range of mature lymphocytes encompassing plasma cells and immunoblasts, that exhibit well-defined germinal centers, and that do not raze the architectural landmarks of the gastrointestinal site usually can be diagnosed assertively as benign and reactive.

The main difficulty in the separation of gastrointestinal lymphomas from lymphoid hyperplasia concerns marginal zone lymphomas of MALT type that are dominated by small lymphocytes and that commonly are associated with germinal-center formation. 25 For such cases, the conventional histologic criteria are not valid (Figure 1, A and B). Many histologically ambivalent gastrointestinal small lymphocytic proliferations prove to be monoclonal and are probably malignant lymphomas, especially of MALT type. 26 The application of immunologic and molecular genetic analyses to gastrointestinal sites, especially gastric small lymphocytic proliferations, has served to vividly alter the traditional histologic criteria and has exposed innumerable inconsistencies in these criteria. 24 At the Armed Forces Institute of Pathology, for example, of 97 cases reviewed from 1970 to 1985, which formerly were diagnosed as gastric pseudolymphoma, 79% were reclassified as malignant lymphoma, and two-thirds of the newly classified lymphoma cases subsequently were designated as lymphomas of MALT type. 27 Lymphoid hyperplasia or atypical lymphocytic infiltrates comprised the remaining cases. As a result, the term pseudolymphoma is currently considered nebulous and obsolescent and is no longer suitable as a diagnostic term. 10

The current perception of small gastrointestinal lymphocytic proliferations that appear mature has changed significantly, not only by refinement of the morphologic criteria, but also by the utilization of immunologic techniques, including immunohistochemistry, in situ hybridization, flow cytometry, and gene rearrangement to analyze the clonality of these lesions. For example, in patients with documented suspicious lymphocytic infiltrates in gastroscopic biopsy specimens, multiple repeated biopsy fragments of the lesion submitted fresh for flow cytometry analysis frequently result in the demonstration of monoclonality and verification of lymphoma. 28 Caution, however, is required in the evaluation of immunoglobulin studies using polymerase chain reaction (PCR) techniques in fixed, paraffin-embedded tissues; small monoclonal bands may occur in extranodal reactive lymphoid hyperplasia, as for example in chronic active gastritis associated with H pylori and associated with lymphoid follicles. 29,30 Therefore, if PCR for immunoglobulin gene rearrangement is to be performed, the test should be limited to those gastric cases with strong morphologic suspicion for actual lymphoma. 24,30

Lymphoid follicles or reactive germinal centers create another conundrum in diagnosis. Germinal centers are a commonly accepted histologic trait of gastric lymphoid hyperplasia, and isolated follicles are a common finding in gastric biopsy specimens. 31 Germinal centers, however, are regular components of many lymphomas of MALT. The critical morphologic characteristic of MALT lymphomas is their simulation of normal MALT as typified by Peyer patches found in the terminal ileum. 24 The neoplastic B lymphocytes of MALT lymphomas are found in marginal-type zones adjoining reactive follicles and often diminished rims of mantle zone lymphocytes. The germinal centers frequently are atrophic owing to encroachment by the encircling small lymphocytes. In MALT lymphomas of stomach, affiliated with peptic ulcer, germinal centers occur at the base of the ulcer and in the adjacent mucosa, where they appear entrapped by the monotonous marginal zone lymphocytes. Frequently, the neoplastic marginal zone lymphocytes invade the germinal centers in a process referred to as “follicular colonization.” 11 When follicles are numerous, follicular colonization may imitate follicular lymphoma. In some cases, the lymphomatous infiltrate may result in architectural destruction with concealment of remaining germinal centers; however, the presence of cryptic germinal centers can be accentuated by the immunohistochemical demonstration of follicular dendritic cells with an antibody against CD21 or CD23. 25,32

Despite honing of the criteria to separate gastrointestinal lymphoid hyperplasia from lymphoma, gastrointestinal lymphoid hyperplasia remains a relatively common histologic alteration. Gastrointestinal lymphoid hyperplasia involves not only stomach, but may occur anywhere in the intestine, as for example the ileum, where Peyer patches may be particularly pronounced. 33 Lymphoid hyperplasia of the gastrointestinal tract may be focal or, rarely, nodular, encompassing long segments of the small and large intestine, where it needs to be distinguished from mantle cell lymphoma and follicular lymphoma. 34 Lymphoid hyperplasia also may affect the rectum and, on occasion, cause a diagnostic challenge. Localized lymphoid hyperplasia of the rectum recently has been referred to as rectal “tonsil.” 35 Patients may present with
Figure 1. Massive gastric infiltrate (A) from an archival case in a study from the late 1960s, labeled as “pseudolymphoma.” The diagnosis of pseudolymphoma most likely was based on the fact that the infiltrate is dominated by small, round lymphocytes with scattered germinal centers (B). With current criteria, this case likely would be labeled gastric marginal zone lymphoma of MALT type (hematoxylin-eosin, original magnifications ×150 [A] and ×300 [B]).

Figure 2. Florid lymphoid hyperplasia in the rectum. At both lower (A) and higher magnifications (B), tingible body macrophages are apparent and indicate that the follicles are reactive and not lymphoma. In the rectum, florid lymphoid hyperplasia has been referred to as rectal “tonsil” and some cases can be mistaken for lymphoma (hematoxylin-eosin, original magnifications ×30 [A] and ×150 [B]).

Figure 3. Large B-cell lymphoma is the most common type of lymphoma in stomach (A). The diagnosis is supported by an immunoperoxidase stain for CD20 (B) (hematoxylin-eosin, original magnification ×300 [A]; original magnification ×300 [B]).
Chlamydial proctitis may be a cause of some... it was previously proposed... NOS, not otherwise specified.

Abbreviations: ALCL, anaplastic large cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; NK, natural killer; T- and natural killer (NK)-cell neoplasms.

Several categories among the mature B-, T- and natural killer cell lymphomas are classified as enteropathy-associated T-cell lymphoma (EATL). In addition, enteropathy-associated T-cell lymphoma may be subdivided into enteropathy-associated T-cell lymphoma of the stomach (with or without extranodal extension) and enteropathy-associated T-cell lymphoma of the intestine (without extranodal extension). The enteropathy-associated T-cell lymphoma of the stomach is often associated with a MALT component or arising in a MALT site.

The diagnosis of large B-cell lymphoma usually is not a problem because of the tendency of the lymphoma to be diffuse, to lack cohesive cell aggregates, and to be composed of cells that are approximately double the size of normal small lymphocytes with open vesicular chromatin and nucleoli, which are either adjacent to the nuclear membrane or, in the case of immunoblasts, central and frequently eosinophilic. In small endoscopic biopsy specimens, the diagnosis may be more tenuous, but immunohistochemical verification of the diagnosis is advised and is particularly valuable in delineating cases of large B-cell lymphoma from undifferentiated gastrointestinal carcinoma. The infiltration by lymphoma around, or into, partially intact gastric and intestinal glands, negative mucin and keratin staining, positive reactivity for B-cell antigens such as CD20, and the lack of syncytial cell aggregates or malignant acinar formation aid in the distinction of large B-cell lymphoma from poorly differentiated or undifferentiated carcinoma, even in small biopsy specimens (Figure 3, A and B). Occasionally, gastrointestinal large B-cell lymphoma requires distinction from other large cell malignant neoplasms that simulate lymphoma, as for example malignant melanoma and myeloid sarcoma.

Small gastrointestinal lymphoid neoplasms, however, are prone to sampling errors and artifactual distortion, and may be necessary to request a second biopsy in order to deliver a more complete diagnosis.

Mantle cell lymphoma is another type of non-MALT lymphoma found in the gastrointestinal tract that can present as a nonspecific lymphocytic infiltrate, but is best known for presentation as multiple lymphomatous polyposis.

Malignant lymphomas of the stomach showed coexistence of a low-grade and a high-grade lymphoma, it was suggested that increased numbers of histologic sections might demonstrate a still higher percentage of cases with a low-grade component. The terms low-grade MALToma and high-grade MALToma formerly were used to describe such lesions, but, as discussed above, the diagnosis of MALT lymphoma currently is restricted to a lymphoma composed principally of small lymphocytes and should not be used to classify large B-cell lymphomas, including those associated with a MALT component or arising in a MALT site.

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This is an unusual, but distinct, gastrointestinal lymphoma characterized by the polyloid accumulation of lymphoma involving long segments of the small and large intestine. Small lymphomatous polyposis has a reported frequency of 4% to 9% among all gastrointestinal B-cell non-Hodgkin lymphomas. Patients generally are middle-aged males who present with weight loss, fatigue, diarrhea, abdominal pain, and often iron deficiency.

The lymphoma forms a series of coalescing polyoid nodules composed of atypical centrocyte-type cells involving mucosa and/or submucosa (Figure 4, A). Occasionally, reactive germinal centers are trapped in the nodular lymphomatous infiltrate and this observation aids in morphologically distinguishing lymphomatous polyposis from follicular lymphoma of the gastrointestinal tract (Figure 4, B). The mantle cells in lymphomatous polyposis exhibit a characteristic CD20, CD5, CD23 phenotype and cyclin D1 overexpression, as well as bcl-1 rearrangements with t(11;14)(q13;q32). Cases of intestinal mantle cell lymphoma also frequently contain the 14q32, and also contain the 24q13.2 (BCL6) gene. However, a subset of lymphomatous polyposis cases are, in fact, follicular lymphomas and such cases appear limited to the small intestine, whereas...
the primary mantle cell cases involve both small and large intestine. As well, patients with clinical presentation of lymphomatous polyposis occasionally have been reported as having marginal zone lymphomas of MALT type. The immunophenotype of the follicular and MALT lymphoma variants of lymphomatous polyposis clearly differs from that of the more common mantle cell cases.

Secondary intestinal dissemination by mantle cell lymphoma also is exceedingly common in patients with generalized, primary lymph node–based mantle cell lymphoma and encompasses cases that exhibit a lymphomatous polyposis pattern with involvement of colon. Approximately 25% of patients with documented nodal mantle cell lymphoma have gastrointestinal symptoms, yet the lymphoma is present histologically in the lower gastrointestinal tract in 77% to 88% of patients and in the upper gastrointestinal tract in 43% to 77%. Moreover, microscopic documentation of mantle cell lymphoma is reported in 84% of patients with normal visual findings by lower endoscopy and in 45% of patients with macroscopically normal findings by upper endoscopy. Such examples can be histologically indistinguishable from focal lymphoid hyperplasia, but immunohistochemical stains, including nuclear cyclin D1 reactivity, confirm gastrointestinal involvement by mantle cell lymphoma. Despite the often subtle microscopic involvement of the gastrointestinal tract in patients with node-based mantle cell lymphoma, aggressive staging evaluation of the gastrointestinal tract has little impact on patient management decisions. Primary mantle cell lymphoma of the gastrointestinal tract, in the form of lymphomatous polyposis, generally has an aggressive clinical course and patients have a median survival of approximately 3 to 4 years.

Primary follicular lymphoma of the gastrointestinal tract is uncommon, but when it occurs it tends to involve the small intestine, especially the duodenum. As considered previously, such cases may present with multiple small polyps, including the appearance of lymphomatous polyposis (Figure 4, C). Histologically, follicular lymphoma of the gastrointestinal tract is similar to node-based follicular lymphoma (Figure 4, D). Most examples are grade 1, but cases of grade 2 and 3 also
occur in the gastrointestinal tract, however, precise grading may prove difficult in small biopsy specimens. The immunophenotype is identical to that of nodal follicular lymphoma (CD20+, CD10+, bcl-6+, bcl-2+) and the cases also exhibit t(14;18). In contrast to nodal follicular lymphoma, the primary gastrointestinal cases frequently express immunoglobulin A (IgA) as well as the α4β7 mucosal homing receptor, to suggest origin from local antigen-experienced B-cells. Unlike nodal follicular lymphoma, duodenal follicular lymphoma also exhibits VH4 gene deviation and lacks activation-induced cytidine deaminase expression; moreover, its dendritic cell meshworks tend to be disrupted. Follicular lymphoma of the duodenum additionally reveals ongoing hypermutation but the mechanisms differ from those in nodal cases and are more in parallel with the antigen-dependent origin of MALT lymphoma. Clinically, patients with primary follicular lymphomas of the gastrointestinal tract tend to have low-stage IE and IIE disease. As compared to mantle cell lymphoma, gastrointestinal follicular lymphoma exhibits an indolent clinical course, with patient survival of 62% or more at 5 years. Moreover, primary stage IE follicular lymphoma of the duodenum is exceedingly indolent and patients who are not treated usually do not develop extraintestinal spread, nor does the disease transform to large cell lymphoma, leading to the recommendation of a “watch and wait” approach.

Immunoproliferative small intestinal disease (IPSID), formerly known as Mediterranean lymphoma or α heavy chain disease, is an uncommon and unusual type of gastrointestinal lymphoma that is included under the umbrella of MALT lymphoma in the current WHO classification scheme. Immunoproliferative small intestinal disease mainly occurs in the Middle East and arises in association with a morphologically benign-appearing infiltrate, often characterized by a dense, plasma cell proliferation in the intestinal mucosa. As opposed to the Western type of lymphoma commonly encountered in Europe and North America, IPSID tends to manifest as malabsorption instead of obstruction, presents in the duodenum or proximal jejunum rather than distal ileum, and exhibits villous atrophy as well as plasma cell infiltration of the adjacent intestine. Immunoproliferative small intestinal disease is either a lymphoma of MALT with a lymphoplasmacytic appearance or large cell, frequently immunoblastic plasmacytoid lymphoma with IgA heavy-chain restriction, which is related to α heavy chain disease with lack of the V region and light chains. The discovery of benign-appearing follicles, together with lymphomatous cells that conform to the centrocyte-like cells of MALT, add credence to the classification of IPSID as a form of extranodal marginal cell lymphoma of MALT type developing in mucosa-associated lymphoid tissue of the small intestine. The exact antigenic stimulus to form reactive follicles in IPSID is unknown, but recent molecular and immunohistochemical studies demonstrate a proposed association with Campylobacter jejuni, although this relationship remains tenuous. Patients at an early stage of mucosal involvement frequently respond to antibiotics, whereas patients whose disease evolves to large cell lymphoma, specifically the immunoblastic variant, classically have a better median survival than Western patients with de novo large B-cell lymphoma of the intestine.

**GASTROINTESTINAL T-CELL LYMPHOMAS, PREDOMINATELY ENTEROPATHY ASSOCIATED**

Most malignant lymphomas that complicate the diagnosis of celiac sprue are not IPSIDs but rather T-cell lymphomas. These cases have been designated as “enteropathy-associated T-cell lymphoma” (EATL) and they are characterized by prominent intramucosal lymphomatous spread and villous atrophy of uninvolved mucosa (Figure 5, A). T-cell lymphomas unassociated with malabsorption also develop in the intestine and cases may simulate the histologic pattern of EATL. T-cell lymphomas can involve any part of the gastrointestinal tract especially in patients in the Far East, and whereas some cases may be examples of EATL, the Far East is nonendemic for celiac disease and most cases in this geographic region are peripheral T-cell lymphomas, not otherwise specified (NOS), NK/T-cell lymphomas of nasal type, and cases linked with the human T-cell lymphotropic virus type 1. In the current WHO classification, EATL is divided into 2 forms. Patients with the first variant have features of celiac disease and may present with abdominal pain and even small intestinal perforation. The lymphomatous nature of the intestinal infiltrate usually is obvious, but the cases are cytologically mutable, ranging from cases containing neoplastic large cells with conspicuous nuclei; cases with pleomorphic, multinucleated cells; and cases dominated by small to medium-sized lymphocytes (Figure 5, B). Most examples of this type of EATL exhibit necrosis and infiltration by inflammatory cells, specifically histiocytes and eosinophils, which can obscure the lymphoma. Although occasionally subtle, the intestinal mucosa adjacent to the main tumor mass frequently exhibits enteropathy with villous atrophy, crypt hyperplasia, increased inflammatory cells in the lamina propria, as well as intraepithelial lymphocytosis.

Unlike the primary form of EATL, the type II variety exhibits villous atrophy, blunting, and intraepithelial lymphocytosis that is usually confined to the area of lymphoma and perhaps adjacent mucosa (Figure 5, C), whereas the more distant nonlymphomatous mucosa is effectively unremarkable and without villous atrophy. Despite inclusion as a form of EATL, paradoxically, most patients with type II disease do not have a history of celiac disease. The morphologic features of the lymphoma also differ, as the lymphomas in the type II cases tend to be more homogeneous and are composed of small to medium-sized lymphocytes with slightly irregular nuclei and small nucleoli surrounded by a rim of pale or clear cytoplasm (Figure 5, D). The type II form of EATL usually expresses CD8 and CD56 in contrast to expression of CD8 in only 20% and CD56 in fewer than 10% of cases of the more classic form of EATL. Both forms exhibit common genetic abnormalities with complex segmental gains of the 9q31.3 chromosomal region or with deletions in 16q12.1. Alternatively, the classic form of EATL associated with celiac disease frequently has chromosomal gains in 1q and 5q, whereas the type II variant is often characterized by 8q24 (MYC) amplifications. The HLA haplotypes also differ. Like patients with celiac disease, more than 90% of patients with the first type of EATL share the HLA-DQ2/DQ8 genotype, while the genotype found in type II EATL is more akin to that of normal white populations.

In Northern Europe, EATL generally is regarded as a complication of celiac disease, but in some patients no
Figure 5. Enteropathy-associated T-cell lymphoma (EATL) in a patient with celiac disease results in infiltration of the adjacent small intestinal mucosa with associated villous atrophy (A). The neoplastic T cells in EATL are frequently pleomorphic (B). In type II EATL, the neoplastic T cells also invade the adjacent mucosa, leading to villous blunting (C). The neoplastic T cells in the type II variant tend to be of medium size and are relatively homogenous (D). In the latter case, the neoplastic T cells expressed CD8 and CD56 versus the usual lack of reactivity for these antigens in classic EATL (not shown). EATL must be distinguished from NK-cell enteropathy, a newly described entity in which atypical cells infiltrate the lamina propria and encircle residual colonic glands (E). Despite the significant atypia, patients with NK-cell enteropathy experience a benign clinical course (hematoxylin-eosin, original magnifications x60 [A], x600 [B and D], x150 [C], and x200/0.75NA [E]). E, Reproduced with permission from Mansoor et al94 and courtesy of Elaine S. Jaffe, MD, Chief, Hematopathology Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland.
history of malabsorption exists and villous atrophy and crypt hyperplasia are discovered only at the time of lymphoma resection. Isaacs and Du and Ashton-Key and associates have demonstrated that EATL may be preceded by refractory celiac disease frequently associated with ulcers and referred to as “ulcerative jejunitis.” Polymerase chain reaction and sequence analysis showed that ulcerative lesions and unremarkable, normal-appearing intraepithelial lymphocytes share the identical monoclonal T-cell receptor rearrangement as the adjacent lymphoma. In refractory celiac disease, the intraepithelial lymphocytes may exhibit a normal CD3+ CD8+ immunophenotype, but they often are phenotypically anomalous with loss of surface CD3, and usually CD8, and also cytogenetically anomalous with partial trisomy of the 1q region in parallel to cases of EATL. Moreover, clonal T-cell gene rearrangements have been recorded in patients with refractory celiac disease who do not present with lymphoma, and in cases in which EATL later develops, the identical clone can be detected in the lymphoma. Such cases are regarded as “cryptic EATL” (EATL in situ) and patients with refractory celiac disease require continual monitoring of both intraepithelial lymphocyte immunophenotype and clonality because of the significant risk of the disease evolving to EATL.

The differential diagnosis of EATL includes not only large B-cell lymphoma of intestine, but also other forms of T-cell lymphoma including peripheral T-cell lymphoma NOS, anaplastic large cell lymphoma, and extranodal NK/T-cell lymphoma, nasal type. For example, the extranodal NK/T-cell lymphomas of nasal type that present in intestine exhibit the usual broad cytologic spectrum of that form of lymphoma, ranging from small to intermediate-size to large cells with marked nuclear pleomorphism. The adjacent mucosa does not exhibit villous atrophy. The lymphoma frequently demonstrates ulceration, angiectacticity, and angioinvasion with fibroid and coagulative necrosis. Phenotypically, the extranodal NK/T-cell lymphomas of nasal type express cytoplasmic, but not surface, CD3, CD5, and CD8. Unlike the type II form of EATL, the extranodal NK/T-cell lymphomas generally are CD8+ and also are negative for bF1. Most importantly, the NK/T-cell lymphomas of nasal type are Epstein-Barr virus positive as opposed to EATL. NK/T-cell lymphomas are clinically aggressive and the extranasal cases, encompassing those in the gastrointestinal tract, convey a statistically significant even worse prognosis. In general, patients with intestinal T-cell lymphoma fare worse than those with intestinal B-cell lymphoma.

One caveat is that EATL and extranodal NK/T-cell lymphoma must be distinguished from 2 similar, if not identical, newly described entities, “NK-cell enteropathy” or “lymphomatoid gastropathy,” especially in small endoscopic biopsy specimens. Patients present with either no or varying gastrointestinal symptoms, but have no features of celiac or inflammatory bowel disease. The atypical NK-cell infiltrates involve either single or multiple sites, including stomach, duodenum, small intestine, and colon. At endoscopy, multiple superficial, discrete, flat or hemorrhagic lesions may be observed or small (less than 1 cm), patchy, superficial ulcers are discovered. Biopsy specimens demonstrate a diffuse, well-circumscribed, mucosal infiltrate of atypical intermediate to large lymphoid cells with clear to eosinophilic cytoplasm and with invasion or destruction of mucosal glands (Figure 5, E). Acute inflammation may accompany the infiltrate. The atypical lymphocytes express cytoplasmic, but not surface, CD3, as well as CD56 and TIA-1. Similar to true NK-cell lymphomas of extranodal nasal type, the T-cell receptor in the enteropathy cases is germline; but, in contrast to NK nasal-type lymphomas, studies for Epstein-Barr virus using Epstein-Barr virus-encoded RNA yield negative results. Of most significance, and as opposed to both extranodal NK/T-cell lymphomas and EATL, patients with NK-cell enteropathy pursue an uneventful clinical course. The etiology of this syndrome is unknown.

GASTRIC LYMPHOMAS, ESPECIALLY MARGINAL ZONE LYMPHOMAS OF MALT TYPE

The morphologic features of extranodal marginal zone lymphoma of MALT type have witnessed gradual changes since the initial descriptions by Isaacs and Wright. Although originally interpreted to be of follicular center cell origin, the lymphoma cells of MALT were later designated as “centrocyte-like” and currently are termed marginal zone cells. Gastric lymphomas of MALT type typically are characterized by an expansion of the marginal-like zones surrounding benign, germinal centers (Figure 6, A and B). Marginal zone cells comprise a variety of cell types ranging from small to intermediate-sized lymphocytes to large cells. The marginal zone or centrocyte-like cells are small to medium-sized lymphocytes with variable nuclear membrane irregularities, resembling a centrocyte. Commonly, the marginal zone cells appear monocytoid with abundant pale-staining cytoplasm and well-delineated borders (Figure 6, C). Other forms of gastric MALT resemble small lymphocytes or are dominated by plasma cells to the extent of simulating a plasmacytoma. Signet ring–type cells also are described in gastric MALT lymphomas and appear to represent a curious type of lymphoepithelial lesion in which the foveolar cells, disaggregated by the lymphomatous infiltrate, attain a globoid, signet ring–type appearance. Regardless of cytoplogic composition, the marginal zone cells of MALT cells share immunophenotypic characteristics. Gastric MALT lymphomas are B cell derived with CD20 expression and frequently contain numerous admixed CD3+ reactive T cells. Despite the B cell phenotype, determination of monoclonality by immunoperoxidase in fixed, paraffin-embedded tissue usually is not possible with the exception of cases containing a conspicuous plasma cell component; however, up to 50% of cases exhibit aberrant coexpression of CD43 that can prove helpful in diagnosis (Figure 6, D). Unlike chronic lymphocytic leukemia/small lymphocytic lymphoma and mantle cell lymphoma, the lymphomas of MALT origin usually lack CD5 and are without bcl-1 gene rearrangements. Mucosa-associated lymphoid tissue lymphomas differ from follicular lymphomas in that they are CD10– and do not exhibit bcl-2 rearrangements. The absence of CD10 in gastric lymphoma with an apparent follicular architecture has been rationalized by the concept of “follicular colonization.” As noted earlier, follicular colonization refers to the replication of follicular lymphoma as a result of invasion by the marginal zone cells of MALT into preexisting reactive follicles (Figure 6, E and F).

The marginal zone cells of MALT invade not only residual reactive follicles but also epithelium. Epithelial invasion with frequent destruction by the B cells of MALT
Figure 6. In classic extranodal marginal zone lymphoma of MALT type, the lymphoid infiltrate in stomach is often massive (A). Residual germinal centers often are evident that are surrounded and encroached upon by the proliferating neoplastic marginal zone lymphocytes (B). The marginal zone lymphocytes exhibit irregular nuclear contours and frequently have pale-staining cytoplasm to impart a monocytoid appearance (C). The neoplastic marginal zone B cells may aberrantly coexpress CD43 in contrast to the absence of CD43 expression in a residual germinal center seen at the upper left (D). Gastric MALT lymphoma also may display a false follicular architecture (E) as the malignant marginal zone cells invade residual germinal centers referred to as “follicular colonization” (F) (hematoxylin-eosin, original magnifications ×60 [A and E], ×150 [B], ×600 [C], and ×300 [F]; immunoperoxidase, original magnification ×150 [D]).
has been referred to as a “lymphoepithelial lesion” and is a vital morphologic attribute in the diagnosis of gastric MALT-derived lymphomas. 4,9,34 An immunohistochemical stain for cytokeratin usually accentuates these lesions. Lymphoepithelial lesions are most noteworthy as a diagnostic trait in the stomach, but are less germane in other extranodal sites, since they may be observed in nonlymphomatous extranodal lymphocytic infiltrates. 10,33

In stomach, lymphoepithelial lesions usually are defined as invasion of gastric epithelium by 3 or more lymphomatous B cells. 20 A decade following the primary proposal for a lymphoma of MALT, a histologic scoring system for gastric MALT lymphoma was proposed in which invasion of epithelial structures or lymphoepithelial lesions is considered paramount to the diagnosis (Table 2). 12

With the scoring system, a definite diagnosis of low-grade B cell lymphoma of MALT is predicated on the existence of a dense, diffuse infiltrate of centrocyte-like cells/marginal zone cells in the lamina propria with prominent lymphoepithelial lesions. Cases regarded as suspicious lymphocytic infiltrates are those in which reactive follicles are surrounded by marginal zone cells that diffusely infiltrate into the lamina propria and into epithelium in small groups. 32 However, caution is required as dense infiltrates, slight cytologic atypia, and also lymphoepithelial-like lesions may be found in cases of lymphoid hyperplasia in the stomach. As well, the criteria may be difficult to apply. In an interobserver study, 9,17 pathologists, including hematopathologists, gastrointestinal pathologists, and general pathologists, reviewed 41 hematoxylin-eosin sections of stomach that ranged from simple gastritis to lymphoma. Interobserver reproducibility was suboptimal and the degree of disagreement was directly related to the experience of the pathologist in evaluating gastric biopsy specimens for MALT lesions. The study recommended that clinical information, extensive sampling, recognition of lymphoepithelial lesions, immunophenotypic information, and cytogenetic results would enhance diagnostic accuracy.99 This recommendation was supported by another report 100 stating that a combination of the morphologic scoring system and B cell clonality analysis by an advanced PCR method accurately discriminated chronic gastritis from covert gastric marginal zone lymphoma. Polymerase chain reaction was particularly valuable in the interpretation of cases that exhibited an ambiguous score of grade 3 or 4.

Currently, it is well established that most gastric marginal zone lymphomas of MALT arise in a setting of "acquired" MALT, whereby nonindigenous extranodal lymphoid tissue is acquired secondary to H pylori infection. 20,101,102 Ample epidemiologic, clinical, and histologic evidence effectively shows a fixed association between gastric MALT lymphomas and H pylori infection. 13,19,20,103–105 For example, in a collaborative study of more than 230,000 patients whose serum had been stored, 33 cases of gastric lymphoma developed in a median of 14 years after serum collection. 103 The patients with gastric lymphoma were significantly more likely than matched controls to have evidence of previous H pylori infection. In contrast, among 31 patients who developed nongastric, non–Hodgkin lymphoma, no association was discovered between this lymphoma and previous H pylori infection. 103 In addition, molecular analysis by PCR has documented the clonal progression from H pylori–associated chronic gastritis to MALT lymphoma of the stomach, and H pylori provides the antigenic stimulus for prolonging the clonal expansion of gastric MALT lymphomas. 13,19,108 Of most significance, antibiotic treatment with obliteration of H pylori usually leads to remission of gastric MALT lymphoma. 12,18,20,21,107

Clinically, gastric MALT lymphomas arise in adults with a peak in the seventh decade of life and with a male to female ratio of approximately 1.5:1. 18 Patients commonly present with nonspecific gastritis and/or a peptic ulcer and at endoscopy, reddened and slightly thickened rugae are often present with superficial spreading of lesions without formation of a tumor mass. 15 The gastric lesions commonly are multifocal and most patients have stage IE disease. 107,108 The link between H pylori and gastric MALT lymphoma led to antibiotic therapy for treatment of low-grade gastric lymphomas of MALT, and this therapy induces sustained remissions in more than 75% of patients. 21,107 Consequently, eradication of H pylori is the recommended primary therapy for almost all patients with MALT lymphoma of stomach irrespective of stage or even documentation of associated H pylori infection. 109,110 With a gastric mapping procedure, an initial follow-up endoscopy is recommended at 3 to 6 months after therapy for H pylori infection, and additional follow-up evaluations should be done at 4- to 6-month intervals for 2 years. 109,110 For patients monitored for up to 2 years whose disease remains refractory to H pylori therapy, other modalities, such as radiotherapy, chemotherapy, or combined treatment are offered; however, no consensus exists for the optimal treatment of primary gastric lymphoma unresponsive to H pylori therapy, particularly

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<thead>
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<th>Grade</th>
<th>Description</th>
<th>Histologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Plasmacytoid cells in LP</td>
</tr>
<tr>
<td>1</td>
<td>Chronic active gastritis</td>
<td>No lymphoid follicles</td>
</tr>
<tr>
<td>2</td>
<td>Chronic active gastritis with florid lymphoid follicle formation</td>
<td>Lymphocyte clusters in LP</td>
</tr>
<tr>
<td>3</td>
<td>Suspicious lymphoid infiltrate in LP, probably reactive</td>
<td>No follicles, LELs</td>
</tr>
<tr>
<td>4</td>
<td>Suspicious lymphoid infiltrate in LP, probably lymphoma</td>
<td>Prominent follicles with surrounding mantle zone and plasma cells</td>
</tr>
<tr>
<td>5</td>
<td>Marginal zone (MALT) lymphoma</td>
<td>Follicles surrounded by lymphocytes that infiltrate diffusely in LP and/or epithelium</td>
</tr>
</tbody>
</table>

Abbreviations: CCL, centrocyte-like; LELs, lymphoepithelial lesions; LP, lamina propria; MALT, mucosa-associated lymphoid tissue; MZC, marginal zone cells.

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GI Lymphoproliferative Disorders—Burke
with evidence of progressive lymphoma, although recent analysis of pooled data proposed that radiotherapy may be most appropriate in this setting. Overall, gastric MALT lymphoma is indolent and in one study of this lymphoma treated by various modalities, the 5-year projected overall survival was 82%.16

One significant issue for pathologists is the interpretation of stomach biopsy specimens after antibiotic therapy for gastric MALT lymphoma. Clearly, no diagnostic problem exists if the biopsy specimen reveals regression of the lymphoma with loss of lymphocytic aggregates in the lamina propria (Figure 7, A) or if the specimen exhibits a total absence of histologic regression with persistence of lymphoma. Parallel to the histologic scoring system used for the initial diagnosis of gastric marginal zone lymphoma, a histologic grading system has been proposed for treated patients which evaluates not only the cellular infiltrate and lymphoepithelial lesions but also stromal changes (Table 3).16–18 The probable minimal disease category does not signify a requirement for further therapy and patients are managed with follow-up as though they were in remission.12–14 For patients with responding residual disease (Figure 7, B) or no change, clinical management consists of as discussed above, careful follow-up and a watch-and-wait approach for up to 2 years in the absence of disease progression.13

Of interest, approximately 50% of patients with histologically negative gastric biopsy findings after antibiotic therapy exhibit persistent monoclonality by PCR, although in some patients the clonality disappears with prolonged follow-up. For other patients, continued monoclonality may result in a delay in realizing remission. However, after antibiotic therapy for gastric MALT lymphoma, the association between ongoing monoclonality and risk of relapse is tenuous. One bone of contention is that serial gastric biopsy specimens frequently exhibit an oscillating clonal status, due perhaps to sampling or recurrent H pylori infection. Therefore, except for clinical investigations, the determination of clonality with PCR currently is not considered pragmatic or recommended in the evaluation of posttherapy gastric MALT lymphoma biopsy specimens.21

The establishment of extranodal gastric marginal zone lymphoma of MALT type as a recognized clinicopathologic entity has progressed to incorporate molecular genetics and specific chromosomal translocations. For MALT lymphomas in general, the genetic abnormalities encompass trisomies 3, 12, and 18, as well as balanced translocations, specifically t(11;18)(q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32), and t(3;14)(p14;q32). The most common translocation in gastric MALT lymphoma arising in approximately 20% to 30% of cases (although at a lower rate in North America) is t(11;18)(q21;q21), which fuses the amino terminal of the API2 gene (that encodes the inhibitor of apoptosis) at 11q21 to the carboxy terminal of MALT1 at 18q21, leading to a chimeric fusion product. The API2-MALT1 fusion protein is detectable by interphase fluorescence in situ hybridization or reverse transcription-PCR (RT-PCR). MALT1 is involved in antigen receptor–mediated nuclear factor (NF)-κB activation and MALT lymphomas that express the translocation exhibit enhanced expression of NF-κB target genes, whereas MALT lymphomas without t(11;18)(q21;q21) support active inflammatory and immune responses. The t(11;18)(q21;q21) translocation is restricted to extranodal MALT lymphomas and has not been reported in other forms of marginal zone lymphoma, such as splenic or nodal, or in chronic gastritis associated with H pylori.

Gastric MALT lymphomas without t(11;18)(q21;q21) often exhibit aneuploidy, for example, trisomy 3, 12, or 18. With endosonographic staging, such (t;11;18)(q21;q21)-positive patients whose condition does not respond to H pylori eradication with antibiotics may have lymphoma that has proliferated beyond the gastric submucosa into muscularis and/or serosa in contrast to patients with lymphoma limited to the mucosa and submucosa who generally are t(11;18)(q21;q21) negative. Moreover, t(11;18)(q21;q21) is uncommon in extranodal diffuse large B-cell lymphoma, and for patients harboring this translocation, the disease rarely metamorphoses to diffuse large B-cell lymphoma. In contrast, patients with aneuploidy, who are t(11;18)(q21;q21) negative with lymphoma unresponsive to H pylori treatment, are at risk of having the disease evolve to diffuse large B-cell lymphoma. For example, microsatellite screening of gastric MALT and large B-cell lymphomas displays allelic imbalances limited to t(11;18)(q21;q21)-negative patients, which are shared by both MALT and diffuse large B-cell lymphomas; this observation advocates that the absence of t(11;18)(q21;q21) is the genesis of most MALT lymphomas that convert to one of large B-cell type. One recent report, however, deviated from this prevailing view by documenting t(11;18)(q21;q21) in 19% (6 of 31) of cases of gastric large B-cell lymphoma. Further investigations obviously are required, but for patients whose condition does not respond to anti-H pylori therapy, it remains of interest to ascertain whether or not the gastric marginal zone lymphoma of MALT type is t(11;18)(q21;q21) positive, since this information carries prognostic and therapeutic repercussions. Nonetheless, routine determination of the t(11;18)(q21;q21) status is controversial since, from a clinical perspective, (t;11;18)(q21;q21)-positive patients also are treated initially for H pylori infection, and no definite data exist to indicate that determining the status of t(11;18)(q21;q21) in the course of follow-up has a direct bearing on therapeutic decisions.

By current criteria, marginal zone lymphoma of MALT type is strictly an indolent or low-grade extranodal lymphoma. Despite the considerable recent emphasis on MALT-type lymphomas, in fact almost 60% of gastric lymphomas are diffuse large B-cell lymphomas. As noted previously, with the exception of small gastroscopic biopsy specimens, differentiation of large cell lymphoma from other large cell malignancies usually is not a morphologic issue, but, immunohistochemical verification is recommended. One consequential diagnostic issue is the observation of large cells in a background of a marginal zone lymphoma of MALT type in a gastric biopsy specimen. No current consensus prevails as to how many large cells are required to establish the evolution from MALT lymphoma to one of diffuse large B-cell type. Undoubtedly, the presence of large cells in discrete nodular aggregates or sheets is likely an indication of transformation; however, diagnostic difficulties ensue for cases in which large cells are numerous and diffusely admixed with small marginal zone lymphocytes.
In one study of 106 patients with gastric MALT lymphomas, the prognostic influence of a large cell component was assessed by semiquantitative analysis of clusters and diffusely intermingled malignant large cells in MALT lymphomas, the observation of a diffuse large cell component in the range of 1% to 10%, with and without nonconfluent clusters of large cells, portended a significantly worse prognosis. Yet, in a report from Italy, the presence of scattered large cells that comprised 5% to 10% of the MALT lymphoma cell population was regarded as prognostically irrelevant, whereas compact clustered large cells that represented more than 10% of the MALT lymphoma proved significant, as they were associated with a worse survival. Cases of putative large B-cell lymphoma in a background of gastric MALT lymphoma typically express bcl-6, but not CD10 and bcl-2.

SUMMARY: A PRAGMATIC GUIDE TO DIAGNOSIS

How then does a surgical pathologist arrive at an accurate diagnosis of suspected gastric marginal zone lymphoma, principally in light of the vagary of the histologic scoring scheme? An appropriate integrated algorithm and diagnostic recommendations have been proposed, but the all-too-common issue of a gastric biopsy specimen containing a solitary enlarged lymphocytic nodule composed of small lymphocytes without evident germinal centers remains ambiguous and a diagnostic conundrum (Figure 8). Such biopsy specimens evoke a broad differential diagnosis ranging from gastritis to malignant lymphoma, which encompasses not only extranodal marginal zone lymphoma of MALT type but also other lymphomas composed of small lymphocytes, including chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, and even follicular lymphoma. In this scenario, the foremost role of the pathologist is vigilant assessment of the histologic features by the conscious determination of whether any cytologic atypia exists, whether the cells appear monocytoid, whether plasma cells are increased, and whether lymphoepithelial lesions are evident. Although morphology remains the standard for diagnosis, the morphologic characteristics require supplementation by an immunoperoxidase panel, primarily CD20 and CD3, as well as CD43 and/or CD5, CD21, and possibly cytokeratin and, if plasma cells are numerous, staining for \( k \) and \( l \) light chains. Such staining will determine whether an aberrant immunophenotype is present, as for example, a predominance of CD20\(^+\) B cells, and whether the B lymphocytes exhibit coexpression with CD43 or CD5, whether the cytokeratin stain highlights lymphoepithelial lesions, whether occult germinal centers exist by positive reactivity for CD21 to imply follicular colonization, and whether a monoclonal plasma cell population is evident with \( k \) or \( l \) light-chain restriction. For example, CD5 coexpression should trigger staining for cyclin D1 to exclude mantle cell lymphoma. If the morphologic and immunophenotypic study results in this setting are strongly suggestive of, but not absolutely diagnostic of,
In this scenario, interpretation of the histologic, immunophenotypic, and molecular studies must be placed in context of the clinical milieu, particularly with the awareness that chronic active gastritis may exhibit immunoglobin gene rearrangements without features of clinical malignant lymphoma in follow-up studies.\textsuperscript{26,30,131} Because of this fact and because ambiguous cases can be treated and usually respond to therapy for \textit{H pylori}, some are of the opinion that routine PCR analysis is unnecessary.\textsuperscript{132} However, our practice prefers to be as resolute as possible in establishing a diagnosis; thus, discovery of a positive B-cell gene rearrangement by PCR is beneficial in the instance of an equivocal lymphocytic infiltrate.\textsuperscript{100} If the PCR study results prove negative, the possibility of lymphoma in the ambivalent lymphocytic infiltrate persists so that a descriptive diagnosis is required and, depending on the clinical features, is a call for repeated biopsy with reservation of fresh tissue to determine clonality, whether by flow cytometry or snap freezing, with suitable immunoperoxidase studies. Although flow cytometry may not be a routine procedure for investigating gastric biopsy specimens, it is a valuable technique for rapidly demonstrating clonality and securing an absolute diagnosis.\textsuperscript{28} At the time of a repeated biopsy, at least 10 samples are submitted without fixative from abnormal-appearing gastric mucosa.\textsuperscript{110} After obtaining and interpreting touch imprints from several biopsy fragments, the multiple biopsy specimens are triaged, with submission of pooled samples to flow cytometry and the remainder for routine microscopy with fixation in B5 and/or formalin. Molecular studies also can be requested at this stage if the new biopsy findings remain suspicious and the flow cytometry and/or snap frozen–tissue studies prove ineffective. Should the new biopsy specimen be successful in providing a definitive diagnosis of gastric MALT lymphoma, but without evidence of \textit{H pylori}, then detection of t(11;18)(q21;q21) by fluorescence in situ hybridization or reverse transcription-PCR remains an option and can also aid in diagnosis.\textsuperscript{25,110,133} Despite these additional ancillary studies, the diagnosis may still remain unresolved. Since significant therapeutic consequences exist in rendering a verdict of extranodal marginal zone lymphoma of MALT type, in a setting of uncertainty, a more fitting, noncommittal diagnosis might be an "atypical lymphocytic infiltrate of uncertain malignant potential."\textsuperscript{22,33,4,135} Regardless of the terminology, it remains incontrovertible that the diagnosis of gastric marginal zone MALT lymphoma depends on adherence to exacting pathologic criteria augmented by immunophenotypic and judicious molecular and/or cytogenetic studies.

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