# GASTRIC LYMPHOMAS:
# 25+ Years of Revolution/Evolution

**Jerome S. Burke, MD**
Department of Pathology
Alta Bates Summit Medical Center
Berkeley, California

The gastrointestinal tract is the most common location of extranodal lymphomas and the stomach in particular serves as an excellent model to illustrate many of the general issues concerning extranodal lymphomas. The stomach is the most frequent site of involvement of extranodal gastrointestinal lymphomas with small intestine second in frequency. Large intestinal and rectal lymphomas are less common, but are found in patients with AIDS and occasionally as a complication of ulcerative colitis and Crohn disease. In a study of 371 patients with primary gastrointestinal lymphomas registered in a German Multicenter Study, stomach accounted for 277 of cases ((74.8%). Curiously, the incidence of primary gastric lymphomas in the United States is increasing, specifically in patients over 60 years of age; this increase appears independent of the AIDS epidemic and the now common diagnosis of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type.

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. Moreover, since the initial descriptions of lymphomas of MALT in 1983 and 1984 by Drs. Peter Isaacson and Dennis Wright, the criteria have evolved and expanded to encompass not only morphologic standards, specifically a more precise definition of various cell types in MALT lymphoma, the 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, but also to embrace immunophenotypic, biologic, molecular genetic and clinical discoveries. Such developments include refinement of the immunophenotype, the association of gastric MALT lymphoma and *Helicobacter pylori* infection, the notion of acquired MALT, the biology of auto-antigen activation and continuous somatic mutations, genetic aberrations, as for example the discovery of the t(11;18)(q21;q21) chromosomal translocation in lymphomas of MALT, and the clinical implications of specific cytogenetic alterations.

## Revolution – Florid Gastric Lymphoid Hyperplasia ("Pseudolymphoma") is Likely Malignant Lymphoma!

In establishing a histologic diagnosis of an extranodal lymphoma, pathologists are aware that various reactive lymphoid hyperplasias exist that mimic extranodal lymphomas clinically and pathologically, such as gastric lymphoid hyperplasia and chronic lymphocytic gastritis. To complicate matters, malignant lymphoma of extranodal marginal zone (MALT) type may develop in association with these reactive lymphoid infiltrates in the stomach.

In the 1960's and 1970's, the morphologic criteria to distinguish extranodal lymphoma from extranodal lymphoid hyperplasia were extrapolated from those used traditionally to distinguish malignant lymphoma from lymphoid hyperplasia in lymph nodes. The major criteria for this distinction included monomorphic lymphocytic infiltrates, cellular atypia, germinal centers and architectural disruption (Table 1).

**Table 1**
***Traditional Histologic Criteria for Distinguishing Extranodal Lymphomas from Lymphoid Hyperplasias***

| Extranodal Lymphomas | Lymphoid Hyperplasias |
|---|---|
| Infiltrate monomorphous | Infiltrate polymorphous (lymphocytes in stages of transformation) |
| Cytologic atypia | Cytologic maturity (lymphocytes, plasma cells, and immunoblasts) |
| Germinal centers uncommon | Germinal centers common (usually in center of infiltrate) |
| Massive infiltration with architectural destruction | Random infiltration with architectural retention |

Because more than 50% of gastric lymphomas are large B cell lymphomas with associated monomorphism, cellular atypia, and architectural destruction (e.g., obliteration of glands), these traditional criteria generally have proven to be reliable and applicable Reactive lymphoid conditions that are at the opposite end of the spectrum equally do not pose diagnostic problems. Lymphocytic infiltrates that exhibit polymorphism, that display a range of mature lymphocytes (including plasma cells and immunoblasts), that are associated with well-defined germinal centers and that do not destroy completely the architectural landmarks of the stomach usually can be diagnosed confidently as benign and reactive.

The main difficulty in the separation of gastric extranodal lymphomas from

lymphoid hyperplasias concerns MALT lymphomas that are composed of small lymphocytes and that frequently are associated with germinal center formation. For these cases, the traditional histological criteria are not applicable. Multiparameter studies have revealed that many histologically ambiguous extranodal small lymphocytic proliferations in stomach are, in fact, monoclonal and, therefore, are presumed to be malignant lymphomas especially of MALT type. The application of immunologic and molecular genetic analyses to gastric small lymphocytic proliferations has served to vividly alter the traditional histologic criteria and has revealed myriad inconsistencies in these criteria (Table 2). For example, in a review of 97 cases originally diagnosed as gastric pseudolymphoma between 1970 and 1985 at the AFIP, 79% were reclassified as malignant lymphoma, with fully two-thirds of the newly classified lymphomatous cases interpreted as lymphomas of MALT type. The remaining cases were regarded as examples of lymphoid hyperplasia or atypical lymphocytic infiltrates. Consequently, the term "pseudolymphoma" is regarded as imprecise and anachronistic and no longer is acceptable as a diagnostic category.

**Table 2**
***Modifications of the Traditional Histologic Criteria for Distinguishing Extranodal Lymphomas From Lymphoid Hyperplasia***

- Extranodal lymphomas may be polymorphous (e.g., peripheral T cell lymphomas)
- Extranodal lymphomas may be composed of cytologically mature-appearing lymphocytes (marginal zone lymphoma of MALT type and other low-grade lymphomas with or without plasma cell differentiation)
- Germinal centers may be observed at the periphery of extranodal lymphomas and in the centers of many low-grade extranodal lymphomas, especially those of MALT type
- Degree of infiltration, architectural and epithelial destruction is highly variable in benign and malignant extranodal lymphocytic infiltrates

The conventional view was that extranodal lymphomas are characterized by nuclear membrane irregularities or atypia. Marginal zone lymphomas of MALT type, however, are cytologically mutable. Although MALT lymphomas typically are composed of marginal zone or centrocyte-like cells in the marginal zones, they also may have a monocytoid appearance, or they be composed of plasma cells, or they may have no, or only subtle, nuclear membrane irregularities similar to the cells of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); the latter variant often is readily confused with extranodal lymphoid hyperplasia. A small lymphocytic proliferation that appears mature is the histologic norm of most cases of gastric lymphoid hyperplasia, yet cytologic maturity or minimal atypia is equally the histologic hallmark of most low-grade malignant lymphomas including those of MALT. How then

can these two groups be distinguished in a small biopsy specimen? In many cases, it is impossible to do when applying only histological criteria. This histologic dilemma prompted the use of the noncommittal term "extranodal small lymphocytic proliferation" to describe histologically ambiguous or indeterminate extranodal lymphocytic infiltrates. Current morphologic criteria used to separate a benign small lymphocytic infiltrate from a malignant small lymphocytic infiltrate includes the designations of whether the infiltrate is monomorphous, dense, or exhibits cytologic atypia or Dutcher bodies and whether this results in destruction of glands, follicles, or other structures indigenous to the stomach. If these morphologic features are unequivocally present, then the lymphocytic infiltrate likely is malignant lymphoma (see Table 3).

Our perspective of the small extranodal lymphocytic proliferations that appear mature has revised dramatically with the application of immunologic markers to analyze the clonality of these lesions. Correlative immunopathologic studies have now reduced the number of cases regarded as atypical or indeterminate. Naturally, cases remain, especially small biopsy specimens, in which the histologic features or immunologic findings remain equivocal; these cases should receive not only a descriptive diagnosis but also a request for a repeat biopsy with reservation of fresh tissues to determine clonality, whether by immunohistochemistry, flow cytometry, molecular techniques, or a combination thereof. When only fixed, paraffin-embedded tissues are available, a consistent determination of clonality in a biopsy specimen dominated by small lymphocytes usually is not possible in most laboratories. In some cases, however, immunologic studies of paraffin-embedded tissues can reveal an aberrant phenotype in the suspicious small lymphocytic population, such as the coexpression of B cell antigen CD20 and T cell antigen CD43. In most instances, the aberrant immunophenotype supports the diagnosis of an extranodal gastric B cell lymphoma. Prudence is necessary in the evaluation of immunoglobulin gene rearrangement studies employing polymerase chain reaction (PCR) techniques in fixed paraffin-embedded tissues; small monoclonal bands may occur in extranodal reactive lymphoid hyperplasias, as for example in chronic active gastritis associated with *Helicobacter pylori*.

As well as diagnostic problems encountered with the gastric lesions dominated by small lymphocytes, benign reactive germinal centers (lymphoid follicles) pose another risk in diagnosis. The presence of germinal centers is a commonly accepted histologic attribute of extranodal lymphoid hyperplasias. Germinal centers, however, are regular constituents of most gastric lymphomas of MALT. The essential morphologic characteristic of MALT lymphomas is their emulation of normal MALT as typified by Peyer patches found in the terminal ileum. The neoplastic B cells of MALT lymphomas are found in marginal-type zones surrounding reactive follicles and frequently attenuated rims of mantle zone lymphocytes. The germinal centers vary in appearance but commonly appear atrophic as a result of impingement by the

surrounding small lymphocytes. In MALT lymphomas of the stomach associated with peptic ulceration, germinal centers occur at the base of the ulcer and in the adjacent mucosa where they seem encroached upon and entrapped by the monotonous marginal zone lymphocytes. In some cases, the neoplastic B cells in the marginal zone invade the germinal centers in a process referred to as "follicular colonization." Follicular colonization may simulate follicular lymphoma in cases where there are numerous follicles. At times, the lymphomatous proliferation may be so extensive as to result in architectural obliteration with masking of any residual germinal centers; however, the presence of former germinal centers can be highlighted by the immunohistochemical demonstration of follicular dendritic cells employing an antibody against CD21 or CD23.

## Evolution – Refinement of Morphologic Criteria, Immunophenotype, Biology, Molecular Genetics and Clinical Therapy of Gastric MALT Lymphomas

The morphologic features of extranodal marginal zone lymphoma of MALT type have witnessed gradual changes since the initial descriptions by Isaacason and Wright. Although originally thought to be of follicular center cell origin, the lymphoma cells of MALT were later designated as "centrocyte-like" and currently are termed as "marginal zone cells." Gastric lymphomas of MALT type typically are characterized by an expansion of the marginal-like zones surrounding benign germinal centers. As described, marginal zone cells constitute a variety of cell types ranging from small, to intermediate-sized lymphocytes, to large cells resembling immunoblasts. The marginal zone or centrocyte-like cells are small to medium-sized lymphocytes with variable nuclear membrane irregularities resembling a centrocyte or small cleaved cell. The most common form has abundant pale-staining cytoplasm and is referred to as monocytoid. Others forms of gastric MALT exhibit plasmacytoid features or resemble small lymphocytes. Occasionally, signet ring-type cells are observed in gastric MALT lymphomas and appear to represent a peculiar type of lymphoepithelial lesion in which the foveolar cells, disaggregated by the lymphomatous infiltrate, acquire a globoid, signet ring-type appearance. Regardless of cytologic composition, the marginal zone cells of MALT cells share immunophenotypic characteristics. Gastric MALT lymphomas are B cell derived with CD20 expression and frequently containing numerous admixed CD3-positive reactive T cells. Up to 50% of cases exhibit aberrant coexpression of CD43 which can prove helpful in diagnosis. Unlike CLL/SLL and mantle cell lymphomas, the lymphomas of MALT origin lack CD5 and are without *bcl*-1 gene rearrangements. MALT lymphomas differ from follicular lymphomas in that they are CD10 negative and do not exhibit rearrangements of the *bcl*-2 proto-oncogene. The absence of CD10 and *bcl*-2 positivity in gastric lymphoma with an apparent follicular architecture has been rationalized by the concept of "follicular colonization". As discussed above, follicular colonization refers to the simulation of a follicular lymphoma as a result of invasion by the marginal zone cells of MALT into pre-existing reactive follicles.

The marginal zone cells of MALT not only are thought to invade residual reactive follicles, but also epithelium. As mentioned previously, epithelial invasion by the centrocyte-like cells of MALT has been referred to as a "lymphoepithelial lesion" and is an important morphologic feature in the diagnosis of gastric MALT-derived lymphomas. Such lesions may be accentuated by an immunohistochemical stain for cytokeratin. Lymphoepithelial lesions are most significant as a diagnostic characteristic in the stomach, but are less relevant in other extranodal sites since they may be observed in non-lymphomatous extranodal lymphocytic infiltrates. In stomach, lymphoepithelial lesions usually are defined as invasion of gastric epithelium by three or more lymphomatous cells. 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 3).

**Table 3**
***Gastric Marginal Zone (MALT) Lymphomas: Histologic Scoring****

| Grade | Description | Histologic Features |
|---|---|---|
| 0 | Normal | Plasma cells in lamina propria<br>No lymphoid follicles |
| 1 | Chronic active gastritis | Lymphocyte clusters in lamina propria<br>No follicles, lymphoepithelial lesions |
| 2 | Chronic active gastritis with florid lymphoid follicle formation | Prominent follicles with surrounding mantle zone & plasma cells<br>No LELs |
| 3 | Suspicious lymphoid infiltrate in LP, probably reactive | Follicles surrounded by lymphocytes that infiltrate diffusely in LP and +/- epithelium |
| 4 | Suspicious lymphoid infiltrate in LP, probably lymphoma | Follicles surrounded by CCL cells (MZC) that infiltrate diffusely in LP & epithelium |
| 5 | MZ (MALT) lymphoma | Dense diffuse infiltrate of CCL cells in LP with prominent LELs |

**Lancet 1993:342:575-577*

Employing the scoring system, a definite diagnosis of low-grade B cell lymphoma of MALT is based on the presence 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. However, caution is required as there may

be dense infiltrates, slight cytologic atypia, and also lymphoepithelial-like lesions in cases of lymphoid hyperplasia in the stomach. As well, the criteria may be difficult to apply. In an interobservor study, 41 H&E sections of stomach that ranged from simple gastritis to lymphoma were reviewed by 17 pathologists, including hematopathologists, gi pathologists and general pathologists. Interobservor reproducibility was suboptimal and the degree of disagreement was directly related to the pathologist's experience in evaluating gastric biopsies for MALT lesions. The study recommended that diagnostic accuracy would be enhanced by clinical information, extensive sampling, recognition of lymphoepithelial lesions, immunophenotypic information and cytogenetic results. This recommendation was supported by another report 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. PCR was particularly valuable in the interpretation of cases that exhibited an ambiguous score of grade 3 or 4.

Paradoxically, most MALT-type lymphomas arise in extranodal sites without normal MALT, such as the stomach, while non-MALT lymphomas, for example Burkitt lymphoma, arise in MALT sites. In order to resolve this apparent paradox, it was proposed that lymphomas in non-MALT sites arise in a setting of "acquired" MALT. This non-indigenous extranodal lymphoid tissue is thought to be acquired secondary to an infection, such as *Helicobacter pylori* in the stomach, or an autoimmune disease. The lymphoid infiltrates in stomach associated with *Helicobacter pylori* seemingly predispose patients to malignant lymphoma. There currently is sufficient histological, clinical, and epidemiologic evidence for the virtually fixed association of gastric MALT lymphomas with *Helicobacter pylori* infection, particularly the CagA strain. For example, in a collaborative study of more than 230,000 patients whose serum had been stored, 33 cases of gastric lymphoma developed a median of 14 years after serum collection. The patients with gastric lymphoma were significantly more likely than matched controls to have evidence of previous *Helicobactor pylori* infection. In contrast, no association was discovered among 31 patients who had developed nongastric non-Hodgkin lymphoma and previous *Helicobactor pylori* infection. In addition, molecular analysis by PCR has documented the clonal progression from *Helicobacter pylori*-associated chronic gastritis to MALT lymphoma of the stomach and *Helicobactor pylori* provides the antigenic stimulus for prolonging the clonal expansion of gastric MALT lymphomas. This view has been supported by Isaacson's group who have exhibited evidence of ongoing Ig gene mutations in most case of MALT-type lymphoma. The discovery of ongoing mutations reinforces the perception that direct antigen stimulation is paramount in the clonal expansion of gastric MALT lymphomas.

Clinically, gastric MALT lymphomas arise in adults with a peak in the seventh decade and with a male:female ratio of approximately 1.5:1. Patients commonly present with nonspecific gastritis and/or a peptic ulcer and at endoscopy, there often are reddened and slightly thickened rugae with superficial spreading of lesions without

formation of a tumor mass. The gastric lesions commonly are multifocal and most patients have stage IE disease. The linkage of *Helicobacter pylori* with gastric MALT lymphoma led to antibiotic therapy for treatment of low-grade gastric lymphomas of MALT and this therapy may induce sustained remissions in about 75% of patients. There are no apparent differences in survival and relapse-free survival between patients treated with antibiotics and with other modalities, such as local treatment, combined treatment, or chemotherapy; in fact, no consensus exists for the optimal treatment of primary gastric lymphoma. In one study of gastric MALT lymphomas treated by various modalities, the five year projected overall survival was 82%. One significant issue for pathologists is the interpretation of stomach biopsy specimens following antibiotic therapy for gastric MALT lymphoma. Clearly, no diagnostic problem exists if the biopsy reveals regression of the lymphoma with loss of lymphocytic aggregates in the lamina propria or if the biopsy exhibits a total absence of histological regression with persistence of lymphoma. Parallel to the histological scoring system employed for the initial diagnosis of gastric marginal zone lymphoma, a histological grading system has been proposed for treated patients. (Table 4).

**Table 4**
***Gastric MZ (MALT) Lymphoma: Post-Therapy Grading****

| Score | Lymphoid Infiltrate | LEL | Stromal Changes |
|---|---|---|---|
| CR | Absent or scattered plasma cells & small lymphoid cells in the LP | – | Normal or empty LP &/or fibrosis |
| pMRD | Aggregates of lymphoid cells or lymphoid nodules in the LP/MM &/or SM | – | Empty LP &/or fibrosis |
| rRD | Dense, diffuse, or nodular extending around glands in the LP | +/- | Focal empty LP &/or fibrosis |
| NC | Dense, diffuse, or nodular | +/- | No changes |

CR, complete histologic remission; pMRD, probable minimal residual disease;
rRD, responding residual disease; NC, no change;
LEL, lymphoepithelial lesions; LP, lamina propria; MM, muscularis mucosa; SM, submucosa
**Gut 2003;52:1656*

The probable minimal disease category (pMRD) does not signify a requirement for further therapy and patients are managed with followup as though they were in remission. Of interest, approximately 50% of patients with histologically negative post-antibiotic therapy gastric biopsies (CR/pMRD) exhibit persistent monoclonality, although in some patients the clone disappears with prolonged followup. In other patients, continued monoclonality may result in a delay in realizing remission.

However, following antibiotic therapy for gastric MALT lymphoma, the association between ongoing monoclonality and risk of relapse is tenuous. One bone of contention is that that serial gastric biopsy specimens frequently exhibit an oscillating clonal status, due perhaps to sampling or recurrent *Helicobacter pylori* infection. Therefore, except for clinical investigations, the determination of clonality employing PCR currently is not considered pragmatic or recommended in the evaluation of post-therapy gastric MALT lymphoma biopsy specimens.

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 20-30% of cases (although lower in North America) is t(11;18)(q21;q21) in which the t(11;18) fuses with amino terminal of the inhibitor of apoptosis *API2* at 11q21 to the carboxyl terminal of *MALT1* at 18q21 leading to a chimeric fusion product. *MALT1* is involved in antigen receptor-mediated NFκB activation. The *API2-MALT1* fusion product is detectable by FISH. The t(11;18)(q21;q21) 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 *Helicobacter pylori*. Gastric MALT lymphomas without a t(11;18)(q21;q21) often exhibit aneuploidy, as for example trisomy 3 or 18.

In this decade, the discovery of t(11;18)(q21;q21) in some patients with gastric MALT lymphoma has led to exciting clinical prognostic correlations. Specifically, patients with gastric MALT lymphoma who prove positive for t(11;18)(q21;q21) often fail to respond to *Helicobacter pylori* therapy and this translocation frequently arises in patients who are *Helicobacter pylori* negative. Employing endosonographic staging, such t(11;18)(q21;q21) positive patients who do not respond to *Helicobacter pylori* eradication with antibiotics are found to have disease that has spread 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 patients with this translocation rarely metamorphose to diffuse large B cell lymphoma. In contrast, aneuploid t(11;18)(q21;q21) negative patients who are unresponsive to *Helicobacter pylori* treatment are at risk to evolve to diffuse large B cell lymphoma. For example, microsatellite screening of gastric MALT and large B cell lymphomas display alleic imbalances limited to t(11;18)(q21;q21) negative patients that are shared by both MALT and diffuse large B cell lymphomas; this observation indicates that t(11;18)(q21;q21) negative patients are the genesis of MALT lymphomas than convert to one of large B cell type. It is therefore paramount to ascertain as to whether or not the gastric marginal zone lymphoma of MALT type is t(11;18)(q21;q21) positive since this information has prognostic and therapeutic repercussions.

In the 1990's, many diffuse large B cell lymphoma cases of stomach were designated as "high-grade MALT lymphoma" based on the belief that these cases had transformed from "low-grade MALT lymphoma" especially when both components were present in a single specimen. Despite the likelihood that such transformations occur, the term "high-grade MALT lymphoma" presently is discouraged and all such cases are interpreted as large B cell lymphoma. By current definition, 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, greater than 50% of gastric lymphomas are high-grade, diffuse large B cell lymphomas. Except in small gastroscopic biopsy specimens, differentiation of large cell lymphoma from carcinoma usually is not a problem in view of the tendency of the lymphomas to be diffuse, massive, and lacking in cohesive cell aggregates. Nonetheless, immunohistochemical verification of diagnosis is recommended and is particularly valuable in delineating cases of large cell lymphoma from gastric adenocarcinoma. The infiltration by lymphoma around, or into, partially intact gastric glands, negative mucin and keratin stains, positive reactivity for CD20, and the lack of syncytial cell aggregates or malignant acinar formation aid in the distinction of large cell lymphoma from poorly differentiated adenocarcinoma, even in small biopsy specimens. Small gastric biopsy specimens, however, are subject to sampling errors and artifactual distortion, and on occasion it may be necessary to request a second biopsy, in order to render a more complete pathologic examination.

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 exists as to how many large cells are required to establish the evolution from MALT lymphoma to one of diffuse large B cell type. Clearly, the presence of large cells in discrete nodular aggregates or sheets is likely an indication of transformation; however, diagnostic difficulties remain for cases in which the large cells are numerous and diffusely admixed with small marginal zone lymphocytes. In one study of 106 patients with gastric MALT lymphomas, the prognostic impact 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 1-10%, with and without non-confluent clusters of large cells, predicted a significantly worse prognosis. In a report from Italy, the presence of scattered large cells that comprised 5–10% 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.

## References

Abbondanzo SL, Sobin LH. Gastric "pseudolymphoma": a retrospective morphologic and immunophenotypic study of 97 cases. Cancer 1997;79:1656-1663.

Algara P, Martinez P, Sanchez L, et al. The detection of B-cell monoclonal populations by polymerase chain reaction: accuracy of approach and application in gastric endoscopic biopsy specimens. Hum Pathol 1993;24:1184-1188.

Almasri NM, Zaer FS, Iturraspe JA, et al. Contribution of flow cytometry to the diagnosis of gastric lymphomas in endoscopic biopsy specimens. Mod Pathol 1997;10:650-656.

Auer IA, Gascoyne RD, Connors JM, et al. t(11;18)(q21;q21) is the most common translocation in MALT lymphomas. Ann Oncol 1997;8:979-985.

Baens M, Maes B, Steyls A, et al. The product of the t(11;18), an *API2-MLT* fusion, marks nearly half of gastric MALT type lymphomas without large cell proliferation. Am J Pathol 2000;156:1433-1439.

Bacon CM, Du MQ, Dogan A. Mucosa-associated lymphoid tissue (MALT) lymphoma: a practical guide for pathologists. J Clin Pathol 2007;60:361-372.

Banks PM. Gastrointestinal lymphoproliferative disorders. Histopathology 2007;50:42-54.

Barth TFE, Barth CA, Kestler HA, et al. Transcriptional profiling suggests that secondary and primary large B-cell lymphomas of the gastrointestinal (GI) tract are blastic variants of GI marginal zone lymphoma. J Pathol 2007;211:305-313.

Bertoni F, Conconi A, Capella C, et al. Molecular follow-up in gastric mucosa-associated lymphoid tissue lymphomas: early analysis of the LY03 cooperative trial. Blood 2002;99:2541-2544.

Burke JS. Histologic criteria for distinguishing between benign and malignant extranodal lymphoid infiltrates. Semin Diagn Pathol 1985;2:152-162.

Burke JS: Extranodal hematopoietic/lymphoid disorders: an introduction. Am J Clin Pathol 1999;111(Suppl 1):S40-S45.

Burke JS: Are there site-specific differences among the MALT lymphomas—morphologic, clinical? Am J Clin Pathol 1999;111(Suppl 1):S133-S143.

Burke JS, Sheibani K, Nathwani, BN, et al. Monoclonal small (well-differentiated) lymphocytic proliferations of the gastrointestinal tract resembling lymphoid hyperplasia: a neoplasm of uncertain malignant potential. Hum Pathol 1987;18:1238-1245.

Campo E, Chott A, Kinney MC, et al. Update on extranodal lymphomas. Conclusions of the Workshop held by the EAHP and the SH in Thessaloniki, Greece. Histopathology 2006;48:481-504.

Chan JKC., Ng CS, Isaacson PG. Relationship between high-grade lymphoma and low-grade B-cell mucosa-associated lymphoid tissue lymphoma (MALToma) of the stomach. Am J Pathol 1990;136:1153-1164.

Cogliatti SB, Schmid U, Schumacher U, et al. Primary B-cell gastric lymphoma: a clinicopathological study of 145 patients. Gastroenterology 1991;101:1159-1170.

Collins RD. Is clonality equivalent to malignancy: specifically, is immunoglobulin gene rearrangement diagnostic of malignant lymphoma? Hum Pathol 1997;28:757-759.

Copie_Begman C, Gaulard P, Lavergne-Slove A, et al. Proposal for a new histological grading system for post-treatment evaluation of gastric MALT lymphoma. Gut 2003;52:1656.

Crump M, Gospodarowicz M, Shepherd FA. Lymphoma of the gastrointestinal tract. Semin Oncol 1999;26:324-337.

De Jong D, Boot H, van Heerde P, et al. Histological grading in gastric lymphoma: pretreatment criteria and clincal relevance. Gastroenterology 1997;112:1466-1474.

De Wolf-Peeters C, Achten R. The histogenesis of large-cell gastric lymphomas. Histopathology 1999;34:71-75.

Deutsch AJA, Aigelsreiter A, Staber PB, et al. MALT lymphoma and extranodal diffuse large B-cell lymphoma are targeted by aberrant somatic hypermutation. Blood 2007;109:3500-3504.

Dierlamm J, Baens M, Wlodarska I, et al. The apoptosis gene *AP12* and a novel 18q gene, *MLT*, are recurrently rearranged in the t(11;18)(q21;q21) associated with mucosa-associated lymphoid tissue lymphomas. Blood 1999;93:3601-3609.

Du M, Diss TC, Xu C, Peng H, et al. Ongoing mutation in MALT lymphoma immunoglobulin gene suggests that antigen stimulation plays a role in the clonal expansion. Leukemia 1996;10:1190-1197.

Du MQ, Peng H-Z, Dogan A, et al: Preferential dissemination of B-cell gastric mucosa-associated lymphoid tissue (MALT) lymphoma to the splenic marginal zone. Blood 1997;90:4071-4077.

Du MQ, Peng H, Liu H, et al. *BCL10* gene mutation in lymphoma. Blood 2000;95:3385-3890.

Du M, Peng H, Singh N, et al. The accumulation of p53 abnormalities is associated with progression of mucosa-associated lymphoid tissue lymphoma. Blood 1995;86:4587-4593.

Du MQ, Xu C-F, Diss TC, et al. Intestinal dissemination of gastric mucosa-associated lymphoid tissue lymphoma. Blood 1996;88:4445-4451.

Eck M, Greiner A, Schmauber B, et al. Evaluation of *Helicobacter pylori* in gastic MALT-type lymphoma: differences between histologic and serologic diagnosis. Mod Pathol 1999;12:1148-1151.

El-Zimaity HMT, Wotherspoon A, de Jong D. Interobserver variation in the histopathological assessment of malt/malt lymphoma: towards a consensus. Blood Cells Mol Disease 2005;34:6-16.

Ferreri AJM, Freschi M, Dell'Oro S, et al. Prognostic significance of the histopathologic recognition of low- and high-grade components in stage I-II B-cell gastric lymphomas. Am J Surg Pathol 2001;25:95-102.

Ferrucci PF, Zucca E. Primary gastric lymphoma pathogenesis and treatment: what has changed over the past 10 years? Br J Haematol 2006;136:521-538.

Ferry JA. Extranodal lymphoma. Arch Pathol Lab Med 2008;132:565-578.

Genta RM, Hamner HW, Graham, DY. Gastric lymphoid follicles in helicobacter pylori infection: frequency, distribution, and response to triple therapy. Hum Pathol 1993;24:577-583.

Graves FD, Linet MS, Travis LB, et al. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 2000;92:1240-1251.

Harris NL, Isaacson PG. What are the criteria for distinguishing MALT from non-MALT lymphoma at extranodal sites? Am J Clin Pathol 1999;111(Suppl.1):S126-S132.

Hsi ED, Eisbruch A, Greenson JK, et al. Classification of primary gastric lymphomas according to histologic features. Am J Surg Pathol 1998:22:17-27.

Hsi ED, Greenson JK, Singleton TP, et al. Detection of immunoglobulin heavy chain gene rearrangement by polymerase chain reaction in chronic active gastritis associated with *Helicobacter pylori*. Hum Pathol 1996;27:290-296.

Hummel M, Oeschger S, Barth TFE, et al. Wotherspoon criteria combined with B cell clonality analysis by advanced polymerase chain reaction technology discriminates covert gastric marginal zone lymphoma from chronic gastritis. Gut 2006;55:782-787.

Hussell T, Isaacson PG, Crabtree JE, et al. The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to *Helicobacter pylori*. Lancet 1993;342:571-574.

Hussell T, Isaacson, PG, Crabtree JE, et al. Immunoglobulin specificity of low grade B cell gastrointestinal lymphoma of mucosa-associated lymphoid tissue (MALT) type. Am J Pathol 1993;142:285-292.

Inagaki H, Oakbe M, Seto M, et al. *API2-MALT1* fusion transcripts involved in mucosa-associated lymphoid tissue lymphoma: multiplex RT-PCR detection using formalin-fixed paraffin-embedded specimens. Am J Pathol 2001;158:699-706.

Isaacson PG. Lymphomas of mucosa-associated lymphoid tissue (MALT). Histopathology 1990;16:617-619.

Isaacson PG, Du MQ. MALT lymphoma: from morphology to molecules. Nature Rev Cancer 2004;4:644-653.

Isaacson PG, Du MQ. Gastrointestinal lymphoma; where morphology meets molecular biology. J Pathol 2005;205;255-274.

Isaacson, PG, Spencer J. Malignant lymphoma of mucosa-associated lymphoid tissue. Histopathology 1987;11:445-462.

Isaacson PG, Spencer J. Malignant lymphoma and autoimmune disease. Histopathology 1993;22:509-510.

Isaacson PG, Spencer J, Finn T. Primary B-cell gastric lymphoma. Hum Pathol 1986;17:72-82.

Isaacson PG, Spencer J, Wright DH. Classifying primary gut lymphomas. Lancet 1988;2:1148-1149.

Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue: a distinctive type of B-cell lymphoma. Cancer 1983;52:1410-1416.

Isaacson, P, Wright DH. Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. Cancer 1984;53:2515-2524.

Isaacson PG, Wotherspoon AC, Pan, L. Follicular colonization in B-cell lymphoma of mucosa-associated lymphoid tissue. Am J Surg Pathol 1991;15:819-828.

Knowles DM, Jakobiec FA. Cell marker analysis of extranodal lymphoid infiltrates: to what extent does the determination of mono- or polyclonality resolve the diagnostic dilemma of malignant lymphoma *v* pseudolymphoma in an extranodal site? Semin Diagn Pathol 1985;2:163-168.

Koch P, del Valle F, Berdel W, et al. Primary gastrointestinal non-Hodgkin's lymphoma: I. anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German multicenter study GIT NHL 01/92. J Clin Oncol 2001;19:3861-3873.

Koch P, del Valle F, Berdel W, et al. Primary gastrointestinal non-Hodgkin's lymphoma: II. combined surgical and conservative or conservative mangement only in localized gastric lymphoma–results of the prospective German multicenter study GIT NHL 01/92. J Clin Oncol 2001;19:3874-3883.

Kurtin PJ. How do you distinguish benign from malignant extranodal small B-cell proliferations? Am J Clin Pathol 1999;111(Suppl.1):S119-S126.

Lévy M, Copie-Bergman C, Gameiro C, et al. Prognostic value of translocation t(11;18) in tumoral response of low-grade gastric lymphoma of mucosa-associated lymphoid tissue type to oral chemotherapy. J Clin Oncol 2005;23:5061-5066.

Liu H, Ye H, Dogan A, et al. t(11;18)(q21;q21) is associated with advanced mucosa-associated lymphoid tissue lymphoma that expresses nuclear BCL10. Blood 2001;98:1182-1187.

Maes B, Demunter A, Peeters B, et al. *BCL10* mutation does not represent an important pathogenic mechanism in gastric MALT-type lymphoma, and the presence of the *API2-MLT* fusion is associated with aberrant BCL10 expression. Blood 2002;99:1398-1404.

Mitchell KA, Finn WG, Owens SR. Differences in germinal centre and non-germinal centre phenotype in gastric and intestinal diffuse large B-cell lymphomas. Leuk Lymphoma 2008;49:1717-1723.

Moore I, Wright DH. Primary gastric lymphoma – a tumour of mucosa-associated lymphoid tissue; a histological and immunohistochemical study of 36 cases. Histopathology 1984;8:1025-1039.

Morgner A, Miehlke S, Fischbach W, et al. Complete remission of primary high-grade B-cell gastric lymphoma after cure of *Helicobacter pylori* infection. J Clin Oncol 2001;19:2041-2048.

Morse HC, Kearney JF, Isaacson PG, et al. Cells of the marginal zone—origins, function and neoplasia. Leuk Res 2001;25:169-178.

Nakamura S, Aoyagi K, Furuse M, et al: B-cell monoclonality precedes the development of gastric MALT lymphoma in *Helicobacter pylori*-associated chronic gastritis. Am J Pathol 1998;152:1271-1279.

Nakamura S, Yao T, Aoyagi K, et al. *Helicobacter pylori* and primary gastric lymphoma: a histopathologic and immunohistochemical analysis of 327 patients. Cancer 1997;79:3-11.

Omonishi K, Yoshino T, Sakuma I, et al. bcl-6 protein is identified in high-grade but not low-grade mucosa-associated lymphoid tissue lymphomas of the stomach. Mod Pathol 1998;11:181-185.

Osborne BM, Pugh WC. Practicality of molecular studies to evaluate small lymphocytic proliferations in endoscopic gastric biopsies. Am J Surg Pathol 1992;16:838-844.

Pan L, Diss TC, Cunningham D, et al. The bcl-2 gene in primary B cell lymphoma of mucosa-associated lymphoid tissue (MALT). Am J Pathol 1989;135:7-11.

Peng H, Du M, Diss TC, et al. Genetic evidence for a clonal link between low and high-grade components in gastric MALT B-cell lymphoma. Histopathology 1997;30:425-429.

Radaszkiewicz T, Dragosics B, Bauer P. Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: factors relevant to prognosis. Gastroenterology 1992;102:1628-1638.

Ranchod M, Lewin KJ, Dorfman RF. Lymphoid hyperplasia of the gastrointestinal tract: a study of 26 cases and a review of the literature. Am J Surg. Pathol 1978;2:383-400.

Rao D, Said JW. Small lymphoid proliferations in extranodal locations. Arch Pathol Lab Med 2007;131:383-396.

Remstein ED, Dogan A, Einerson RR, et al. The incidence and anatomic site specificity of chromosomal translocations in primary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in North America. Am J Surg Pathol 2006;30:1546-1553.

Remstein ED, James CD, Kurtin PJ. Incidence and subtype specificity of *API2-MALT1* fusion transcripts in extranodal, nodal, and splenic marginal zone lymphomas. Am J Pathol 2000;156:1183-1188.

Remstein ED, Kurtin PJ, James CD, et al. Mucosa-associated lymphoid tissue lymphomas with t(11;18)(q21;q21) and mucosa-associated lymphoid tissue lymphomas with aneuploidy develop along different pathogenetic pathways. Am J Pathol 2002;161:63-71.

Rosenwald A, Ott G, Stilgebauer S, et al. Exclusive detection of the t(11;18)(q21;21) in extranodal marginal zone B cell lymphomas (MZBL) of MALT type in contrast to other MZBL and extranodal large B cell lymphomas. Am J Pathol 1999;155:1817-1821.

Sagaert X, De Wolf-Peeters C, Noels H, et al. The pathogenesis of MALT lymphomas: where do we stand? Leukemia 2007;21:389-396.

Savio A, Franzin G, Wotherspoon AC, et al. Diagnosis and posttreatment follow-up of Helicobacter pylori-positive gastric lymphoma of mucosa-associated lymphoid tissue: histology, polymerase chain reaction, or both? Blood 1996;87:1255-1260.

Severson RK, Davis S. Increasing incidence of primary gastric lymphoma. Cancer 1990;66:1283-1287.

Spencer J, Diss TC, Isaacson PG. Primary B cell gastric lymphoma: a genotypic analysis. Am J Pathol 1989;135:557-564.

Starostik P, Greiner A, Schultz A, et al. Genetic aberrations common in gastric high-grade large B-cell lymphoma. Blood 2000;95:1180-1187.

Starostik P, Patzner J, Greiner A, et al. Gastric marginal zone b-cell lymphomas of MALT type develop along 2 distinct pathogenetic pathways. Blood 2002;99:3-9.

Streubel B, Lamprecht A, Dierlamm J, et al. t(14;18)(q32;q21) involving *IGH* and *MALT1* is a frequent chromosomal aberration in MALT lymphoma. Blood 2003;101:2335-2339.

Takeshita M, Iwashita A, Kurihara K, et al. Histologic and immunohistologic findings of 40 cases of gastric large B-cell lymphoma. Am J Surg Pathol 2000;24:1641-1649.

Thieblemont C, Bastion Y, Berger F, et al. Mucosa-associated lymphoid tissue gastrointestinal and nongastrointestinal lymphoma behavior: analysis of 108 patients. J Clin Oncol 1997;151624-1630.

Thiede C, Wündisch T, Alpen B, et al. Long-term persistence of monoclonal B cells after cure of *Helicobacter pylori* infection and complete histologic remission in gastric mucosa-associated lymphoid tissue B-cell lymphoma. J Clin Oncol 2001;19:1600-1609.

van Krieken JHJM, Raffeld M, Raghoebier S, et al. Molecular genetics of gastrointestinal non-Hodgkin's lymphomas: unusual prevalence and pattern of c-*myc* rearrangements in aggressive lymphomas. Blood 1990;76:797-800.

Wang G, Auerbach A, Wei M, et al. t(11;18)(q21;q21) in extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in stomach: a study of 48 cases. Mod Pathol 2009;22:79-86.

Wolber RA, Owen DA, Anderson FH, et al. Lymphocytic gastritis and giant gastric folds associated with gastrointestinal protein loss. Mod Pathol 1991;4:13-15.

Wotherspoon AC, Doglioni C, Diss, TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. Lancet 1993;1342:575-577.

Wotherspoon AC, Doglioni C, Isaacson PG. Low grade gastric B-cell lymphoma of mucosa-associated lymphoid tissue (MALT): a multifocal disease. Histopathology 1992;20:29-34.

Wotherspoon AC, Ortiz-Hildago C, Falzon MR, et al. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. Lancet 1991;338:1175-1176.

Wu TT, Hamilton SR. Lymphocytic gastritis: association with etiology and topology. Am J Surg Pathol 1999;23:153-158.

Wündisch T, Neubauer A, Stolte M, et al. B-cell monoclonality is associated with lymphoid follicles in gastritis. Am J Surg Pathol 2003;27:882-887.

Wündisch T, Thiede C, Morgner A, et al. Long-term follow-up of gastric MALT lymphoma after *Helicobacter pylori* eradication. J Clin Oncol 2005;23:8018-8024.

Yamashita H, Watanabe H, Ajioka K, et al. When can complete regression of low-grade gastric lymphoma of mucosa-associated lymphoid tissue be predicted after *Helicobacter pylori* eradication? Histopathology 2000;37:131-140.

Ye H, Liu H, Attygalle A, et al. Variable frequencies of t(11;18)(q21;q21) in MALT lymphomas of different sites: significant association with CagA strains of *H pylori* in gastric MALT lymphoma. Blood 2003;102:1012-1018.

Ye H, Liu H, Raderer M, et al. High incidence of t(11;18)(q21;q21) in *Helicobacter pylori*–negative gastric MALT lymphoma. Blood 2003;101:2547-2550.

Zucca E, Bertoni F, Roggero E, et al. Molecular analysis of the progression from *Helicobacter pylori*-associated chronic gastritis to mucosa-associated lymphoid-tissue lymphoma of the stomach. N Engl J Med 1998;338:804-810.

Zucca E, Bertoni F, Roggero E, et al. The gastric marginal zone B-cell lymphoma of MALT type. Blood 2000;96:410-419.

Zukerberg LR, Ferry JA, Southern JF, et al. Lymphoid infiltrates of the stomach: evaluation of histologic criteria for the diagnosis of low-grade gastric lymphoma on endoscopic biopsy specimens. Am J Surg Pathol 1990;14:1087-1099.