Diagnosis of Primary Gastrointestinal Lymphomas and Mimics

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1 Introduction

Primary gastrointestinal (GI) lymphomas typically refer to a lymphoma that predominantly involves any section of the GI tract from the oropharynx to the rectum (Bautista-Quach, Ake, Chen, & Wang, 2012). While the disease often involves a single primary site, multiple sites within the GI tract may be involved, as can local and distant lymph nodes. Primary GI tract lymphomas are uncommon, while secondary involvement of the GI tract by lymphoma is relatively frequent (Lewin, Ranchod, & Dorfman, 1978). Nonetheless, primary lymphomas of the GI tract are important since their evaluation, diagnosis, management and prognosis are distinct from that of lymphoma at other sites and other cancers of the GI tract (Dawson, Cornes, & Morson, 1961).

1.1 Background

The amount and nature of GI tract associated lymphoid tissue varies greatly within the GI tract, thus influencing the type of lymphomas developing in each location (Radic-Kristo et al., 2010). The character of these lymphoid tissues is determined by innate genetic factors and acquired immune stimulation, often directed by exposure to the innumerable dietary and microbial antigens and inflammatory responses. The normal esophagus essentially has no lymphoid tissue associated with the mucosa. Likewise, B-lymphocytes, plasma cells, and granulocytes are almost completely absent in the normal stomach (Cardona, Layne, & Lagoo, 2012). A few CD8+ T-cells are present in intraepithelial locations and CD4+ T-cells are localized mainly in the lamina propria of stomach, accompanied by macrophages and very few CD1-positive Langerhans' cells (Brenchley et al., 2004; Cardona et al., 2012). In contrast, the intestines contain a large amount of lymphoid tissue, concentrated in the mucosa and submucosa, which is collectively referred to as mucosa associated lymphoid tissue or MALT (Isaacson PG, 2008).

Intestinal MALT is the primary site for eliciting adaptive immune responses towards mucosal antigens and can be divided into three components including Peyer’s patches, isolated lymphoid follicles, and efferent lymphatics. Most well-known among these are the organized lymphoid aggregates called Peyer's patches, which first appear during 19th week of gestation on the antimesenteric border of the entire small intestine starting at the upper jejunum. Their numbers appear to be predetermined but their size steadily increases until puberty, followed by gradual involution in old age. They resemble miniature lymph nodes and contain both B- and T-cells, segregated in the follicles and interfollicular areas, respectively. The luminal antigens are carried to the Peyer's patches through specialized epithelial cells called M cells, present in the intestinal lining covering the dome region of the patch, and presented to the dendritic cells (Burke, 2011). Structures closely related to Peyer's patches but containing only an isolated lymphoid follicle develop after exposure to intestinal commensals and are particularly numerous in the colon, which lacks Peyer's patches. Efferent lymphatics from the Peyer's patches carry memory B-cells and plasma cells to mesenteric lymph nodes and hematogenous lymphocytes traffic through MALT by virtue of specific adhesion molecules (Isaacson PG, 2008).

Gastrointestinal lymphomas comprise a group of distinctive clinicopathological entities of B- or T-cell type, with primary gastrointestinal Hodgkin's disease being extremely uncommon (Devaney & Jaffe, 1991). Most low-grade B-cell gastrointestinal lymphomas are MALT type, so called because they recapitulate the features of MALT rather than those of lymph nodes. Paradoxically, however, most MALT lymphomas arise in the stomach, which normally contains no organized lymphoid tissue. The gastrointestinal (GI) tract is the predominant site of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), accounting for 30–40% of cases of all extranodal
lymphomas (Isaacson PG, 2008). Although B-cell lymphomas are by far the most frequent type found in this location, gastrointestinal lymphomas are a diverse group of neoplasms, many of which are characterized by distinctive clinicopathologic settings. Diffuse large B-cell lymphoma (DLBCL) and MALT lymphoma are commonly encountered, but other less common entities can pose diagnostic challenges, mimicking both benign, reactive conditions and each other (Bautista-Quach et al., 2012).

Primary GI lymphomas are derived from lymphoid tissue of the MALT and lymph nodes of the intestine (including Peyer’s patches). In western countries, the estimated frequency of GI lymphomas based on the site are stomach (48%) > small bowel (26%) > colon (12%) > pancreas (2%) > esophagus (rare). In the Middle East and Mediterranean basin, small bowel lymphoma is most common, and accounts for up to 75 percent of primary GI lymphomas. The incidence of Burkitt lymphoma (BL) in Africa is approximately 50-fold higher than it is in the US, and its classic GI presentation is that of an obstructing lesion in the terminal ileum (Koch et al., 2001).

1.2 Predisposing Conditions

The conditions that predispose to GI lymphoma include (Andrews et al., 2008; Isaacson PG, 2008):

- **Helicobacter pylori infection** — *H. pylori* infection is highly associated with the development of MALT lymphoma of the stomach (Suzuki, Saito, & Hibi, 2009).

- **Autoimmune diseases** — A variety of autoimmune diseases, including rheumatoid arthritis, Sjögren’s syndrome, systemic lupus erythematosus and granulomatosis with polyangiitis (previously Wegener's granulomatosis), have been associated with an increased risk of lymphoma. Immunosuppression, rather than the disease itself, is thought to be responsible for the increased risk.

- **Immunodeficiency and immunosuppression** — Congenital immunodeficiency syndromes (eg, Wiskott-Aldrich syndrome, severe combined immunodeficiency syndrome, ataxia-telangiectasia, X-linked agammaglobulinemia) and acquired immunodeficiency (eg, HIV infection, iatrogenic immunosuppression) are associated with an increased incidence of B cell lymphoma. Lymphomas occurring in this setting tend to be aggressive and widespread at the time of diagnosis (Jamieson, Thiru, Calne, & Evans, 1981; Sandler & Kaplan, 1996).

- **Celiac disease** — Patients with gluten-sensitive enteropathy (celiac disease) are at increased risk of developing enteropathy-associated T cell lymphoma (EATL) (Smedby et al., 2005).

- **Inflammatory bowel disease** — An association between inflammatory bowel disease (IBD) and lymphoma has been described, as has been a possible association between tumor necrosis factor-alpha inhibitors and hepatic gamma delta T-cell lymphoma (Aithal & Mansfield, 2001; Kandiel, Fraser, Korelitz, Brensinger, & Lewis, 2005; Thayu et al., 2005).

- **Nodular lymphoid hyperplasia** — Nodular lymphoid hyperplasia, also known as follicular lymphoid hyperplasia, is a benign condition that has been implicated as a possible risk factor for primary lymphomas of the small intestine (Burke, 2011).

1.3 Clinical Presentation

The clinical signs and symptoms of GI lymphomas are typically nonspecific, attributable to the site of involvement:
Gastric lymphoma is the most common site of GI lymphoma and typically presents with nonspecific symptoms such as epigastric pain or discomfort, anorexia, weight loss, nausea and/or vomiting, occult GI bleeding, and/or early satiety. The diagnosis is usually established during upper endoscopy with biopsy. The vast majority (greater than 90 percent) of gastric lymphomas is approximately equally divided between extranodal marginal zone B cell lymphoma of gut-mucosa (gut)-associated lymphoid tissue (MALT) type (referred to as MALT lymphoma in this chapter) and diffuse large B cell lymphoma. Lymphoma of the small intestine is the second most common site and the clinical presentation varies depending upon whether the tumor is associated with immunoproliferative small intestinal disease (IPSID), celiac disease (enteropathy-associated T cell lymphoma, EATL), or neither. The diagnosis may be suggested on computed tomography (CT) and/or contrast radiography, but requires a biopsy for confirmation.

Colorectal lymphoma is an uncommon form of GI lymphoma and may present with abdominal pain, overt or occult bleeding, diarrhea, intussusception, or rarely, bowel obstruction. Colonoscopy with biopsy is the principal diagnostic modality for colorectal lymphomas. The most common histologic types include diffuse large B cell lymphoma, mantle cell lymphoma, and Burkitt lymphoma. Esophagus is perhaps the most uncommon site for primary GI lymphoma, which appears to more commonly involve the distal esophagus. Most patients are asymptomatic or present with complaints of dysphagia or odynophagia. There is a diverse appearance on imaging and the diagnosis is made by endoscopic biopsy in most cases.

1.4 Staging

Lymphoma of the GI tract is staged using the Ann Arbor System, with the GI tract being considered an extranodal site (Boot, 2010):

- I-Single nodal or extranodal site
- II-More than one nodal group on same side of diaphragm or single extranodal group with adjacent lymph nodes
- III- Multiple nodal sites on both sides of diaphragm
- IV-Bone, central nerve system (CNS), diffuse visceral involvement

2 Lymphomas by Anatomic Location

2.1 Gastric Lymphoma

The stomach is the most common extranodal site of lymphoma. Primary gastric lymphoma accounts for 3 percent of gastric neoplasms and 10 percent of lymphomas (Isaacson PG, 2008; Lewin et al., 1978). Stomach is the most common site of GI tract involved by lymphoma, accounting for 68 to 75 percent of GI lymphomas (Koch et al., 2001). Gastric lymphoma reaches its peak incidence between the ages of 50 to 60 years. There is a slight male predominance.

Gastric lymphoma is clinically heterogeneous. While the vast majority of cases occur in individuals infected with Helicobacter pylori, the cases can show a range of histologies and can follow diverse natural histories. Tumors may comprise mainly small cells, contain predominantly large cells with a small-cell component, or consist entirely of large cells, similar to diffuse large B-cell lymphomas.
occurring in nodes or other extranodal tissues (Cardona et al., 2012; Starostik et al., 2002). The disease originates on inflammatory background brought about by a chronic Helicobacter pylori infection that initiates buildup of MALT in originally lymphoid follicle-free stomach. Further development of lymphoma out of the MALT is the result of continuous antigen-dependent growth of B lymphocytes in the early phase that then progresses into a stage of autonomous proliferation of a true low-grade lymphoma. That lymphoma can and in some cases does develop into a high-grade lymphoma (Starostik et al., 2002).

The diagnosis of gastric lymphoma is usually established during upper endoscopy with biopsy. The vast majority (greater than 90 percent) of gastric lymphomas are approximately equally divided into two histologic subtypes, gastric extranodal marginal zone B cell lymphoma of MALT type (MALT lymphoma), and DLBCL (Isaacson PG, 2008; Koch et al., 2001; Lewin et al., 1978). The remaining cases of gastric lymphoma may represent any histology including mantle cell lymphoma (1 percent), follicular lymphoma, and peripheral T cell lymphoma.

2.2 Lymphoma of the Small Intestine

Small intestine has abundant mucosal lymphoid tissue which contains both B- and T-cells and lymphomas of both cell types occur in this location. Reactive lymphohistiocytic infiltrate due to infections can occur and mimic Hodgkin lymphoma in immunocompromised patients. The most common lymphoma in adults is DLBCL, but in children Burkitt lymphoma is more common (Matuchansky et al., 1985). Some lymphomas are rather unique to the small intestine or have unique features when they occur in this GI tract site.

These lymphomas may be broadly categorized into three main groups, 1) Immunoproliferative small intestinal disease (IPSID, also called alpha heavy chain disease, Mediterranean lymphoma, or Seligmann disease). This lymphoma is a variant of MALT lymphoma which secretes alpha heavy chains, 2) Enteropathy-associated T cell lymphoma (EATL), also called intestinal T cell lymphoma, is a tumor that is highly associated with gluten-sensitive enteropathy (celiac disease), and 3) Other western-type non-IPSID lymphomas, including diffuse large B cell lymphoma, mantle cell lymphoma, Burkitt lymphoma, follicular lymphoma (Mori et al., 2010). In the Middle East and Mediterranean basin, primary small intestinal lymphoma, usually of the IPSID type, accounts for up to 75 percent of primary GI lymphomas (Salem et al., 1987). Although uncommon, enteropathy-associated T cell lymphoma (EATL) is most common in areas with a high incidence of gluten-sensitive enteropathy (celiac disease), such as the Western part of Ireland and Northern Europe (Verbeek et al., 2008).

IPSID-associated lymphomas generally appear as a diffuse infiltrating lesion of the proximal small intestine, sometimes resembling cobblestoning. The presence of multiple polyps of varying size within the bowel (lymphomatous polyposis) is particularly common in mantle cell lymphoma. Patients with enteropathy-associated T cell lymphoma of the jejunum typically demonstrate large circumferential ulcers without overt tumor masses. Biopsies of the involved mucosa demonstrate lymphoma, while biopsies of the normal appearing mucosa usually show villous atrophy characteristic of celiac disease (Salem et al., 1987).

Patients with mantle cell lymphoma may demonstrate typical small nodular or polypoid tumors (2 mm to more than 2 cm in size), with or without normal intervening mucosa referred to as "lymphomatous polyposis" (Bautista-Quach et al., 2012).
Patients with primary intestinal follicular lymphoma most often (commonly) present with multiple small (1 to 5 mm) polypoid lesions in the descending part of the duodenum. The lesions are solitary in approximately 15 percent of cases and may grossly resemble adenomas (Iwamuro et al., 2013).

### 2.3 Colorectal Lymphoma

Colorectal lymphomas are uncommon, accounting for approximately 3 percent of the GI lymphomas and 0.3 percent of large intestinal malignancies (Koch et al., 2001; Lewin et al., 1978). There is a male predominance, twice as often in males compared with females (Aledavood et al., 2012). The diagnosis of colorectal lymphoma is dependent upon the histologic evaluation of an adequate biopsy specimen. The most common lymphomas seen in this region include: DLBCL, mantle cell lymphoma, Burkitt lymphoma, and follicular lymphoma. Almost all primary colorectal lymphomas reported from the West have B-cell lineage, but rare T-cell lymphomas are reported in the East. While MALT lymphomas are relatively uncommon in large intestine, DLBCLs may show a low grade component in a minority of cases. In immunocompetent patients the cecum is involved most often but in immunodeficient patients, the rectum (and anal canal) is more likely to be involved (Koch et al., 2001). The difference could be due to the viral infectious etiology (Hyder & Mackeigan, 1988).

### 2.4 Esophageal Lymphoma

Primary esophageal lymphoma is very rare, accounting for less than 1 percent of primary GI lymphomas. More commonly, lymphoma may involve the esophagus as an extension of mediastinal or gastric involvement. Only case reports and series of primary esophageal lymphoma have been reported in the literature (Kalogeropoulos et al., 2009). Primary esophageal lymphoma appears to more commonly involve the distal esophagus. Most patients are asymptomatic or present with complaints of dysphagia or odynophagia. There is a diverse appearance on imaging and the diagnosis is made by endoscopic biopsy in most cases (Ghai, Pattison, O’Malley, Khalili, & Stephens, 2007).

### 3 Morphologic Classification

In this section, the characteristic pathological, immunophenotypic, and genetic features of different GI lymphomas categorized according to World Health Organization (WHO) classification are discussed. The epidemiological, clinical, and pathological features of lymphomas occurring in each part of the GI tract are summarized and the key points regarding lymphomas at each site are emphasized.

#### 3.1 Overview

The current lymphoma classification is based on morphological, immunophenotypic, genetic, and clinical features (Isaacson PG, 2008). In addition to characteristic cell morphology, most GI lymphomas also demonstrate fairly typical architectural features which are useful in diagnosis. Specific cytogenetic abnormalities are seen in many lymphomas and appear to influence their clinical behavior to a great extent. Making the correct diagnosis, according to the WHO classification, is critical because treatments can vary widely from a simple "wait and watch" approach to local radiation or surgery to high dose chemotherapy with or without stem cell transplantation. No separate classification for gastrointestinal lymphomas is offered by the World Health Organization (WHO), although extranodal marginal zone
lymphoma of MALT (including immunoproliferative small-intestinal disorder) and enteropathy-associated T-cell lymphoma form 2 distinct categories among the mature B-, T- and natural killer (NK)—cell neoplasms. The distinguishing clinicopathological features of the major types of lymphomas occurring in the GI tract are summarized in Table 1.

<table>
<thead>
<tr>
<th>Hodgkin Lymphoma</th>
<th>T-cell lymphomas</th>
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<tbody>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>type II (non-enteropathy associated)</td>
</tr>
<tr>
<td>B-cell lymphomas</td>
<td>NK/T, nasal type</td>
</tr>
<tr>
<td>Extranodal marginal zone lymphoma, MALT type</td>
<td>Gamma-Delta type</td>
</tr>
<tr>
<td>IPSID (heavy chain disease)</td>
<td>Anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>Mantle cell (lymphomatous polyposis)</td>
<td>Peripheral T-cell lymphoma, not otherwise specified</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>Adult T-cell lymphoma</td>
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<tr>
<td>Burkitt lymphoma</td>
<td>Precursor T-lymphoblastic lymphoma</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>Others</td>
</tr>
<tr>
<td>Precursor B-lymphoblastic lymphoma</td>
<td></td>
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<tr>
<td>Plasmacytoma</td>
<td></td>
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<tr>
<td>Plasmablastic lymphoma</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
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</table>

**Table 1**: Classification of Primary Gastrointestinal Lymphomas Histologic Type.

### 3.2 B-Cell Lymphomas

**I. Extranodal marginal zone mucosa associated lymphoid tissue (MALT) lymphoma**

MALT lymphomas comprise over 50% of primary gastric non-Hodgkin lymphomas, occurring predominately in patients older than 50 years, with a noted peak in the seventh decade and a male: female ratio of about 1.5:1 (Psyrri, Papageorgiou, & Economopoulos, 2008). Patients commonly present with nonspecific gastritis and/or a peptic ulcer. Endoscopy commonly demonstrates erythematous and slightly thickened rugae with superficial spreading of lesions without formation of a distinct mass. The gastric lesions commonly are multifocal, and most patients have stage I or II disease (Isaacson PG, 2008; Nakamura et al., 2008). Cases of MALT transformation to DLBCL have also been recognized (Isaacson PG, 2008; Nakamura et al., 2008).

**Pathogenesis**

A strong association between chronic *H. pylori* infection and gastric MALT lymphoma has been demonstrated in 80 to 90% of cases, and it is widely accepted that the bacterial infection plays a crucial role in the pathogenesis of this tumor (Isaacson PG, 2008; Nakamura et al., 2000; Psyrri et al., 2008). Chronic *H. pylori* infection provides the antigenic stimulus, resulting in the clonal expansion of lymphoid cells leading to the evolution of MALT lymphoma. According to the study by Arnold and colleagues, *H. pylori* strains expressing the cytotoxin-associated gene A (*CagA*) protein carry the major histocompatibility complex (MHC) class II T cell epitope. Therefore, infection with this specific strain induces activation of CD4+ T cells which has been postulated to instigate neoplasia (Arnold et al., 2011; Mills, Kurjanczyk, & Penner, 1992).
On the other hand, lymphomagenesis has also been hypothesized to evolve independent of *H. pylori* infection (Farinha & Gascoyne, 2005; Isaacson PG, 2008), particularly in the setting of translocation (11;18)(q21;q21) positive cases (Nakamura *et al.*, 2000). This aberration is further described under molecular abnormalities. Transformation to DLBCL has been documented in cases independent of *H. pylori* infection, as well as in cases harboring genomic alterations of the MYC, p53, p15, p16, and retinoblastoma (Rb) genes (Farinha & Gascoyne, 2005).

**Morphology and immunophenotype**

Gastric MALT lymphomas are characterized by lymphoepithelial lesions (LEL) (Figure 1) with glandular invasion by neoplastic centrocyte-like cells or small lymphoid cells with irregular nuclear contour, nuclear clefting, hyperchromasia, and with scant to fair amount of cytoplasm. Occasional atypical plasmacytoid/plasmacytic lymphocytes and/or plasma cells may also be observed. Nevertheless, care must be taken to avoid over-interpretation of LELs as these lesions may also appear in benign settings including reactive lymphoid infiltrates. Lymphoepithelial lesions are not reliable in distinguishing chronic active H. Pylori gastritis from MALT-lymphoma since they can occur in both (Aledavood *et al.*, 2012).

![Image](image.png)

**Figure 1**: H&E stained section of extranodal marginal zone lymphoma, MALT type lymphoma of stomach. The dense atypical lymphoid infiltrate in MALT lymphoma extends deeper into the lamina propria. Immunohistochemistry for CD20 highlights sheets of B-cells and lymphoepithelial lesions. Cytokeratin (CK) stain shows the glandular epithelial cells. CD3 stain is positive in the reactive non-neoplastic T-cells.

The distinction between reactive LEL and neoplastic LEL may be very difficult. A large infiltrate, a relatively monotonous lymphoid population, cytologic atypia and numerous Dutcher bodies are supportive of a malignant diagnosis. The presence of halos around LEL’s and broad interconnecting bands of atypical lymphoid cells (centrocyte-like or monocytoid B cells) are features supporting the diagnosis of lymphoma. With progression, the LEL's are destroyed, reactive follicles are infiltrated and replaced and the process extends outside the gland (Bautista-Quach *et al.*, 2012; Isaacson PG, 2008). Reactive germinal centers, common in the deeper mucosa associated with *H. pylori* gastritis, may be
colonized by lymphoma cells, with obliteration of mantle zone and the appearance of so-called “naked” follicles. The atypical lymphoid infiltrate usually expands the lamina propria or submucosa. Muscularis mucosae infiltration and disruption can be a useful clue to the diagnosis in small biopsy specimens. In more extensive cases, the lymphoma can create mucosal ulcers and can infiltrate through the muscularis propria.

While MALT lymphoma does not show a specific immunohistochemical profile, there is usually an overabundance of neoplastic B cells as highlighted by CD20 immunostain. Large series have demonstrated that up to 50% of the cases may also aberrantly co-express CD43 and/or BCL2 by these neoplastic B cells (Isaacson PG, 2008; Psyrri et al., 2008). The tumor cells show variable surface and cytoplasmic immunoglobulin reactivity, with most cases expressing IgM, and a few cases showing IgA or IgG reactivity, whereas IgD expression is rare. The neoplastic B cells are negative for CD10, CD23, and cyclin D1, and typically do not co-express CD5, although rare cases of CD5-positive MALT lymphomas have been documented (Terada, 2012). In cases with extensive or nearly complete plasmacytic differentiation, immunostains for kappa and lambda light chains can be extremely useful in highlighting possible monotypic plasma cell population (Bautista-Quach et al., 2012).

**Molecular abnormalities**

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 the amino terminal of the apoptosis inhibitor API2 at 11q21 to the carboxyl terminal of MALT1 at 18q21 leading to a chimeric fusion protein (Sugano, 1998). MALT1 is involved in antigen receptor-mediated nuclear factor kB (NF-kB) activation (32,33). However, t(11;18)(q21;q21) is usually not associated with *H. pylori* gastritis; hence, such cases are believed to show resistance to antibiotic therapy (Nakamura et al., 2000).

All aforementioned translocations induce activation of the nuclear factor kB (NF-kB) oncogenic pathway (Psyrri et al., 2008). It has been postulated that chronic inflammation leads to activation of NF-kB pathway via the antigen receptor signaling in MALT lymphoma cells. Antigen stimulation and CD40 triggering synergize NF-kB activation through formation of CARMA1–BCL10–MALT1 ternary complex. In addition, the continuous and sustained antiapoptotic stimuli driven by API2-MALT1 are most likely to play key roles in the pathogenesis of MALT lymphomas (Farinha & Gascoyne, 2005; Sagaert, De Wolf-Peeters, Noels, & Baens, 2007).

**Prognosis**

The response of low grade MALT lymphoma to *H. pylori* eradication is predicted by stage. Complete regression of low-grade, early stage MALT lymphoma following successful *H. pylori* eradication has been confirmed in about 75-80% of cases (Chiang, Wang, Cheng, Lin, & Su, 1996; Isaacson PG, 2008). Studies have documented that complete response has been achieved in nearly all patients where disease is limited to the gastric mucosa or submucosa. Complete response rates have decreased in cases where disease extended to the muscularis propria or serosa (Freeman, Berg, & Cutler, 1972). Furthermore, it has been shown that no patients with nodal disease achieved complete response with *H. pylori* eradication alone (Nakamura et al., 2008).
It is important to note, however, that approximately 10% of gastric MALT lymphomas have the t(11;18)(q21;q21) translocation and are resistant to *H. pylori* antibiotic therapy, suggesting importance of strict follow up, and if clinically indicated, a trial of chemotherapy, immunotherapy (i.e., Rituximab), and/or radiotherapy for localized disease, may be pursued (Isaacscon PG, 2008; Nakamura et al., 2008). Studies suggest that medical therapy alone is superior to surgery, although surgical intervention may be appropriate in specific circumstances such as in cases with gastric outlet obstruction and/or other complications (Yoon, Coit, Portlock, & Karpeh, 2004).

**Diagnosis of gastric MALT lymphoma**

It should be emphasized that essentially not all of the above described histopathologic features are seen in every case of low-grade gastric MALT lymphoma, and virtually everyone can be seen in other neoplasms or even benign reactive conditions. Even prominent lymphoepithelial lesions, often regarded as among the features most suggestive of MALT lymphoma, can be seen in florid follicular gastritis as well as non-MALT lymphomas. Thus, the histologic diagnosis of gastric MALT lymphoma is based on analysis of the gestalt of features present, rather than on the presence of any individual feature. These difficulties are magnified in small mucosal biopsies, where limited sampling and crush artifact can further limit assessment.

In general, it has been suggested that an unequivocal diagnosis of low grade MALT lymphoma be made on the basis of histologic analysis of small gastric mucosal biopsies only if all three of the following features are present in full flower: 1) a dense, extensive, interfollicular lymphoid infiltrate (sometimes defined as occupying at least half of a low-power field using a 4X objective), 2) the predominance within the infiltrate of atypical centrocyte-like cells, with or without clear cytoplasm, and 3) prominent lymphoepithelial lesions, generally associated with expansion and distortion of glandular structures, and eosinophilic degeneration of the epithelial cytoplasm. Specimens showing lesser degrees of atypia should be termed "suspicious lymphoid infiltrates"; in such cases repeat biopsies to provide material for immunophenotyping and lymphoid antigen receptor gene rearrangement studies could be helpful if warranted clinically. The histologic scoring system initially described by Wotherspoon et al. (1993) for assessment of post-therapy biopsies (but equally applicable to initial diagnostic specimens) is reproduced here (Table 2), and can be useful in categorizing suspicious lymphoid infiltrates (Copie-Bergman et al., 2003).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Histological Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Scattered plasma cells in LP. No LFs</td>
</tr>
<tr>
<td>1</td>
<td>Chronic active gastritis</td>
<td>Small clusters of lymphocytes in LP. No LFs. No LELs.</td>
</tr>
<tr>
<td>2</td>
<td>Chronic active gastritis with florid LF formation</td>
<td>Prominent LFs with surrounding MZ and plasma cells. No LELs.</td>
</tr>
<tr>
<td>3</td>
<td>Suspicious lymphoid infiltrate in LP, probably reactive</td>
<td>LFs surrounded by small lymphocytes that infiltrate diffusely in LP and occasionally into epithelium</td>
</tr>
<tr>
<td>4</td>
<td>Suspicious lymphoid infiltrate in LP, probably lymphoma</td>
<td>LFs surrounded by CCL cells that infiltrate diffusely in LP and into epithelium in small groups</td>
</tr>
<tr>
<td>5</td>
<td>Low-grade B-cell lymphoma of MALT</td>
<td>Presence of dense diffuse infiltrate of CCL cells in LP with prominent LELs</td>
</tr>
</tbody>
</table>

LP = Lamina propria, LF = lymphoid follicle, LEL = lymphoepithelial lesion, MZ = mantle zone, CCL = centrocyte-like, MALT = mucosa associated lymphoid tissue

**Table 2:** Histologic grading system for gastric MALT lymphoma.
Although less common than gastric primaries, MALT lymphomas also not infrequently present in the intestines. Most involve the small intestine; colorectal tumors are rare. The most common form of intestinal MALT lymphoma histopathologically and immunophenotypically resembles gastric MALT lymphoma, and is diagnosed in the same manner. It apparently shows a somewhat less favorable prognosis than gastric primaries, however. Despite its occurrence throughout the world, this form is termed the "Western type" of intestinal MALT lymphoma, largely to distinguish it from a form endemic in the Mediterranean and Middle East, previously referred to a "Mediterranean lymphoma", but now more commonly referred to as immunoproliferative small intestinal disease (IPSID)(Salem et al., 1987). This latter entity is the subject of the next section.

II. Immunoproliferative Small Intestinal Disease (IPSID)

IPSID is a variant form of MALT lymphoma arising in the small intestine that has also been described as alpha heavy chain disease (alpha-HCD). The neoplastic cells of IPSID show a characteristic production of alpha immunoglobulin heavy chains without light chain, which occurs as a paraprotein in the serum, leading this alternate designation. IPSID or alpha-HCD is the most common form of the heavy chain diseases (HCD). It accounts for about one-third of all GI lymphomas in the Middle-East areas. IPSID occurs in a younger age population, with most patients presenting at the age of 20 to 30 years. Molecular and immunohistochemical studies demonstrated an association with epidemiology of Campylobacter jejuni (Salem et al., 1987). The typical presentation in young adults is as a malabsorption syndrome. Pathologically, it can be thought of a low grade B-cell MALT lymphoma with marked plasma cell differentiation, showing a dense lymphoplasmacytic infiltrate which expands and blunts the intestinal villi.

Pathogenesis

As in cases of H. pylori associated MALT lymphoma, an infectious etiology has been suspected in cases of IPSID. Studies have mirrored the efficacy of antimicrobial therapy in disease regression. Lecuit, et al demonstrated C. jejuni as a possible stimulus for this proliferation (Lecuit et al., 2004). C. jejuni has been shown to persist in Peyer’s patches and mesenteric lymph nodes, and is capable of eliciting strong IgA mucosal response. Persistent infection may lead to sustained stimulation of B cells eventually resulting in the production of monotypic IgA such as that seen in IPSID (Peterson, 2004).

Morphology and immunophenotype

IPSID is morphologically characterized by small bowel infiltration by a monotypic lymphoplasmacytic cells, and is associated with a variety of histopathological changes which range from small to medium atypical lymphoid propagation to DLBCL. The centrocyte-like lymphocytes are CD20 positive, and both atypical lymphocytic and plasmacytic populations will stain strongly with IgA heavy chain, with absence of light chain staining (7).

Molecular abnormality

Much like H. pylori associated MALT lymphoma, IPSID appears to arise from monoclonal overgrowth secondary to chronic immune stimulation by an infectious organism in this case by C. jejuni (7). Deletions of alpha heavy chain gene are observed which lead to expression of a faulty heavy chain that precludes binding of light chain to form an intact immunoglobulin molecule (7, 41).
**Prognosis**

The disease follows a variable clinical course, but in its early phases may respond to broad spectrum antibiotics, again suggesting the possibility of an infectious etiology, possibly *C. jejuni*. Nonetheless, transformation to DLBCL is not uncommon (7). The diagnosis is made in a manner similar to other forms of MALT lymphoma.

**III. Diffuse large B cell lymphoma (DLBCL)**

Diffuse large B-cell lymphoma is the 2nd most common lymphoma of the stomach after MALT lymphoma. About 75% of all cases arise *de novo* whereas the rest are transformations of MALT lymphoma and other low grade lymphomas (Koch *et al.*, 2001). The normal architecture is replaced by a diffuse proliferation of large lymphoid cells. The tumors may form large gastric mass or an ulcer with perforation. DLBCL of the gastrointestinal tract, either *de novo* or transformed from another low grade type, is an aggressive lymphoma, more commonly affecting males with a median age range of 50 to 60 years (Aledavood *et al.*, 2012; Isaacson PG, 2008; Zhang, Shen, Shen, & Ni, 2012).

**Pathogenesis**

MALTomas may transform into a diffuse large B-cell lymphoma. There is usually nothing specific appearance or immunophenotype of the large cell lymphoma itself to suggest MALT origin, but rather the existence of a prior or coexistent low grade MALT lymphoma which permits the inference that a particular large B-cell lymphoma is derived from MALT. Since many gastrointestinal large B-cell lymphomas are discovered without any known previous or coexistent low grade MALT lymphoma, this raises the interesting question of whether all gastrointestinal diffuse large B-cell lymphomas are of MALT origin (discussed further below). Current research suggests that the transformation from low grade to high grade MALT lymphoma may involve decreased expression of *bcl-2* and acquisition of increased p53 abnormalities resulting in overexpression of the p53 protein product (Psyrri *et al.*, 2008; Zhang *et al.*, 2012). No definite risk factors for gastric DLBCL have been identified, although some evidences suggest that this neoplasm may arise in a background of atrophic gastritis, particularly in the setting of immunodeficiency.

**Large Cells in Gastric B-cell Lymphomas**

Primary gastric DLBCL is a heterogeneous disease entity that includes patients with and without detectable MALT lymphoma components. Foci of DLBCL may be found in MALT lymphomas, ranging from small number of transformed cells to predominant large cell population with minimal residual MALT lymphoma (2). Distinction of the latter from DLBCL can be difficult, and may require correlation of identical rearranged immunoglobulin (Ig) genes with co-existent low-grade MALT lymphoma (Isaacson PG, 2008). A case can be made that most are of MALT origin given a common pattern of oncogene expression in gastric low grade MALT lymphomas and large cell lymphomas compared with node-based tumors.

It is generally accepted that DLBCL can be diagnosed when large lymphoid cells with distinct nucleoli are present in compact clusters, confluent aggregates, or sheets (not counting large cells confined to apparent colonized follicles), although if the high grade tumor is a minor component within a larger low grade MALT lymphoma, it should be so noted. If the tumor is predominantly of large cell type, there is no significant difference in behavior if a low grade component can be identified, although again it is suggested that the presence of the minor component be noted. Shrinkage artifact in poorly fixed
specimens can sometimes obscure the recognition of large cells, which may be difficult to tell from the surrounding centrocyte-like cells, which may have somewhat open chromatin and small nucleoli. It has been suggested that large cells be counted as such only if they show distinct nucleoli and a rim of amphiphilic cytoplasm (Burke, 2011). Given the heterogeneity of the large cell component in some tumors, failure to detect a high grade large cell component in mucosal biopsies does not exclude the possibility of transformation, and a re-biopsy should be suggested in cases where the clinical suspicion is high (e.g., a significant clinical mass lesion, or failure to respond to antibiotic therapy)(Isaacson PG, 2008).

In hematopathology, a large lymphoid cell is by definition larger than the nucleus of a histiocyte. This "internal yardstick" is helpful to avoid incorrect assessment due to swelling of cells(Cardona et al., 2012). MALT lymphomas typically contain a mixture of large and small lymphoid cells, but presence of up to 10% large cells dispersed throughout does not change the outcome. The WHO classification does not recommend categorization as "high grade MALT lymphoma" for cases with higher number of large cells mixed with small cells. However, when large cells are present in confluent sheets or clusters with other areas showing typical MALT lymphoma morphology, the diagnosis should be “DLBCL associated with MALT lymphoma in stage I or II gastric lymphomas.” DLBCL with associated low grade MALT component appear to have a better outcome than DLBCL without associated MALT component, prolonging the event free survival but not necessarily the overall survival. De novo DLBCL is also not uncommon in the stomach (Aledavood et al., 2012; Psyrri et al., 2008).

**Morphology and immunophenotype**

DLBCL is characterized by large lymphoid cells (Figure 2), with nuclei greater than twice the size of a small lymphocyte, and frequently larger than nuclei of tissue macrophage (Stein, 2008). The tumor cells are medium to large sized cells and contain round, oval, or slightly irregular nuclei with vesicular nuclear chromatin, prominent nucleoli, and moderate to ample amount of basophilic cytoplasm, and show a moderate to high proliferation index marker Ki-67 (usually >40%). In most cases, the predominant cells resemble either large centroblasts or immunoblasts; nonetheless, a mixture of these two cell types is also commonly encountered. Histologically, there is an intense cellular infiltration of the lamina propria (Boot, 2010).

Transformed MALT lymphomas may be distinguished from de novo germinal center DLBCL by immunophenotype. Both transformed MALT lymphomas and DLBCLs show BCL6 positivity; however, DLBCLs with a germinal center-like phenotype are frequently CD10 and BCL2 positive, whereas transformed MALT lymphomas are CD10 and BCL2 negative (Burke, 2011).

**Molecular abnormalities**

A number of genetic variability in DLBCLs has been documented. Studies continue to subdivide these processes into separate disease entities with associated overall clinical circumstances. However, approximately 30% of DLBCL has been demonstrated to show BCL6 abnormalities. BCL2 translocation has been documented in about 25%, and presence of c-MYC rearrangements have been postulated to occur at an average of about 10% of patients (42, 47).

**Prognosis**

Several factors affect the prognosis of gastrointestinal DLBCL. Age, stage of disease, lactate dehydrogenase (LDH) level, and use of chemotherapy are independently and significantly associated with survival. A more aggressive clinical course has been reported in patients with more extensive disease,
Figure 2: Gastric diffuse Large B-cell Lymphoma arising MALT lymphoma. The H&E stained sections show confluent collections sheets of large atypical lymphoid cells and high cell proliferation index marker Ki-67 (>40%). Evidence of an underlying MALT lymphoma is seen in this case as lymphoepithelial lesions and presence of a polymorphous infiltrate including plasma cell. CD20 stain is positive in the sheets of B-cell infiltrate.

such as presence of systemic symptoms, bulky lymphadenopathy, and elevated serum LDH levels. Interestingly, patients with CD10-positive disease showed a significantly higher survival rate compared to patients with CD10-negative lymphomas. The prognostic and diagnostic roles of some molecular variables, like microsatellite instability, allelic imbalance and chromosomal trisomies, are matters of continued investigation (Akaza et al., 1995; Boot, 2010).

IV. Burkitt lymphoma (BL)

Burkitt lymphoma is a substantially much more aggressive mature B cell neoplasm mainly in children and young adults. This entity has three recognized clinical variants: endemic form which is usually associated with EBV infection, sporadic variant where only about 30% of the cases are related to EBV infection, and immunodeficiency-associated BL (Howell et al., 2012; Lewin et al., 1978; Sugano, 1998). Extranodal disease is frequently observed but GI tract involvement varies among the three clinical subtypes, with the sporadic variant usually presenting as an abdominal mass, commonly in the terminal ileum. Rare cases of gastric and cecal BL have also been described (Faltas & Kramer, 2009; Sugano, 1998).

Pathogenesis

All three variants harbor chromosomal rearrangement of c-MYC oncogene which modifies cell cycle regulation, cellular metabolism, adhesion, differentiation and apoptosis ultimately leading to tumor formation. Baumgaertner and colleagues reported a case of \textit{H. pylori}-associated Burkitt lymphoma with complete disease remission after \textit{H. pylori} eradication therapy. This occurrence may imply probable role of \textit{H. pylori} in some cases of BL (Faltas & Kramer, 2009; Grewal et al., 2008).
**Morphology and immunophenotype**

BL displays a diffuse, monotonous infiltrate of medium-sized neoplastic lymphoid cells with round nuclei showing finely clumped and dispersed chromatin, with multiple basophilic nucleoli (Figure 3). The profoundly basophilic cytoplasm generally encloses multiple lipid vacuoles on Wright-Giemsa or Diff-Quick stained smears. Frequent mitotic figures and apoptotic bodies are encountered; the apoptotic body-containing scattered tingible body macrophages impart the characteristic “starry sky” pattern.

![Figure 3: Burkitt lymphoma of colon. The lymphoma cells are medium sized with round nuclei, coarse chromatin, multiple nucleoli, and frequent mitoses. Numerous tingible-body macrophages create a starry sky pattern. By immunohistochemistry, the tumor cells are diffusely positive for B-cell marker CD20 with co-expression of CD10 and very high cell proliferation index marker Ki-67 (nearly 100%).](image)

The tumor cells co-express pan B-cell markers such as CD19, CD20, as well as CD10, BCL6, and demonstrate light chain restriction, but are generally negative for BCL2 and TdT. In rare cases, Bcl-2 can be weakly positive. The neoplastic cells show an extremely high proliferation index with nearly 100% of Ki-67 reactivity (Bautista-Quach *et al.* 2012; Burke, 2011).

Currently Burkitt's lymphoma can be divided into three main clinical variants: the endemic, the sporadic and the immunodeficiency-associated variants. The endemic variant occurs in equatorial Africa. It is the most common malignancy of children in this area. The sporadic type of Burkitt lymphoma (also known as "non-African") is found outside of Africa. Sporadic lymphomas are rarely associated with the Epstein-Barr virus. Immunodeficiency-associated Burkitt lymphoma is usually associated with HIV infection or occurs in the setting of post-transplant patients who are taking immunosuppressive drugs (Bellan *et al.*, 2003).

**Molecular abnormalities**

As previously mentioned, all three subtypes of BL typically demonstrate any of three c-MYC translocations at band 8q24; the most common of which is with immunoglobulin heavy (IgH) chain gene at 14q32, and infrequently with Ig kappa (IgK) at 2p12 or Ig lambda (IgL) at 22q11. However, c-MYC rearrangement is not specific for BL (Sugano, 1998). The WHO criteria for Burkitt lymphoma include demonstration of a translocation involving *MYC* oncogene on chromosome 8 with one of the immunoglobulin
genes, involving kappa, IgH, and lambda, respectively) in small to medium, uniform B-cells which express CD10 and BCL6 and surface immunoglobulin but lack expression of BCL2 and TdT (Sugano, 1998). The proliferation fraction, as measured by Ki67 immunostaining, is 99% or higher (Cogliatti et al., 2006). The characteristic morphology (diffuse proliferation of uniform, small non-cleaved cells with cytoplasmic vacuoles and a starry sky appearance) must be accompanied by the translocation involving MYC and immunoglobulin gene for a diagnosis of BL.

**Prognosis**

BL is chemosensitive and the advent of high intensity, multi-agent chemotherapeutic regimen has led to an astoundingly high remission rate. Because BL specific aggressive chemotherapy protocols offer a chance of cure, whereas routine chemotherapy such as CHOP used for DLBCL is usually associated with suboptimal response, every effort should be made to provide the accurate diagnosis (Burke, 2011). In one case, a BL patient with concomitant *H. pylori* infection benefitted from *H. pylori* eradication (44).

**V. Gray zone lymphoma**

Approximately 28-50% of GI tract, *de novo* DLBCLs, and DLBCL, unclassifiable, with features intermediate between DLBCL and BL (DLBCL/BL) show c-MYC translocation with a non-Ig gene partner, complex karyotype, and simultaneous BCL2, BCL6 and/or PAX5 translocations. These are referred to as “double or triple hit” lymphoma. The 2008 WHO classification resurrects the concept of a high-grade B-cell lymphoma occupying a gray zone between BL and DLBCL in a new category with the ungainly title of “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL,” which is commonly abbreviated DLBCL/BL (Hasserjian et al., 2009). DLBCL/BL is one of the two officially sanctioned “gray zone” lymphomas in the updated 2008 WHO classification. Morphological overlap exists between BL and high-grade DLBCL and/or DLBCL/BL; therefore, it is imperative to differentiate BL from DLBCL and DLBCL/BL, particularly since the latter two entities are more resistant to chemotherapy and carry a poorer prognosis overall (47). Currently, the category of previous Burkitt-like lymphoma is usually defined as a lymphoma with features intermediate between Burkitt lymphoma and diffuse large B-cell lymphoma. The immunophenotype is similar to Burkitt lymphoma, but some cases are BCL2 positive and the cell morphology is less uniform and resembles DLBCL. Furthermore, the cytogenetic abnormalities may involve both MYC and BCL2 or BCL6 genes (Hasserjian et al., 2009).

**VI. Mantle cell lymphoma**

Small cell lymphomas other than low grade MALT lymphomas can involve the GI tract, including CLL/SLL, follicular lymphoma, and, most notably mantle cell lymphoma. Mantle cell lymphoma may involve virtually any portion of the gastrointestinal tract, which is the most common site of extranodal involvement by this tumor (Akaza et al., 1995; Boot, 2010; Burke, 2011). Overall, between 20% and 30% of mantle cell lymphoma cases involve the GI tract, not uncommonly as the primary site of involvement. A particularly characteristic form of GI tract involvement is the presence of multiple polypoid lesions, most commonly in the ileocecal region (where regional lymph nodes are also frequently involved), a condition termed lymphomatous polyposis (Figure 4). Lymphomatous polyposis has been regarded as synonymous with mantle cell lymphoma in the past, but it is now clear that other forms of non-Hodgkin’s lymphoma, especially follicular lymphoma, may on occasion present in an identical fashion, so attention to pertinent diagnostic cytoarchitectural features is important (Howell et al., 2012). In other cases, GI mantle cell lymphomas may present clinically as discrete masses, ulcers, and mucosal thickenings which may more closely mimic other lymphomas (Howell et al., 2012).
Figure 4: Mantle Cell Lymphoma involvement GI tract can be multifocal, known as “lymphomatoid polyposis”. The lymphoma cells are monomorphic small to medium sized with co-expression of CD5 and CD20. Nuclear staining of variable intensity with Cyclin D1 is characteristic.

Because of its worse prognosis (median survival 2-3 years) compared with other small cell lymphomas, it is important to distinguish mantle cell lymphoma of the GI tract from its histologic mimics, particularly the much more indolent low grade MALT lymphomas. The histologic features of mantle cell lymphoma include a monomorphic population of small lymphocytes, typically resembling small cleaved cells, but with nuclei which may range from round to frankly convoluted. In contrast to MALT lymphoma, there is a paucity of other admixed cell types such as large non-cleaved lymphocytes. The tumor cells are usually present in diffuse sheets, although a mantle zone pattern, with tumor cells surrounding naked germinal centers, may provide a clue in some cases. A nodular pattern has also been reported on occasion. An increased mitotic rate may be seen, particularly in the blastic variant. Unlike low grade MALT lymphomas, lymphoepithelial lesions are uncommon.

Mantle cell lymphoma shows a variety of immunophenotypic characteristics which can be quite useful in arriving at the correct diagnosis. By frozen section or flow immunophenotyping, the cells appear as B-cells with immunoglobulin light chain restriction which are CD5+ and CD23-, an immunophenotype virtually diagnostic of mantle cell lymphoma, given that the only other common CD5+ small cell lymphoma, CLL/SLL, is characteristically CD23+. Even if only paraffin-embedded material is available, immunophenotyping is still helpful, as CD43 coexpression is usually seen, which, though not specific for mantle cell lymphoma, does suggest a B-cell neoplasm. In addition, cyclin D1 overexpression can be detected by antibodies which work well in paraffin sections. This overexpression, which represents activation of the PRAD1/CCND1 gene at the bcl-1 locus at 11q13 by the characteristic t(11;14) translocation found in most mantle cell lymphomas, appears to date to be quite specific for mantle cell lymphoma.

VII. Intestinal Follicular Lymphoma

Primary FL of the GI tract is a predominantly female lymphoma that most frequently involves the small intestine with a predilection to the ileum (Damaj et al., 2003). This entity is recognized as a variant of follicular lymphoma in the 2008 edition of WHO classification (Figure 5).
Figure 5: Follicular lymphoma in the duodenum which is the usual site of involvement by follicular lymphoma, but may occur anywhere along the GI tract. The follicular architecture is variably prominent on H & E staining. Immunohistochemical stains show the atypical follicle centers are positive for CD20 and CD10 which confirm the follicular center origin of the lymphoma. In addition BCL2 positive staining (not shown) confirms the malignant nature of the follicles.

Since the endoscopic and clinical presentation may not be different from secondary GI involvement by a nodal follicular lymphoma or lymphomatous polyposis, which is often associated with mantle cell origin of tumor cells, it is mandatory to perform an immunohistological and, if possible, a molecular analysis of GI lymphoma. A comprehensive recent review show that this lymphoma is similar to node based follicular lymphoma with regard to morphology and immunophenotype (CD10+, BCL6+, BCL2+), but has a superior prognosis compared to nodal disease (Damaj et al., 2003). It is often detected as an incidental polyp or plaque in the duodenum or terminal ileum during endoscopy, but more advanced techniques such as double balloon endoscopy or capsule endoscopy shows multifocal involvement of the entire small intestine in many cases. The course of the disease is indolent and does not differ from nodal FL. Thus, therapy may not be required unless significant clinical symptoms are present or until disease progression. Nevertheless, a majority of patients may not require specific treatment (Boot, 2010; Burke, 2011).

VIII. AIDS-Related lymphomas

Non-Hodgkin’s lymphomas represent the most common malignancy in AIDS patients after Kaposi’s sarcoma, and unlike KS, occur with increased frequency in all AIDS risk groups. About 30% of AIDS-related non-Hodgkin’s lymphomas involve the GI tract at presentation (Sandler & Kaplan, 1996; Wotherspoon et al., 1996), with the stomach and small intestine representing the most common sites of involvement. Pain, ulceration with bleeding, obstruction, and constitutional symptoms are all seen as presenting complaints. The vast majority of AIDS-related lymphomas have been reported to correspond to one of three "diffuse aggressive". Frequently, it is difficult to precisely sub-classify AIDS-related lymphomas, as many display histopathologic features which vary significantly within the tumor (Imrie et al., 1995). Precise histologic sub-classification may be of largely semantic interest, however, since in
AIDS patients, essentially all of these lymphomas behave in an aggressive, high-grade fashion, with reported median survivals of 5 to 11 months in most series (Imrie et al., 1995; Simcock et al., 2007). Histologically, all tend to show a high mitotic rate with significant necrosis. Virtually all are B-cell lymphomas, and are generally thought to develop secondary to the impaired immunosurveillance which occurs in AIDS. Many cases (including a majority of the immunoblastic lymphomas) show evidence of EBV infection, and most show evidence of c-MYC proto-oncogene activation which may be etiologic. High grade Burkitt’s and Burkitt’s-like lymphomas also commonly involve the GI tract in non-AIDS patients, particularly among pediatric and young adult patients.

Some uncommon variants of large B-cell lymphoma are seen in this population. Their diagnosis may be challenging due to their atypical morphology and immunophenotype. Plasmablastic lymphomas and extra-cavitary variant of primary effusion lymphoma deserve special mention (Sarode, Zarkar, Desai, Sabane, & Kulkarni, 2009). The former is most commonly seen in the oral cavity of chronically HIV infected patients but can occur in other parts of the GI tract including the anorectal region and a majority of cases are associated with EBV (Figure 6).

![Figure 6](image)

**Figure 6**: Plasmablastic Lymphoma usually occurs in the oral cavity of HIV positive patients. Anorectal location has been noted, but other parts of the GI tract such as the small intestine, esophagus, as in this case, can be involved. The lymphoma cells do not express CD45 or CD20 (not shown), but are CD138+, and restrictive kappa cytoplasmic light chain+. In situ hybridization shows EBV early RNA (EBER) expression.

On the other hand, primary effusion lymphoma is associated with HHV8 (or Kaposi Sarcoma herpes virus, KSHV) and often presents as pleural effusions but can occur as a solid tumor. KSHV may be seen in a relatively high proportion of aggressive B-cell lymphomas in HIV patients and all morphological and immunophenotypic characteristics should be considered for appropriate diagnosis. A plasmacytoid morphology or an immunophenotype that is closer to plasma cells than to B-cells is observed in these lymphomas as both lymphomas often lack expression of pan B-cell antigen CD20 and PAX5, but often express CD79a and always express MUM1, CD38 and CD138. Distinction of these lymphomas from plasmablastic myeloma may be difficult as they share nearly identical immunophenotypic profiles, but is important for correct treatment (Cardona et al., 2012; Vega et al., 2005). The only significant difference
between plasmablastic lymphoma and plasma cell myeloma was the presence of EBV-encoded RNA, which was positive in all plasmablastic lymphoma cases tested and negative in all plasma cell myelomas (Vega et al., 2005). Marked reactive lymphoid hyperplasia may produce localized masses referred to as "Anorectal Tonsils", which must be distinguished from low grade lymphomas (Burke, 2011).

IX. Post-transplant lymphoproliferative disorders (PTLDs)

Transplant patients receiving immunosuppressive drugs constitute the other major class of immunocompromised hosts to experience high rates of non-Hodgkin’s lymphomas (Semakula, Rittenbach, & Wang, 2006). As in AIDS, most are EBV-driven B-cell proliferations, but in contrast to AIDS, these proliferations are a heterogeneous group which range from benign hyperplasias to frankly malignant high grade lymphomas. Most patients with PTLDs have extranodal involvement, with the GI tract being the principal site of clinical presentation. Most of these GI involving cases are of B-lymphocyte origin and are associated with Epstein-Barr virus infection. Overall, the GI tract is involved in about 35% of PTLD cases, with the small bowel being the most common site. In many cases, it is difficult to determine from routine histopathologic examination whether the lesions are benign or malignant, leading to use of the more general term PTLD (Lai et al., 2006; Nalesnik, 1990). A variety of classification schemes for PTLDs have been proposed over the years. The 2008 World Health Organization (WHO) classification system recognizes 4 major histopathologic subtypes of PTLD: (1) early hyperplastic lesions, (2) polymorphic lesions (which may be polyclonal or monoclonal), (3) monomorphic lesions, and (4) classic Hodgkin-type lymphomas (Glotz et al., 2012; Pitman et al., 2006).

3.3 T-Cell Lymphomas

I. Enteropathy-associated T-cell lymphoma (EATL)

Two components of intestinal MALT are present more diffusely in the mucosa. Firstly, lamina propria immune cells are a heterogeneous collection of antigen presenting macrophages and dendritic cells, antibody producing plasma cells and helper T-cells. Few eosinophils and mast cells are also present, particularly in the small intestine. Secondly, intra-epithelial lymphocytes are predominantly cytotoxic T-cells, present diffusely in low numbers throughout the intestines, with somewhat higher proportions in small intestines. Distinct types of lymphomas arise from the three components of intestinal MALT and recapitulate the structure and function of the cells of origin to a variable degree.

While virtually any T-cell lymphoma can affect the GI tract, EATL is perhaps the most distinctive one. Most cases occur in elderly individuals, many of whom have histories of malabsorption syndromes, particularly celiac disease. Clinically, the jejunum is most frequently involved, often as multiple well-circumscribed ulcers without a clinical mass lesion (Chan et al., 2011; Smedby et al., 2005). Biopsies or resection specimens show lymphoid infiltrates which typically resemble a large cell lymphoma, but which may vary considerably, even within a given patient, with other areas resembling small cell lymphomas or even Hodgkin’s disease. Tumor cells commonly invade the overlying epithelium, sometimes in aggregates resembling lymphoepithelial lesions (Figure 7). The presence of numerous associated eosinophils, and other inflammatory cells related to the ulceration, together with the often polymorphous nature of the infiltrate, may mask the neoplastic nature of this disorder, which should nonetheless be suspected in this clinical setting. Most cases previously described in the literature as "ulcerative jejunitis" are now suspected of being EATLs, given some studies which have found clonal T-cell receptor gene rearrangements by PCR (Chan et al., 2011; Smedby et al., 2005). Most cases (classical
Figure 7: Enteropathy associated T-cell Lymphoma (EATL) type II in the small intestine: The uniform small cells in this lymphoma closely mimic cells of mantle cell lymphoma. Immunohistochemistry shows the lymphoma cells are positive for CD3, CD8, and CD56, as well as TIA-1 and Granzyme B (not shown).

type I EATL) have a characteristic CD3+, CD7+, CD4-, and CD8- immunophenotype. As this is also the typical immunophenotype for intestinal intraepithelial T-cells, and an origin from native intraepithelial T-cells has been proposed. The tumor tends to follow an aggressive clinical course, with frequent dissemination to multiple body sites (Andrews et al., 2008). Type II EATL develops sporadically and is independent of celiac disease (Yang, Batth, Chen, Borys, & Phan, 2012), and it comprises 10 to 20% of EATL cases. It is a distinct aggressive T-cell lymphoma with frequent gamma-delta (γδ) T-cell receptor expression (Chan et al., 2011; Smedby et al., 2005). This type of EATL is mainly composed of medium-sized cells, which are positive for CD3, CD7, CD8, and CD56. Recent studies suggest to separate type II EATL from the EATL category as a distinct form of lymphoma, for which it was proposed the designation of "monomorphic intestinal T-cell lymphoma" (Burke, 2011; Chan et al., 2011).

II. Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma presents with marked hepatosplenomegaly in the absence of lymphadenopathy. The great majority of cases are of γδ T-cell origin. Most patients are male, with a peak incidence in young adults. There is an association with iatrogenic immunosuppression, both in solid organ transplant recipients and in patients with Crohn’s disease receiving immunosuppressive agents, in particular purine analogs and infliximab, an inhibitor of tumor necrosis factor. Although patients may respond initially to chemotherapy, relapse has been seen in the majority of cases, and the median survival is <3 years. Allogeneic hematopoietic cell transplantation has led to long-term disease-free survival in some cases.

The cells of hepatosplenic T-cell lymphoma are usually moderate in size, with a rim of pale cytoplasm (Figure 8). The nuclear chromatin is dispersed, with small inconspicuous nucleoli. The pattern of infiltration mimics the homing pattern of γδ T cells with marked sinusoidal infiltration in liver and spleen. Abnormal cells are usually present in the sinusoids of the bone marrow but may be difficult to identify
Figure 8: Gamma-delta T-cell lymphoma of the liver. Malignant T cells are small to intermediate in size with regular oval or folded nuclei; occasional cells may be larger with highly atypical nuclei. The lymphoma cells are diffuse positive for T-cell marker CD3, but are double negative for CD4 and CD8.

without immunohistochemical stains. The neoplastic cells also have a phenotype that resembles that of normal resting γδ T cells. They are often negative for both CD4 and CD8, although CD8 may be expressed in some cases. CD56 is typically positive. The neoplastic cells express markers associated with cytotoxic T cells, such as TIA-1. However, perforin and granzyme B are usually negative, suggesting that these cells are not activated. Isochromosome 7q is a consistent cytogenetic abnormality, and is often seen in association with trisomy 8 (Thayu et al., 2005). Cases of αβ T-cell derivation have similar immunophenotypic and genetic features, but are more common in females, with an older age distribution. Interestingly, they have a gene expression profile very similar to tumors of γδ T-cell derivation (Burke, 2011).

III. Extranodal NK/T cell lymphoma, nasal type (ENKTL)

This aggressive entity primarily occurs in the nasal cavity, nasopharynx and paranasal sinuses but also involves a number of extranasal locations including the GI tract where it may present as ulceration or perforation (Bautista-Quach et al., 2012). The disease is more commonly seen in Asians, Mexicans and natives of Central and South America, and more frequently affects males than females. Virtually all cases of ENKTL are associated with EBV infection (Burke, 2011).

The infiltrate often effaces the mucosal architecture and consists of varying sizes of pleomorphic neoplastic lymphoid cells with irregular, convoluted nuclear contour with indistinct nucleoli (Figure 9). The larger lymphoid cells show irregular nuclei with vesicular chromatini. The moderate to abundant cytoplasm is usually clear or faint. In particular, the neoplastic lymphoid infiltrates characteristically show an angiocentric and angiodestructive pattern where they aggregate around and infiltrate blood vessel wall. Admixed inflammatory cells consisting of histiocytes, plasma cells and small lymphocytes, ulceration of the overlying mucosa and geographic necrosis are frequently observed (Sun, Lu, Yang, & Chen, 2011). The tumor cells are distinctively CD2, CD56, cytoplasmic CD3 positive and express
Figure 9: Extranodal NK/T cell lymphoma, nasal type in the esophagus. The neoplastic lymphoid cells are invading and destroying the wall of a blood vessel. The neoplastic cells are positive for CD56, and CD3 as well as EBV by EBER in situ hybridization.

cytotoxic molecules (Granzyme B, TIA-1 and/or perforin) but are negative for surface CD3 and other T or NK cell markers such as CD4, CD5, CD8, TCR delta, beta F1, CD16 and CD57. Some cases demonstrate reactivity for CD7 or CD30 (Burke, 2011).

3.4 Other Rare Type of Primary Gastrointestinal Lymphomas

The primary GI tract Hodgkin lymphoma, myeloid sarcoma, histiocytic sarcoma, dendritic cell sarcoma, extramedullary plasmacytoma or other rare types of primary GI tract B-cells lymphomas (T-cell histiocytes rich large B-cell lymphoma, B lymphoblastic lymphoma, lymphomatoid granulomatosis etc) or T-cells lymphomas (anaplastic large cell lymphoma, peripheral T-cell lymphoma and T-lymphoblastic lymphoma etc) should also be considered if unusual morphologic and immunophenotypical features are present. A complete morphologic immunophenotypical and molecular study analysis is required for the differential diagnosis.

3.5 Mimics of Gastrointestinal Lymphomas

1. Distinguishing between reactive lymphoid hyperplasia and MALT lymphoma

This has been discussed in the section on low grade MALT lymphoma above. While reactive lymphoid follicles can be present in virtual any gastrointestinal biopsy, the presence of an extensive dense interfollicular lymphoid infiltrate, a predominance of centrocyte-like cells (which may include monocyte-toid cells) in the infiltrate, deep extension of the infiltrate into the wall, and prominent destructive lymphoepithelial lesions should alert one to the possibility of a low grade MALT lymphoma (Figure 10).

The suspicious of MALT lymphoma is relied on histology in combination with immunohistochemistry and ancillary studies if available, but diagnose unequivocally only if most or all of the above features are present. A monomorphous dense lymphoid infiltrate should raise suspicion of a non-MALT lymphoma, such as mantle cell lymphoma, follicular lymphoma, or small lymphocytic lymphoma. Ancillary studies are recommended to support the diagnosis.
2. Inflammatory pseudotumor (IPT) and lymphomas

Inflammatory pseudotumor (inflammatory myofibroblastic tumor) is a benign, chronic inflammatory disorder of unknown cause that manifests as a solid mesenteric mass, indistinguishable from malignancy. IPT can be differentiated from lymphoma because IPT has both T and B cells, in contradistinction to lymphoma, in which a clonal population of T or B cells is present (Figure 11) (Burke, 2011). Some pseudotumors are thought to be secondary to infection. Various organisms have been implicated in pathologic specimens, including mycoplasmata and nocardiae in lung pseudotumors, actinomycetes in liver pseudotumors, Epstein-Barr virus in splenic and nodal pseudotumors, and mycobacteria in spindle cell tumors. Histologically, the lesions were characterized by a fibrous/inflammatory process that showed marked heterogeneity associated with both acute and chronic inflammation, including lymphocytes and plasma cells, myofibroblastic spindle cells, and collagen (a fibrous reaction). IPT of lymph node represents an evolving, dynamic process that may adopt different morphological appearances depending on its stage of evolution (Makhlouf & Sobin, 2002).

Some IPTs have been found to be associated with IgG4-related sclerosing disease, a systemic disease in which there is extensive IgG4-positive plasma cell and T-cell infiltration of various tissues. This condition manifests itself as autoimmune pancreatitis, sclerosing cholangitis, cholecystitis, sialadenitis, retroperitoneal fibrosis, tubulointerstitial nephritis, interstitial pneumonia, prostatitis, IPT, and lymphadenopathy. IgG4-related IPTs have been found in patients with and those without autoimmune pancreatitis (Cheuk & Chan, 2010).

3. NK-cell enteropathy or lymphomatoid gastropathy

Recently, benign, indolent NK-cell enteropathy or lymphomatoid gastropathy have been described, and therefore should be differentiated from the aggressive ENKTL. Mansoor and associates documented eight cases of atypical NK-cell proliferation limited to the GI tract (stomach, duodenum and colon) (Mansoor et al., 2011). The atypical cells express NK cell markers such as CD56, cytoplasmic CD3, CD7, TIA-1 and/or Granzyme B, but are non-reactive for CD4, CD8, CD5, CD10, CD20, CD30, CD68, or CD138.
The proliferative index marker Ki-67 nuclear staining is usually low. Furthermore, in contrast to ENKTL, NK-cell enteropathy or lymphomatoid gastropathy is not typically associated with EBV infection. This lesion clinically behaves in a benign and an indolent manner. Disease persistence was observed in 67% to 75% of the patients, with recurrence in one patient two years after spontaneous regression of the disease. Moreover, none of the patients showed evidence of disease progression, and there was no reported mortality (Mansoor et al., 2011). It is therefore essential to distinguishing this entity from the more aggressive NK/T-cell lymphomas in order to avoid unnecessary therapy and its associated risks.

4. Non-lymphoid disease

Non-hematolymphoid lesions such as poorly differentiated carcinoma or melanoma morphologically can mimic GI tract lymphoma (Burke, 2011). In addition, many system diseases have GI tract involvement; therefore the clinical and radiological correlation is required for differential diagnosis. A complete immunohistochemistry work up is helpful in order to figure out the origin or the disease processes. For example, systemic mastocytosis and Langerhans' histiocytosis can be distinguished with CD117 and CD1a immunostains, respectively (Bautista-Quach, et al., 2012).

4 Diagnostic Approach for Suspected GI Lymphomas

In every case of GI tract lymphoma, the goal is to provide a diagnosis according to the WHO classification so that the correct treatment can be given. Detailed algorithms or practical guide to diagnosis with relatively modest ancillary techniques have been published but must be adopted for the individual practice situation. A judicious use of immunohistochemistry can provide a great deal of information with relatively low cost. Generous sampling during endoscopy, prompt fixation, and optimal processing are required to produce consistently high quality H&E sections, which must form the basis for decisions about additional ancillary testing. In general, diffuse large B-cell lymphomas, which form the largest...
single type of GI lymphomas, are unlikely to be mistaken for a benign process but may mimic non lymphoma entities. Immunohistochemical staining for CD20 may be sufficient to arrive at the correct diagnosis in most of these cases. Staining with CD45, CD138, pancytokeratin and S-100 antibodies is robust and usually reliable in cases of acute leukemia, plasma cell neoplasm, poorly differentiated carcinoma and melanoma, respectively (Burke, 2011; Cardona et al., 2012). The infiltrates composed of small or mixed lymphoid cells prove most challenging as do the presence of lymphoid follicles. The pathologist should be familiar with the characteristics of reactive follicles (presence of zonation, tingible body macrophages, and complete mantle zones), but BCL2 immunohistochemistry may be required to make the distinction between reactive and neoplastic follicles and follicular colonization by mantle zone or marginal zone lymphoma cells. The pathologist should also remember that benign reactive lymphoid follicles may co-exist with extranodal marginal zone lymphoma involving GI tract.

The clinical context is extremely important in deciding which ancillary tests are required. Because most chronic gastritis and gastric MALT lymphoma patients are initially treated with antibiotics, the exact distinction may not be necessary. Demonstrating the proportion of B-cells with one or two immunostains may be adequate. However, distinction between mantle cell lymphoma, EATL type II and other reactive small lymphocytic infiltrates is crucial and Cyclin D1 staining should be included in any GI tract lymphoma composed of small cells. Clinical correlation is essential in every case of suspected lymphoma and GI tract lymphomas have no exception. In particular, the distinction between primary GI tract lymphoma and secondary involvement of GI tract by lymphoma cannot be performed on the basis of pathological examination alone. The prognosis for primary and secondary GI tract lymphoma of the same WHO type may be entirely different, supposed to be due to the low clinical stage of the primary lesions. The presence of HIV infection or other causes of immunodeficiency (for example, post-transplant status) should be noted because of the possibility of unusual types of lymphomas and the vastly inferior prognosis to the usual types.

In summary, GI lymphomas are common extranodal lymphomas occurring in all age groups. Accurate diagnosis of the types of lymphoma is vitally important for correct treatment and determining prognosis. The close connection between chronic inflammation in GI tract and lymphoma has shed much light on the growth and natural history of the lymphomas.

References


