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Perspectives in pathology

The recognition and classification of lymphoproliferative disorders of the gut☆

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Summary Gastrointestinal lymphomas can be difficult to diagnose, particularly in small samples, when early in development, or when of unusual types. In this review, we describe lymphoid proliferations in the gastrointestinal tract in a location-based manner, including, mouth, esophagus, stomach, small intestine, and large bowel. For the purpose of differential diagnosis, benign mimics of lymphoma are also described. Lymphoma types that are specifically addressed include plasmablastic, extranodal natural killer/T-cell–nasal type, extranodal marginal zone lymphoma (eg, mucosa-associated lymphoid tissue lymphoma), diffuse large B cell, primary follicular of small intestine, enteropathy-associated T cell, and Burkitt and mantle cell. Immunohistochemical markers useful in the diagnostic approach are elaborated in detail.

1. Introduction

The gastrointestinal (GI) tract is a common site of presentation for extranodal lymphomas [1]. A broad range of lymphoproliferative disorders occur in the GI tract and, with only few exceptions, most of these exhibit features similar to those encountered in their nodal or other extranodal sites. It is the goal of this review to consider some of the specific diagnostic findings allowing distinction of specific types within the broad range of lymphoid proliferations in the GI tract, with emphasis for application by the general surgical pathologist.

Primary GI lymphomas make up 5% to 10% of primary GI neoplasms [1] (Tables 1-3). Nevertheless, the GI tract is the most common site of extranodal lymphomas, with increasing incidence worldwide [2,3]. The stomach comprises 50% to 60% of these cases, with an additional 30% arising in small intestine, most of which are in the proximal portion. Ten percent occur in the large intestine. Oral lymphomas are rare, and esophageal lymphomas are exceedingly rare. The most common type of GI tract lymphoma, diffuse large B cell lymphoma (DLBCL), is the commonest type arising in other extranodal as well as nodal sites. It comprises about 45% of cases of GI lymphoma with extranodal marginal zone lymphoma accounting for about 17% of cases [2,4,5].

There are some notable racial associations: Asian, Native American, and Pacific Islander populations have an increased incidence of GI lymphomas [4]. African Americans have a low incidence and Caucasians have an incidence

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Table 1 Most frequent sites of occurrence of gastrointestinal lymphomas

Site	Oropharynx	Esophagus	Stomach	Small intestine	Large intestine	Rectum
DLBCL	+	+	+	+	+	+
PBL	++					+
MCL	+	+	+	++	++	+
FL				+[a]		
ENKTL	++			+		
BL	+			+	+	
EATL	+	+	+	++	+	+
EMZL	+	+	++	+	+	+

Abbreviations: DLBCL, diffuse large B cell lymphoma; PBL, plasmablastic lymphoma; MCL, mantle cell lymphoma; FL, follicular lymphoma; ENKTL, extranodal nasal type NK/T cell lymphoma; BL, Burkitt lymphoma; EATL, enteropathy associated T-cell lymphoma; EMZL, extranodal B marginal zone lymphoma; +, found in this site; ++, classic GI site of this lymphoma type.

[a] Specific clinical entity "follicular lymphoma of small intestine". Typical systemic follicular lymphoma may occur at all sites.

intermediate between these groupings. Except in cases of perforation, surgical resection has no specific effect on long-term survival [4,6].

It is important to remember that the difficulty in diagnosis of lymphoma in the GI tract is usually 2-fold: (1) the small size of biopsies, limiting the extensive evaluation usually performed on comparable lymph node samples and (2) confusion of lymphoma with benign and reactive lymphoid proliferations in the GI tract [7-9]. However, the latter can be addressed by improved skill at recognizing benign lymphoid proliferations in GI biopsy specimens. In particular, with consideration of clinically or pathologically defined background settings a higher suspicion and further evaluation for lymphoproliferative disease will achieve better diagnostic accuracy (Tables 4 and 5; Fig. 1).

Table 2 Primary GI non-Hodgkin lymphoma cases according to GI site and histologic type

	% by site	% of all sites
Esophagus		
BCL-NOS	100	0.7
Stomach		
DLBCL	38	10
EMZL	37	17
MCL	3	1
Small intestine		
DLBCL	38	10
FL	23	6
EATL	10	3
PTLD	10	3
BL	8	2
EMZL	5	1
Colon		
DLBCL	50	9
EMZL	23	4
FL	8	1
MCL	4	0.7
PTLD	4	0.7
Multiple GI Sites		
DLBCL	31	3
MCL	31	3
EMZL	8	0.7
BL	15	1
FL	8	0.7
PTLD	8	0.7

Abbreviations: BCL-NOS, B-cell lymphoma, not otherwise specified; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; EATL, enteropathy associated T-cell lymphoma; EMZL, extranodal marginal zone lymphoma ("MALT lymphoma"); FL, follicular lymphoma; MCL, mantle cell lymphoma; PTLD, post-transplant lymphoproliferative disorder.

NOTE. Adapted from Howell et al 2012 [2].

In evaluating GI tract lymphoid lesions we should consider and compare normal components, immune hyperplasias and lymphoproliferative disorders. Throughout the GI tract there are normally lymphoid and plasma cells in the submucosal lymphoepithelial complexes and in the lamina propria. In some sites, these are frequently inconspicuous and small in number, so that they are rarely noticed. The entire length of the GI tract is exposed to antigen, and a functional immune response actively occurs in all sites [5].

2. Approach by location

It is of benefit to consider lymphoid infiltrates in relation to their location in the GI tract (Table 1). According to each site, specific combinations of benign and neoplastic processes are more common, although, as will be noted, some lymphoproliferative disorders can arise anywhere in the GI tract. Incidences of lymphomas differ in relation to specific regions (Table 2).

3. Lymphoid hyperplasias – benign processes

Lymphoid hyperplasias of the GI tract can be divided by their anatomic distribution: focal or diffuse. Focal lymphoid hyperplasias of the GI tract are most often localized to the ileum and occasionally the colon. Young patients typically