A practical approach to small lymphoid cell infiltrates in the lower gastrointestinal tract

Anita S Iyer

Abstract

The intestines contain the largest accumulation of lymphoid tissue in the body. Hence it is not surprising that a variety of lymphoid lesions are found here. The spectrum ranges from focal or diffuse reactive lymphoid hyperplasias to post transplant lymphoproliferative disorders to full-blown lymphomas. In fact, the GI tract is the most common extranodal site of non-Hodgkin lymphoma (NHL), often arising in a setting of immunosuppression or immune dysregulation. The distinction therefore, of reactive lesions from low grade NHLs especially the small cell type, is of clinical significance, as the management is different. The diagnosis in these lymphoid lesions is best made through familiarity with the histologic patterns of injury, systematic approach to diagnosis and full knowledge of the clinical setting. This review will provide an overview of the normal mucosal immune system and discuss the lymphoid pathology of the lower GIT with emphasis on a practical approach to small cell infiltrates.

Keywords extranodal non-Hodgkin lymphomas; GI lymphomas; lymphomatoid polyposis; reactive lymphoid lesions

Introduction

The GIT houses more lymphoid tissue than the remainder of combined anatomic sites. Hence it is not surprising that the GIT is the predominant site of extranodal lymphoma involvement[1,2] accounting for 30–50% of all lymphomas considered. The vast majority are NHLs, although Hodgkin lymphoma has been reported. Primary lymphomas of the GI tract are rare accounting for 1–4% of all gut malignancies, while secondary GI involvement is relatively common, especially so in advanced disease (up to 60%). Despite their rarity, primary lymphomas of the GIT are important since their evaluation, diagnosis, management and prognosis are distinct from that of lymphomas at other site.

Within the GIT, 68–75% occur in the stomach, approximately 30% in the small bowel, and up to 3% in the large colon and rectum combined. The relative incidences of primary GI lymphomas show considerable geographic variation.[3,4] In the US, gastric lymphoma of the MALT type is more common rather than the primary small intestinal lymphoma. The latter however, accounts for 75% of the small bowel lymphomas in the Middle East and Mediterranean basin. While Burkitt's lymphoma in Africa is approximately 50-fold higher than it is in US.

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The lymphomas within GIT often arise in a clinical setting of long standing inflammation (e.g. celiac disease, inflammatory bowel disease), long standing/recurrent infection (*Campylobacter jejuni*, *Helicobacter pylori* infection) or immunosuppressed states (AIDS, Post transplantation, iatrogenic). The mechanism is persistent infection and/or chronic antigenic stimulation resulting in reactive or aberrant immune response eventually culminating into full-blown lymphoma. The morphologic correlation here translates into a florid, but heterogeneous lymphoid cell proliferation in the initial reactive phases to an expansile, monotonous, clonal population of lymphoid cells, without overt signs of destruction especially in the low grade NHL.

The distinction of reactive versus neoplastic lymphoid infiltrates therefore, requires awareness of the clinical setting, familiarity with the histologic spectrum and a thoughtful consideration of the possible differential diagnoses. In this review, we will provide a brief overview of the normal intestinal immune system and discuss the various lymphoid pathologies of the lower GIT with emphasis on a practical approach to small cell infiltrates.

Normal intestinal mucosal immune system

The gastrointestinal system is endowed with a rich immune system as humans are exposed to an enormous load of environmental antigens through the GIT. The immune system must thus balance antigenic tolerance against immune defense. The function of the intestinal immune system is best understood on the basis of the microscopic anatomy. The entire length of the small and large bowel displays nodules of lymphoid tissue within the mucosa or both mucosa and submucosa. Within the distal ileum, these nodules become confluent to produce Peyer's patches (Figure 1). The surface epithelium overlying the lymphoid tissue contains both columnar absorptive cells and the M (membranous) cells, the latter found only in the small and large intestinal lymphoid sites and not seen by light microscopy. M cells are capable of transporting antigenic macromolecules, intact from the lumen to the underlying lymphocytes. The cytotoxic T lymphocytes are scattered within the surface epithelium throughout the intestine, usually at the base of the epithelial layer. These are referred to as intraepithelial lymphocytes (IELs)

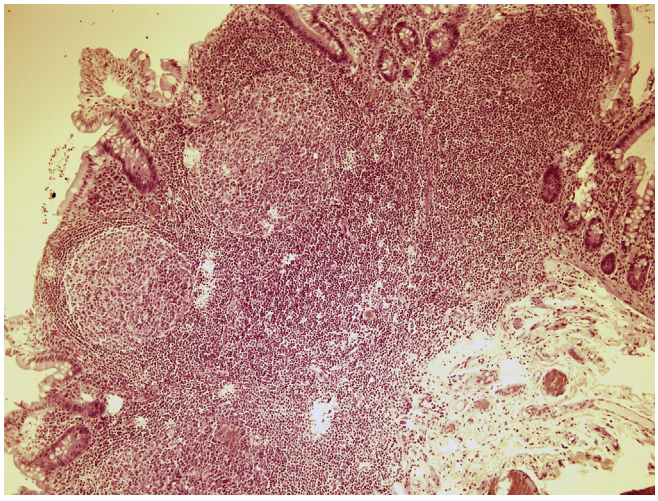

Figure 1 Confluent lymphoid aggregates in the ileum produce Peyer's patches with broadening of the overlying villi.

and are of the CD8+ phenotype. In healthy individuals, the IEL counts can vary from 1.8 to 26 per 100 epithelial cell nuclei.[5] A modest elevation in the IEL counts accompanies many types of inflammatory conditions of the colon.

The lamina propria contains helper T cells (CD4+), educated B cells, plasma cells, mast cells and eosinophils. The intestinal lymphoid nodules and mucosal lymphocytes, together with isolated lymphoid follicles in the appendix and mesenteric lymph nodes constitute the mucosa-associated lymphoid tissue (MALT).

Reactive lymphoid lesions

Focal lymphoid hyperplasia

This condition occurs in the terminal ileum and seen commonly in children and young adults. In children, the nodules may serve as a nidus for ileocecal intussusception, or an appendicitis-like illness. The histology reveals hyperplasia of Peyer's patches with preservation of sharply defined follicles. The adults, however may present with more severe symptoms lasting several weeks and sometimes, with a right lower quadrant mass. The histology likewise reveals a more severe pathology including follicular hyperplasia with ulceration and accentuation of the marginal zone. There is dense lymphoplasmacytic infiltrate, extending transmurally. Sometimes eosinophils may be prominent feature. Lymphoepithelial lesions may also be seen on tangential section. The overall morphology may thus closely resemble MALT lymphoma and clonality assays may be required for definite distinction in difficult cases.

Diffuse nodular lymphoid hyperplasia

It is also called as follicular lymphoid hyperplasia. This may occur in the small bowel and/or the large bowel. In children, this condition tends to have a benign course and usually regresses spontaneously. In adults, however the condition is associated with immunodeficiency (e.g. common variable immunodeficiency or selective IgA deficiency) and giardiasis, and the prognosis is less certain.

On endoscopy, the bowel reveals numerous nodules mimicking lymphomatous polyposis (mantle cell lymphoma). Hence a biopsy often becomes necessary to confirm the benign nature of the nodules. (The morphologic challenges and the methods to resolve are discussed in detail in the section of Diagnostic pitfalls.) There is well-documented association of diffuse nodular hyperplasia to MALT type of lymphoma when occurs in the absence of immunodeficiency.[6,7]

Lymphomas of the small intestine

These lymphomas can be broadly classified into three main groups:

- IPSID (also called alpha heavy chain disease, Mediterranean lymphoma, Seligman disease), a variant of extranodal marginal zone lymphoma of MALT that secretes alpha heavy chains.
- Other western-type non-IPSID lymphomas (e.g. diffuse large B-cell lymphoma, mantle cell lymphoma, Burkitt's lymphoma, follicular lymphoma).
- Enteropathy-associated T cell lymphoma (EATL) which is T cell lymphoma arising in a background of gluten-sensitive enteropathy.

For the purposes of this review, we will focus on the differential considerations of small cell lymphomas such as IPSID, the western-type extranodal marginal zone lymphoma, SLL/CLL, the follicular lymphoma and the mantle zone lymphoma.

Extranodal marginal zone B-cell MALT lymphoma

These are the most frequent lymphomas of the intestine in the western world, but are much less frequent than the gastric MALT lymphomas.

Clinical features: the majority is seen in middle-aged adults or older patients with a slight male predominance. This lymphoma can be located in any portion of the small or large bowel, though a large number have been reported in the rectum.[8,9] The disease has an indolent course being largely localized in the small bowel with typically no systemic spread. Patients typically present with abdominal pain and weight loss. Unlike the gastric counterpart, a clear association with an infectious agent is lacking. However, some cases reportedly respond to antibiotics implicating a bacterial agent in at least a subset of lymphomas.[10]

The prognosis is better when compared to other histologic types of lymphoma, but less favorable when compared with the gastric MALT lymphoma. Long term survival (10 year survival rate of up to 82%) and cure are common.

Pathology:

Gross – the lymphomas typically present as ulcerated exophytic mass, sometimes they can present as raised lesions with erosion and erythema. The majority is single, but occasionally can be multiple. Typically they show deep mural invasion, although sometimes they can be superficially invasive.

Microscopy: the lesion initially reveals hyperplastic reactive B-cell follicles separated by neoplastic marginal zone cells, which often show plasma cell differentiation (Figure 2c). At this stage, the lesion can be easily misinterpreted as benign particularly in a biopsy specimen, if the interfollicular region is not carefully scrutinized (see the discussion under "Diagnostic pitfalls"). As the lesion advances, the infiltrate could erode and overrun the follicles resulting in partial or total effacement of the nodular architecture (Figure 2a). Sometimes, clusters of neoplastic cells can be seen invading the mucosal glands, causing eosinophilic degeneration of the epithelium and eventual destruction (described as "lymphoepithelial lesion"). This feature is not as striking as in the gastric counterpart, however, can almost always be found (Figure 2b). Hence one must be careful not to over interpret this feature, especially in the terminal ileum where intraepithelial lymphocytes can be normally seen in the epithelium overlying the lymphoid follicles. If clusters or sheets of large cells are noted, then this may indicate a large cell transformation to diffuse B-cell lymphoma and the finding, therefore has to be noted in the report.

Immunohistochemistry and molecular pathology: the immunophenotype is positive for CD20 and CD21; CD5 is usually negative or weakly expressed; but CD23, CD10 and BCL6 are usually negative. Plasma cell differentiation may be detected by immunoglobulin light-chain restriction. CD43 is coexpressed in the neoplastic B cells in one-third of the cases.