

15.10.4 Gastrointestinal lymphomas 2892

15.10.4 Gastrointestinal lymphomas 2892

section 15 Gastroenterological disorders 2892 15.10.4 Gastrointestinal lymphomas Kikkeri N. Naresh ESSENTIALS Primary gastrointestinal lymphoma is the most common extranodal lymphoma and is almost exclusively of non-Hodgkin type. It is defined as lymphoma that has presented with the main bulk of disease in the gastrointestinal tract, with or without involvement of contiguous lymph nodes. MALT lymphoma is an indolent B-cell lymphoma whose histology recapitulates the features of mucosa-associated lymphoid tissue (MALT). It most commonly affects the stomach, presenting with nonspecific dyspepsia. Most cases appear to be driven by *Helicobacter pylori*, with 75% regressing following eradication of the organism with appropriate antibiotics. Deeply invasive lymphomas and those with adverse histological or cytogenetic features are unlikely to respond. Mantle cell lymphoma and duodenal-type follicular lymphoma are adult B-cell lymphomas that can present as gastrointestinal lymphomas. Diffuse large B-cell lymphoma is an aggressive lymphoma that is relatively frequently encountered in gastrointestinal locations. Burkitt lymphoma is also an aggressive B-cell lymphoma, and is the most frequent childhood gastrointestinal lymphoma. Enteropathy-associated T-cell lymphoma is an intestinal lymphoma of intraepithelial T lymphocytes that occurs most commonly in the jejunum or ileum and is associated with coeliac disease. It presents with abdominal pain, often due to intestinal perforation. The prognosis is usually poor, with death frequently resulting from abdominal complications in patients already weakened by uncontrolled malabsorption. Monomorphic epitheliotropic intestinal T cell lymphoma (MIETL) has been recently identified as a distinct type of high-grade T cell lymphoma. Introduction The gastrointestinal (GI) tract is the most common extranodal location for lymphomas. Designation as 'primary GI lymphoma' requires disease to be limited to the GI tract and contiguous lymph nodes at presentation. Such lymphomas are almost entirely non-Hodgkin lymphomas (NHLs), and while there are many types of non-Hodgkin lymphomas, a small subset of types account for most GI lymphomas, with most being B cell in origin. Diffuse large B-cell lymphoma (DLBCL) and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) are particularly more frequent. Many other types of lymphomas can present in the GI tract, but each of them accounts for few of all GI lymphomas and these will not be discussed in this chapter. Common primary GI lymphomas are listed in Table 15.10.4.1. Epidemiology

Epidemiological aspects of some of the GI lymphomas are distinct. These include primary gastric MALT lymphoma, immunoproliferative small intestinal disease (IPSID), Burkitt lymphoma, and enteropathy-associated T-cell lymphoma (EATL). MALT lymphoma The stomach is the most common site for MALT lymphoma, and MALT lymphoma accounts for nearly 50% of primary gastric lymphomas. A relatively high incidence is recorded in some parts of the world, such as north-east Italy. Gastric MALT lymphoma has a strong association with *Helicobacter pylori* infection. IPSID is a rare disease and type of MALT lymphoma. This is mostly seen in the Middle East and in the Cape region of South Africa, and is associated with *Campylobacter jejuni* infection. Burkitt lymphoma Burkitt lymphoma occurs in three forms: endemic, nonendemic (sporadic), and immunodeficiency associated. Endemic Burkitt lymphoma is endemic in the malarial belt of equatorial Africa and Papua, New Guinea. It is a childhood malignancy. Immunodeficiency-associated Burkitt lymphoma is mostly seen in patients infected with HIV and is often the initial presentation of AIDS. Enteropathy-associated T-cell lymphoma A type of EATL is more common in areas of high prevalence of coeliac disease, such as Northern Europe. Aetiology There have been insights into the aetiology of some of the GI lymphomas such as MALT lymphoma, Burkitt lymphoma, and EATL (Table 15.10.4.2). The aetiology of other lymphomas is unclear. MALT lymphoma and infective agents *H. pylori* is implicated in the pathogenesis of gastric MALT lymphoma. There is a significantly higher frequency of preceding *H. pylori* infection in patients with gastric lymphoma, and *H. pylori* Table 15.10.4.1 Common primary GI lymphomas B cell Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) Mantle cell lymphoma (MCL) and lymphomatous polyposis Duodenal-type follicular lymphoma (FL) Diffuse large B-cell lymphoma (DLBCL) Burkitt lymphoma T cell Enteropathy-associated T-cell lymphoma (EATL)

15.10.4 Gastrointestinal lymphomas 2893 is demonstrated in many gastric MALT lymphomas. It is fascinating that normal gastric mucosa is devoid of organized lymphoid tissue. *H. pylori* infection induces acquisition of lymphoid tissue, and *H. pylori*-associated follicular gastritis is a precursor lesion to gastric MALT lymphoma. Further evidence of the aetiological association comes from the fact that the cells of low-grade gastric MALT lymphoma respond to *H. pylori* antigens via a T-cell-mediated mechanism in an in vitro setting. This is further corroborated by regression of *H. pylori*-associated MALT lymphoma following eradication of *H. pylori* using appropriate antibiotics. Similar to *H. pylori*, *C. jejuni* is associated with IPSID, which is a form of MALT lymphoma involving proximal small intestine. Burkitt lymphoma, malaria, and Epstein-Barr virus Nearly all cases of endemic Burkitt's lymphoma show an association with Epstein-Barr virus (EBV), with EBV being present within the neoplastic B cells. A lesser proportion (approximately 30%) of other forms of Burkitt's lymphoma is also associated with EBV. The precise role played by EBV in lymphomagenesis is still a matter of debate. Infection of B cells by EBV results in activation and enhanced proliferation within the germinal centres. This enhanced proliferation increases the chances of errors in DNA replication and acquisition of chromosomal translocations. In addition, EBV products such as EBV nuclear antigen 1 and EBV-encoded small RNAs suppress apoptosis and enhance tumourigenicity respectively, and contribute to lymphomagenesis. Endemic Burkitt's lymphoma also occurs in the same regions that are endemic to *Plasmodium falciparum* malaria. *P. falciparum* is thought to reduce patient immunity and cause exhaustion of the EBV-specific T-cell response. *P. falciparum* is also thought to stimulate latently EBV-infected memory B cells via the Toll-like receptor 9. These processes lead to activation and expansion of EBV-infected B cells, contributing to lymphomagenesis. Enteropathy-associated T-cell lymphoma There is a strong association between coeliac disease and a sub type of EATL. These patients also have other features associated with

coeliac disease, such as expression of HLA DQ2 or HLA DQ8, hyposplenism, and dermatitis herpetiformis. Pathogenesis Many B-cell GI lymphomas are associated with specific chromosomal translocations, and these play pathogenetic roles. Genes involved in the translocations include oncogenes and tumour suppressor genes (Table 15.10.4.2). Many of the B-cell lymphomas limited to the GI tract express $\alpha\beta$ -integrin, which is a homing receptor that binds to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) that is expressed on endothelial cells of GI mucosa. Infections and associated immune mechanisms also play a role in lymphomagenesis. Well-established precursor lesions also exist for some of these lymphomas. MALT lymphoma *H. pylori* is associated in up to 90% of gastric MALT lymphomas. As stated previously, normal gastric mucosa does not show any significant lymphoid tissue, and acquisition of lymphoid tissue, which is triggered by *H. pylori*, precedes development of MALT lymphoma. Hence, *H. pylori*-associated gastritis is a precursor lesion for *H. pylori*-associated gastric MALT lymphoma. Trisomy of chromosome 3, 18, or others is not an infrequent finding in GI MALT lymphomas. A small subset of GI MALT lymphomas is associated with chromosomal translocations involving MALT1 or BCL10 genes. These translocations target and activate the nuclear factor kappa B (NF- κ B) pathway. Table 15.10.4.2 Frequently associated genetic abnormalities and infective agents in GI lymphomas, and well-recognized precursor lesions

Chromosomal abnormalities	Genes involved	Infective agent	Precursor lesions
MALT lymphoma t(11;18)(q21;q21) t(14;18)(q32;q21) t(1;14)(q22;q32) +3 +18	API2-MALT1	MALT1	BCL10
<i>H. pylori</i> C. jejuni <i>H. pylori</i> gastritis	MCL t(11;14)(q13;q32) CCND1-IGH	None	In situ mantle cell neoplasia
Duodenal-type FL t(14;18)(q32;q21) t(2;18)(p12;q21) t(18;22)(q32;q11)	Others	BCL2-IGH IGH-BCL2 BCL2-IGL	None
In situ follicular neoplasia DLBCL t(14;18)(q32;q21) 3q27 abnormalities 8q24 translocations	Others	BCL2-IGH BCL6 MYC	Epstein-Barr virus (infecting neoplastic cells)
in a minority of cases	None	Burkitt lymphoma t(8;14)(q24;q32) t(2;8)(p12;q24) t(8;22)(q24;q11)	MYC-IGH IGH-MYC MYC-IGL
Epstein-Barr virus (infecting neoplastic cells)	None	EATL +9q34 -9p/-9p21 -17p12-13.2 -16q12.1	None
Refractory coeliac disease	MEITL +9q34.3 +8q24	MYC	None

section 15 Gastroenterological disorders 2894 Mantle cell lymphoma Over 95% of these lymphomas are associated with a CCND1-IGH translocation. Duodenal-type follicular lymphoma Most are associated with a BCL2 translocation resulting in increased and inappropriate BCL2 protein expression. BCL2 is a key antiapoptotic protein. Burkitt lymphoma The key cytogenetic abnormality is translocation of the MYC gene. In an overwhelming majority of cases, IGH partners the MYC gene, and in a few cases the partnering gene is IGH or IGL. Most cases do not show additional cytogenetic abnormalities (simple MYC), but MYC mutations are frequent. Abnormalities involving TP53, p73, BAX, p130/RB2, and p16 also occur. Enteropathy-associated T-cell lymphoma Most patients with adult-onset EATL have a previous history of coeliac disease or are diagnosed as having coeliac disease in the same clinical episode in which the lymphoma is diagnosed. A few patients have a history of childhood-onset coeliac disease. In some cases, there is a prodromal period of refractory coeliac disease that is sometimes accompanied by intestinal ulceration (ulcerative jejunitis). A clonal population of T cells evolves during the transition from coeliac - disease to refractory coeliac disease, and further clonal expansion occurs during transition from refractory coeliac disease to EATL. EATL is associated with complex cytogenetic abnormalities that include segmental amplifications of 9q34 region or deletions of 16q12.1 regions in most cases. EATL is associated with gains of 1q and 5q. Clinical presentation The age at presentation, site of frequent occurrence, presenting symptoms, and endoscopic features of different GI lymphomas are variable (Table 15.10.4.3). MALT lymphoma Gastric MALT lymphoma typically occurs in patients

over 40 years of age, but can occur at any age. The sex incidence is equal. The presenting symptoms are usually those of nonspecific dyspepsia and more suggestive of gastritis or peptic ulcer than a neoplastic lesion. Most MALT lymphomas of the stomach arise in the antrum, and macroscopically are characterized by an ill-defined thickened, inflamed, and ulcerated mucosa, rather than a tumour mass. Most GI MALT lymphoma patients present in stage IE or IIE disease. Multiple extranodal sites may be involved in one-quarter of gastric MALT lymphomas and in about one-half of other GI MALT lymphomas. About one-third of patients have an IgM paraprotein. IPSID is a disease of young adults and patients usually present with severe malabsorption. Most patients with IPSID demonstrate an aberrant alpha heavy chain in peripheral blood. Mantle cell lymphoma Primary GI MCL characteristically presents as multiple polypoidosis in the small and large intestine, although presentation as ulcers, mucosal thickening, and as tumour masses is not uncommon. Median age of presentation is about 60, with a male predominance. Duodenal-type follicular lymphoma Most cases of primary GI follicular lymphoma occur in the small intestine, with the duodenum being the most frequent site, especially its second part. Most patients are adults with a median age in the fifties. On endoscopy they are typically seen as small polyps. Unlike nodal follicular lymphoma, most patients with duodenal-type follicular lymphoma have localized disease presenting as stage IE or IIE disease. Burkitt lymphoma Presentation depends on the clinical type of Burkitt's lymphoma. Endemic Burkitt's lymphoma patients are typically children, who usually present with rapidly growing bulky disease with high tumour burden. Symptoms are typically of only a few weeks duration.

Table 15.10.4.3 Clinical presentation and endoscopic features of common GI lymphomas				
Median age	Sex predilection	Frequent site	Common presentation	Endoscopic appearance
MALT lymphoma ~60 years	Similar	Stomach	Nonspecific dyspepsia	Gastritis
Peptic ulcer	Ill-defined thickened, inflamed, and ulcerated mucosa	MCL ~60 years	Male	Small and large intestine
Multiple polyposis	Ulcers	Mucosal thickening	Tumour masses	Multiple polyps
Ulcers	Mucosal thickening	Duodenal-type FL ~50 years	Female	Duodenum
Small polyps	Small polyps	DLBCL ~60 years	Male	Ileocaecal
Tumour mass - Burkitt lymphoma	Dependent on type	Male	Ileocaecal	Rapidly growing tumour mass
EATL	Jejunum	Abdominal pain	Intestinal perforation	Long-standing history of coeliac disease

15.10.4 Gastrointestinal lymphomas 2895 Most patients are typically in stages III or IV. Some patients can present with leukaemic central nervous system involvement. Diffuse large B-cell lymphoma Among primary GI DLBCLs, the stomach and ileocaecal regions are the most frequent presenting sites. Presentation is related to the rapidly enlarging tumour mass. Enteropathy-associated T-cell lymphoma Most patients present with abdominal pain, often associated with intestinal perforation. Many with EATL have a previous history of coeliac disease.

Pathology: histomorphological features Morphological features of each of the types of GI lymphomas are fairly distinctive (Table 15.10.4.4), hence it is possible to suggest a likely diagnosis based purely on morphological features, although confirmation of diagnosis with immunohistochemistry and (in some cases) cytogenetic or molecular genetic studies is essential.

MALT lymphoma The histological features closely simulate those of Peyer's patches (Fig. 15.10.4.1a). Reactive nonneoplastic follicles are surrounded

Table 15.10.4.4 Characteristic histomorphological features of common GI lymphomas		
Pattern	Cytological features	Other characteristic features
MALT lymphoma	Diffuse pattern	Marginal zone pattern
Follicular	Colonization	Centrocyte-like $\pm$ plasmacytic differentiation
Scattered larger cells	Lymphoepithelial lesions	MCL
Diffuse pattern	Nodular pattern	Mantle zone pattern
Monomorphic centrocytes	Duodenal-type FL	Follicular pattern
Follicle centre	Centrocytes and centroblasts	DLBCL
Diffuse		

pattern Centroblasts Immunoblasts Anaplastic cells Variable reactive component Burkitt lymphoma Diffuse pattern Monomorphic, cohesive medium-sized lymphoid cells with deeply basophilic cytoplasm, round nuclei, and multiple paracentrally located nucleoli Prominent mitoses and apoptoses Starry-sky pattern EATL Diffuse pattern Variable Relatively monomorphic medium-sized to large cells Marked pleomorphism with multinucleated cells Inflammatory component within the tumour Varying degrees of enteropathy in adjacent mucosa MEITL Diffuse pattern Monomorphic small to medium-sized round cells with darkly staining nuclei Florid infiltration of intestinal crypt epithelium (a) (b) (c) Fig. 15.10.4.1 (a) Peyer's patch comprising a B-cell follicle surrounded by a mantle zone external to which is the marginal zone. There are collections of small B lymphocytes within the dome epithelium. (b) Gastric MALT lymphoma. The tumour cells surround the reactive B-cell follicle in the marginal zone and invade gastric glands to form lymphoepithelial lesions. The overall structure is similar to the Peyer's patch. (c) Detail of the neoplastic infiltrate in a gastric MALT lymphoma showing 'centrocyte-like' cells invading gastric glands to form lymphoepithelial lesions (bottom right) and eosinophilic change in gastric gland epithelium (centre).

section 15 Gastroenterological disorders 2896 by the neoplastic lymphoid infiltrate in the region corresponding to the marginal zone in Peyer's patch. The infiltrate extends into surrounding lamina propria and invades individual gastric glands to form characteristic lymphoepithelial lesions. The cytological appearances of the cells of MALT lymphomas are characteristically centrocyte like, with more cytoplasm than the neoplastic cells of MCL or those of normal mantle cells (Figs. 15.10.4.1b and 15.10.4.1c). Rarely, cells can be smaller. Scattered larger cells are usually present amid centrocyte-like cells. Plasma-cell differentiation is prominent in about a third of cases, and this is characteristically seen beneath the surface epithelium. The lymphoma cells may colonize, and as a result partially or completely replace, reactive follicle centres. In later stages of disease, lymphomatous infiltrate extends beyond the mucosa into submucosa and invades the muscularis propria and beyond. In about 20% of cases, perigastric lymph nodes are involved by lymphoma. Differential diagnosis between MALT lymphoma and florid H. pylori-associated chronic gastritis (follicular gastritis) can be difficult in some cases, necessitating establishment of B-cell monoclonality by molecular methods for a diagnosis of MALT lymphoma. In some cases, disease progression coincides with an increase in the proportion of larger nucleolated neoplastic lymphoid cells. Eventually this can result in sheets of large lymphoid cells, heralding transformation of MALT lymphoma to DLBCL (Fig. 15.10.4.2). The histology of IPSID is similar to MALT lymphoma, except that plasma-cell differentiation is much more prominent both in the intestine and mesenteric lymph nodes. Fig. 15.10.4.2 MALT lymphoma showing transformation from low-grade (small cell) histology (upper half of figure) to high-grade (large cell) lymphoma (bottom half of figure). (c) (d) (e) (a) (b) Fig. 15.10.4.3 Mantle cell lymphoma: (a) Polyploid lymphoid lesion in duodenum involving the mucosa. (b) There is a diffuse monomorphic infiltrate of lymphoid cells with morphology of small cleaved cells or centrocytes. Lymphoid cells express CD20 (c); CD5 (d); and cyclin D1 (e).

15.10.4 Gastrointestinal lymphomas 2897 Mantle cell lymphoma Morphological features of GI MCL are similar to those when the condition occurs elsewhere. There is a monomorphic infiltrate of centrocytes with scanty cytoplasm, minimally indented nuclei, and coarse chromatin. The infiltrate has a diffuse or a nodular pattern, or a combination of both. Lymphoepithelial lesions are not seen (Figs. 15.10.4.3a and 15.10.4.3b). Duodenal-type follicular lymphoma Morphological features of duodenal-type follicular lymphoma is highlighted by presence of neoplastic follicles in mucosa and

sub mucosa. Follicles are devoid of mantle zones, and composed of centrocytes and centroblasts lacking zonation. Centroblasts are scanty; morphological features are usually of grade 1, and rarely grade 2 (Figs. 15.10.4.4a and 15.10.4.4b). Burkitt lymphoma Morphological features of GI Burkitt's lymphoma are similar to those when the condition occurs elsewhere. It characteristically shows monomorphic diffuse sheets of medium-sized lymphoid cells, which are cohesive with deeply basophilic cytoplasm, round nuclei, and multiple paracentrally located nucleoli. Mitoses and apoptoses are prominent. Tumour cells are accompanied by phagocytic histiocytes imparting a 'starry-sky' appearance (Figs. 15.10.4.5a and 15.10.4.5b). Diffuse large B-cell lymphoma Morphological features of GI-DLBCL are similar to those when the condition occurs elsewhere. The morphology is variable: tumour cells can have features of centroblasts, immunoblasts, anaplastic large cells, or other forms of large cell morphology, and the infiltrate can either be monomorphic or pleomorphic. The pattern of involvement is typically diffuse, with variable degree of background fibrosis. The reactive component is also variable and includes small lymphocytes, histiocytes, and, less frequently, other inflammatory cells (Figs. 15.10.4.6a and 15.10.4.6b). Enteropathy-associated T-cell lymphoma Lesions usually present as multiple ulcerating raised mucosal masses. They can also present as one or more ulcers or as a large exophytic mass. Cytological features are variable. In most cases, the tumour cells are relatively monomorphic medium-sized to large cells with round or angulated vesicular nuclei, prominent nucleoli, and moderate to abundant, pale-staining cytoplasm. In others, the tumour exhibits marked pleomorphism with multinucleated cells. Most cases show infiltration by inflammatory cells, including large numbers of histiocytes and eosinophils, and in some cases the inflammatory component can obscure the tumour cells. Necrosis is a prominent feature (Fig. 15.10.4.7). Infiltration of the epithelium of individual crypts is present in many cases. Intestinal mucosa adjacent to the tumours (particularly jejunum), usually shows varying degrees of enteropathy comprising villous atrophy, crypt hyperplasia, increased lamina propria lymphocytes and plasma cells, and intraepithelial lymphocytosis (Fig. 15.10.4.8). In some, this may consist only of an increase in intraepithelial lymphocytes. Monomorphic epitheliotropic intestinal T cell lymphoma (MIETL) In this condition the neoplastic cells are small to medium sized, round and monomorphic, with darkly staining nuclei and a narrow (a) (b) (c) (d) (f) (g) (e) Fig. 15.10.4.4 Duodenal-type follicular lymphoma: (a-c) Duodenal mucosa is replaced by a dense lymphoid infiltrate with a prominent follicular pattern. (d) lesional cells are mostly centrocytes; with only occasional centroblasts; they express CD10 (e); CD10 (f); and BCL2 (g).

section 15 Gastroenterological disorders 2898 rim of pale cytoplasm (Fig. 15.10.4.9).

Characteristically, there is florid infiltration of intestinal crypt epithelium. The adjacent intestinal mucosa shows villous atrophy and crypt hyperplasia, with striking intraepithelial lymphocytosis involving both crypt and surface epithelium. MEITL lacks the inflammatory component and necrosis is relatively less significant. In most cases, small intestine remote from the site of the tumour show changes identical with those of coeliac disease— villous atrophy with crypt hyperplasia, plasmacytosis of the lamina propria, and an increase in intraepithelial small lymphocytes. In MEITL, the degree of intraepithelial lymphocytosis may be extreme.

Pathology: immunohistochemistry Documenting characteristic immunophenotypes of different types of GI lymphoma is absolutely essential for definitive diagnosis and optimal patient management. This is best achieved by immunohistochemistry on paraffin sections (Table 15.10.4.5). MALT lymphoma Lymphoma cells express pan-B-cell antigens CD19, CD20, CD79a, and PAX5. They also express surface and to a lesser extent cytoplasmic IgM. They are typically negative for IgD and other heavy chains, and they show light-chain restriction. The cells express

other mature B-cell antigens such as CD21 and CD35, but are typically negative for CD5 and CD10, although rare cases may show aberrant expression of CD5. CD43 expression is more common. They are negative for other T-cell antigens. They consistently express BCL2, but are negative for BCL6 and cyclin D1, and variably positive for MUM1. CD21 and CD23 identify reactive, remnant, or colonized follicles. Proliferation as measured by Ki67 expression is usually less than 40%. Mantle cell lymphoma Lymphoma cells express pan-B-cell antigens CD19, CD20, CD79a, and PAX5. They also express surface IgM and IgD, show light-chain restriction, show aberrant expression of CD5 and CD43, and are negative for CD10 and CD23, mostly negative for BCL6 and MUM1, and negative for other T-cell antigens. They consistently express BCL2. The overwhelming majority (>95%) of cases express cyclin D1, and most express SOX11. CD21 and CD23 identify a nodular pattern if present (Figs. 15.10.4.3c–15.10.4.3e). Duodenal-type follicular lymphoma Lymphoma cells express pan-B-cell antigens CD19, CD20, CD79a, and PAX5. Most cases express IgA. They express follicle centre cell markers CD10, BCL6, and similar others. They characteristically express BCL2, and most cases of grade 1–2 FL do not express MUM1. They are negative for cyclin D1, CD5, and CD43, and most are negative for CD23. CD21 and CD23 identify follicular dendritic cell (FDC) meshworks within neoplastic follicles (Figs. 15.10.4.4c–15.10.4.4e). Burkitt lymphoma Lymphoma cells express pan-B-cell antigens CD19, CD20, CD79a, and PAX5. They also express IgM and often CD43, and express (a) (b) (c) Fig. 15.10.4.5 Burkitt lymphoma: (a) Mucosa of stomach shows a dense lymphoid infiltrate with a diffuse pattern. (b) Lymphoid cells are relatively monomorphic and medium sized. They have multiple paracentrally located nucleoli. (c) Almost all lymphoid cells express Ki-67. Lymphoid cells harboured MYC-IGH translocation (not shown).

15.10 Gastrointestinal lymphomas 2899 (a) (b) (c) (d) (e) Fig. 15.10.4.6 Diffuse large B cell lymphoma: (a) Mucosa of stomach shows a dense lymphoid infiltrate with a diffuse pattern. (b) Lymphoid cells are large and have multiple prominent nucleoli. Lymphoid cells express CD20 (c); MUM1 (d); and BCL2 (e). (a) (b) (c) Fig. 15.10.4.7 EATL. Three different cases showing the cytological variability. In (a) the tumour is composed of large polymorphic lymphocytes; in (b) the tumour shows striking pleomorphism; and in (c) tumour cells are overrun by inflammatory cells, principally eosinophils.

section 15 Gastroenterological disorders 2900 follicle centre cell markers CD10, BCL6, and CD38. They characteristically express c-MYC, but not BCL2. They are also negative for CD44, CD5, cyclin D1 and TdT, and most are negative for MUM1. A proportion of cases are EBV associated, which is demonstrated by in situ hybridization with an EBER1 probe. Ki67 expression is typically seen in greater than 95% of the neoplastic cells (Fig. 15.10.4.5c). Diffuse large B-cell lymphoma Lymphoma cells express pan-B-cell antigens CD19, CD20, CD79a, and PAX5. DLBCL is a heterogeneous disease, and expression of various antigens/proteins varies among the subtypes of DLBCL, which is beyond the scope of this chapter (Fig. 15.10.4.6c–15.10.4.6e). Enteropathy-associated T-cell lymphoma In EATL, the tumour cells express CD3, CD7, CD103, and cytotoxic molecules, and are typically negative for CD5, CD4, and CD56. Most cases express TCRβ+, and a small minority (<20%) express CD8. In almost all cases, a varying proportion of the tumour cells express CD30. The CD3-positive intraepithelial lymphocytes in the adjacent enteropathic mucosa may show an abnormal immunophenotype, lacking expression of CD5, CD4, and CD8 (Fig. 15.10.4.8c and 15.10.8d). Monomorphic epitheliotropic intestinal T-cell lymphoma In MEITL, the tumour cells express CD3, CD7, CD8, TCRβ, CD56, CD103, and cytotoxic molecules, and are typically negative for CD5 and CD4. The intraepithelial lymphocytes in

the adjacent mucosa have a similar immunophenotype. Fig. 15.10.4.8 MEITL. The lymphoma is composed of monomorphic small lymphocytes. (b) (a) (c) (d) Fig. 15.10.4.9 Uninvolved mucosa adjacent to EATL showing (a) increased intraepithelial lymphocytes that are (b) CD3 positive, (c) CD8 negative, and (d) CD56 negative.

15.10.4 Gastrointestinal lymphomas

2901 Management MALT lymphoma All patients with gastric MALT lymphoma who are *H. pylori* positive should be given eradication therapy, following which those with early-stage disease can be managed by surveillance endoscopy with multiple biopsies. Those who have early-stage *H. pylori*-negative disease are typically treated with local radiotherapy. Immunotherapy (rituximab, an anti-CD20 monoclonal antibody), with or without chemotherapy, is offered to patients whose disease fails to respond or recurs after radiotherapy, and those with advanced-stage disease. Targeted treatments, for example, ibrutinib (a tyrosine kinase inhibitor), and autologous haemopoietic cell transplantation are used in some cases.

Mantle cell lymphoma Most patients require treatment at the time of diagnosis. Options include conventional chemotherapy/immunotherapy (e.g. bendamustine and rituximab) followed by maintenance rituximab, conventional chemotherapy/immunotherapy followed by autologous haemopoietic cell transplantation, conventional chemotherapy/immunotherapy with radiotherapy, or intensive chemotherapy.

Duodenal-type follicular lymphoma Most patients with disease limited to duodenum have an indolent disease course, and treatment may not be required (watch-and-wait). They would rarely require treatment. In patients with nodal involvement, possibly of conventional FL also involving the duodenum or the gastrointestinal tract needs to be considered.

Burkitt lymphoma There is no wide consensus on the best treatment for adults with Burkitt's lymphoma. Intensive combination chemotherapy is typically given, along with central nervous system prophylaxis. The high risk of tumour lysis syndrome can be mitigated by intravenous hydration and rasburicase.

Diffuse large B-cell lymphoma Molecular analysis helps to direct therapy, which for patients without MYC and BCL2 gene rearrangements typically involves rituximab in combination with anthracycline-based chemotherapy.

Enteropathy-associated T-cell lymphoma Treatment is with combination chemotherapy, as used for other aggressive lymphomas.

Prognosis

MALT lymphoma Most gastric MALT lymphomas are associated with *H. pylori*, and nearly 75% of these regress following eradication of *H. pylori* using appropriate antibiotics. Deeply invasive lymphomas, those in which there are foci of high-grade transformation, and cases with t(11;18) usually do not respond to antibiotics and require conventional chemotherapy. Overall, MALT lymphomas respond favourably to therapy and there is an excellent overall survival, approximating 90% at 10 years. The survival for cases in which there is evidence of transformation to DLBCL is significantly worse: only 45% at 10 years.

Mantle cell lymphoma In general, patients with this condition have a median survival in the range of 3 to 5 years.

Duodenal-type follicular lymphoma Survival is extremely good, even without treatment.

Burkitt lymphoma This is a potentially curable disease. With intensive regimens, cure rates of up to 90% in limited stage disease and 60 to 80% in patients with advanced stage disease are achievable.

Diffuse large B-cell lymphoma Cure can be achieved in many patients with DLBCL with appropriate treatment. Identifying subsets of DLBCL with different biology using protein and gene expression and mutation analysis (by next-generation sequencing) is an area of active research and beyond the scope of this chapter.

Enteropathy-associated T-cell lymphoma The prognosis is usually poor, with death frequently resulting from abdominal complications in patients already weakened by uncontrolled malabsorption.

Table 15.10.4.5 Characteristic immunophenotype of common GI lymphomas

Antigens positive for	Antigens negative for	Other characteristic features
MALT lymphoma	CD19, CD20, CD79a, PAX5, BCL2, and IgM	CD5, CD10, BCL6, and cyclin D1
CD43+/-	CD21/CD23+	FDC meshworks
MCL	CD19,	

CD20, CD79a, PAX5, BCL2, IgM, IgD, CD5, CD43, cyclin D1, and SOX11 CD10 and CD23 CD21/CD23 + FDC meshworks in nodular areas Duodenal-type FL CD19, CD20, CD79a, PAX5, CD10, BCL6, and BCL2 CD5 and cyclin D1 CD21/CD23 + FDC meshworks DLBCL CD19, CD20, CD79a, and PAX5, Cyclin D1 Variable expression of other markers Burkitt lymphoma CD19, CD20, CD79a, PAX5, CD10, BCL6, and CD38 TdT, CD5, cyclin D1, CD44, and BCL2 CD43+/-, Ki67>95%, EBER-/+ EATL CD3, CD7, CD103, TCRβ+, and cytotoxic molecules CD5, CD4, and CD56 CD30+/- CD8-/+ MEITL CD3, CD7, CD8, TCRβ, CD56, CD103, and cytotoxic molecules CD5 and CD4 –

Revision #1

Created 2026-01-22 16:38:30 UTC by Omar Ayman

Updated 2026-01-22 16:38:30 UTC by Omar Ayman