

REVIEW

Recent advances in upper gastrointestinal lymphomas: molecular updates and diagnostic implications

Periklis G Foukas,¹  Bettina Bisig²  & Laurence de Leval¹ 

¹Second Department of Pathology, National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece, and ²Department of Laboratory Medicine and Pathology, Institute of Pathology, Lausanne University Hospital and Lausanne University, Lausanne, Switzerland

Foukas P G, Bisig B & de Leval L.

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Approximately one-third of extranodal non-Hodgkin lymphomas involve the gastrointestinal (GI) tract, with the vast majority being diagnosed in the stomach, duodenum, or proximal small intestine. A few entities, especially diffuse large B-cell lymphoma and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, represent the majority of cases. In addition, there are diseases specific to or characteristic of the GI tract, and any type of systemic lymphoma can present in or disseminate to these organs. The recent advances in the genetic and molecular characterisation of lymphoid neoplasms

have translated into notable changes in the classification of primary GI T-cell neoplasms and the recommended diagnostic approach to aggressive B-cell tumours. In many instances, diagnoses rely on morphology and immunophenotype, but there is an increasing need to incorporate molecular genetic markers. Moreover, it is also important to take into consideration the endoscopic and clinical presentations. This review gives an update on the most recent developments in the pathology and molecular pathology of upper GI lymphoproliferative diseases.

Keywords: differential diagnosis, duodenum, enteropathy-associated T-cell lymphoma, fluorescent in situ hybridization, gastrointestinal lymphomas, indolent lymphoproliferative disorders, MALT lymphoma, molecular pathology, small intestine, stomach

Introduction

Lymphomas involving the gastrointestinal (GI) tract account for approximately 30–40% of extranodal lymphomas.^{1,2} The notion of primary GI lymphomas, in principle, refers to tumours arising in the GI tract with the bulk of the tumour localised to a specific GI organ, with or without regional involvement. By extension, the term also encompasses situations in which the clinical presentation is related to

lymphoma involvement of a GI site, and staging reveals disseminated disease. In addition, the GI tract can be affected by contiguous involvement or dissemination of a systemic disease. Primary oesophageal lymphomas are extremely rare, accounting for <1% of GI lymphomas,^{2–4} with most cases probably representing extension from posterior mediastinal masses or gastric primaries. The stomach alone accounts for the majority of GI lymphomas (60% of the cases), ~30% arise in the duodenum or small intestine and ileocaecal region, and ~10% affect the colon.^{1–6}

Most GI lymphoma cases correspond to entities that are not specific to the GI tract, with specific tumour entities primarily arising in the GI tract representing

Address for correspondence: L de Leval, MD, PhD, Institute of Pathology, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 25, CH-1011, Lausanne, Switzerland. e-mail: laurence.deleval@chuv.ch

a smaller proportion, including duodenal-type follicular lymphoma (FL) and intestinal T-cell lymphomas. The prevalence of the different lymphoma entities varies according to the site of involvement, i.e. stomach versus duodenum and small intestine versus colon (Table 1).

In this article, we present an update on the pathological and molecular features of the lymphoid neoplasms that most commonly involve the upper GI tract, with an emphasis on the new guidelines derived from the latest updates of the World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues⁷ and the digestive system,⁸ and a focus on more recent developments.

Small B-cell lymphomas

Although essentially any small B-cell lymphoma may infiltrate the upper GI tract, primary GI presentation is dominated by extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in the stomach and the small intestine in general, and duodenal-type FL in that specific site. A diagnostic approach to lympho(plasma)cytic infiltrates in the upper GI mucosa is shown in Figure 1, and Table 2 summarises the antibodies commonly used to assist in the differential diagnosis in routine practice.

Table 1. Relative prevalence of lymphomas in different parts of the gastrointestinal tract

Lymphomas	Stomach (%)	Small intestine (%)	Colon (%)
Gastrointestinal lymphomas	60	25–30	5–10
Primary neoplasms	<5	30–50	<1
Diffuse large B-cell lymphomas	40–50	40–60	>40
MALT lymphoma	40–50	5–15	25
Follicular lymphoma	Rare	1–10	Rare
Mantle cell lymphoma	<5	<5	25
Burkitt lymphoma	<1	<5	<1
Intestinal T-cell lymphomas	Rare	15	Rare
Post-transplant and ID-related	Rare	Rare	Rare

ID, Immunodeficiency; MALT, Mucosa-associated lymphoid tissue.

MALT LYMPHOMA

MALT lymphoma, an indolent B-cell lymphoma recapitulating the morphology and architectural features of mucosa-associated lymphoid tissue (MALT), accounts for 40–50% of primary gastric lymphomas and a much smaller proportion (5–15%) of lymphomas arising in the small intestine.^{1–3,9,10} Patients are usually adults and present with non-specific symptoms such as dyspepsia, nausea, epigastric pain, or bleeding, or may be asymptomatic. Immunoproliferative small intestinal disease (IPSID) is a rare variant of intestinal MALT lymphoma associated with the secretion of defective α heavy chains, and is largely restricted to the eastern Mediterranean area, the Middle and Far East, and Africa. This disease, which usually develops in the duodenum and jejunum, affects young adults of lower socioeconomic status and living in poor hygienic conditions, who present with malabsorption, diarrhoea, abdominal pain, and weight loss.^{11,12}

Association with infectious agents

MALT lymphomas usually occur in tissues naturally devoid of MALT, and develop in a context of chronic inflammation induced by infections or autoimmune disorders.^{13,14} Epidemiological, biological and therapeutic studies have shown a strong link between *Helicobacter pylori* infection and gastric MALT lymphoma.^{15,16} Following an initial study by Wotherpoon *et al.*, several groups have confirmed that eradication of *H. pylori* following antibiotic therapy induces regression of MALT lymphoma in ~75% of early-stage tumours.^{17–20} In earlier reports, *H. pylori* infection was demonstrated in >90% of cases.^{21–23} However, recent analyses have shown a significant reduction in the prevalence of *H. pylori* infection in gastric MALT lymphomas in Europe as compared with the early 1990s.²⁴ In a retrospective study of >400 cases diagnosed in France between 2002 and 2010, only 57% of the cases were associated with *H. pylori*.²⁵ Another point is that the density and detectability of *H. pylori* have been reported to decrease in association with lymphoma progression.^{26,27} In intestinal MALT lymphomas, an association with *Campylobacter jejuni* infection has been reported, but evidence for a causal link is lacking.²⁸

Pathological features

Endoscopically, MALT lymphoma may present as subtle gastritis-like lesions, erosions, and ulcerations, or as diffuse infiltrates and thickened folds, which may form polypoid or exophytic mass lesions. Endoscopic

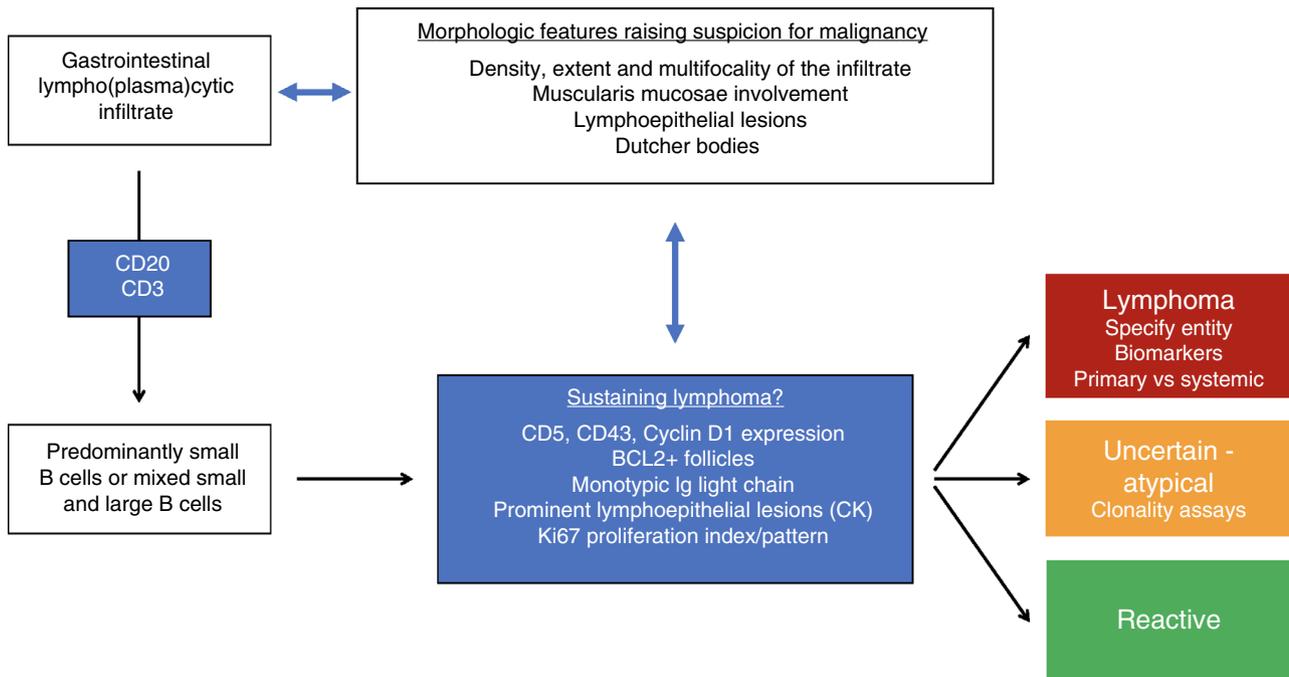


Figure 1. Diagnostic approach to lympho(plasma)cytic infiltrates in the gastrointestinal mucosa. CK, cytokeratin.

ultrasonography is the most accurate staging method for assessment of the depth of invasion and the status of regional lymph nodes.^{29,30} The Lugano and Paris staging systems are most commonly used, with the second describing more accurately the depth of gastric wall invasion, a parameter that may predict the response to anti-*H. pylori* treatment.³⁰

Histologically, the cardinal features of MALT lymphoma are: (i) a diffuse and/or nodular infiltrate of neoplastic lymphoid B cells cytologically resembling marginal zone B cells; (ii) lymphoepithelial lesions; and (iii) reactive lymphoid follicles with germinal centres.^{31,32} The neoplastic population comprises small to medium-sized lymphoid cells, with a centrocyte-like or monocytoid appearance, which infiltrate diffusely into the mucosa and frequently colonise reactive germinal centres (Figure 2). There can be cytological variation: some tumours contain a relatively monotonous population, whereas others feature a mixture of cell types. The neoplastic infiltrate also usually contains scattered, large, transformed blastic cells resembling centroblasts or immunoblasts. Plasma cell differentiation is seen in ~30% of cases (Figure 3). The neoplastic plasma cells may appear as normal mature plasma cells, have crystalline inclusions in the cytoplasm, or possess nuclei with Dutcher bodies. Lymphoepithelial lesions, defined as the invasion of

individual gastric pits and/or glands by aggregates (three or more) of neoplastic cells, often resulting in oxyphilic changes in the epithelium, constitute a characteristic feature of gastric MALT lymphoma, but are found infrequently in MALT lymphomas of the small intestine. The destruction and disintegration of the epithelial structures induce degenerative epithelial changes manifested by eosinophilic or oncocyctic metaplasia. Notably, although lymphoepithelial lesions in the stomach are highly suggestive of MALT lymphoma, occasional lymphoepithelial lesions may be seen in florid gastritis, so they are not specific for a diagnosis of malignancy. Moreover, other lymphomas may show epitheliotropism and produce alterations resembling lymphoepithelial lesions. In particular, epitheliotropism is a defining property of monomorphic epitheliotropic intestinal T-cell lymphoma, which, by morphology alone, may mimic MALT lymphoma in the stomach. Epitheliotropism is commonly seen in extranodal natural killer (NK)/T-cell lymphoma, which rarely involves the stomach, and is occasionally encountered in other B-cell lymphoma types such as diffuse large B-cell lymphoma (DLBCL) or, less commonly, mantle cell lymphoma (MCL).

The lymphoma cells are positive for pan-B-cell antigens (CD19, CD20, CD79a, and PAX5), and usually

Table 2. Antibodies used in the (differential) diagnosis of gastrointestinal B-cell lympho(plasma)cytic infiltrates

Antigens	Normal cells	Diagnostic utility
CD20 PAX5 CD79a	B-cell lineage antigens	Usually strong and diffuse expression in B-cell lymphomas. Weak CD20 staining in CLL/SLL. Reduced or absent CD20 expression in patients with previous immunochemotherapy comprising anti-CD20 antibodies. Weak or negative in plasmablastic lymphoma
CD3 CD5	T-cell antigen Weakly expressed in mantle cells of follicles	CD5 expression in CLL/SLL and MCL, rarely in MALT lymphoma, and in a subset of DLBCLs NOS
CD10	Germinal centre B cells	CD10 expression in FL, BL, and a subset of DLBCLs NOS (germinal centre-B-cell like). Rarely positive in blastoid MCL. Positive in reactive follicles in MALT lymphoma
CD21	Mature B cells and FDCs	Helpful to identify reactive or neoplastic follicular structures in MALT lymphoma and FL
CD23	Activated B cells, mantle B cells of follicles, FDCs	CD23 expression CLL/SLL, and a subset of FLs and DLBCLs. Lack of CD23 expression in MCL. Helpful to identify reactive or neoplastic follicular structures in MALT lymphoma and FL
CD43	Pan-T-cell antigen, monocytes, activated B cells	CD43 expression in MCL and CLL/SLL (most cases, but sometimes not detectable on routine sections), positive in a subset of MALT lymphomas
bcl-2	Antiapoptotic molecule down-regulated in germinal centre B cells	bcl-2+ neoplastic follicles in FL bcl-2-reactive follicles in MALT lymphomas Lack of bcl-2 expression typical of BL Expression in >50% of neoplastic cells defines bcl-2+ (bcl-2+) DLBCL; usually very strong and diffuse positivity in <i>BCL2</i> -rearranged lymphomas
bcl-6	Transcription factor of germinal centre B cells and follicular helper T cells	bcl-6 expression in FL, BL, a subset of DLBCLs NOS, and high-grade B-cell lymphomas
Cyclin D1	No expression by normal B cells. Positive endothelial cells and macrophages are internal controls	Very sensitive and highly specific marker for MCL. Also expressed in some DLBCLs and in proliferation centres of CLL/SLL
LEF1	Activated T cells	Expressed in CLL/SLL cells
SOX11	No known expression in normal lymphoid tissues	Expressed in a subset of MCLs, useful to identify the rare cyclin D1-negative MCL
Ki67	Nuclei of cycling cells	Ki67 proliferative index reflective of high-grade and low-grade entities. Usually low in small B-cell lymphomas, with residual Ki67-high germinal centres in MALT lymphomas; prognostic factor in MCL. Ki67 index close to 100% in BL and variably high in other aggressive B-cell neoplasms
κ and λ light chains	B cells (membrane Ig expression) and plasma cells (cytoplasmic Ig expression). Normal κ to λ ratio: 2:1	Restricted (monotypic) light chain expression in neoplastic cells versus polytypic expression in reactive lymphoproliferations
Cytokeratins	Surface epithelium, crypts and glands	Demonstration of lymphoepithelial lesions

bcl-2, B-cell lymphoma 2; bcl-6, B-cell lymphoma 6; BL, Burkitt lymphoma; CLL, Chronic lymphoid leukaemia; DLBCL, Diffuse large B-cell lymphoma; FDC, Follicular dendritic cell; FL, Follicular lymphoma; Ig, Immunoglobulin; LEF1, Lymphoid enhancer factor 1; MALT, Mucosa-associated lymphoid tissue; MCL, Mantle cell lymphoma; NOS, Not otherwise specified; SLL, Small lymphocytic lymphoma; SOX11, SRY-box transcription factor 11.

negative for CD5, with aberrant coexpression of CD43 in approximately one-third of the cases.³³ The rare cases of CD5+ MALT lymphoma must be

distinguished from small lymphocytic lymphoma (SLL) and MCL. MALT lymphoma cells are negative for the germinal centre markers CD10 and B-cell

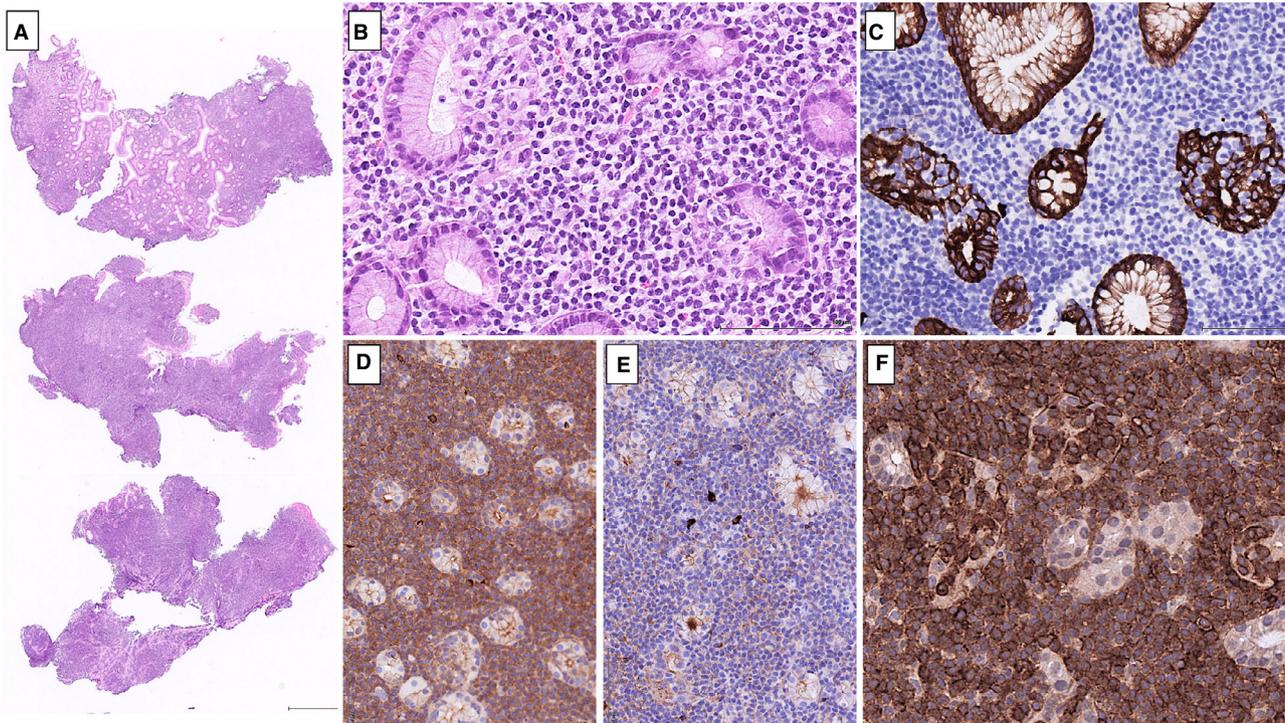


Figure 2. Gastric mucosa-associated lymphoid tissue lymphoma. A, Panoramic view showing a diffuse lymphoid infiltrate, disrupting the glands and the muscularis mucosae [haematoxylin and eosin (H&E)]. B, A diffuse infiltrate of small centrocyte-like cells with moderate amounts of clear cytoplasm, forming lymphoepithelial lesions (H&E). C, Cyokeratin immunostain highlighting the lymphoepithelial lesions. D, Positivity for lambda light chains. E, Negativity for kappa light chains. F, Immune receptor translocation-associated protein 1 (IRTA 1) positivity of lymphoma cells, especially pronounced among the subset of intraepithelial lymphocytes.

lymphoma 6 (*bcl-6*), negative for the MCL markers cyclin D1 and SRY-box transcription factor 11 (*SOX11*), and usually express B-cell lymphoma 2 (*bcl-2*). They are negative for IgD and express monotypic IgG, IgM or IgA with either kappa or lambda light chain, a feature best demonstrated in cases with plasmacytoid differentiation. Antibodies against keratins highlight lymphoepithelial lesions, and follicular dendritic cell markers, such as CD21, CD23, and CD35, are useful for highlighting follicular structures and identifying follicular colonisation. The Ki67 proliferation index is low outside of residual germinal centres. Immune receptor translocation-associated protein 1 (IRTA1) was recently characterised as a potentially useful biomarker with which to identify MALT lymphomas and distinguish them from other small B-cell lymphomas. IRTA1 belongs to a family of immunoglobulin-like proteins that mediate B-cell immune responses, and is normally expressed in benign monocytoid B cells, some marginal zone cells, and intraepithelial B cells.³⁴ IRTA1 expression has been reported in 40% to >90% of MALT lymphomas,

whereas other small B-cell lymphomas are, with few exceptions, IRTA1-negative.^{35,36}

Molecular genetics/pathogenesis

Adding to the growth signals provided by infiltrating *H. pylori*-specific T cells,^{37,38} activation of the B-cell receptor (BCR) and nuclear factor- κ B (NF- κ B) signalling pathways plays a major role in gastric MALT lymphoma development. Sequence analysis of immunoglobulin (IG) gene rearrangements shows evidence of somatic hypermutations, with an active ongoing somatic hypermutation machinery resulting in intraclonal variation and a biased usage of certain immunoglobulin heavy chain (IGH) genes, such as IGHV3-7 and IGHV1-69, indicating a selective pressure towards antigen-driven clonal expansion.³⁹⁻⁴³

Several recurrent chromosomal translocations are associated with MALT lymphomas. They are mutually exclusive, and their relative frequencies vary with the primary site of involvement. The most frequent in the GI tract is the *t(11;18)(q21;q21)/BIRC3-MALT1* translocation, found in approximately 25% of gastric

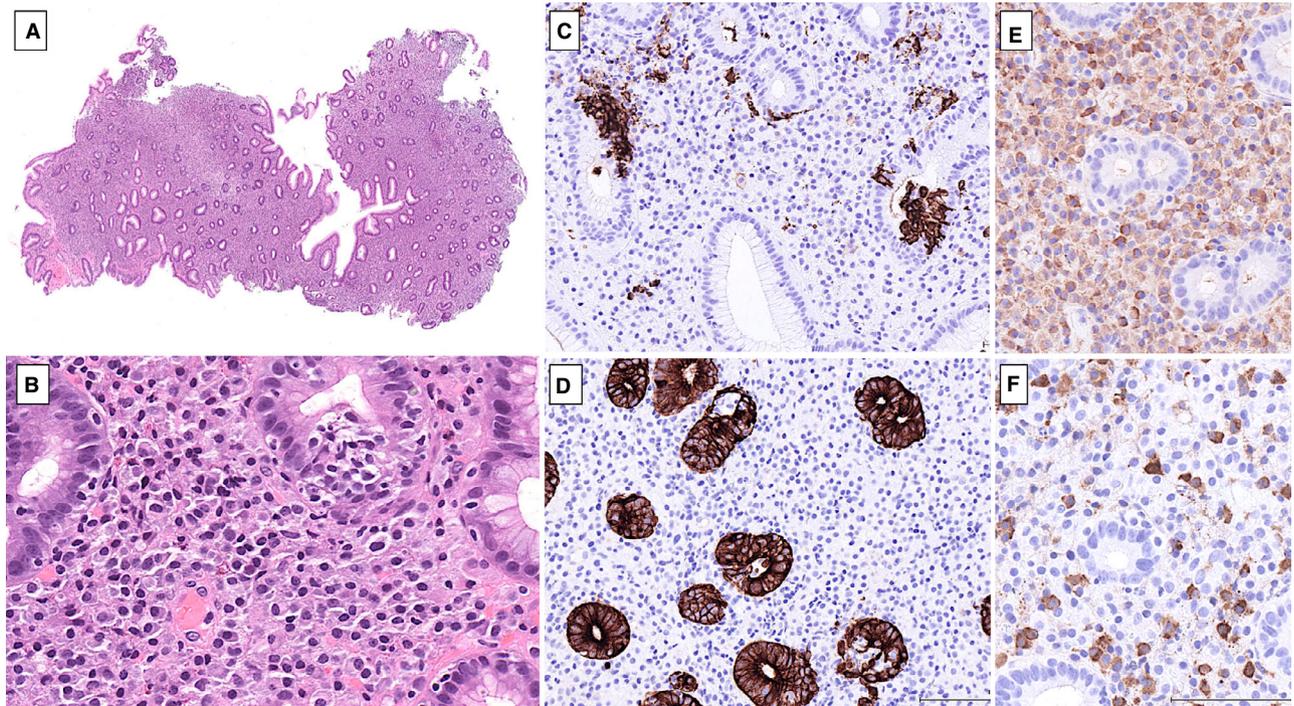


Figure 3. Gastric mucosa-associated lymphoid tissue lymphoma with marked plasmacytic differentiation. A, A panoramic view showing a diffuse mucosal infiltrate with atrophy and rarefaction of the glands [haematoxylin and eosin (H&E)]. B, Lymphoepithelial lesions and a diffuse plasmacytic infiltrate in the lamina propria (H&E). C, CD20 highlighting the aggregates of intraepithelial lymphocytes, and only a few cells between the glands. D, Cytokeratin immunostain highlighting the lymphoepithelial lesions. E, Staining for lambda light chains of the majority of plasma cells. F, A few were kappa chain-positive plasma cells.

and 10–50% of intestinal MALT lymphomas. Its oncogenic activity is attributed to overexpression of MALT1, which is an important mediator of activation of the canonical and non-canonical NF- κ B pathways.^{44–48} Other recurrent translocations, more commonly observed at extra-GI sites, have been reported in <5% of GI MALT lymphomas in most published series. They include the t(14;18)(q32;q21)/IGH–MALT1, t(1;14)(p22;q32)/IGH–BCL10, and t(3;14)(p14.1;q32)/IGH–FOXP1 translocations.^{49,50} In gastric MALT lymphomas, the t(11;18)(q21;q21) translocation is more prevalent in *H. pylori*-negative cases, correlates with higher-stage disease, and is a factor in the poor response to alkylating agents.^{51,52} Conversely, t(11;18)-positive MALT lymphomas are less prone to transformation to DLBCL.⁵³ When it is present in *H. pylori*-positive cases, the t(11;18)(q21;q21) translocation is predictive of non-response to or relapse after antibiotic therapy.^{21,54} Therefore, fluorescence *in-situ* hybridisation (FISH) testing for t(11;18) is recommended at initial diagnosis or for the cases that fail to respond to anti-*H. pylori* therapy.^{30,55} The clinical significance of the infrequent IGH–BCL10 rearrangement is not clear, although a

small study suggested that cases with t(1;14) or strong nuclear expression of B-cell lymphoma 10 (bcl-10) most likely do not respond to *H. pylori* eradication.⁵⁶

Other aberrations variably reported in gastric MALT lymphoma are deletions of TNFAIP3/A20 (6q23), which encodes an inhibitor of NF- κ B, and trisomies/gains of chromosomes 3, 8, and 18.^{57–60}

In recent years, a few studies have examined the mutational landscape of MALT lymphomas by means of whole exome sequencing or targeted next-generation sequencing (NGS) technologies.^{57,61–63} Distinct genetic profiles were observed in MALT lymphomas from different sites.⁶³ Overall, only a small number of gastric MALT lymphomas have been analysed, with variations in the methodology in the different studies. Recurrent mutations in genes involved in activation of NF- κ B signalling pathways, such as TRAF3 (33%) and TNFAIP3 (25%), were identified, and in general were mutually exclusive with the BIRC3–MALT1 translocation. Interestingly, MALT lymphoma essentially lacks mutations in MYD88, CD79A, or CARD11, which are frequently found in other B-cell

lymphomas characterised by constitutive NF- κ B activation. Mutations are also found in genes related to B-cell differentiation, notably *NOTCH1* (11–25%), and epigenetic modifications (*CIITA*, *TBL1XR1*, and *TET2*), and in tumour suppressor genes.⁶¹ Mutations in *GPR34* and *PIK3CD*, which are frequently found in MALT lymphomas of the salivary glands and thyroid, have not been detected in gastric MALT lymphomas.⁶³

Differential diagnosis

A common diagnostic challenge is differentiating gastric MALT lymphoma from *H. pylori*-associated gastritis. An expansile, destructive infiltrate, the cytological characteristics of the infiltrating cells, Dutcher bodies, infiltration of the muscularis mucosae and prominent lymphoepithelial lesions favour lymphoma, but many biopsies may lack some of these features. Monotypic immunoglobulin expression and/or coexpression of CD43 by the B cells establish malignancy. Morphological assessment with the Wotherspoon scoring system helps in identifying the cases that may benefit from clonality testing.^{19,64}

Differentiating MALT lymphoma from other small B-cell lymphomas, notably MCL, which shows tropism for the GI mucosa, but also SLL/chronic lymphocytic leukaemia (CLL) and FL, can also be challenging. Immunohistochemistry is key in establishing the correct diagnosis (see below). Because of the morphological overlap between MCL and MALT lymphoma, cyclin D1 immunohistochemistry should be performed in all cases of GI small B-cell lymphoma.³⁰ MALT lymphomas with extensive plasmacytic differentiation should be distinguished from plasma cell neoplasia, either extramedullary plasmacytoma or dissemination of a multiple myeloma, which occur rarely in the GI tract (Figure 4).⁶⁵

Although large cells are typically present and admixed with the small B cells in MALT lymphoma, sometimes representing up to 20% of the total cells, transformation to DLBCL should be considered when sheets or confluent clusters of large, transformed cells are found outside follicles. Clusters of at least 20 cells or a proportion of >30% large cells are needed to consider a diagnosis of large-cell transformation. Conversely, diffusely scattered large cells, representing 5–10% or even up to 20% of the total population, are not associated with a worse prognosis, as long as they do not form clusters.^{66–68} If a component of MALT lymphoma is noted in a gastric or intestinal DLBCL, it should be mentioned in the report. Reactive germinal centres in MALT lymphomas, which can be identified by their germinal centre immunophenotype,

should not be mistaken as foci of large-cell transformation.

Follow-up biopsies in gastric MALT lymphomas

Irrespective of stage, *H. pylori* eradication is the initial treatment of choice, and it is recommended that follow-up biopsies are taken 2–3 months after treatment and subsequently twice yearly for 2 years.³⁰ The evaluation of histological response is based on the Groupe d'Etude des Lymphomes de l'Adulte (GELA) scoring system.^{69,70} In this scheme, patients with *complete response* or *probable minimal residual disease*, in which small residual lymphoid aggregates are recognised, should be managed with observation and regular follow-up. Although molecular assays have shown that such lymphoid aggregates may harbour the same clonal IG gene rearrangements as the initial lymphoma, molecular testing is not recommended, as no firm correlation has been established between a positive molecular test result and a higher risk of relapse.^{71–73} Patients with *responding residual disease* or *no-change/stable disease* can also be managed with observation for several months, as long as they are asymptomatic, because responses may occur as late as >18 months after the completion of antibiotic therapy.^{72,74} In patients not responsive to antibiotic therapy or with progressive disease, there are several therapeutic options, including radiation therapy, chemotherapy, and/or immunotherapy.³⁰

As higher rates of epithelial preneoplastic lesions (intestinal metaplasia, atrophic gastritis, and dysplasia) and a six-fold increased risk for gastric adenocarcinoma have been reported in patients with gastric MALT lymphoma,^{75–78} it is important, in follow-up biopsies, not only to assess the lymphoid infiltrates but also to screen the biopsies for (pre)neoplastic epithelial lesions.

DUODENAL-TYPE AND PRIMARY INTESTINAL FL

Primary intestinal FL accounts for 5–10% of primary intestinal lymphomas overall, and affects middle-aged to older adults. Approximately half of the cases occur in the second portion of the duodenum,^{1,2,79,80} and because these show distinct clinicopathological features—duodenal presentation, low histological grade, indolent behaviour, and excellent outcome—they are now recognised as a distinct disease entity, namely duodenal-type FL.⁷ FL cases developing elsewhere along the GI tract, usually in the small intestine or colon, are referred to as primary intestinal FL (Table 3). Most duodenal-type FL cases are discovered incidentally during upper GI endoscopy for

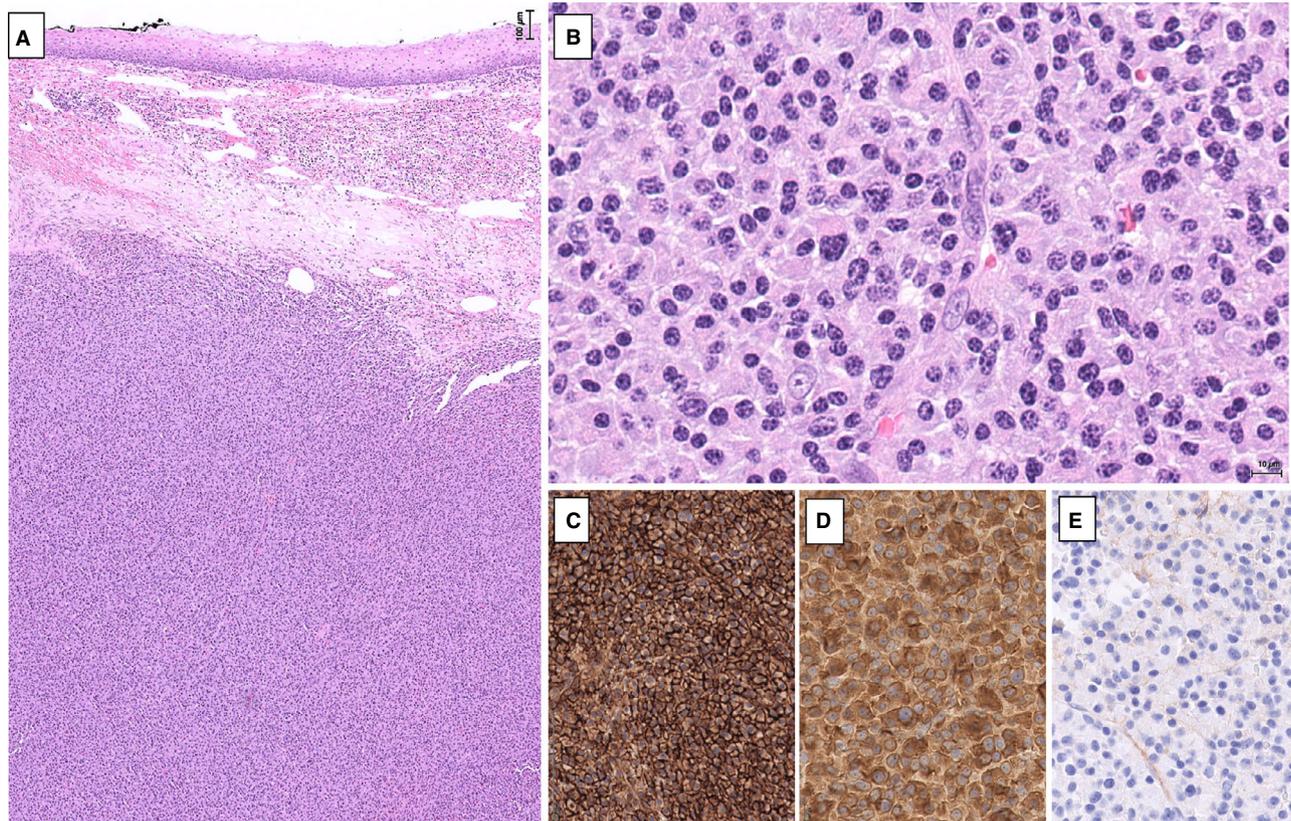


Figure 4. Oesophageal involvement by multiple myeloma. A, A panoramic view showing a dense and diffuse mucosal infiltrate, and the overlying normal epithelium [haematoxylin and eosin (H&E)]. B, The infiltrate consisted of sheets of plasma cells, ranging from mature to atypical (H&E). C, Strong and diffuse CD138 positivity. D, Monotypic expression of kappa light chains. E, Absence of immunostaining for lambda light chains.

surveillance of unrelated pathologies, such as gastritis, gastro-oesophageal reflux disease, or other malignancies, and only a minority of patients present with mass effect symptoms such as obstructive jaundice.^{79,81–83} Endoscopically, the lesions appear as one or more nodules or small polyps in the second portion of the duodenum, but multifocal involvement of more distal regions of the intestine, mainly the jejunum, is not uncommon.^{81,82} Duodenal-type FL is an indolent disease for which a watchful waiting approach is generally recommended.^{82,84} Nodal involvement (stage II) is a risk factor associated with progression.⁸⁵ Only a few case reports have documented transformation to DLBCL.^{86–88} Non-duodenal-type FLs tend to produce larger symptomatic tumour masses that may be obstructive or cause bleeding, and staging is essential to differentiate primary intestinal disease from secondary GI involvement by a systemic (nodal) FL.

Pathological features

In duodenal-type FL (Figure 5A–D), the neoplastic follicles expand the duodenal mucosa/submucosa

and show features of grade 1–2 FL, i.e. non-polarised neoplastic follicles composed primarily of centrocytes with few centroblasts, and lacking a starry-sky appearance, an attenuated mantle zone, and infiltration of centrocytes in the lamina propria outside the follicles. The B cells are CD10+, bcl-6+, and bcl-2+, with a low Ki67 proliferation index. One characteristic feature of duodenal-type FL is the frequent distribution of CD21+ CD23+ follicular dendritic cells at the periphery of the neoplastic germinal centres, referred to as a ‘hollowed-out’ appearance. Furthermore, duodenal-type FL neoplastic cells preferentially express IgA over IgM,^{89,90} and the mucosal homing receptors $\alpha 4\beta 7$ integrin and CCR9 chemokine receptor, which direct lymphocyte trafficking to the intestinal mucosa.^{91,92}

Non-duodenal-type FL (Figure 5E–G) tends to be transmural, encompasses cases ranging from grade 1–2 to grade 3, and may be accompanied by sclerosis. It is histologically and phenotypically indistinguishable from systemic FL.

Table 3. Key points in comparison between primary intestinal and duodenal-type follicular lymphoma (FL)

	Primary intestinal FL <4% of primary GI lymphomas	Duodenal-type FL <4% of primary GI lymphomas
Localisation	Small and large intestine Rare in the stomach	Duodenum (D2) ± simultaneous involvement of the jejunum or ileum
Macroscopy	Infiltrative, usually transmural ± regional LN involvement Lymphomatous polyposis	Polypoid lesions, mucosa and submucosa, no LN involvement
Presenting features	Middle-aged (50 years) Abdominal discomfort, obstruction, bleeding	Slightly older (60 years) Asymptomatic (incidental endoscopic finding) or abdominal discomfort
Pathology	Centrocytes and centroblasts CD20+ CD10+ bcl-2+ bcl-6+ Most cases t(14;18)+ (IGH-BCL2)	
	Grade 1–2 > grade 3 bcl-6 and CD10 can be down-regulated	All cases grade 1–2 CD21+ FDCs at the periphery of the nodules, preferential IgA expression

bcl-2, B-cell lymphoma 2; bcl-6, B-cell lymphoma 6; FDC, Follicular dendritic cell; GI, Gastrointestinal; LN, Lymph node.

Molecular genetics

Both duodenal-type and other intestinal FLs harbour the t(14;18)(q32;q21)/IGH-BCL2 translocation in the majority of the cases. In duodenal-type FL, the active somatic hypermutation machinery is related to the expression of BTB and CNC homolog 2 (BACH2) instead of activation-induced cytidine deaminase (AID).^{83,93} In an effort to shed light on the molecular differences between duodenal-type FL and nodal FL and explain the indolent clinical behaviour of duodenal-type FL, recent studies analysed the genetic landscape of the neoplastic cells and the expression profile of the immune microenvironment.^{94,95} Comparison of the mutational landscapes of duodenal-type FL and nodal FL showed no significant differences in the mutation rates of the most recurrently altered genes, including CREBBP, TNFRSF14/HVEM, and EZH2. In contrast, duodenal-type FL showed fewer biallelic or multiple mutations in the histone methyltransferase KMT2D/MLL2 gene and a high frequency of mutations in HVCN1 and EEF1A1, in 22% and 35% of cases, respectively.⁹⁴ Interestingly, HVCN1 mutations

were reported to correlate with longer progression-free survival in patients with systemic FL.⁹⁶

Conversely, factors related to the microenvironment appear to play a significant role in duodenal-type FL lymphomagenesis. Selective usage of the IGHV4 gene segment in most cases indicates an antigen-driven mechanism of lymphomagenesis.^{93,97} Furthermore, gene expression analyses have shown a distinct immune microenvironment profile in duodenal-type FL, characterised by a chronic inflammation gene signature and overexpression of proinflammatory cytokines and chemokines such as CXCL6, TNFSF15, CCL11, CXCL1, CCL21, and CCL20 with its ligand CCR6, with consequent recruitment of Th17 and activated CD4+ T-helper cells into the lymphoma microenvironment.^{94,95}

MCL

MCL is an aggressive type of B-cell lymphoma, accounting for approximately 3–5% of primary GI lymphomas.^{2,98} MCL mainly affects elderly and predominantly male individuals. As a primary GI disease, it may present as multiple mucosal polyps, so-called multiple lymphomatous polyposis, more commonly in the lower GI tract.^{99,100} Gastric involvement manifests as large cerebriform folds. Presenting symptoms may include abdominal pain, weight loss, diarrhoea, or bleeding. Staging frequently reveals widespread extraintestinal disease (stage IV). Microscopic GI tract involvement is also extremely frequent (84%) in patients with systemic MCL.^{101,102}

Pathological features

MCL is composed of a monotonous small to medium-sized lymphoid cell population, with clefted nuclei, indistinct nucleoli, and scant cytoplasm, that infiltrates the mucosa and submucosa in a nodular or diffuse fashion (Figure 6). Occasionally, infiltration of epithelial structures is found, resembling lymphoepithelial lesions.¹⁰³ Two aggressive cytological variants are recognised, namely blastoid and pleomorphic. Immunophenotypically, the cells typically express CD20, PAX5, CD5, CD43, IgD, bcl-2, and cyclin D1, and are negative for CD23, CD10, and bcl-6. Rare cases with aberrant phenotypes, namely CD5-, CD10+, or bcl-6+, have been described. SOX11 expression is a useful diagnostic marker in the rare cyclin D1- MCL cases.¹⁰⁴ A Ki67 proliferation index of >30% identifies patients with a poor prognosis, and should be reported.⁷

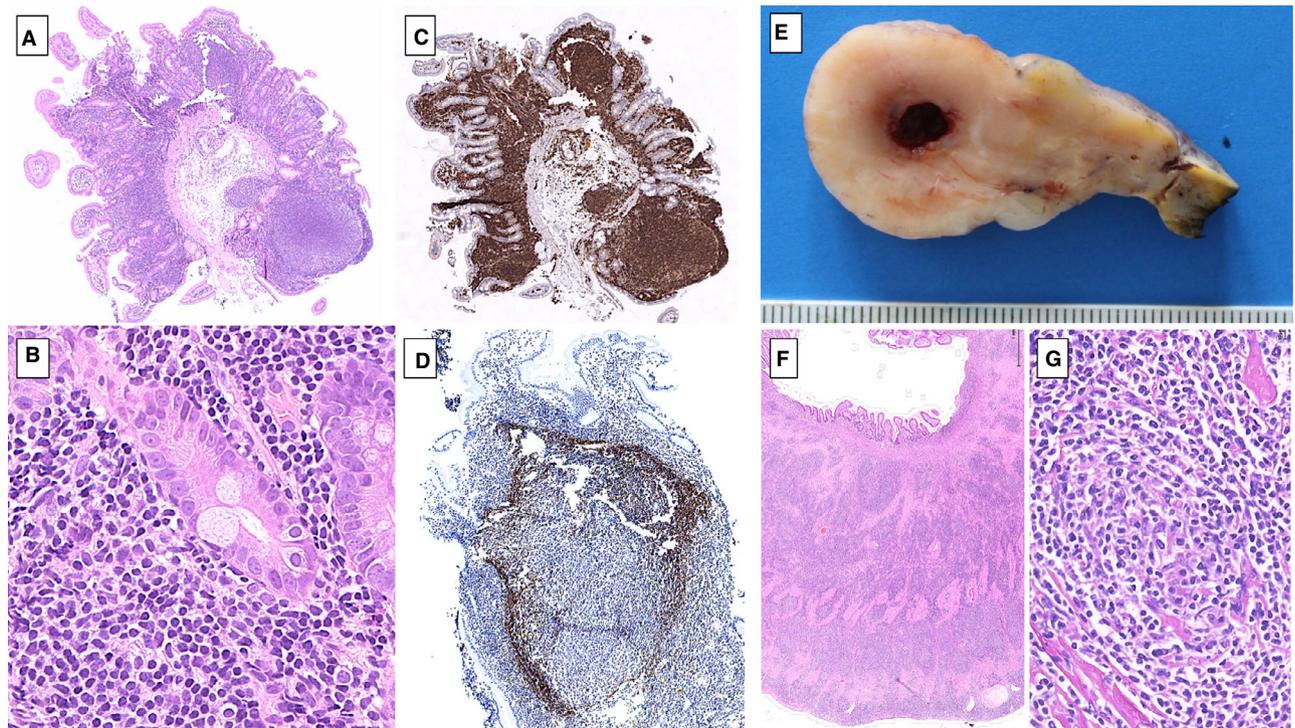


Figure 5. Intestinal follicular lymphoma. A–D, Duodenal-type follicular lymphoma. A, The lesion presented as a mucosal polyp with nodular and partly diffuse involvement of the lamina propria [haematoxylin and eosin (H&E)]. B, Cytologically, most cells were small, resembling centrocytes (H&E). C, Diffuse positivity for B-cell lymphoma 2 (bcl-2). D, CD21 immunostaining showing follicular dendritic-cell meshworks pushed to the outer rim of the follicles. E–G, Primary follicular lymphoma of the small intestine. E, The lesion presented as a circumferential and transmural infiltrate causing obstruction, and required surgical excision. F, A panoramic view of the intestinal wall involved by the lymphoma infiltrate (H&E). G, Neoplastic follicles associated with sclerosis, comprising in this case mostly centrocytes (H&E).

Molecular genetics

The characteristic genetic signature of MCL is the t(11;14)(q13;q32) translocation resulting in IGH–CCND1 fusion and cyclin D1 overexpression, whereas cases that lack cyclin D1 expression often show alternative CCND2 or CCND3 rearrangements.^{105,106} Immunogenetic studies have shown a biased usage of certain IGHV genes (IGHV3-21, IGHV4-34, IGHV1-8, and IGHV3-23), suggesting antigen-driven selection, whereas completely unmutated IGHV genes are detected in ~30% of the cases, which have a worse prognosis than cases with IGH somatic hypermutations.^{107,108} The genomic landscape of MCL is heterogeneous, and comprises mutations in genes involved in DNA damage response (*ATM* and *TP53*) and Notch signalling (*NOTCH1* and *NOTCH2*), and in genes affecting RNA metabolism and splicing (*EWSR1*, *DAZAP1*, and *HNRNP1*). Mutations in *TP53*, *SMARCA4*, *CELSR3*, *CCND1* and *KMT2D* have been found to negatively affect the response to venetoclax-based therapies.^{109–111}

The median survival is 3–5 years, and the majority of cases remain incurable, with multiple relapses. Besides standard chemotherapy, treatment options currently comprise many new drugs such as ibrutinib, lenalidomide, bortezomib, temsirolimus, and venetoclax.¹¹²

SLL

Although rare cases of primary SLL of the GI tract have been described,¹¹³ most of them represent secondary involvement in patients with known CLL. It usually consists of a dense and diffuse infiltrate of small round lymphocytes, which may constitute proliferation centres. The lymphoma cells are CD20+ (often with heterogeneous or weak expression), CD5+, CD23+, CD43+, cyclin D1–, and lymphoid enhancer binding factor 1 (LEF1)+.^{114,115} Secondary lymphoid follicles or lymphoepithelial lesions typical of MALT lymphoma are usually not seen.

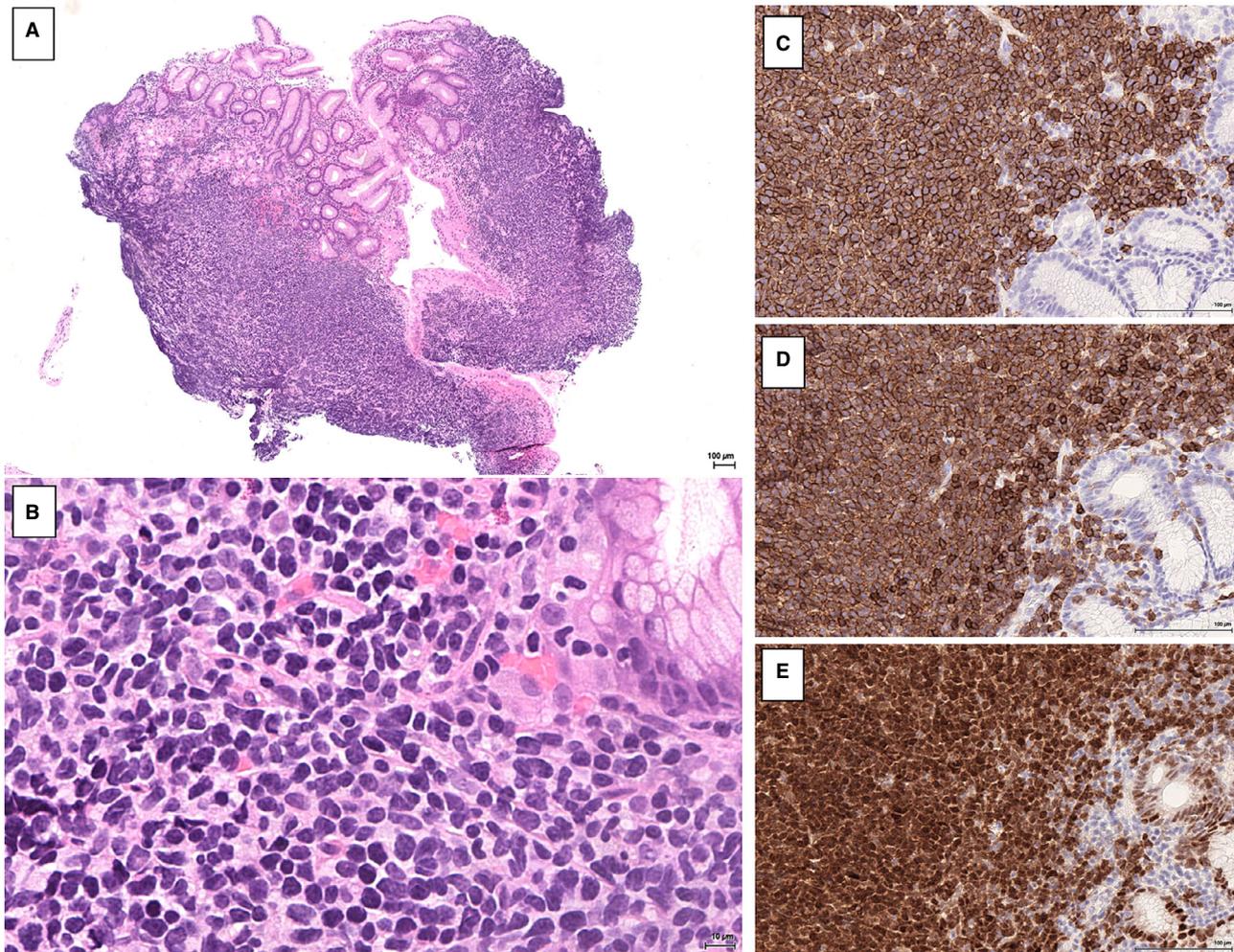


Figure 6. Mantle cell lymphoma of the stomach. **A**, A panoramic view showing a dense basophilic lymphoid infiltrate [haematoxylin and eosin (H&E)]. **B**, A monotonous infiltrate of small cells with irregular nuclei, adjacent to a residual gastric gland (H&E). **C**, CD20 positivity. **D**, CD5 expression. **E**, Cyclin D1 nuclear positivity.

Aggressive B-cell lymphomas

DLBCL, including the not otherwise specified (NOS) type (DLBCL, NOS) and specific variants, is the most common aggressive lymphoma of the upper GI tract.^{2–6} Burkitt lymphoma (BL) and high-grade B-cell lymphomas (HGBCLs) occur less frequently. Two HGBCL entities were created in the revised WHO classification of lymphoid neoplasms, to classify a group of aggressive B-cell lymphomas that are clinically and biologically distinct from DLBCL, NOS and BL. HGBCLs with *MYC* and *BCL2* and/or *BCL6* rearrangements [so-called double-hit (DH) or triple-hit (TH) lymphomas; HGBCL-DH/TH] are defined by their genetic features, irrespective of the morphology. HGBCL, NOS encompasses cases previously termed

‘unclassifiable, with features intermediate between DLBCL and BL’, or showing blastoid morphology, but lacking DH/TH translocations.^{7,116}

The current diagnostic approach to aggressive lymphomas of B-cell lineage according to the 2017 WHO guidelines is summarised in Figure 7. The first level of assessment remains cytomorphology, which encompasses large cells (centroblastic, immunoblastic, plasmablastic or anaplastic types), Burkitt-type morphology (monomorphic medium-sized cells with basophilic cytoplasm, coarse chromatin and several medium-sized nucleoli, densely packed and associated with a starry-sky pattern), intermediate cases (comprising somewhat pleomorphic cells with features intermediate between Burkitt cells and large cells, often featuring prominent apoptosis and a starry-sky

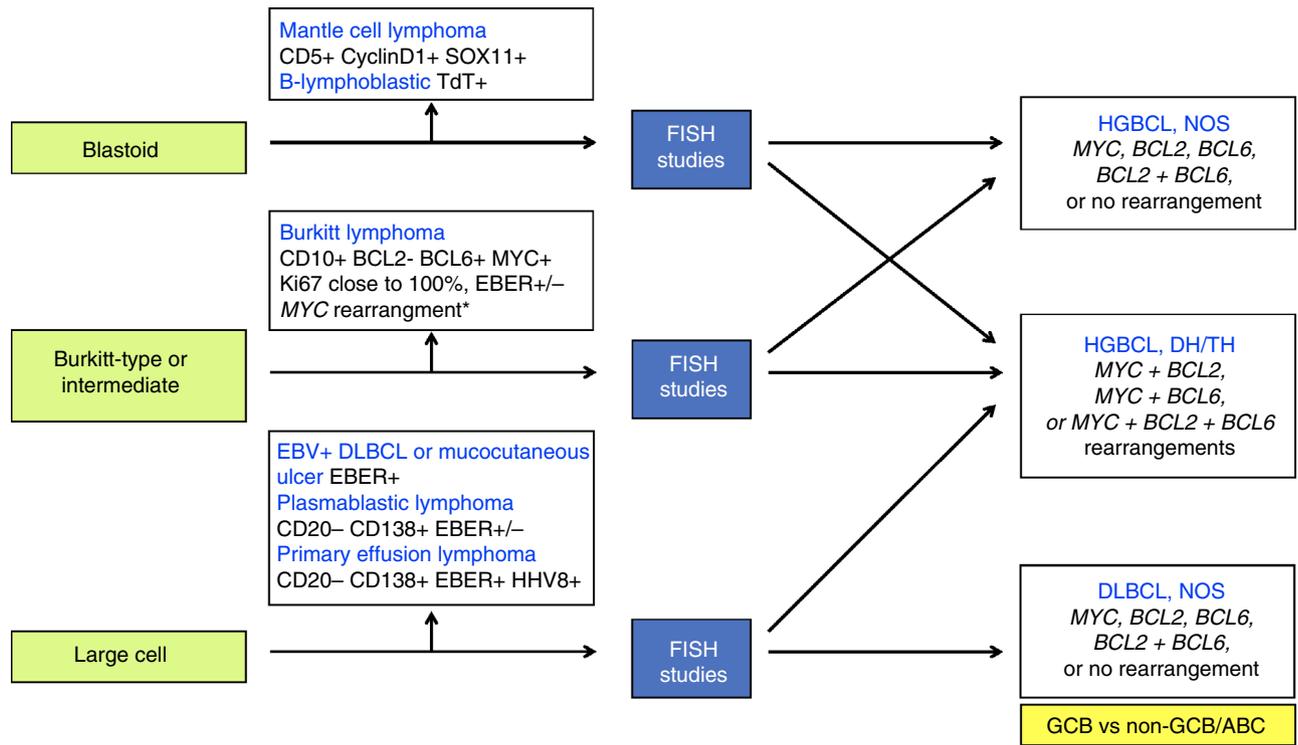


Figure 7. The diagnostic approach to high-grade B-cell lymphomas. ABC, activated B-cell-like; GCB, germinal centre B-cell-like; HGBCL-DH/TH, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (double-hit/triple-hit). HGBCL, NOS, high-grade B-cell lymphoma, not otherwise specified. *Demonstration of a *MYC* rearrangement may not be mandatory in cases with typical morphology and immunophenotype.

pattern), and blastoid tumours (comprising medium-sized cells with fine chromatin, indistinct nucleoli, and scant cytoplasm). Cases with blastoid morphology may represent blastoid MCL or lymphoblastic neoplasms, which are best identified with an appropriate panel of immunostains. BL is a rather uniform entity, and in cases with typical morphology the diagnosis is confirmed by the demonstration of the expected immunophenotype (CD20+ CD10+ bcl-2- bcl-6+ MYC+, and a Ki67 proliferation close to 100%), and association with Epstein–Barr virus (EBV) infection in a subset of the cases. In cases with typical morphology and immunophenotype, confirmation of a *MYC* rearrangement by the use of FISH is optional; in cases showing deviations from the typical features (mild cytological pleomorphism and bcl-2 expression), FISH studies are mandatory to assess the *MYC* status and exclude a DH lymphoma (Figure 8). The majority of lymphomas composed of large B cells remain under the umbrella term of DLBCL, NOS. However, specific entities that may occur as GI neoplasms, such as EBV+ entities (EBV+ DLBCL and EBV+ mucocutaneous ulcer), plasmablastic lymphoma, and the solid form of primary effusion

lymphoma, have to be excluded, and FISH studies are also mandatory to identify the small subset of large B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements, because these are classified as HGBCL-DH/TH.⁷

DLBCL, NOS

DLBCL, NOS usually presents *de novo*, but some cases represent transformation of a pre-existing systemic or GI small B-cell lymphoma.^{5,6} In particular, transformation of systemic FL may occur in the small intestine, whereas MALT lymphoma represents the most common primary GI small B-cell lymphoma that undergoes transformation to DLBCL. DLBCL usually presents as symptomatic ulcerated tumour masses or mucosal thickening. The majority of cases are localised (stage I or II) at diagnosis.^{117–119} The tumour is composed of large or medium to large lymphoid cells, with centroblastic and/or immunoblastic and, less commonly, anaplastic morphology. The growth is diffuse and obliterates the crypts or glands without the formation of typical lymphoepithelial lesions. A small-cell component may be present in transformed cases,

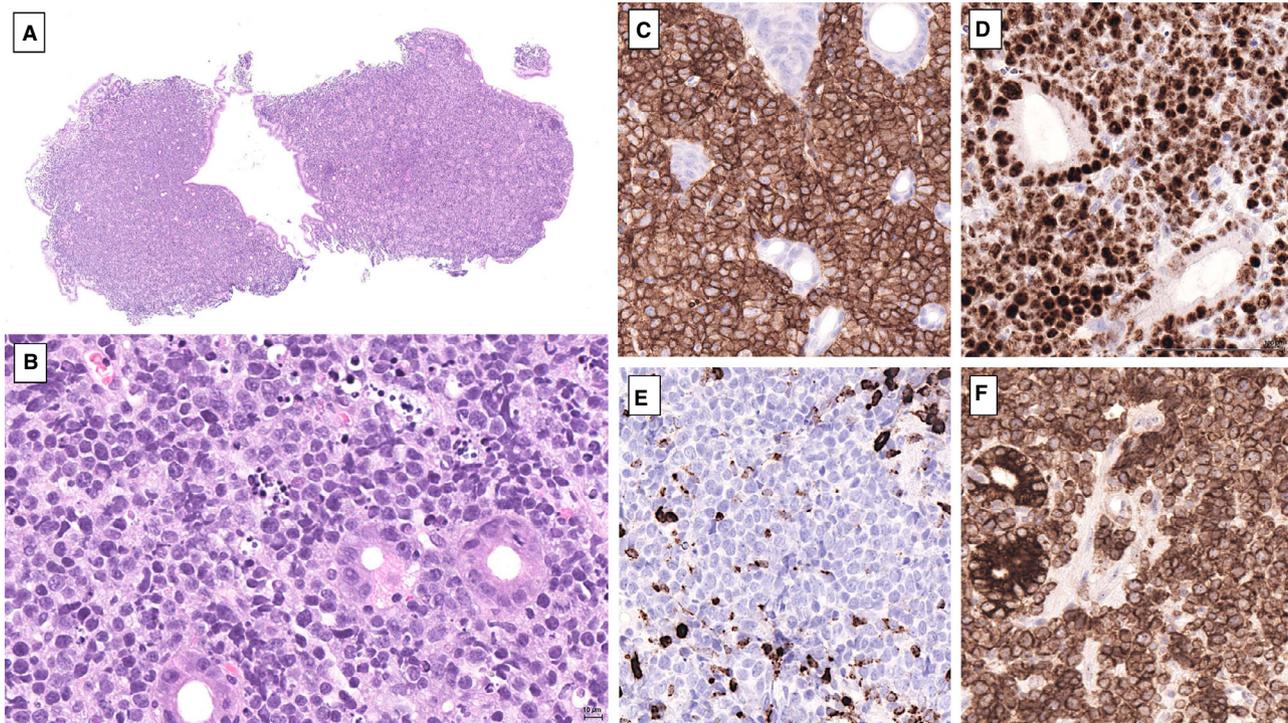


Figure 8. High-grade B-cell lymphoma with concomitant rearrangement of *MYC* and *BCL2* (double-hit lymphoma). A, A low-power view showing a diffuse mucosal basophilic infiltrate [haematoxylin and eosin (H&E)]. B, Cytomorphology was intermediate between medium and large cells, with a focal starry-sky pattern (H&E). C, Strong CD10 positivity. D, The Ki67 proliferation index was very high. E, Lack of B-cell lymphoma 2 (*bcl-2*) expression as shown by use of the usual Dako antibody (clone 124). F, Conversely, the clone E17 *bcl-2* antibody demonstrated diffuse *bcl-2* expression. This pattern was probably due to a *BCL2* mutation interfering with immunoreactivity of the epitope recognised by the Dako clone 124 antibody.

and the presence of residual follicular dendritic cell meshworks may denote an underlying MALT lymphoma. The lymphoma cells express pan-B-cell antigens (CD20, CD19, CD22, CD79a, and PAX5) and monotypic surface and/or cytoplasmic immunoglobulin, usually IgM, and rarely coexpress CD5.¹¹⁸ A subset of gastric DLBCLs are associated with *H. pylori* infection, and there have been sporadic case reports and one prospective study suggesting that *H. pylori* eradication might be an effective treatment for limited-stage *de-novo* *H. pylori*-positive gastric DLBCLs.^{120–122} In a recent retrospective study from China, it was found that a positive *H. pylori* status in gastric DLBCL was associated with a higher proportion of stage I–II disease and was a predictor of less aggressive behaviour and better outcome.¹¹⁷ It is mandatory, according to WHO recommendations, that DLBCL, NOS be classified into ‘germinal centre B-cell-like (GCB)’ and ‘non-GCB’ or ‘activated B-cell-like (ABC)’ subtypes.⁷ In diagnostic practice, this is usually achieved by means of immunohistochemical algorithms designed as surrogates of mRNA-based

expression signatures. The Hans classifier, based on the assessment of three markers (CD10, *bcl-6*, and MUM1) is one of the most widely used.¹²³ Other alternatives incorporating other markers, such as FOXP1 and/or GCET-1, have been proposed.¹²⁴ Methods based on mRNA expression profiling that are applicable to routinely processed samples are also available, e.g. the Lymph2Cx assay or multiplex ligation-dependent probe amplification (MLPA) assay, but they are less widely used.^{125,126} In the stomach, the non-GCB/activated cases outnumber tumours with a GCB immunophenotype (58–70% versus 30–42%)^{68,117,118,127,128}; conversely, intestinal DLBCLs are more often of the GCB type.^{129–131} Those transformed from MALT lymphomas are more often CD10– and *bcl-2*– than are *de-novo* DLBCLs, but usually express *bcl-6*.^{26,127,132} The diagnostic work-up of DLBCL, NOS should also include the assessment of *bcl-2* and *MYC* expression, with positive cut-offs set at 50% of cells with cytoplasmic *bcl-2* expression and 40% with *MYC*+ nuclei. Many cases are immunohistochemically *bcl-2*+ or *MYC*+ in the absence of *BCL2*

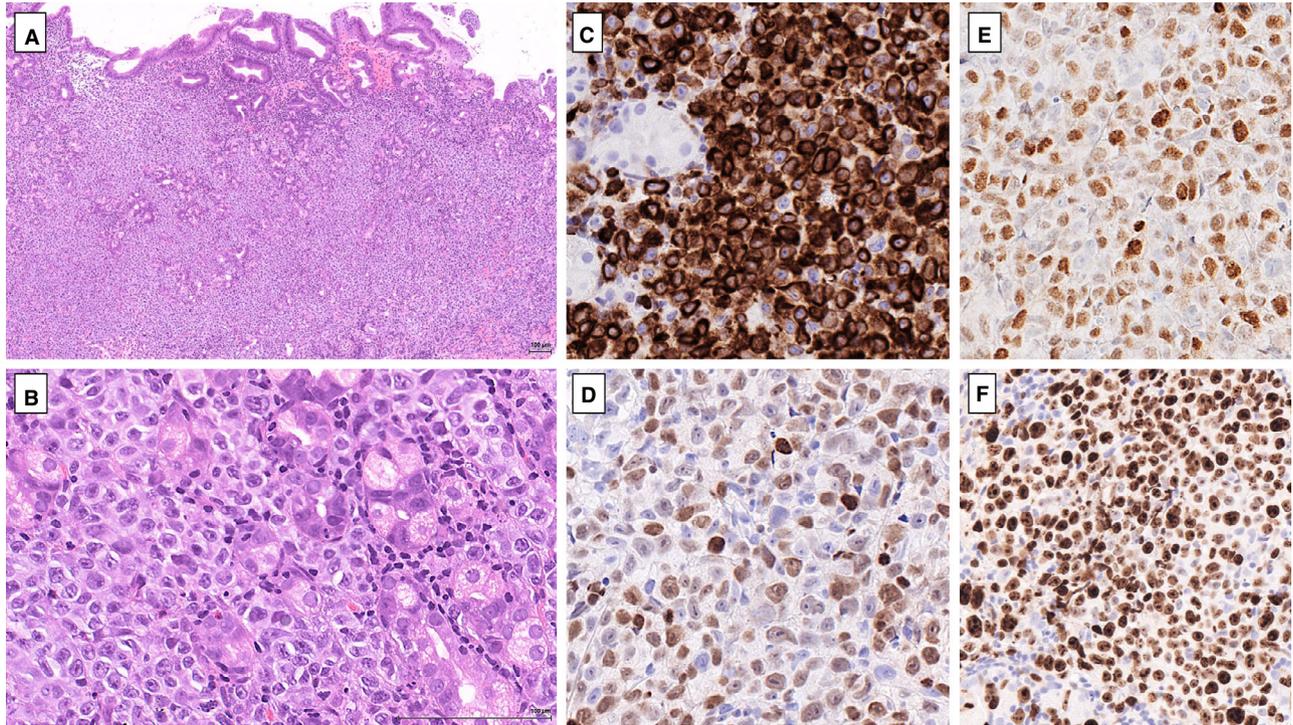


Figure 9. Gastric diffuse large B-cell lymphoma, not otherwise specified. A,B, Diffuse mucosal infiltrate comprising large lymphoid cells [haematoxylin and eosin (H&E)]. C, Strong B-cell lymphoma 2 (*bcl-2*) expression. D, MUM1 positivity in the majority of nuclei (this case had an overall activated B-cell-like immunophenotype). E, Nuclear positivity for *MYC* was present in the majority of nuclei. F, The Ki67 proliferation index was high.

or *MYC* rearrangements. Importantly, the so-called 'double-expressor' *bcl-2*+/*MYC*+ status (Figure 9) identifies a group of patients who have more aggressive disease and poorer outcomes.^{133,134}

Although a subset of primary gastric DLBCLs arise by transformation of MALT lymphomas, specific translocations associated with MALT lymphoma, such as the *t(11;18)/BIRC3-MALT1* translocation, are rare in DLBCLs, supporting the view that these cases are less prone to transform.¹³⁵ Regarding the recurrent translocations associated with DLBCL, *BCL2* rearrangements are overall rarely found in primary GI DLBCL, and ~10% carry *MYC* translocations, which is similar to the rate in nodal cases.^{136–139} *BCL6* rearrangements, which have been found in association with transformation of MALT lymphoma, are present in 48% of gastric DLBCLs and 30% of intestinal DLBCLs.^{132,139} Some studies suggest that *BCL6* rearrangements may be associated with a better prognosis.^{127,140} Recently, two seminal studies using a multiplatform genomic approach, consisting of gene expression profiling, whole exome sequencing, structural variants, and DNA copy number analysis, led to

the identification of several genetic subgroups based on enrichment of driver mutations and signalling pathways.^{141,142} Interestingly, both studies identified a genetic subgroup defined by the association of structural alterations of *BCL6* and *NOTCH2* mutations, encompassing both non-GCB and GCB gene expression signatures, which may be related to marginal zone lymphomas.

EBV-ASSOCIATED DISEASES

A variety of large B-cell lymphoma entities are characterised by a more or less frequent association with EBV infection (Table 4).⁷ Overall these entities are rare, but may involve the GI tract. They have in common the tendency to occur in individuals with some dysfunction of the systemic or local immune system. Given the spectrum of EBV-associated entities, the relevance of EBV testing for proper diagnosis, and the clinical importance of recognising EBV-associated entities, we advocate performing EBV testing by means of *in-situ* hybridisation for EBV-encoded small RNAs (EBERs) in a broad range of settings.

Table 4. Epstein–Barr virus (EBV)-associated B-cell lymphoproliferations

Entities defined by EBV association
EBV+ diffuse large B-cell lymphoma
EBV+ mucocutaneous ulcer
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary effusion lymphoma (EBV+ and HHV-8+)
Entities frequently associated with EBV infection
Plasmablastic lymphoma
Post-transplantation lymphoproliferative disorders
HIV-associated lymphomas
Lymphoproliferative disorders associated with primary immune deficiencies
Indications for EBER testing
Elderly individuals
Large-cell proliferations presenting as ulcers
DLBCLs with a non-GC immunophenotype
CD30 expression, Reed–Sternberg-like cells
Plasmablastic lymphoma
Clinical context: HIV+, post-transplantation, immune deficiencies, children

DLBCL, Diffuse large B-cell lymphoma; EBER, Epstein–Barr virus-encoded small RNA; GC, Germinal centre; HHV-8, Human herpesvirus 8; HIV, Human immunodeficiency virus.

EBV+ DLBCL, NOS (Figure 10) and **EBV+ mucocutaneous ulcer** include a broad range of clinicopathological features, ranging from highly aggressive diseases to self-limited localised conditions, with some overlap between the two entities.¹⁴³ The lesions contain EBV+ CD20+ large cells, often including scattered Reed–Sternberg-like cells, and a polymorphic inflammatory background. The immunophenotype is usually of the activated B-cell type, with frequent CD30 expression, but a subset of cases are CD10+.¹⁴⁴ EBV+ DLBCL, NOS is generally reported in patients without any known immune deficiency disorder (after exclusion of ‘specific’ types of EBV+ DLBCL, such as plasmablastic lymphoma), and can occur at any age, but usually in older adults. In a series from Asia, EBV+ DLBCLs represented approximately 7–10% of gastric primaries, and the presence of EBV was negatively correlated with outcome.¹¹⁹ EBV positivity was found

to correlate with higher expression of programmed death-ligand 1 (PD-L1) in the tumour microenvironment, a finding that might have therapeutic impact in the immunotherapy era.¹¹⁸ EBV+ mucocutaneous ulcer causes superficial ulcerative lesions in the skin or mucosae in elderly individuals, in the setting of iatrogenic immunosuppression (methotrexate, azathioprine, cyclosporine, mycophenolate) for rheumatoid arthritis or inflammatory bowel disease, in human immunodeficiency virus (HIV)-infected individuals, or post-transplantation.^{145–147} Whereas EBV+ mucocutaneous ulcer has a predilection for the lower GI tract, a recent study from Japan reported that GI EBV+ DLBCLs occurring in non-immunosuppressed individuals have a predilection for the stomach, which was the main localisation of disease for low-stage lesions and was often involved in cases with multifocal lesions.¹⁴⁴

Plasmablastic lymphoma is composed of large cells, ranging from immunoblasts to plasmablasts with or without a component of mature plasma cells, and is characterised by extinction of the B-cell transcription programme and a plasma cell immunophenotype.¹⁴⁸ Recent data provide evidence that the transcriptome of plasmablastic lymphoma is more closely related to that of multiple myeloma than to that of other B-cell malignancies.¹⁴⁹ The GI tract is the most common site of presentation, after the oral cavity, and ~50% of primary GI plasmablastic lymphomas are diagnosed in the stomach or proximal small intestine.^{150–153} Although plasmablastic lymphoma was initially described in HIV+ individuals, the majority of cases nowadays occur in HIV– patients with other causes of immunosuppression or apparently immunocompetent.^{151,154,155} Plasmablastic lymphoma is essentially negative for CD45, CD20, and PAX5, negative or variably positive for CD79a, and positive for CD38, CD138, and VS38c, with expression of the transcription factors PRDM1/BLIMP-1, MUM1, and XBP1. Epithelial membrane antigen (EMA) and CD30 are also commonly expressed. Cytoplasmic immunoglobulin is detected in 50–70% of the cases, and CD56 is variably expressed.^{150,151,153} Approximately half of the cases are EBV+ (EBER+; Epstein–Barr nuclear antigen 1 (EBNA1)+).^{150,151,153} *MYC* rearrangements are found in 50% of the cases, usually with an *IG* gene as the translocation partner.^{151–153,156} Recent NGS-based studies have reported recurrent mutations affecting the JAK–STAT (*STAT3*, *JAK1*, *SOCS1*, *JAK2*, and *PIM1*), RAS–mitogen-activated protein kinase (MAPK) (*NRAS*, *KRAS*, *BRAF*, and *MAP2K1*) and Notch (*NOTCH1*, *SPEN*, and *NCOR2*) signalling pathways, providing the genetic basis for new therapeutic interventions.^{149,157}

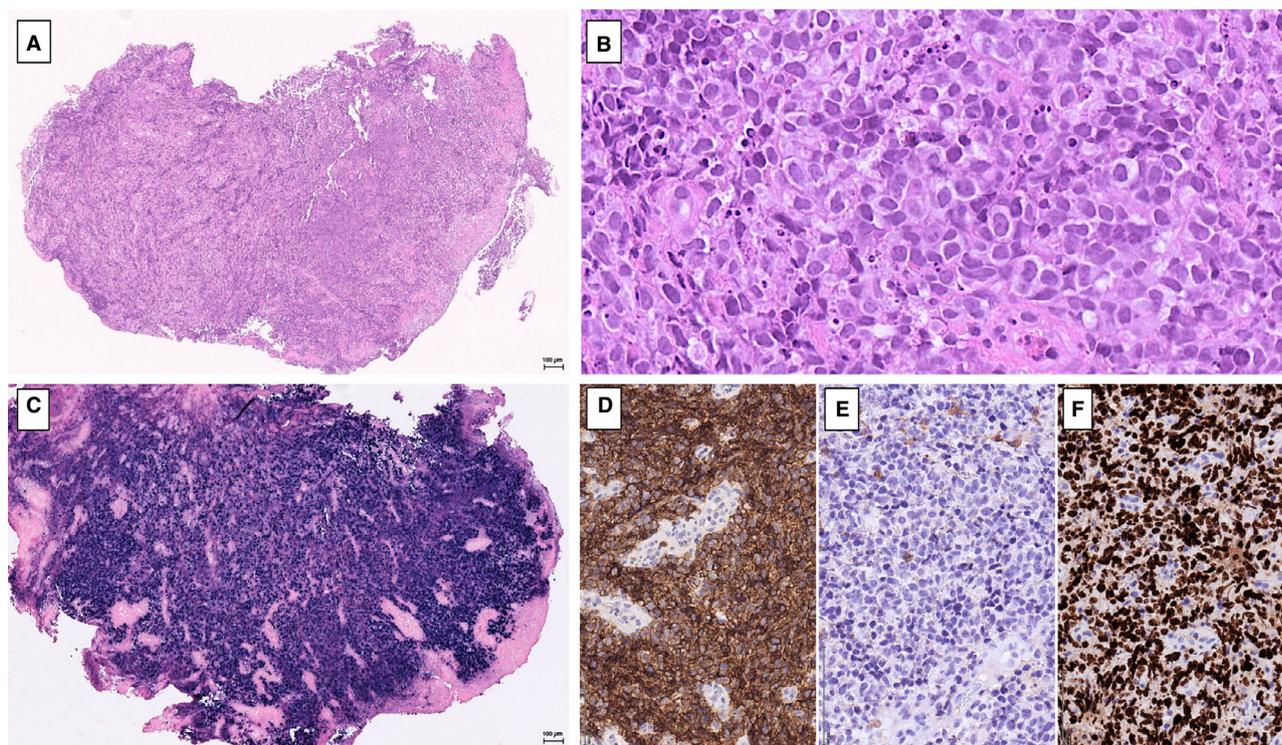


Figure 10. Epstein–Barr virus (EBV)-positive diffuse large B-cell lymphoma, not otherwise specified. A, Diffuse involvement of the gastric mucosa by an ulcerated eosinophilic lymphoproliferation [haematoxylin and eosin (H&E)]. B, A high-power view showing medium-sized to large lymphoid cells with fine chromatin, and nucleoli, associated with single-cell necrosis and apoptosis (H&E). C, EBV-encoded small RNA (EBR) *in-situ* hybridisation was positive in most cells. D, Strong positivity for CD20. E, Lack of CD10 expression. F, A Ki67 proliferation index of >90%.

T-cell neoplasms

GI T-cell neoplasms are overall markedly less frequent than B-cell lymphomas, but they encompass several distinct entities. Although the majority of the cases develop in the intestine, a small proportion of the cases may arise in or disseminate to the stomach, duodenum or, uncommonly, oesophagus. The recently revised WHO classification introduced significant changes in the classification of intestinal T-cell lymphomas. The two subtypes of enteropathy-associated T-cell lymphoma (EATL), types I and II, which were previously considered to be variants of the same disease, have been reclassified as two distinct diseases [EATL, formerly type I EATL, and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), formerly type II EATL], owing to differences in their epidemiology and clinical features, morphology, phenotype, and genetic features, as highlighted in recent studies.^{7,158,159} Intestinal T-cell lymphoma, NOS is a novel category created to include the cases of primary intestinal T-cell lymphoma not meeting the criteria for either EATL or MEITL. In addition, indolent T-cell lymphoproliferative disorder of the GI tract (ITLDP)

represents a newly recognised group of clonal monomorphic proliferations of small T cells showing a superficial/mucosal distribution along the GI tract, and usually characterised by indolent behaviour and a chronic relapsing course.^{160,161} NK-cell enteropathy (NKCE) represents another rare indolent disorder derived from NK cells. Other mature T/NK-cell lymphoma entities, such as extranodal NK/T-cell lymphoma, nasal type (ENKTCL), can also primarily or secondarily involve the GI tract, and their diagnosis may be challenging.

EATL

EATL, the most common form of primary intestinal T-cell lymphoma, is a neoplasm derived from intraepithelial T cells, and occurs in individuals with coeliac disease (CD) (gluten-sensitive enteropathy). The prevalence is highest in Europe, and especially northern Europe, whereas the disease is essentially non-existent in Asia.^{162–165} The median age at presentation is >60 years. Patients typically have a history of CD or refractory CD (RCD), but a substantial proportion of the cases arise *de novo*, and these may be

associated with a better outcome. Patients with EATL present with GI symptoms that often culminate in intestinal perforation and peritonitis, or obstruction. B symptoms are common (30–40%). EATL most commonly affects the small bowel, and rarely the large intestine or stomach (8% of the cases).^{163,164} Lesions are frequently multifocal. The prognosis is poor, with a median survival of 7 months.¹⁶⁶

Pathological features

EATL (Figure 11) presents as ulcerative lesions or tumour masses. Histologically, EATL is composed of pleomorphic, medium-sized to large, occasionally anaplastic, lymphoid cells with a high mitotic rate. A mixed inflammatory infiltrate is typically present, usually rich in histiocytes and eosinophils, and may sometimes obscure the lymphoma cells.⁸ Angiocentricity and angioinvasion can lead to extensive necrosis. Enteropathic features [villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytosis (IEL)] may be seen in the adjacent or distant mucosa. The neoplastic cells are CD2+ CD3+ CD4– CD5– CD7+ CD8–/+ CD56– with an activated cytotoxic phenotype and a

high Ki67 index. CD30 is usually expressed by a large proportion of cells.¹⁶⁷ The majority of the cases are negative for T-cell receptor (TCR) expression ('TCR-silent'); ~25% are positive for TCR $\alpha\beta$, and TCR $\gamma\delta$ expression has been described in a few cases. Expression of CD103 (human mucosal lymphocyte antigen 1, integrin $\alpha\text{E}\beta 7$), which is found in normal intraepithelial lymphocytes, is often at least partially preserved. Overexpression of p53 is seen in many cases.

Molecular and genetic features

Clonal T-cell receptor (TR) gene rearrangements are detected in the majority of the cases.^{168–170} EATL shows multiple chromosomal imbalances: 9q gains and almost mutually exclusive losses at 16q12.1, gains of chromosome 7, frequent gains of chromosomes 1q and 5q, and losses involving 8p22–23.2, 16q21.1, 11q14.1–q14.2, and 9p21.2–p21.3.^{158,171–175} The mutational landscape of EATL is characterised by recurrent activating mutations in genes of the JAK–STAT pathway, most commonly *JAK1* and *STAT3*, and rarely *JAK3*, *STAT5B*, *TYK2*, and *SOCS1*.^{158,159,176} Mutations in genes of the MAPK

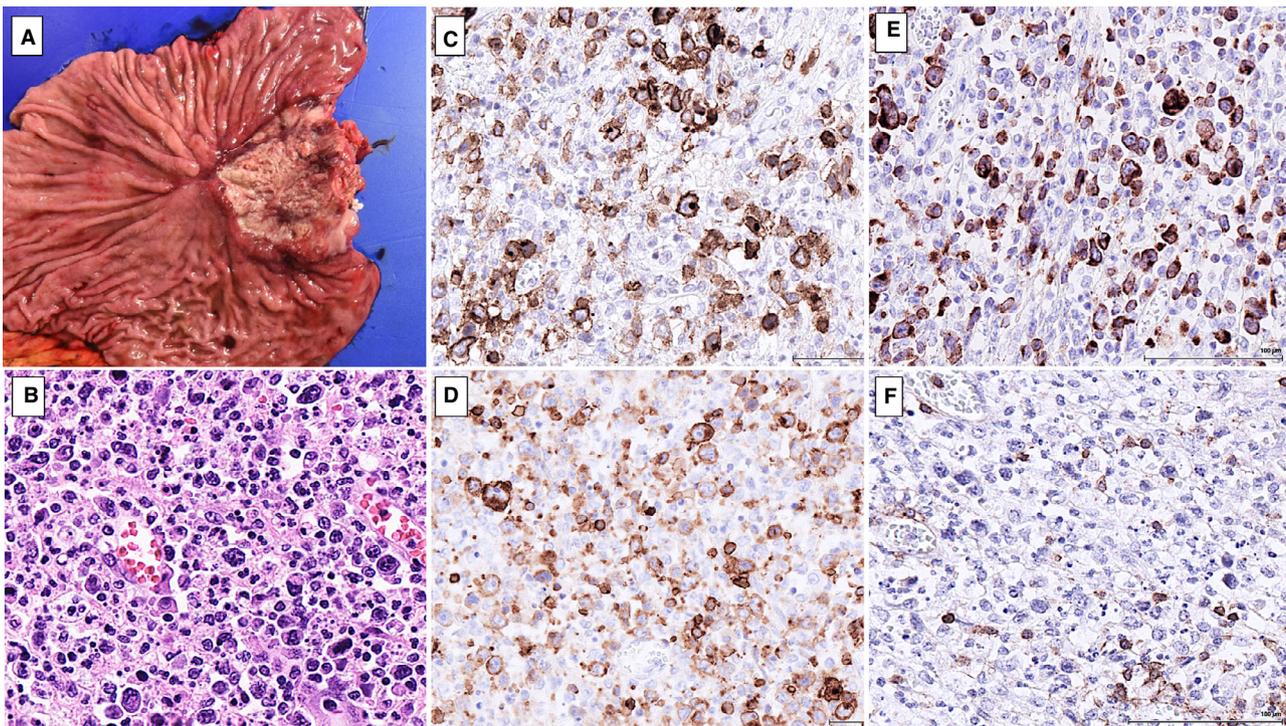


Figure 11. An enteropathy-associated T-cell lymphoma presenting as a subcardial gastric ulcer. A, A macroscopic view of the gastrectomy specimen showing a large, ulcerated subcardial lesion. B, The tumour consisted of a pleomorphic, predominantly large-cell, lymphoid infiltrate, including cells with anaplastic-type morphology (haematoxylin and eosin). C, Strong CD7 expression. D, CD30 positivity was detected in most cells. E, An activated cytotoxic phenotype highlighted by perforin expression. F, Lack of T-cell receptor (TCR)- β F1 expression in the neoplastic cells (in contrast to the few reactive lymphocytes in the field) (TCR δ was also negative in this case, which was overall TCR-silent).

pathway (*KRAS*, *NRAS*, and *BRAF*) are present in 20% of the cases, and *TP53* mutations have been reported in 10–15% of the cases. Alterations in *SETD2* are less common than in MEITL.

Whole transcriptome sequencing showed differences in the gene expression profiles of EATL and MEITL, further supporting their reclassification as distinct entities.¹⁵⁸ Genes expressed at higher levels in EATL include *STAT3*, *STAT5A*, *IRF1/4*, and *TGM2*, which encodes transglutaminase 2, a known autoantigen in CD, highlighting the association of EATL with this disorder. Furthermore, EATL was also characterised by overexpression of interferon- γ signalling pathway genes, a pattern reported in untreated CD patients.¹⁷⁷

Differential diagnosis

The diagnosis of EATL in the upper GI tract may be challenging, especially that of *de-novo* cases if enteropathic features are not identified. In those instances, if the pathological findings are consistent, a diagnosis of EATL should be proposed, and tested with serological investigations and human leukocyte antigen genotyping. In cases with no evidence of CD, a diagnosis of intestinal T-cell lymphoma, NOS is more appropriate. Cases with an anaplastic large-cell morphology and strong CD30 expression may histologically resemble anaplastic large-cell lymphoma (ALCL), but primary intestinal ALCL is very rare, and this diagnosis can be considered only after thorough clinical investigation to exclude underlying CD.

A clinical context of RCD may raise the differential diagnosis between EATL and type II RCD. Type II RCD features villous atrophy and intraepithelial expansion of slightly atypical lymphocytes, which are usually monoclonal and immunophenotypically abnormal, similar to that found in EATL, including loss of surface CD3 expression by flow cytometry, and loss of CD4 and CD8 expression. However, type II RCD is an '*in-situ*' precursor to EATL, lacking the inflammatory background, predominantly large-cell morphology, infiltration with possible mass formation, necrosis and angioinvasion seen in EATL. CD30 expression is rarely seen in type II RCD, and is considered to be a sign of progression to EATL.^{8,178}

MEITL

MEITL is a lymphoma derived from intraepithelial lymphocytes. It is unrelated to CD, and is composed of medium-sized cells with round nuclei and pale cytoplasm, featuring epitheliotropism to the adjacent

mucosa and lacking the inflammation and necrosis characteristic of EATL. MEITL occurs worldwide, but is the main form of primary intestinal T-cell lymphoma in Asia.^{163,179,180} The disease occurs in older adults, with a male predominance.

Patients may have non-specific symptomatology, such as abdominal pain and diarrhoea, or present with perforation, obstruction, abdominal masses, bleeding, or ascites. MEITL usually involves the jejunum, and less commonly the ileum or duodenum, sometimes with concurrent colonic lesion(s). Presentation in the colon or stomach is rare. Dissemination to regional lymph nodes and various distant organs may occur. The bone marrow is rarely involved (5%).^{180–183} The prognosis is universally poor, despite aggressive treatment, and the median overall survival is 7–14.8 months.^{179,180}

Pathological features

MEITL (Figure 12) usually presents as an ulcerated, sometimes bulky, mass. The tumour comprises monotonous, small to medium-sized lymphoid cells with pale cytoplasm, dispersed chromatin, and inconspicuous nucleoli. Some cases show some pleomorphism but, unlike in EATL, there is no prominent inflammatory infiltrate, and necrosis is limited to the surface. The peritumoral mucosa shows prominent epitheliotropism and lesser involvement of the submucosa and muscularis propria. The distant mucosa may contain patchy foci with increased IEL without villous atrophy.^{179,181,183,184} Nevertheless, rare reports of cases with concomitant CD challenge the sporadic nature of the neoplasm.¹⁸⁵

Immunohistochemically, the tumour cells are typically CD2+, CD3+, CD7+, CD4–, and CD5–.^{163,176,179,181,183} Most cases are positive for CD8, CD56, and TIA1. Granzyme B is detected in two-thirds of the cases. Aberrant expression of CD20 or other B-cell antigens occurs in 20% of the cases, and CD30 is mostly negative. Either TCR $\alpha\beta$ or TCR $\gamma\delta$ is usually expressed, whereas a small subset are TCR-silent.^{179–181,186,187} *MATK* expression has been reported as a characteristic marker in the majority of the cases.^{179,188} A recent study identified spleen tyrosine kinase (*SYK*) as a distinctive marker for MEITL (95% versus 0% in EATL), pointing to a role of enhanced TCR signalling in MEITL.¹⁸⁶ *EBER* expression may be seen in scattered B cells, but is consistently absent in the neoplastic T cells.

Molecular and genetic features

The majority of cases show monoclonal rearrangements of the TR genes.^{179,180,189} Genomic copy

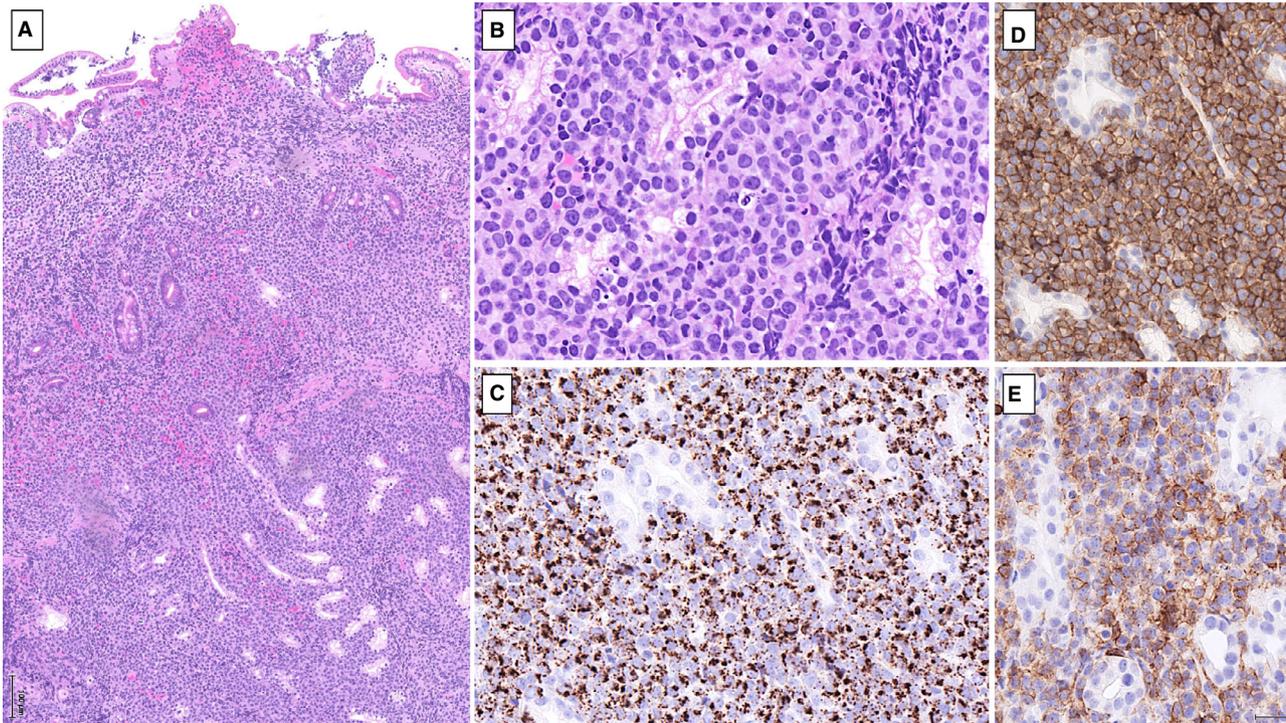


Figure 12. Monomorphic epitheliotropic intestinal T-cell lymphoma involving the duodenum. A, A dense lymphoma infiltrate obliterating the mucosa and submucosa [haematoxylin and eosin (H&E)]. B, Medium-sized cells densely infiltrating the lamina propria and showing epitheliotropism to Brunner's glands (H&E). C, Strong TIA1 expression. D, Diffuse positivity for CD56. E, Heterogeneous CD8 expression.

number alterations in common with EATL include gains of chromosomes 9q, 1q, and 7q.^{158,172,184} Alterations of chromosome 8, i.e. loss or gain of 8q, which includes *MYC*, are significantly more frequent in MEITL than in EATL.^{172,179} A characteristic feature of MEITL consists of *SETD2*-disruptive mutations or deletions, which are present in >90% of the cases.¹⁵⁹ *SETD2* encodes a lysine methyltransferase responsible for trimethylation of lysine 36 in histone H3. Immunohistochemically, *SETD2*-mutated cases have undetectable or reduced *SETD2* expression, with concomitant low expression of histone H3 trimethylated on lysine 36.¹⁵⁹ Mice with *SETD2* loss showed expansion of $\gamma\delta$ T cells, suggesting novel roles of the gene in T-cell development and an early event in lymphomagenesis.¹⁵⁸ Inactivation of *SETD2* has been demonstrated in many different tumour types, and seems to play a role in both disease initiation and disease progression.¹⁹⁰ Other genes mutated in MEITLs and related to epigenetics include the histone acetyltransferase gene *CREBBP* (26%) and *EP300*, *EZH2*, and *ARID1*, which are frequently mutated in B-cell lymphomas, whereas other genes that are frequently mutated in peripheral T-cell lymphomas (PTCLs),

such as *TET2*, *DNMT3A*, and *IDH1/2*, are usually wild-type in MEITLs.¹⁵⁹

Mutations activating the JAK–STAT pathway (especially in *STAT5B*, *JAK3*, and *SH2B3*) are present in a large proportion of the cases. Mutually exclusive alterations affecting the MAPK pathway (*BRAF*, *KRAS*, *NRAS*, and *TP53*) are observed more frequently than in EATL, collectively in ~80% of the cases.^{159,176} Mutations of *GNAI2*, which is a gene encoding a subunit of guanine nucleotide-binding protein, have been reported in 21% of MEITLs.¹⁹¹

Whole transcriptome sequencing analysis showed that genes overexpressed in MEITL as compared with EATL include *FASLG*, *SYK*, *TGBR1*, and *NCAM1* (consistent with CD56 expression).¹⁵⁸ Furthermore, enrichment for an NK-like cytotoxic signature, a known function of intraepithelial lymphocytes, was detected in MEITL.¹⁹²

Differential diagnosis

The features of MEITL are usually sufficiently distinctive from those of EATL. Even if an increase in IEL may be seen in the mucosa distant from MEITL, villous atrophy is, in principle, absent. Expression of

CD56 (and CD8) may suggest a diagnosis of ENKTCL (Figure 13), but MEITL is EBV-. In some cases, expression of B-cell markers may be confusing, and lead to consideration of a B-cell lymphoma.

Indolent T/NK-cell entities

INDOLENT T-CELL LYMPHOPROLIFERATIVE DISORDER (ITLPD) OF THE GI TRACT

ITLPD of the GI tract is a new provisional entity defined as a clonal T-cell lymphoproliferation involving the GI mucosa, usually following a chronic and indolent course.⁷ ITLPD can occur at any age, but it usually occurs in middle-aged adults, with a slight male predominance (1.5:1). Symptoms include diarrhoea, vomiting, bloating, and abdominal pain. Some patients have been misdiagnosed as having RCD, and others have a history of inflammatory bowel disease, autoimmunity, or infection.^{161,193,194} Mucosal involvement is frequently multifocal, with a predilection for the small bowel and colon rather than the stomach. Mesenteric lymph nodes may be enlarged. Isolated cases of progression to other sites have been reported.^{161,193–197} Most patients are alive with persistent disease after several years of follow-up. Complete remission has been

reported in two cases,^{161,198} and death from disease progression has been reported at 10–27 years after diagnosis in seven patients.^{194,196,199–201}

Pathological features

Endoscopy may show nodules, mucosal polyps, fissures, and erosions. Some cases have no mucosal anomalies. Histologically, ITLPD features a non-destructive proliferation of small, monomorphic lymphocytes, which may infiltrate the muscularis mucosae or submucosa, and is associated with crypt hyperplasia. Mitoses and apoptoses are both inconspicuous; vascular invasion and necrosis are absent. Villous atrophy is infrequent, but IEL may be encountered. Scattered granulomas, lymphoid follicles or admixed eosinophils may be seen. Transformed cases comprise atypical cells and resemble PTCL.

Immunohistochemically, ITLPD is positive for CD3, CD2, and TCR β F1.^{161,194,201} Some cases show down-regulation or loss of CD5 and/or CD7 expression. Most reported cases are CD4+, and less frequently CD8+, but double-negative (CD4- CD8-) or double-positive (CD4+ CD8+) immunophenotypes have been described. They are negative for T follicular helper-cell markers. A recent study investigating the cell of origin found that the CD4+ and double-positive cases

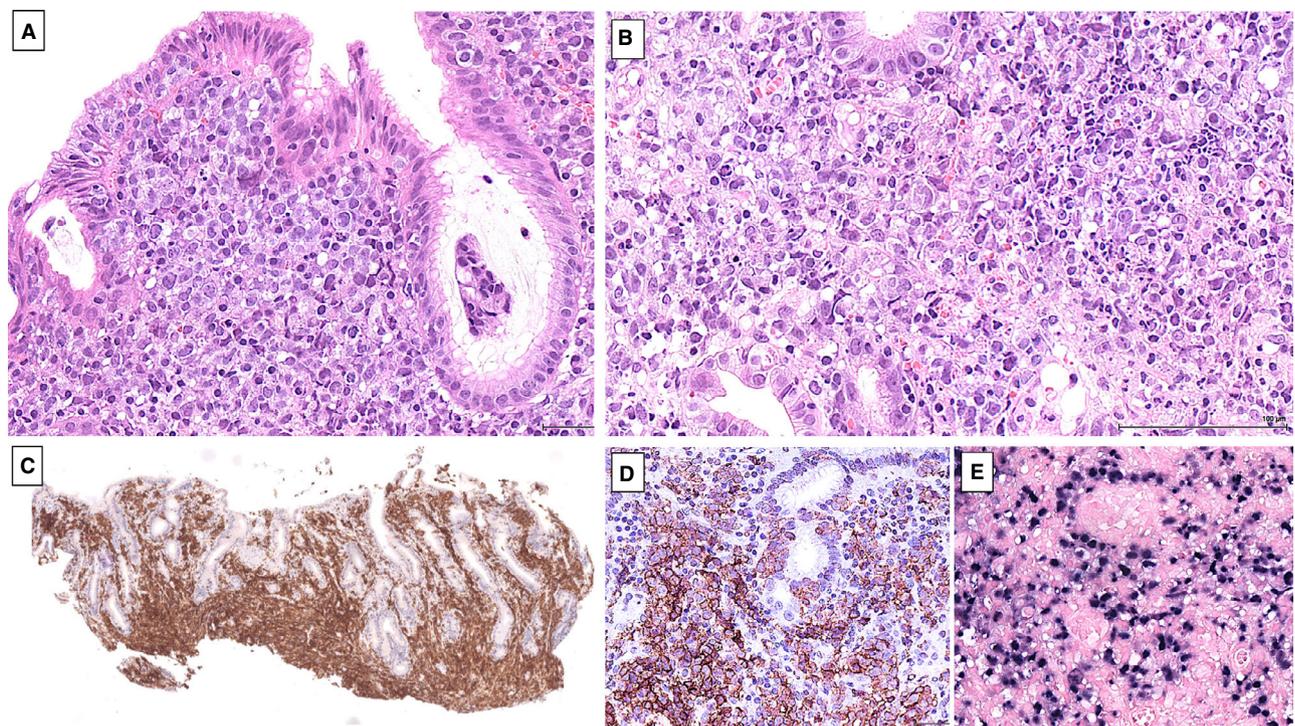


Figure 13. Extranodal natural killer/T-cell lymphoma, presenting in the stomach. A,B, Diffuse mucosal infiltrate comprising pleomorphic medium-sized to large cells (haematoxylin and eosin); note some epitheliotropism (A) and focal necrosis (B). C, Diffuse CD3 expression. D, Positivity for T-cell receptor- δ . E, Positivity for Epstein-Barr virus by *in-situ* hybridisation.

featured Th1 (T-bet+), Th2 (GATA3+) or hybrid Th1/Th2 (T-bet+ GATA3+) profiles, whereas the majority of CD8+ cases and the double-negative cases showed a Th2-polarised (GATA3+) phenotype.¹⁹⁴ CD8+ cases express TIA1, but are negative for other cytotoxic markers. CD103 may be expressed, CD56 is usually negative, and there is no association with EBV. The Ki67 proliferation index is typically very low (<5%). In one case, aberrant expression of CD20 was observed. Transformed cases may express MUM1/IRF4, CD30, CD25, perforin, and granzyme B.

Molecular genetics

Genetic data on ITLPD are scarce, but indicate a burden of genetic aberrations lower than that in EATL/MEITL, and suggest a different pathogenesis for CD4+ and CD8+ cases.^{161,194,201} A study focused mostly on CD8+ ITLPD did not find phospho-STAT3 expression or *STAT3* mutations.¹⁶¹ A *STAT3-JAK2* fusion was reported in four of five cases of CD4+ ITLPD by Sharma *et al.*,²⁰¹ but a lower prevalence was found in subsequent studies, and the fusion has not been identified in CD8+, CD4+ CD8+ or CD4⁻ CD8⁻ cases.¹⁹⁴ Cases harbouring the *STAT3-JAK2* fusion show phosphorylation of STAT5, and

might be sensitive to JAK inhibitors.^{201,202} *STAT3* mutations and *SOCS1* deletion are other recurrent alterations found essentially in CD4+ cases.^{161,194} Other genetic aberrations include loss-of-function mutations in epigenetic modifier genes (*TET2*, *DNMT3A*, and *KMT2D*) and structural alterations of *IL2* in CD8+ cases.¹⁹⁴

Differential diagnosis

ITLPD should be distinguished from inflammatory disorders, and from primary intestinal lymphomas. This distinction is particularly important, because the natural history is completely different, and ITLPDs do not either require or respond to chemotherapy. Clues to the correct diagnosis include the superficial nature of the lesions; the absence of mass formation and/or a destructive growth pattern; the bland cytology; and, the low proliferation index.

NK-CELL ENTEROPATHY (NKCE)/LYMPHOMATOID GASTROPATHY

NKCE was introduced in 2011 to designate indolent GI mucosal lymphoproliferations derived from NK cells, with a benign course and no clinicopathological

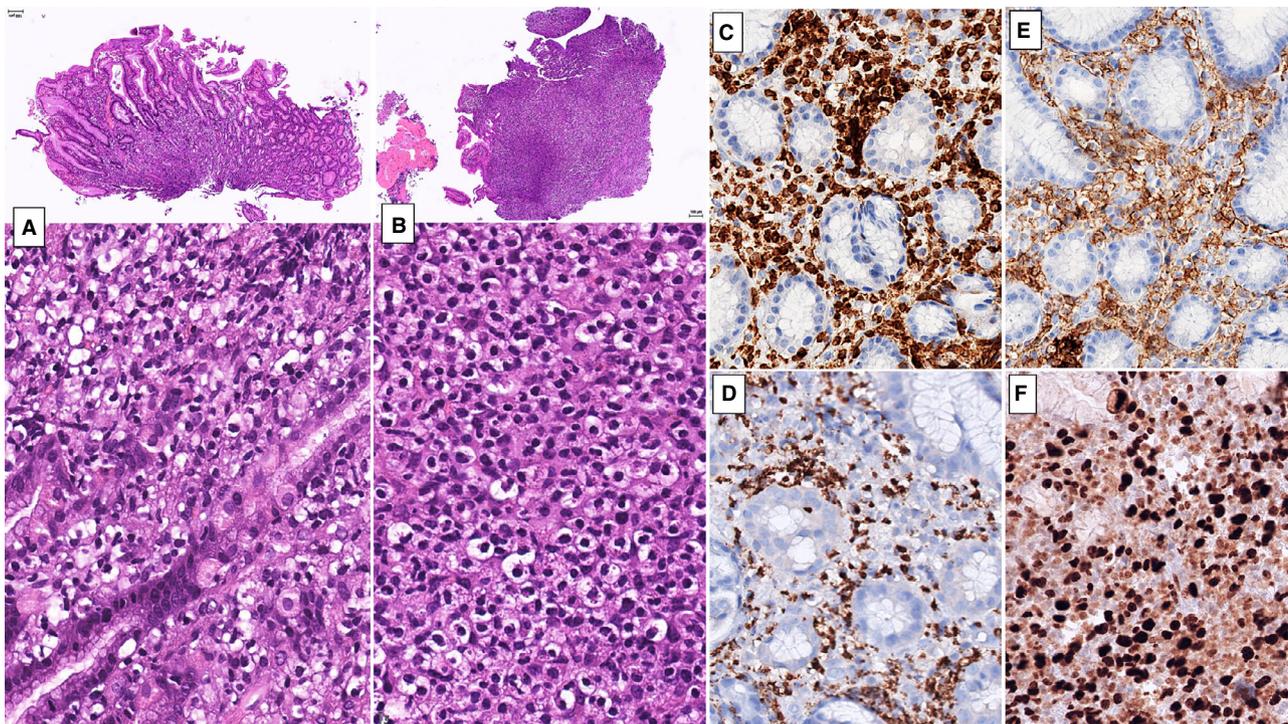


Figure 14. Natural killer-cell enteropathy involving the stomach (lymphomatoid gastropathy). A–D, Morphological features consisting of a mucosal infiltrate between the glands or partially destructive (C,D), composed of medium-sized cells with clear cytoplasm (B,D) (haematoxylin and eosin). E, CD3 immunopositivity. F, Perforin expression. G, CD56 expression. H, The Ki67 proliferation index was high in this case. Note that, on next-generation sequencing analysis, this case had a small in-frame hotspot deletion in *JAK3*.

evidence to substantiate NK-cell lymphoma.²⁰³ The disorder was first described in the stomach, and has also been reported as 'lymphomatoid gastropathy'.^{204–206} NKCE is a rare disease, with <50 cases documented so far (reviewed in Dargent *et al.*; see references therein).^{178,203–209} Most cases occurred in middle-aged to older individuals, who were either asymptomatic or presented with mild and rather non-specific GI symptoms. The majority of the cases occurred in the stomach, duodenum, or several upper GI sites, or involved both the upper and lower GI mucosa. Several gastric cases had concomitant *H. pylori* infection. The clinical course entails spontaneous resolution or persistence of the lesions for up to several years in some patients, despite various types of therapy. Unlike IITLPD of the GI tract, it has not yet been shown to progress to a more aggressive disease or cause nodal involvement.

At endoscopy, the altered mucosa often consists of erythematous, flat or polypoid lesions, superficial erosions, or ulcers. Histologically (Figure 14), NKCE features an atypical diffuse lymphoid infiltrate composed of medium-sized to large cells, with moderate clear or slightly eosinophilic cytoplasm, fine nuclear chromatin, and inconspicuous nucleoli. The infiltrate expands the lamina propria, with occasional epitheliotropism and glandular destruction, but lacks angiocentricity and necrosis. The atypical cells feature a CD2^{+/-} CD3⁺ CD4⁻ CD5⁻ CD7⁺ CD8^{-/+} CD56⁺ NK-cell immunophenotype, with an activated cytotoxic profile. The Ki67 proliferation index is variable, and is sometimes elevated.^{203,205–208} The cells in NKCE are EBV⁻, which is a major feature distinguishing it from ENKTCL.

All cases lack clonal TR gene rearrangements, consistent with an NK-lineage derivation. In a recent study using a large haematology-oriented NGS panel, a somatic *JAK3* mutation consisting of a small in-frame deletion in exon 12 was identified in three of 10 NKCE cases.²⁰⁷ Other non-recurrent mutations involving *PTPRS*, *AURKB*, *AXL*, *ERBB4*, *IGF1R*, *PIK3CB*, *CUL3*, *CHEK2*, *RUNX1T1*, *CIC*, *SMARCB1* and *SETD5* were found in other cases.²⁰⁷ These findings support the neoplastic nature of the disorder, and may suggest potential therapeutic targets in some patients.²⁰⁷

Conclusion

A variety of lymphomas occur in the upper GI tract, and they are primarily diagnosed on endoscopic biopsies, which pose specific challenges, owing to limited sampling. The diagnosis of lymphoid infiltrates in

these tissues primarily relies on careful morphological assessment complemented by immunophenotypic studies. Clonality assays, FISH studies and additional molecular genetic tests are complementary tools that are becoming increasingly useful or even mandatory to provide complete characterisation and accurate categorisation of the tumours. Importantly, endoscopic and clinical features are essential for providing a correct interpretation of the rare T-cell proliferations encountered in the stomach or small intestine.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Data sharing

Data sharing is not applicable to this article, as no new data were created or analysed in this study.

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