Review

Gastrointestinal lymphoproliferative lesions: a practical diagnostic approach

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Summary

The gastrointestinal (GI) tract is the primary site of lymphoproliferative lesions, spanning from reactive lymphoid hyperplasia to overt lymphoma. The diagnosis of these diseases is challenging and an integrated approach based on clinical, morphological, immunohistochemical and molecular data is needed. To reach to confident conclusions, a stepwise approach is highly recommended. Histological evaluation should first assess the benign versus neoplastic nature of a given lymphoid infiltrate. Morphological and phenotypic analyses should then be applied to get to a definite diagnosis. This review addresses the key histological features and diagnostic workup of the most common GI non-Hodgkin lymphomas (NHLs). Differential diagnoses and possible pitfalls are discussed by considering distinct groups of lesions (i.e. small to medium B-cell NHLs; medium to large B-cell NHLs; T-cell NHLs; and mimickers of Hodgkin lymphoma). The key clinical and epidemiological features of each entity are also described.

Key words: lymphoma, gastrointestinal lymphoma, Hodgkin lymphoma, B-cell lymphoma, T-cell lymphoma

Introduction and clinical relevance

The gastrointestinal (GI) tract plays several immunologic functions, including fine-tuning the intestinal microbiome, mediating tolerance toward food antigens and mounting immune responses against enteric pathogens 1. Such functions rely on dedicated anatomical structures, widely spread along the stomach, the small and large bowel (i.e. Peyer’s patches and rectal tonsil) 1,2. The physiologic and/or neoplastic expansion of such structures gives rise to a broad spectrum of lesions, spanning from benign lymphoid hyperplasia to malignant B and T cell lymphomas 3. Gastrointestinal lymphoid proliferations are commonly found in the surgical pathology practice and their diagnosis can be challenging even for trained pathologists. This is due to their disguising and overlapping histological features, the small amount of diagnostic material and sampling artifacts. Despite such limitations, histology is the gold standard for the diagnosis of GI lymphoproliferative disorders (LPDs) and guides the management of patients 4. For these reasons, when dealing with lymphoid infiltrates in the GI tract, every effort should be taken to get to a diagnosis as accurate and informative as possible. This review will discuss the histological features of GI LPDs and non-Hodgkin lymphomas (NHLs), specifically addressing the key diag-
nostic features and pitfalls of each entity. A practical approach will be followed, by grouping GI LPDs into major diagnostic categories, discussing their general features and considering their differential diagnosis. This work is intended to support the surgical pathology practice. For a detailed discussion of the clinical and pathophysiological features of each entity, the reader is referred to the many excellent reviews published on this topic 5-10.

The diagnosis of GI LPDs: benign versus malignant lesions

The first most compelling issue concerning GI LPDs is to define whether they are benign or malignant in nature. Clues favoring a diagnosis of lymphoma over reactive lymphoid hyperplasia include: (i) tissue effacement by confluent sheets of lymphoid cells (even with polyp formation), (ii) infiltration and disruption of glandular units (i.e. "lymphoepithelial lesions"; LELs), (iii) atypical follicles, follicular colonization or expanded mantle zones, (iv) the monomorphic composition of the lymphoid infiltrate, and (v) the documentation of cytologically or phenotypically atypical elements, singly or in aggregate. None of these findings is pathognomonic of lymphoma per se, nor all lymphomas disclose each of these features. It is rather the integration of multiple parameters that leads to a correct diagnosis (Fig. 1).

Molecular biology may also support the differential diagnosis between reactive hyperplasia and lymphoma, the former being associated with polyclonal rearrangements of the immunoglobulin and T cell receptor genes, the latter showing monoclonal gene patterns. Exceptions nonetheless exist to this rule. In fact, antigen-driven monoclonal populations are commonly found in inflammatory, infectious or autoimmune responses 11 and polyclonal patterns may characterize highly mutant NHLs, as a result of limited primer annealing and poor amplification of the monoclonal sequences 12. Thus, the finding of a monoclonal peak does not necessarily imply a diagnosis of lymphoma and the results of molecular biology should always be integrated with the clinical-pathological findings. Despite extensive phenotypic and molecular characterization, in a minority of cases a definite diagnosis cannot be made. In such instances, the degree of uncertainty should be stated in the pathology report and provisional statements of "atypical lymphoid hyperplasia/infiltrates," "lymphoid infiltrate of uncertain potential/significance," or "lymphoid infiltrate suspicious but not certain for lymphoma" may be proposed 13. The management of such lesions will depend on the clinical picture, the endoscopic findings and the severity of histological atypia.

Primary GI lymphomas versus secondary involvement by systemic disease

Once the neoplastic nature of a lymphoid infiltrate has been established, another important issue is defining its origin. The GI tract can indeed host both primary NHLs and secondary localizations of systemic disease. The clinical criteria distinguishing these two groups of neoplasms were first proposed by Dawson in 1961. A NHL is considered of primary GI origin if, at presentation: (i) peripheral and/or mediastinal lymphadenopathies are lacking; (ii) blood cell counts are normal; (iii) the lesion is predominantly localized within the GI tract and the only affected lymph nodes are adjacent to such lesion; and (iv) the liver and spleen are spared 14.

By applying Dawson’s criteria, primary GI NHLs account for about 30-40% of all extra-nodal lymphomas and for 1-4% of GI malignancies 15. Secondary GI involvement is by far more frequent, being reported in 5-20% of NHLs 16. The anatomic distribution of GI NHLs varies across geographical areas: the stomach is primarily involved in Western countries 17, while the small bowel is mostly affected in Middle East regions 18. In all, gastric and small intestinal NHLs account for 80-85% of all GI cases.

Primary GI NHLs are mostly of B-cell lineage (90% of cases), spanning from indolent to very aggressive neoplasms. Peripheral T-cell lymphomas are less common and typically associated with poor prognosis. In contrast to patients with known classic Hodgkin lymphoma (cHL), great caution is required before making a diagnosis of primary cHL in extranodal sites (stage IE is extremely rare: 0.25-1% of cases). Mimickers of cHL are well documented and will be addressed in a separate section of this review. Finally, the GI tract is frequently site of post-transplant LPDs (PTLDs). These lesions are frequently driven by EBV infection and include benign, non-destructive lymphoid or plasma cell proliferations (i.e. follicular hyperplasia, plasma cell hyperplasia, infectious mononucleosis-like LPDs), polymorphic and monomorphic B and T/NK-cell PTLDs (Tab. I).

**Non-Hodgkin B cell lymphomas of the GI tract**

For diagnostic purposes, B-cell NHLs can be grouped in two broad disease categories: (i) tumors consisting of small to medium size B-cells; and (ii) tumors consisting of medium to large size B-cells. The first group encompasses extra-nodal marginal zone lymphoma
Figure 1. Differential diagnosis between benign and malignant GI lymphoid proliferations. The table summarizes the key morphological features favoring a diagnosis of neoplastic over reactive lymphoid infiltrate. (A) Reactive infiltrates are non-destructive and encompass well-demarcated lymphoid nodules (left figure); non-Hodgkin lymphomas are instead characterized by dense infiltrates occupying the entire lamina propria (right figure). (B) Reactive infiltrates are polymorphic and include variable numbers of small lymphocytes, granulocytes, histiocytes and plasma cells (left figure). Non-Hodgkin lymphomas mostly consist of monomorphic, atypical lymphocytes (right figure). (C) In reactive conditions, intra-glandular cells are mainly granulocytes and/or scattered, small lymphocytes (left figure); in non-Hodgkin lymphomas, native glands are infiltrated/effaced by neoplastic lymphocytes (“lymphoepithelial lesions”) (right figure; arrow). (H&E stain; original magnification, 10x and 20x).

| Gastrointestinal Lymphoid Infiltrates | Atypical findings requiring further histological evaluation |
|--------------------------------------|--------------------------------------------------|
| Benign features | Malignant features |
| 1. Dense monotonous population of lymphocytes | |  |
| 2. Striking intraepithelial lymphocytosis and/or lymphoepithelial lesions | |  |
| 3. Gland destruction and/or lamina propria effacement | |  |
| 4. Atypical follicles (lack of polarization and tingible body macrophages; absent/poorly formed mantle zones; monotonous cytology) | |  |
| 5. Expanded mantle zones | |  |
| 6. Multiple lymphoid polyps | |  |
| 7. Any population of highly atypical lymphoid cells (singly or in aggregate) | |  |
(ENMZL), mantle cell lymphoma (MCL), follicular lymphoma (FL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The second group mainly includes Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBL) not otherwise specified (HGBL NOS), HGBL with MYC and/or BCL2 rearrangements (i.e. double/triple-hit lymphoma, DHL/THL), large B-cell lymphoma (LBCL) with IRF4 rearrangements, and plasmablastic lymphoma (PBL).

**SMALL TO MEDIUM SIZE B-CELL NHLs**

This group includes entities primarily arising in the GI tract or secondarily spreading to this site. A stepwise immunohistochemical approach supporting their diagnosis is proposed in Figure 2.

**Extra-nodal marginal zone lymphomas (ENZML)** are indolent B-cell NHLs, mostly arising in the mucosa-associated lymphoid tissue (MALT) of the stomach and small bowel. A consistent number of cases develop after chronic antigen stimulation by *H. pylori* (gastric ENZML) or *C. jejuni* (small intestinal ENMZL) infection 5. Alpha heavy chain disease (also known as ‘immunoproliferative small intestinal disease; IPSID) is a clinical-pathological variant of small bowel ENMZL, characterized by monoclonal alpha heavy chain secretion with no immunoglobulin light chains. IPSID affects adolescents and young adults of Mediterranean origin and presents with malabsorption, diarrhea, fever, and weight loss 16.

Histologically, ENMZLs disclose sheets of B-cells, expanding the lamina propria with possible extension to the muscolaris mucosae and submucosa. Reactive germinal centers (GCs) are scattered throughout the tumor, often with features of GC colonization (i.e. effacement of GCs and disruption of follicular dendritic cell [FDC] meshworks). Neoplastic cells also infiltrate the surrounding glands, producing LELs (Fig. 3A). These are defined as intra-epithelial aggregates of ≥3 marginal zone cells that disrupt the gland architecture. Epithelial cells of LELs frequently undergo eosinophilic degeneration (i.e. oxyphilic change). The neoplastic population consists of small to medium-sized mature

**Table I. Classification of GI lymphomas**

| Histologic subtype | Predilection site |
|--------------------|-------------------|
| **B Cell Origin (90% of cases)** | |
| Extramedullary marginal zone lymphoma, MALT type | Stomach, small intestine |
| Alpha heavy chain disease (IPSID) | Jejunum, ileum |
| Diffuse large B cell lymphoma, NOS | Stomach, ileocecal |
| Burkitt lymphoma | Ileocecal, stomach, small intestine |
| Plasmablastic lymphoma | Anorectum |
| Mantle cell lymphoma | Any sites |
| Follicular lymphoma | Duodenum, large intestine |
| Posttransplant lymphoproliferative disorder | Any sites |
| **T/NK cell origin (5-9% of cases)** | |
| Enteropathy associates T cell lymphoma (EALT) | Small intestine |
| Monomorphic epitheliotropic intestinal T cell lymphoma (MEILT) | Small intestine |
| NK/T-cell lymphoma, nasal type | Small intestine, large intestine |
| Peripheret T cell lymphoma, NOS | Large intestine, small intestine |
| Indolent T/NK lymphoproliferative disorder | Small intestine, large intestine |
| Posttransplant lymphoproliferative disorders | Any sites |
| **Classical Hodgkin Lymphoma (<5% of cases)** | Rectum |

**Figure 2.** Immunohistochemical algorithm for the diagnosis of small to medium-sized B-cell NHLs. Notes: *CD10-negative follicular lymphomas can be encountered; ** A similar phenotype is shared by lymphoplasmacytic lymphoma, which is not included in this review due to its exceptional occurrence in the GI tract.
B cells with variable amounts of plasma cells and scattered large B blasts. The mature cell component has variable cytological features, spanning from marginal zone to monocytoid, centrocyte-like, small-cell and plasmacytic morphology. Marginal zone cells are medium-sized, have pale cytoplasm, slightly irregular nuclear contours, moderately dispersed chromatin and inconspicuous nucleoli. Monocytoid cells have larger amounts of paler cytoplasm, while centrocyte-like cells are small to medium-sized with irregular/cleaved

**Figure 3.** Histological features of ENMZL and primary duodenal FL. (A) ENMZL presents as a dense infiltrate of small to medium B-cells, with frequent LELs (H&E, high power picture). Phenotypically, CD10 and Bcl6 are negative, while Bcl2 is diffusely positive. MNDA expression supports the diagnosis, while the Ki67 proliferation index is low. (B) Primary duodenal FL presents as superficially located lymphoid nodules with villous widening and lamina propria expansion. The neoplastic population includes numerous centrocytes with sparse centroblasts (large box, insert). CD20, CD10, Bcl6 and Bcl2 are diffusely positive. CD21 immunostain highlights peripheral ring-shaped FDC networks, while the Ki67 index is low-to-moderate and lacks polarization. (H&E, Giemsa and immunoperoxidase stain; original magnification 7x, 20x and 80x).
nuclei and dense chromatin. Small cell morphology consists of mature B-cells with round nuclear contours and clumped chromatin, resembling SLL/CLL. Plasmacytic differentiation occurs in one third of gastric ENMZL and may include plasma cells with intra-nuclear immunoglobulin inclusion (i.e. Dutcher bodies). Such histological features are even more prominent in IPSID, where they occur together with villous widening and pseudo-atrophy. LELs are limited to residual B-cell areas.

On immunohistochemistry (IHC), ENMZLs express the pan-B cell antigen CD20 and are negative for CD10, Bcl6, CD23, Cyclin D1 and CD5. IgM are usually positive in ENMZL, while IgA heavy chains are characteristically expressed in IPSID. Positivity for IR-1A1 has been reported in subsets of cases (mostly with monocytoid morphology) and supports the diagnosis. MNDA and CD43 are also variably expressed (Fig. 3A). In case of plasma cell differentiation, light chain restriction can be documented by kappa and lambda immunostains. The diagnosis of ENMZL may prove challenging on occasion. This holds particularly true for chronic inflammatory conditions (e.g. H. pylori-related gastritis) or post-treatment assessments, in which the border between reactive lymphoid hyperplasia and ENMZL is blurred. In such instances, uncertainty should be reported through validated scoring systems, such as the Wotherspoon score (for treatment-naive cases) and GELA score (for post-treatment evaluations) (Tab. II).

The differential diagnosis of ENMZL includes a number of entities. First, ENZML must be distinguished from other small-to-medium B-cell NHLs. As marginal zone markers (e.g. MNDA and IRTA1) have only limited sensitivity or specificity, the diagnosis of ENMZL is often one of exclusion and requires thorough immunophenotyping (Fig. 2). In the pediatric population, ENMZL must also be distinguished from “atypical marginal zone hyperplasia” (AMZH). This lesion occurs in the appendix and tonsil of children and adolescents, as a consequence of unknown inflammatory triggers. Histologically, AMZH recapitulates the morphological features of ENMZL with frequent lambda-chain restriction on immunophenotyping, being nonetheless characterized by polyclonal rearrangements of the immunoglobulin genes and never progressing to locally-spread or systemic disease. When the plasmacytic differentiation is so prominent to occupy most of the tissue sample, the risk of a misdiagnosis of extramedullary plasmacytoma does exist. The clinical features and search for an associated B-cell compo-

### Table II. Scoring systems for treatment-naive and post-treatment ENMZL

| Score | Diagnosis | Histological features |
|-------|-----------|-----------------------|
| 0     | Normal mucosa | Scattered lymphocytes and plasma cells in the lamina propria; no lymphoepithelial lesions |
| 1     | Active gastritis | Inflammatory lymphoid infiltrate in the lamina propria; no lymphoepithelial lesions |
| 2     | Active gastritis with lymphoid follicles | Inflammatory lymphoid infiltrate with follicles; no lymphoepithelial lesions |
| 3     | Suspicious lymphoid infiltrate, probably reactive | Dense lymphoid infiltrate with follicles surrounded by small lymphocytes that infiltrate diffusely the lamina propria with occasional lymphoepithelial lesions |
| 4     | Suspicious lymphoid infiltrate, probably lymphoma | Dense lymphoid infiltrate with follicles surrounded by marginal zone lymphocytes that infiltrate diffusely the lamina propria and the glandular epithelium with focal lymphoepithelial lesions |
| 5     | ENMZL | Dense lymphoid infiltrate effacing gastric mucosa with diffuse lymphoepithelial lesions |

| Score | Diagnosis | Histological features |
|-------|-----------|-----------------------|
| CR    | Complete histological remission | Scattered lymphocytes and plasma cells in the lamina propria; no lymphoepithelial lesions; empty or fibrotic lamina propria |
| pMRD  | Probable minimal residual disease | Lymphoid aggregates in the lamina propria, muscularis mucosa or submucosa; no lymphoepithelial lesions; empty or fibrotic lamina propria |
| rRD   | Responding residual disease | Dense periglandular lymphoid infiltrate with/without lymphoepithelial lesions; focal empty or fibrotic lamina propria |
| NC    | No change (persistent ENMZL) | Dense lymphoid infiltrate effacing gastric mucosa, mostly with lymphoepithelial lesions |

Notes: *modified from ref. 20; **modified from ref. 21. Note that molecular biology tests are not included in either scoring system. Even in post-treatment settings, monoclonal peaks per se cannot be assumed as evidence of residual disease. Nonetheless, the documentation of identical peaks in pre- and post-treatment samples is highly suggestive of pMRD/rRd.
ment in subsequent sections usually allows for a reliable diagnosis. Finally, ENMNL with increased large cell fractions must be distinguished from DLBCL. By definition, any sheet-like proliferation of large cells (i.e., aggregates >20 large cells and/or areas with >10% of cohesive large cells) excludes ENMNL and prompts a diagnosis of DLBCL. If both high and low-grade areas are present, a diagnosis of DLBCL with accompanying ENMNL is advised and the percentage amount of each component should be reported 3.

In the GI tract, follicular lymphoma (FL) occurs as either primary disease or (more frequently) as secondary involvement by systemic cases 23. Primary FL of the GI tract usually arises in the duodenum, with possible synchronous seeding to the jejunum and ileum 23,24. Primary-duodenal FL is a disease variant with possible synchronous seeding to the jejunum and ileum. It affects middle-aged to elderly patients and presents as nodal/extra-nodal disease, with frequent GI involvement (15-30% of cases). In the large bowel, it may occasionally appear as multiple polypoid lesions, known as lymphomatous polyposis. Histologically, classic MCL consists of diffuse, vaguely nodular or (rarely) perifollicular lymphoid infiltrates localized in the lamina propria and submucosa. Unlike ENMNL, native glands are spared, LELs are rarely found and the infiltrate is more deeply seated with limited effacement of the superficial lamina propria. The neoplastic infiltrate consists of small to medium-sized cells with irregular nuclear contours (Fig. 4A). Blastoid, pleomorphic and (more rarely) small or marginal zone cell variants are reported. The immunophenotype of MCL is highly characteristic, with strong positivity for CD5, Cyclin D1, and SOX11. Negativity for one of such markers is nonetheless possible and correlates with specific clinical-prognostic features. In particular, CD5-negative MCLs typically present as extra-nodal disease (also in the GI tract) and bear more favorable prognosis (Fig. 4A) 25. CD10, Bcl6 and CD23 are usually (yet not invariably) negative 3,26. The proliferation index varies and should always be assessed, as values >30% correlate with worse prognosis 27. Over 95% of MCLs bear the t(11;14)(q13:32), which juxtaposes the IGH with the Cyclin D1-coding CCND1 gene. In selected cases, Fluorescence In Situ Hybridization (FISH) analysis for this translocation supports the diagnosis 3 (Fig. 4A). Small subsets of Cyclin D1-positive cells properly located in the mantle zone of otherwise reactive follicles can be discovered in inflammatory infiltrates of patients with Cyclin D1-positive monoclonal B-cell lymphocytosis. In the absence of manifest lymphoma, this picture should not be diagnosed as clinically overt MCL 28.

The major differential diagnosis of MCL is chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). This is an indolent B-cell neoplasm, usually affecting elderly people with peripheral blood and/or nodal involvement 3. Despite CLL/SLL never occurs as primary GI lymphoma, subtle interstitial and intravascular infiltrates may be encountered in the stomach, bowel and appendix as a result of systemi-
ic dissemination. This is also true for specimens removed for complicated diverticulitis or carcinoma: in this setting, CLL/SLL cells are likely recruited by the inflammatory milieu and appear as multiple, discrete and monotonous lymphoid nodules (Pizzi M, Bellan A; unpublished data) (Fig. 4B). Histologically, CLL/SLL is...
characterized by an interstitial, diffuse or vaguely nodular infiltrate, made of small lymphocytes with round nuclei and dark chromatin. Paler pseudo-follicles enriched in medium-sized nucleolated paraimmunoblasts are commonly seen. On IHC, CLL/SLL is positive for CD20, CD23 and CD5, but (unlike MCL) it stains negative for Cyclin D1 and SOX11 \(^3\) (Fig. 4B). CD200 and LEF1 are also usually positive \(^29\).

**Medium to large size B-cell NHLs**

This group includes a variety of clinically aggressive entities (BL, DLBCL, HGBL NOS, DHL/THL, LBCL with IRF4 rearrangements and PBL), presenting with bulky lesions, intestinal occlusion, GI bleeding and/or perforation. They occur in immunocompetent as well as immunocompromised patients \(^3\).

**Burkitt lymphoma** (BL) is an aggressive NHL, typically occurring in extra-nodal sites or as leukemic disease. Three epidemiological variants are described: (i) endemic BL, (ii) sporadic BL, and (iii) immunodeficiency-associated BL. Endemic BL occurs in equatorial Africa, affects children and young adolescents and presents as bulky lesions of the jaws and facial bones. Sporadic and immunodeficiency (mostly HIV)-associated cases are reported throughout the world, have a broad age distribution and account for about 1-2% of adult lymphomas in Western countries \(^30\). Immunodeficiency-associated BL usually presents with nodal or leukemic disease, while sporadic BL mostly occurs in the GI tract and abdominal cavity \(^3\).

The histological and cytogenetic features of BL are highly characteristic. In prototypical cases, the tumor shows a diffuse, cohesive and monotonous proliferation of medium-sized lymphocytes with squared-off borders, round nuclei, finely clumped chromatin, inconspicuous nucleoli and scant basophilic cytoplasm with lipid vacuoles. The latter are more readily appreciable in cytological preparations or by adipophilin immunostain \(^31\). Rare (usually immunodeficiency-related) cases disclose a more pleomorphic cytology and/or plasmacytoid differentiation. Irrespective of the morphological variants, tingible body macrophages are scattered throughout the lesion, imparting the classic “starry sky” pattern (Fig. 5A). Phenotypically, tumor cells are almost invariably positive for CD10 and Bcl6 and negative (or only weakly positive) for Bcl2. The Ki-67 proliferation index is equal (or close) to 100%. Myc protein is diffusely and strongly expressed in > 80% of neoplastic cells. Negative staining may nonetheless occur in a minority of cases and does not prevent the diagnosis, if all other BL features are present \(^30\). CD38, MUM1, CD43 and SOX11 expression is variable, while TdT, Cyclin D1, CD23, and CD5 are consistently negative (Fig. 5A). Positivity for EBER in situ hybridization is documented in most endemic and immunodeficiency-associated BLs, while it is less common in sporadic cases. Most BLs bear translocations juxtaposing MYC to one of the immunoglobulin genes (IGH, IGK and/or IGL); the resulting t(8;14)(q24;q32) or alternative t(2;8) (p12;q24) and t(8;22)(q24;q11) play a key pathogenic role and help to confirm the diagnosis (Figure 5A).

By definition, BCL6 and/or BCL2 rearrangements are not present \(^3\). Of note, about 10% of otherwise classical BLs lacks MYC rearrangements \(^33,34\), indicating that alternative pathogenic mechanisms may occur. In such cases, strict clinical, morphological and phenotypic criteria should be applied to rule out possible BL mimickers.

The diagnosis of BL is usually straightforward. Small or poorly representative biopsy samples may nonetheless pose the differential diagnosis with other high-grade B-cell NHLs with medium size or blastoid morphology (i.e. blastoid MCL, B-cell lymphoblastic leukemia/lymphoma [B-ALL], HGBL or, rarely, DLBCL, and Burkitt-like lymphoma with 11q aberration). Negativity for CD5 and Cyclin D1 excludes blastoid MCL, while negativity for TdT (and other immaturity markers, such as CD34) argues against B-ALL \(^35\). HGBLs (NOS or DHL/THL) and DLBCL have features that more commonly diverge from the classical morphological, phenotypic and cytogenetic presentation of BL (e.g. pleomorphic or large-sized cells, negativity for CD10 and/or Bcl6; diffuse, strong positivity for Bcl2; lack of MYC translocations; occurrence of BCL2 and/or BCL6 translocations) \(^3\). Helpful immunohistochemical algorithms have been reported in challenging cases \(^36\). Finally, Burkitt-like lymphoma with 11q aberration is a rare, aggressive B-cell NHL, mostly occurring at nodal sites in children, young adults and in the post-transplant setting. The differential diagnosis with BL relies on a greater degree of cytological pleomorphism, a vaguely nodular (or even follicular) growth pattern and on the less intense positivity for Myc protein. MYC rearrangements are typically lacking, while chromosome 11q alterations (proximal gains and telomeric losses) are present by definition (Figs. 5B, 6) \(^3,37\).

**Diffuse large B-cell lymphomas** (DLBCLs) are clinically and biologically heterogeneous neoplasms, defined by purely morphological criteria (i.e. diffuse growth pattern of large B cells). DLBCLs account for about 45-50% of all primary GI NHLs and develop as either primary disease or secondary evolution of a prior low-grade lymphoma (ENMZL; FL or CLL/SLL) or MCL \(^38\). The identification of secondary cases is based on the clinical history, disease presentation, and on the histological documentation of a clonally related (prior or coexisting) indolent component.
Figure 5. Histological features of BL and Burkitt-like lymphoma with 11q aberrations. (A) BL presents with bulky GI lesions, featuring a diffuse proliferation of monomorphic, medium-sized lymphocytes with squared-off borders and inconspicuous nucleoli. A starry sky pattern is usually present. Phenotypically, BL is positive for GC markers (CD10, Bcl6) and negative/weakly positive for Bcl2. The Ki-67 index approximates 100% and c-Myc is strongly and diffusely expressed. MYC translocations are present in >90% of cases (c-Myc box, insert; break apart probes). Tumor cells are also positive for adipophilin, a marker of deranged lipid metabolism. (B) Burkitt-like lymphoma with 11q aberrations discloses more cytological heterogeneity (H&E, insert) and weaker c-Myc expression than conventional BL. MYC translocations are not documented (c-Myc box, insert; break apart probes), while 11q aberrations (gain/loss signals at FISH) are present by definition. (H&E, Giemsa, immunoperoxidase and DAPI stain; original magnification 10x, 20x and 80x).
Despite several DLBCL variants are described, the NOS subtype is by far the most common. The tumor typically presents as a bulky, ulcerated lesion with extensive infiltration of the affected organ. Tumor cells resemble centroblasts (medium to large-sized blasts with multiple membrane-bound nucleoli), immunoblasts (large-sized blasts with a single, centrally located nucleolus) or have anaplastic morphology. Spindle or signet-ring cytology is rarely found. In the GI tract, immunoblastic morphology is by far the most frequent (Fig. 7A).

Given their biological heterogeneity, DLBCLs have highly variable phenotypes. Blast cells are strongly positive for panB-cell markers (CD20, CD19, PAX5, CD79a), though some of them may exceptionally be lacking, with variable expression of CD10, Bcl6, MUM1, Bcl2 and Myc (Fig. 7A). CD30, CD23 and CD5 can be occasionally positive, while Cyclin D1, SOX11 and TdT are consistently negative. The Ki-67 proliferation index is variable, but typically exceeds 25-30%. EBER in situ hybridization is positive in a minority of cases and is usually documented in elderly patients. These lymphomas fall within the WHO category of “EBV-positive, DLBCL NOS” and should be diagnosed as such (Fig. 7B). EBV positivity may also be documented in immunodeficiency-related cases and in the post-transplant setting.

For prognostic purposes, newly diagnosed DLBCLs should be stratified according to the putative cell of origin into germinal center-derived (GCB) or non-GCB types. In the routine practice, this is possible by applying IHC algorithms, including the Visco-Young, Choi and/or Hans algorithm. The latter is most widely used and is based on the sequential assessment of CD10, Bcl6 and MUM1 expression. All DLBCL cases should also be stained for Myc and Bcl2, as double expressor cases bear significantly worse prognosis and should be reported as such (cutoffs for Myc and Bcl2 positivity: 40% and
50% of neoplastic cells, respectively) 43 (Fig 7A). Of note, Myc/Bcl2 double expression is not a surrogate marker of MYC and BCL2 gene rearrangements, although Myc protein positivity in > 70% of the neoplastic cells is more likely sustained by MYC translocations 44. As such, in defined clinical and pathological settings, Myc and Bcl2 joint positivity should prompt FISH analyses for DHL/THL, as recently stated by a consensus paper from the Italian Hematopathology Group 45. A subset of high-grade B-cell NHLs discloses ambig-
uous features, not perfectly fitting within the BL and/or DLBCL categories. These cases (formerly known as “large B-cell lymphomas with features intermediate between DLBCL and BL”) are currently referred to as high-grade B-cell lymphomas (HGBL) and further sub-classified into: (i) HGBL NOS and (ii) HGBL with rearrangements of MYC and BCL2 and/or BCL6 (i.e. DHL/THL) 3,46. Most often, these tumors have large-cell or blastoid morphology (i.e. medium-sized blasts with finely dispersed chromat and inconspicuous nucleoli). Their phenotype is variable and the proliferation index is usually high, reflecting the heterogeneous (yet very aggressive) nature of these neoplasms. CD10, Bcl6, Bcl2 and Myc are variably expressed in such cases (yet very aggressive) nature of these neoplasms. CD10, Bcl6, Bcl2 and Myc are variably expressed in HGBL NOS, while they are typically positive in DHL/THL 3,47. TdT and Cyclin D1 are invariably negative, thus excluding a diagnosis of B-ALL and blastoid/plasmacytic MCL. By definition, DHL/THL harbor MYC translocations together with BCL2 and/or BCL6 rearrangements. Instead, HGBLs NOS are not translocated or feature rearrangements in only one of such genes.

Large B-cell lymphoma (LBCL) with IRF4 rearrangement is a recently described lymphoid neoplasm, included as a provisional entity in the revised 4th edition of the WHO Classification 3. The tumor primarily occurs in children and young adults, accounting for <1% of all high-grade B-cell NHLs. Despite the presence of IRF4, these tumors are typically positive in DHL/THL 3,47. TdT and Cyclin D1 are invariably negative, thus excluding a diagnosis of B-ALL and blastoid/plasmacytic MCL. By definition, DHL/THL harbor MYC translocations together with BCL2 and/or BCL6 rearrangements. Instead, HGBLs NOS are not translocated or feature rearrangements in only one of such genes.

Plasmablastic lymphoma (PBL) is an aggressive NHL with plasmacytic differentiation, most commonly arising in immunocompromised or elderly patients. The tumor typically develops in extra-nodal locations (mostly the oral cavity and head and neck region). Primary PBL of the GI tract accounts for about 20% of cases and occurs in the stomach, terminal ileum, large bowel, rectum and anal canal 49. In these locations, the tumor presents with large, ulcerated lesions causing abdominal pain, bleeding, diarrhea and/or constipation. Monoclonal components in the peripheral blood are only rarely documented. Histologically, PBL is characterized by sheets of large cells, spanning from immunoblasts to plasmablasts (i.e. blasts with eccentrically located nuclei, evident nucleoli and abundant cytoplasm). Immunoblast morphology frequently occurs in the oral and nasal cavity of HIV-positive patients, while plasmablastic differentiation is more characteristic of other anatomic sites. A starry sky pattern and abundant mitotic figures are common. A plasma cell component at various stages of maturation is not a feature of PBL and should prompt consideration of alternative diagnoses (e.g. anaplastic plasmacytoma/multiple myeloma). On IHC, PBL discloses sharp plasmacytic differentiation with positivity for CD38, CD138, MUM1, IgG and either kappa or lambda chains. The Ki-67 proliferation index is very high (80%). CD30 and EMA are frequently expressed, while CD79a, CD56 and c-Myc are positive in subsets of cases. CD45, CD20 and PAX5 are negative or only focally positive, thus ruling out DLBCL NOS and other high-grade B-cell NHLs. Most PBLs (75% of cases) are positive for EBER in situ hybridization (Fig. 8A). This feature and the overall clinical presentation are extremely helpful in differentiating PBL from extramedullary anaplastic plasmacytoma and multiple myeloma, which are rarely associated with EBV infection. In some instances, however, the distinction is not feasible and a descriptive diagnosis of “plasmablastic neoplasm, consisting with PBL or anaplastic plasmacytoma” is advisable 3,50. In PBL, negativity for ALK1 and HHV8 rules out other CD20-negative NHLs with plasmablastic morphology, such as ALK1-positive large B-cell lymphoma and extra-cavitary primary effusion lymphoma (Fig. 8B).

Non-Hodgkin T cell lymphomas of the GI tract

T-cell NHLs represent an absolute minority of GI lymphoid neoplasms. Despite any T-cell neoplasm may eventually involve the GI tract, some entities localize electively to the small intestine. These include: (i) enteropathy-associated T-cell lymphoma (EATL); (ii) monomorphic epitheliotropic intestinal T-cell lymphomas (MEITL); (iii) some cases of extra-nodal NK/T-cell
lymphoma (ENKTL), nasal type; (iv) rare intestinal T-cell lymphomas, NOS; and (v) the so-called ‘indolent T-cell LPDs of the GI tract’.

Enteropathy-associated T-cell lymphoma (formerly known as type 1 EATL) is a rare and very aggressive T-cell neoplasm, affecting patients with prior or concomitant history of coeliac disease (CD). It accounts for <5% of all GI NHLs and mostly occurs in Western

**Figure 8.** Histological features and differential diagnosis of PBL. (A) PBL consists of sheets of large cells with plasmablastic/plasmacytoid features. Tumor cells are characteristically negative for CD20 and express plasma cell markers, such as CD138 and MUM1. Light chain restriction is documented by kappa and lambda immunostains. The vast majority of cases is driven by EBV infection (positive EBER in situ hybridization). (H&E and immunoperoxidase stain; original magnification 10x, 20x and 40x). (B) Diagnostic flow chart for GI neoplasms with plasmablastic morphology.
countries. In Italy, it constitutes about two thirds of all primary GI T-cell neoplasms, with an estimated incidence among CD patients of 0.2-2/100,000/year \(^{51,52}\). The disease typically occurs in the jejunum or ileum sometimes with multifocal lesions, and presents with ulcerated, perforated or stenotic masses that cause abdominal pain, bleeding, intestinal occlusion and systemic symptoms. Patients also complain of CD-related symptoms \(^{53}\).

Histologically, EATL is characterized by a diffuse proliferation of polymorphic atypical cells of medium to large size that colonize the surface epithelium and deeply infiltrate the intestinal wall. Anaplastic features are documented in about 40% of cases, while angioinvasion, angiocentricity and necrotic areas are commonly observed. The neoplastic population is accompanied by a rich inflammatory infiltrate, consisting of histiocytes, eosinophils and small lymphocytes (Fig. 9A). Spreading to regional lymph nodes, liver, skin and other extra-abdominal organs is frequent. The uninvolved small intestinal mucosa discloses the classical histological features of CD (variable degrees of villous atrophy with increased intra-epithelial CD3-positive T lymphocytes) (Fig. 9A). On IHC, EATL expresses the panT cell markers CD3 and CD7, with variable loss of CD2 and CD5. Neoplastic cells disclose an activated cytotoxic phenotype (positivity for TIA1, granzyme B and perforin) and are almost invariably positive for CD30. The latter is expressed at higher intensity in cases with anaplastic cytology. EATL is usually negative for CD4, CD8 and CD56 and does not express T-cell receptor (TCR) antigens (Fig. 9A). EBER \textit{in situ} hybridization is typically negative and its documentation should prompt consideration of an immunodeficiency-related LPD or other NK/T-cell entities (see below) \(^5\).

The main differential diagnoses of EATL include refractory CD and secondary GI involvement by systemic T-cell NHLs (mostly anaplastic large cell lymphoma; ALCL). Refractory CD (RCD) is defined as CD not responding to > 6-12 months of strictly gluten-free diet. Two forms of RCD are described: (i) type 1 RCD, which is histologically indistinguishable from classic CD; and (ii) type 2 RCD, which is characterized by > 50% atypical intraepithelial T-cells, closely resembling EATL (i.e. positivity for CD3; double negativity for CD8 and CD4) \(^{54}\). Several lines of evidence suggest that type 2 RCD is the precursor lesion of EATL \(^{55}\). The differential diagnosis between the two entities relies on RCD being an intra-epithelial disease of mostly small atypical cells, whereas EATL is a large cell lymphoma and massively infiltrates the intestinal wall. Like EATL, ALCL is characterized by large atypical blasts with a defective T-cell phenotype, diffuse expression of CD30 and positivity for T-cell cytotoxic markers \(^{56}\). In ALCL, however, there is no history of CD, the uninvolved intestinal mucosa lacks features of enteropathy and the positivity for CD30 is much more intense and diffuse than in EATL. However, if CD features are not seen on the tissue samples and there is no history of CD, the differentiation can be challenging and CD clinical investigation should be suggested.

\textit{Monomorphic epitheliotropic T-cell lymphoma} (MEITL; formerly known as type 2 EATL) is another aggressive T-cell NHL, typically arising in the small bowel. Unlike EATL, it is not associated with CD and accounts for the vast majority of primary GI T-cell NHLs in Asia \(^7\). Histologically, intestinal villi are distorted and widened by sheets of monotonous medium-sized cells with pale cytoplasm, sparse chromatin and small nucleoli. Epitheliotropism is striking, while angiotropism, necrotic areas and/or accompanying inflammatory cells are characteristically absent (Fig. 9B). The phenotype of MEITL differs from EATL in that the neoplastic cells are positive for CD8 and CD56 with negativity for CD30. MATK, TCR-\gamma chains and TIA1 are usually positive, while perforin and granzyme B are more variable \(^{3,57}\) (Fig. 9B). About 25% of cases aberrantly express CD20, but negativity for PAX5, CD19, CD79a and other B-cell markers supports the diagnosis of a T-cell neoplasm \(^{58}\). EBER \textit{in situ} hybridization is consistently negative, thus excluding ENKTL, nasal type \(^3\). Extra nodal NK/T-cell lymphoma (ENKTL) is an EBV-driven aggressive lymphoma, most commonly occurring in the upper respiratory tract. The GI is the primary site of disease in 2-7% of cases, but secondary involvement by extra-intestinal neoplasms is reported. ENKTL, nasal type usually arises in the jejunum and ileum of middle-aged males, presenting as large ulcerated lesions with bleeding and/or perforation. Key histological features are the prominent angiotropism, the presence of large necrotic areas and/or ulceration without epitheliotropism and the diffuse positivity of neoplastic cells for EBER (Fig. 9C). Tumor cells are cytologically variable, spanning from relatively small to large atypical blasts with “sternbergoid” features in a mixed inflammatory background. Most cases disclose a NK phenotype, with positivity for CD56, cytoplasmic CD3 and cytotoxic markers. Surface CD3, CD5, CD4 and CD8 are negative, while CD2, CD7 and CD30 are variably expressed \(^{59}\) (Fig. 9C). Rare cases with T-cell (either TCR-\gamma or TCR-\delta) phenotype do also occur \(^60\). Irrespective of the cell lineage, EBER positivity is always documented and its negativity should prompt consideration of other entities (e.g. MEITL, PTCL NOS and indolent T-cell LPDs of the GI tract; see below). Molecular biology supports the differential diagnosis, as monoclonal TCR gene rearrangements

### Note

- EATL stands for Enteropathy-associated T-cell lymphoma.
- CD stands for Celiac disease.
- RCD stands for Refractory CD.
- ALCL stands for Anaplastic large cell lymphoma.
- MEITL stands for Monomorphic epitheliotropic T-cell lymphoma.
- ENKTL stands for Extra nodal NK/T-cell lymphoma.
- PTCL NOS stands for Primary cutaneous T-cell lymphoma, not otherwise specified.
are not documented in most ENKTL, nasal type (i.e. cases of NK derivation), while are usually present in other T-cell entities.

Rare intestinal T-cell NHLs do not fulfill the diagnostic criteria of EATL, MEITL and ENKTL, nasal type. These tumors, currently referred to as intestinal T-cell lymphomas NOS, are not a specific disease entity, but a diagnostic category to be used when other more common neoplasms are ruled out or not assessable (i.e. small biopsy samples lacking surface epithelium or inadequate material for immunophenotyping) 3. These cases are not associated with CD, usually arise in the large bowel or the stomach and have a very aggressive clinical course. The morphological and immunohistochemical features are highly variable, yet most cases disclose a cytotoxic phenotype and lack TCR expression. The differential diagnosis with secondary GI involvement by peripheral T-cell lymphoma NOS is based on clinical data and imaging studies 61. In recent years, indolent T-cell LPDs of the GI tract have also been described 62. These cases mostly occur in the stomach, small intestine and large bowel and present with abdominal pain, weight loss, diarrhea or dyspepsia. Endoscopically, the mucosa of af-
fected sites is thickened, polypoid or hyperemic with superficial erosions. Histology discloses a dense, lamina propria-limited, non-angioinvasive lymphoid infiltrate, displacing (yet not infiltrating) the mucosal glands or surface epithelium \( ^{62} \). Epithelioid granulomas and occasional eosinophils may be present, yielding the differential diagnosis with Crohn disease. Cytologically, neoplastic cells are monomorphic and small to medium-sized. Cases with NK phenotype disclose brightly eosinophilic cytoplasmic granules. On IHC, most indolent T-cell LPDs have a non-activated cytotoxic phenotype \( \text{(i.e. positivity for CD3, CD8 and TIA1; negativity for perforin and granzyme B)}, \) but positivity for CD4 or even NK cell markers has been reported \( ^{63,64} \). Irrespective of the cell lineage, these lesions have very low proliferation index (usually < 10% of neoplastic cells) and a protracted clinical course, with limited response to conventional chemotherapy. Molecular biology shows monoclonal TCR rearrangements in all cases \(^3\).

**Hodgkin lymphoma mimickers in the GI tract**

Primary classic Hodgkin lymphoma (cHL) is extremely rare in the GI tract. Occasional GI LPDs may nonetheless feature neoplastic elements that closely resemble Hodgkin and Reed-Sternberg (HRS) cells. **EBV-positive mucocutaneous ulcer (EBVMCU)** is the most challenging of such entities. This recently described disease affects immunosuppressed and elderly males and presents as large ulcerated lesions of the skin, oral cavity, and GI tract \(^3,66\). In the latter site, the rectum and sigmoid colon are most commonly involved. The clinical course is usually benign, with nearly all cases responding to reduction of immunosuppressive therapy \(^{65}\). Radiation and chemotherapy are also effective. Systemic spread is very rare, but relapse and local progression have been reported \(^3\).

Histologically, EBVMCU appears as a well-demarcated ulcer with a dense, polymorphic sub-epithelial lymphoid infiltrate. The latter includes small lymphocytes, plasma cells, histiocytes and eosinophils. Variable numbers of large atypical cells are also present, resembling either immunoblasts or HRS cells \( \text{(i.e. very large cells with multi-lobated nuclei, eosinophilic nucleioli and abundant cytoplasm)} \). The deepest margin of the lesion is sharp and consists of a band-like infiltrate of reactive lymphocytes (Fig. 10A). Necrotic areas and angioinvasion are frequently documented. On IHC, the atypical cells are positive for CD30, MUM1, PAX5, CD79a and OCT2. Expression of CD20 is variable and CD15 is found in about 50% of cases. CD10 and Bcl6 are usually negative. A key diagnostic feature is the strong and diffuse positivity for EBER in the large atypical blasts as well as in small to medium-sized B cells. The background lymphoid infiltrate and deep margin of the lesion mainly consists of CD8-positive T-cells (Fig. 10A). Molecular biology shows monoclonal rearrangements of the immunoglobulin genes in about 50% of cases \(^{65}\).

Depending on the amount and morphological features of the large atypical cells, EBVMCU enters the differential diagnosis with cHL, monomorphic/polymorphic PTLD and EBV-positive DLBCL NOS. Distinction from cHL is based on the clinical presentation and on the sharp circumscription of the lesion (deep band-like margin of T cells). The positivity for EBER even in small lymphocytes and the B-cell phenotype of the atypical cells are also not features of cHL. The differential diagnosis with monomorphic/polymorphic PTLD and EBV-positive DLBCL NOS is more challenging and largely depends on the clinical findings and the localized, non-infiltrative nature of EBVMCU \(^{66}\) (Fig. 10B). Finally, small and superficial biopsies of EBVMCU may lead to the wrong impression of florid granulation tissue associated with benign mucous ulcers. In such instances, only a high degree of suspicion and careful histological examination leads to the correct diagnosis. Immunophenotyping for CD30, MUM1 and EBER help highlighting the atypical cell component, thus favoring EBVMCU over reactive inflammation.

**Conclusions**

Non-Hodgkin lymphomas of the GI tract constitute a broad spectrum of neoplasms with variable clinical and biological features. The management of such entities is based on an integrated diagnostic framework, considering morphological, immunophenotypic and molecular/cytogenetic data. As discussed in this review, a step-wise approach is highly recommended to reduce the spectrum of differential diagnoses and to get to confident conclusions. Key features for any diagnostic evaluation are the assessment of tumor cell cytology \( \text{(typical vs atypical; small vs large size)} \) and lineage of differentiation \( \text{(B versus T cell proliferations)} \). This first evaluation will guide any subsequent ancillary test, reducing the number of unnecessary \( \text{(or even confounding)} \) analyses. Several factors may limit the diagnostic reliability of the biopsy findings \( \text{(sampling artifacts; little amount of diagnostic material; overlapping features among different entities)} \). Pathologists should be aware of such limitations, stating all of them in the final report. This will likely limit the over-interpretation of the histological findings, favoring the teamwork between pathologists and clinicians and the proper management of patients.
Figure 10. Histological features of EBVMCU and monomorphic PTLD. (A) EBVMCU is an ulcerated, sharply demarcated lymphoid lesion with a band-like CD3-positive T-cell infiltrate at the base (large box, *insert*). Hodgkin/Reed Sternberg-like cells are characteristically present (high power picture, *arrow*) and express CD30, multiple B-cell markers (*e.g.* CD20, CD79a), MUM1 and EBER. CD15 is present in subsets of cases. These features need to be distinguished from cHL, whose primary involvement of the GI tract is extremely rare. (B). The differential diagnosis of EBVMCU encompasses various EBV-positive LPDs, including monomorphic PTLD. This consists of sheets of atypical blasts with variable histological features (the case reported here has lymphomatoid granulomatosis-like features with marked angiotropism). CD20, CD30 and MUM1 are typically expressed, EBER positivity is strong and diffuse (large box, *insert*) and the Ki67 index is high. (H&E, immunoperoxidase stain; original magnification 2x, 10x, 20x and 40x).
ABBREVIATIONS:

AMZH: atypical marginal zone hyperplasia; B-ALL: B-cell lymphoblastic leukemia/lymphoma; BL: Burkitt lymphoma; CD: coeliac disease; cHL: classic Hodgkin lymphoma; CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL: diffuse large B-cell lymphoma; EALT: enteropathy-associated T-cell lymphoma; EBVMCU: EBV-positive mucocutaneous ulcer; ENKTL: extra-nodal NK/T-cell lymphoma; ENMZL: extra-nodal marginal zone lymphoma; FDC: follicular dendritic cell; FISH: Fluorescence In Situ; FL: follicular lymphoma; GC: germinal centers; GCD: germinal center-derived; GI: gastrointestinal tract; HGBL: high-grade B-cell lymphoma; HGBL NOS: high-grade B-cell lymphoma not otherwise specified; HPF: high-power field; HRS: Hodgkin and Reed-Sternberg cells; IHC: immunohistochemistry; IPSID: immunoproliferative small intestinal disease; LBCL: large B-cell lymphoma; LELs: lymphoepithelial lesions; LPDs: lymphoproliferative disorders; MALT: mucosa-associated lymphoid tissue MALT; MCL: mantle cell lymphoma; MEITL: Monomorphic epitheliotropic T-cell lymphoma; NHLs: non-Hodgkin lymphomas; PBL: plasmablastic lymphoma; PTLDs: post-transplant LPDs; RCD: Refractory CD; TCR: T-cell receptor.

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