We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Primary Gastrointestinal Lymphoma

Ramiz Bayramov and Ramila Abdullayeva

Abstract

The gastrointestinal tract (GIT) is the most common (30–40%) extranodal site involved in lymphoma. Although primary gastrointestinal lymphoma (PGIL) is a rare disease, comprising only 1–4% of gastrointestinal (GI) malignant tumors, its incidence is increasing. Different regions of the GIT are involved in different subtypes of PGIL with a various frequency that reflects the diversity of the causative agents and predisposing factors for each site and subtype of PGIL. Even though these malignant diseases are categorized under the common term of “lymphoma” they represent a heterogeneous group of malignant neoplasms which are different entities in terms of etiologic factors, predisposing conditions, pathogenesis, immunohistochemical profile, treatment strategy and prognosis. In this chapter the epidemiology of all subtypes of PGIL, factors and disorders contributing to the development of them, non-inherited and inherited conditions associated with a higher risk of them, diagnostic difficulties and pitfalls, and novel treatment strategies were comprehensively and concisely illuminated.

Keywords: gastrointestinal lymphoma, gastric lymphoma, intestinal lymphoma, extranodal lymphoma, non-Hodgkin lymphoma

1. Introduction

The incidence of lymphoma, especially extranodal lymphoma, such as non-Hodgkin lymphoma (NHL) of the central nervous system (CNS), GI and cutaneous lymphomas has been increasing over the last decades [1–3].

The definition of PGIL has differed among different authors but typically refers to a lymphoma that develops in any part of the gastrointestinal tract (GIT) from the oropharynx to the anal canal. PGIL is the most common type of extranodal lymphoma comprising 25–40% of the latter depending on geographic regions [4, 5]. PGIL, however, is a rare malignancy, accounting for 1% to 4% of the malignant lesions in GIT [3, 6]. GIT several times more frequently is involved secondarily from nodal lymphoma [4].

Dawson's criteria that were suggested 6 decades ago are used for the definition of PGIL, that include (1) absence of peripheral lymphadenopathy at the time of presentation; (2) lack of enlarged mediastinal lymph nodes (LNs); (3) normal total and differential white blood cell count; (4) predominance of bowel lesion at the time of laparotomy with only LNs affected in the immediate vicinity (LNs which are confined to the drainage area of the primary tumor site); and (5) no involvement of liver and spleen [7].

Histopathologically, almost 90% of the PGILs are of B-cell lineage, and T-cell lymphomas (TCLs) and Hodgkin lymphoma (HL) are rarely encountered in GIT [4, 8, 9]. Some histological subtypes of lymphoma have a relative propensity to develop in specific sites as mucosa-associated lymphoid tissue (MALT) lymphoma in the stomach, follicular lymphoma (FL) in the duodenum, enteropathy-associated T-cell lymphoma (EATL) in the jejunum, mantle cell lymphoma (MCL) in the terminal ileum and colon [10].

Due to the rarity of PGIL, opinions upon some aspects of this neoplasm are still controversial. The increasing incidence of this malignancy, makes it necessary for clinicians to understand the characteristic clinical manifestation, diagnostic properties, treatment and prognosis of PGIL more comprehensively [11].

In the last decades, a great achievement has been reached in the diagnosis, staging and management of PGIL attributed to a better understanding of its etiology and molecular aspect including signaling pathways [4]. The therapeutic approach to the cure of PGIL has completely changed over the last decade, including innovative conservative options to reduce the complication rate following treatment [11]. Nevertheless, the prognostic and diagnostic significance of mutational analysis in daily practice and its role in novel targeted therapy remains and requires to be determined [12].

2. Epidemiological properties

PGIL, as mentioned above, is a rare malignancy, constituting 1% to 4% of the GIT cancer [4, 6]. Although theoretically lymphoma can arise from any region of the GIT stomach is the most frequently involved site (60–75%) followed by the small intestine [20–30%], ileocecal region (7%) and colon (6–12%). More than one gastrointestinal (GI) site is involved in 6–13% of the cases [4, 6, 13–15].

Primary esophageal lymphoma (PEL) is extremely rare comprising <1% of all PGILs. Less than 30 cases of PEL have been reported in the literature [4]. Primary gastric lymphoma (PGL) accounts for up to 5% of all malignancies of the stomach [16]. Primary small intestinal lymphoma (PSIL) constitutes 15–20% of all small bowel neoplasms [4]. Primary colorectal lymphoma (PCRL) comprises only 0.2% of all malignancies arising from the colorectum with caecum, ascending colon and rectum more frequently involved in decreasing order [14].

PGIL approximately 2–3 times more frequently is seen in men compared to women [4, 8, 11]. This ratio can be varied depending on the sites of PGIL and pathological subtypes. For example, DLBCL is seen in males 1.2–2 times more [17, 18], and FL affects males and females equally [19] or demonstrates a clear female predominance [20].

The age of the patients with PGIL can range from 19 to >90 years with a median age of 55 years [4, 8, 21]. The age range (and median age) depends on involved sites and pathological subtypes of PGIL. The median age of patients with TCL is usually by 10–14 years younger compared to B-cell lymphoma (BCL) [8, 22].

Different entities of the PGILs of B-cell lineage can demonstrate different peak ages. MALT lymphoma and MCL are most commonly detected between the age of 50 and 60 years [23]. On the contrary immunoproliferative small intestine disease (IPSID) is mainly seen in adolescents and younger adults [24, 25] and endemic Burkitt's lymphoma (BL) is mainly detected in children [26].

Some forms of PGIL have a tendency to increase in its incidence in younger age group of people, the other ones tend to be encountered among some ethnics or have different geographical distribution. It has been observed that the incidence of MALT lymphoma has increased significantly in people older than 40 years [27].

Monomorphic epitheliotropic intestinal TCL (MEITL) is more common in people of Hispanic descent and is the most frequent primary intestinal TCL being detected in Asia [28]. PGL is the most common extranodal site of lymphoma in the USA. The predominant part of this neoplasm is either extranodal marginal zone lymphoma (MZL) of MALT or DLBCL. PSIL, while uncommon in Western countries, comprises up to 75% of PGIL in the Middle East, North and South Africa, and Mediterranean basin, because of that is commonly called “Mediterranean type lymphoma”. Endemic BL, the most common type of BL, has a geographical distribution identical to that of *Plasmodium falciparum* [29]. That is why the incidence of BL in Africa is nearly 50-fold higher than that in the USA [11, 24].

3. Predisposing factors and disorders

Certain risk factors and disorders can be involved in the pathogenesis of PGIL including *Helicobacter pylori*, *Campylobacter jejuni*, human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), human T-cell lymphotropic virus-1 (HTLV-1), celiac disease, inflammatory bowel disease (IBD) and immunosuppression [4, 30].

Chronic gastritis related to *H. pylori* infection has been considered a major predisposing factor for the development of MALT lymphoma [11] and the latter is strongly associated with *H. pylori* infection. This pathogen is the most common infectious agent related to global malignancy (5.5% of total cancers) [31]. The prevalence of *H. pylori*-related gastritis is dependent on geographical regions, socio-economic status, education level, living environment, occupation and age [32]. Patients with *H. pylori* gastritis have a great risk for the development of gastric MALT lymphoma, and the development of this neoplasm requires some circumstances or co-factors [33]. Studies demonstrated that only 1 of the 13 different tested *H. pylori* strains was capable of inducing B-cell proliferation and making T-cells produce IL-2 [25]. However, unlike gastric MALT lymphoma, esophageal MALT lymphoma is not associated with *H. pylori* infection [4].

MALT lymphoma can be divided into *H. pylori*-positive or negative based on association with *H. pylori* infection. Typically, gastric MALT lymphoma is a low-grade (LG) neoplasm, but it can be transformed into a high-grade (HG) lymphoma. In the last years, it has been discovered that *H. pylori* infection plays a role in the development of gastric DLBCL as well [34] and few studies have shown complete remission of that after eradication therapy alone [35]. Recent studies detected that CagA-positive strains of *H. pylori* are more frequent in DLBCL than in LG MALT lymphoma of the stomach [36]. It should be noted that although “LG MALT lymphoma” is widely used in the literature despite its official name is “extranodal MZL of MALT” in the 2016 revision of WHO classification (for comprehensive explanation see subsection 5). However, following the commonly used by most of the authors terminology “LG MALT lymphoma” will be employed in this chapter keeping the original style of spelling of the authors.

The role of *H. pylori* in the pathogenesis of PCRL has not been fully clarified. Niino et al. reported that in five of the eight cases (63%) endoscopic examination showed that the rectal MALT lymphoma had disappeared following antibiotic therapy which was confirmed histologically [37]. These results indirectly discover the role of unknown infection, which is a target for antibiotics in the development of rectal MALT lymphoma.

IPSID, also recognized as an alpha-chain disease, is considered as a variant of MALT lymphoma related to *C. jejuni* (sometimes to *Campylobacter coli*) infection that prevalently involves the proximal part of the small intestine. The disease is

characterized by a lymphoid infiltrate of mucosa composed of plasma cells and lymphocytes with centrocyte features. The plasma cells secrete truncated immunoglobulin, consisting of the heavy chains without associating light chains [24].

Pathogenesis of primary PGIL can also be associated with other infectious agents like EBV, HIV, HBV and HTLV-1 [11]. The role of EBV-infection in the pathogenesis of B-cell NHL has been established [38]. Hui et al. reported 11 cases of PGL that harbor the EBV encoded small messenger RNA, EBER-1, detected by fluorescence in situ hybridization (FISH). The cases comprised 18% of 61 consecutive PGL. Nine of the 11 (81.8%) EBER-1-positive PGL cases were DLBCL-type without LG components. None of the EBER-1-positive gastric BCLs showed histological features characteristic of LG lymphoma of MALT-type being common in Western countries. Of the two patients with TCL, one had a pleomorphic TCL and the other had an angiocentric lymphoma. They concluded that a significant proportion of PGL in Hong Kong Chinese are EBV-related and that they show histological features more similar to conventional nodal lymphomas than to MALT-type lymphomas [39].

BL has three recognized clinical variants: endemic form, sporadic variant and immunodeficiency-associated BL. There is clear evidence regarding the role of EBV and *P. falciparum* as a co-factor in the pathogenesis of endemic BL. It demonstrates an association with HIV-1 as well, but the data is insufficient to support the role of those factors in sporadic cases, where the association with EBV is observed in only 20–30% of the patients [29, 40].

EBV infection is also associated with the EBV-positive DLBCL, recently recognized as a definite entity. The term “elderly” in the 2008 WHO classification has been substituted by NOS (not otherwise specified) because this lymphoma can be encountered in younger patients as well [12].

A recently recognized entity, EBV-positive mucocutaneous ulcer (MCU) is characteristically associated with iatrogenic immunosuppression (for autoimmune or inflammatory conditions and solid organ transplantation), HIV-infection and age-related immunosenescence that leads to inadequate immune surveillance for EBV. It is characterized by the propagation of EBV-positive atypical large B-cells affecting the skin or mucous sites, presumably related to local trauma or inflammation [41, 42]. Most cases of EBV-positive MCU are detected in the elderly (due to predisposing age-associated immunosenescence in half of the patients), but the patients with iatrogenic immunosuppression usually have a younger age. Patients treated by immunosuppressive therapy for IBD may be all the more vulnerable due to the presence of local tissue injury related to the mentioned disease [19].

NK/T cell neoplasms are invariably associated with EBV infection and are mostly aggressive; thus, differentiation from a benign NK-cell enteropathy is paramount [15]. BL is associated with EBV and HIV/AIDS, and most commonly affects children [26].

GI lesions as the most frequent extranodal manifestation of HIV-associated NHL lymphoma (occurs in 5–10% of individuals with HIV-infection), are late events of HIV-infection with severe immunosuppression and are mostly diagnosed in advanced stages of the disease. They are characterized by HG B-cell histology, frequently multifocal location in the GIT, high rates of life-threatening complications (bleeding, perforation or obstruction) [43, 44]. NHL is the second most common type of malignancy in HIV-patients following Kaposi sarcoma [45]. The high incidence of GI NHL prompted Powitz et al. to commence a prospective survey on 93 of 341 HIV-infected patients with GI symptoms who were examined by endoscopy, some selected patients by endoscopic ultrasound (EUS). NHL of the GIT was detected in seven of 93 endoscopically examined patients (7.5%) [44].

Nearly 70–90% of AIDS-related lymphomas are highly aggressive and are almost exclusively BL and an immunoblastic variant of DLBCL. Compared to the general

population, the relative risk for highly aggressive lymphomas is higher >400-fold overall [46], and 260-fold and 650-fold for BL and DLBCL, respectively among HIV-infected people [47]. BL can be one of the diseases associated with the initial manifestation of AIDS [48]. The indolent lymphomas are less common, comprising <10% of AIDS-related lymphomas. Compared to the general population, the relative risk is increased nearly 15-fold for indolent lymphomas and TCLs in the HIV-positive population [46, 47, 49]. However, TCLs are less common in HIV-infected people as well despite the increased relative risk. Of note, 40–50% of cases of HIV-associated BL are positive for EBV [48].

The epidemiologic association between HBV-infection and NHL, notably DLBCL is well established. Most studies concerning this association have been conducted in endemic areas. Some researchers report up to 2.5 times higher risk of NHL in HBV-infected people. Deng et al. studied HBV-infection status and clinicopathologic features of 587 patients with DLBCL in HBV-endemic China. Eighty-one (13.8%) patients were HBsAg-positive, 20 of which (25%) had DLBCL in GIT. Compared to HBsAg-negative DLBCL, HBsAg-positive DLBCL demonstrated a younger median onset age by 10 years, more advanced stages of the disease and significantly worse outcome [50].

PGL with a T-cell phenotype is very rare, comprising only 7% of PGLs in endemic areas of HTLV-1 infection. Primary gastric TCL without HTLV-1 infection is extremely rare, and sporadic cases have been occasionally reported [51].

PGIL is one of the major and serious complications of different diseases and conditions presenting with immunodepression, both congenital (Wiskott-Aldrich syndrome, ataxia-telangiectasia, X-linked agammaglobulinemia) and acquired immunodeficiency (HIV-infection, iatrogenic immunosuppression). Lymphomas developed in the setting of the diseases associated with immunodepression are pathologically and clinically heterogeneous, but share some hallmarks such as frequent involvement of extranodal sites, association with EBV-infection, B-cell lineage genesis, and aggressive behavior. Although PGIL associated with congenital immunodeficient conditions seems to be an infrequent occasion despite the higher prevalence of post-transplantation lymphoproliferative disorders GIT is one of the most involved sites of lymphoma [43]. It should be noted that PEL in an immunocompetent patient is very rare [52].

The three most common systemic autoimmune diseases—rheumatoid arthritis, primary Sjögren's syndrome (PSS) and systemic lupus erythematosus, are characterized by an increased risk of lymphoma. Of these diseases, the highest risk of lymphoma is associated with PSS [53]. The development of the NHL is the most serious complication of PSS. Up to 25% of NHL associated with PSS is PGL that predominantly demonstrates MALT lymphoma. NHLs complicated PSS are not associated with viral agents known to be present in other types of lymphoma [54].

TCL of the small bowel comprises 10–25% of all primary intestinal lymphomas (PIL) primarily occurring as EATL, and most of them are often associated with Crohn's disease [55, 56]. Intestinal EATL, type I in particular, usually occurs in the setting of celiac disease [15]. T-cell gene rearrangement confirms clonality [57]. MEITL was formerly known as type II EATL. Even in this older classification, it had been recognized that the “type II” form of the disease had rarely demonstrated (if demonstrated) association with underlying gluten-sensitive enteropathy [19].

4. Pathogenesis

Although the stomach is devoid of lymphoid tissue, it is the organ most commonly involved of MALT lymphoma, especially the antrum and distal body.

Lymphoid cells are attracted and transformed into gastric MALT tissue by a chronic *H. pylori* infection. Lymphoid follicles develop in the setting of chronic inflammation (gastritis) associated with *H. pylori* infection. It is evidenced by the fact that the rate of *H. pylori* infection prevalence is >90% in patients with MALT lymphoma. These lymphoid follicles resemble LN tissue and are composed of activated plasma cells, B-cells and reactive T-cells. When these cells are continuously stimulated by *H. pylori*, the B-cells undergo clonal expansion [57, 58]. Overtime, B-cell clones that still depend on antigens for growth and survival, acquiring unknown genetic mutations, will give rise to MALT lymphoma. At this stage, the proliferation is monoclonal but not yet able to spread beyond the site of inflammation. With the acquisition of additional mutations, including chromosomal abnormalities, the tumor becomes antigen-independent and capable of systemic spread [11]. In addition to B-cells, T-cells and macrophages play an important role in MALT lymphoma-genesis [57, 58].

The association of gastric MALT lymphoma with *H. pylori* is undeniable. *E. coli* and *C. jejuni* were also tested, two Gram-negative intestinal bacteria which share different antigens with *H. pylori*, and they failed to induce B-cell proliferation in culture, so *H. pylori* strains have a specific role [25]. In addition, *H. pylori* can translocate the CagA protein directly into B-cells resulting in extracellular signal-regulated kinase activation and *BCL2* expression up-regulation, leading to apoptosis inhibition [59].

In normal B and T-cells signals produced by the interaction of antigen with antigen receptors on the cell surface cause the protein bcl-10 (B-cell leukemia/lymphoma 10) to bind to the protein MALT1 (lymphoma-associated translocation protein 1) [60]. During *H. pylori* infection, normal B-cells are transformed into malignant clones via three chromosomal translocations—t(14;18)(q32;q21), t(1;14)(p22;q32) and t(11;18)(q21;q21), which produces activation of nuclear factor kappa B (NF- κ B), a transcription factor that promotes cell survival and plays a role in immunity, inflammation, and apoptosis [61, 62]. These events result in enhancing the survival of extranodal lymphoma cells [63].

The t(14;18)(q32;q21) fuses the *IGH* gene on chromosome 14 with the *MLT/MALT1* gene on chromosome 18. The rare t(1;14)(p22;q32) translocation fuses the coding sequence of *BCL10* gene on chromosome 1 to the *IGH* promoter/enhancer elements [11, 64]. These all lead to overexpression of the *BCL10* gene, which causes cellular transformation [65] and guarantees a survival advantage to the neoplastic B-cells. Nuclear expression of bcl-10 or NF- κ B in gastric MALT lymphoma is characterized by resistance of those cases to the *H. pylori* eradication therapy, even in the cases without the t(11;18)(q21;q21) translocation [66]. The t(3;14)(p13;q32) translocation fuses the *FOXP1* gene on chromosome 3 to the *IGH* gene and leads to upregulation of the FOXP1 transcription factor [67]. MALT lymphoma cases with *FOXP1* rearrangement appear to grow into DLBCL more frequently compared with those with t(11;18)(q21;q21) translocation the mechanism of that is unclear [68].

In *H. pylori*-negative gastric MALT lymphomas, the theory suggesting that infection leads to lymphomagenesis loses validity. Today, many propose that there are various mechanisms by which pathogenesis occurs in the development of *H. pylori*-negative gastric MALT lymphoma, including the relationship between genetic alterations and other activation pathways [11]. Recently, the t(11;18)(q21;q21) translocation is associated with LG MALT lymphoma, extranodal MZL [69]. The t(11;18) rearrangement fuses the apoptosis inhibitor gene *API2* (apoptosis inhibitor 2 gene) on chromosome 11 with the novel *MLT/MALT1* gene, a human paracaspase, on chromosome 18 [70, 71]. According to the data in literature, *H. pylori*-negative MALT lymphoma tends to have a high positive rate for t(11;18)(q21;q21) translocation than *H. pylori*-positive MALT lymphoma [69]. Studies show that t(11;18)

(q21;q21) was found to be more prevalent in patients with CagA-positive *H. pylori* strains compared to CagA-negative *H. pylori*-infection [72]. Some authors reported this translocation to be closely associated with *H. pylori*-negative gastric MALT lymphoma [73]. It should be noted that the t(11;18)(q21;q21) has mainly been observed in LG MALT lymphomas of the GIT. Recent studies have also demonstrated that the t(11;18)(q21;q21) translocation presents important biological characteristics since this translocation is associated with resistance to antibiotic treatment in cases of *H. pylori*-positive gastric MALT lymphoma and with a more aggressive clinical behavior in cases of *H. pylori*-negative gastric MALT lymphoma [69, 74, 75]. The publications have also reported that t(11;18)(q21;q21) is never seen in early gastric MALT lymphomas that regressed after *H. pylori* eradication treatment [74]. In gastric LG MALT lymphomas, the reported frequency of t(11;18)(q21;q21) ranges from 0% to 48% (mean, 30%). It should be noted that the t(11;18)(q21;q21) translocation or the *API2-MLT/MALT1* fusion transcript has been detected in some percentage of patients with extranodal MZL of MALT (LG MALT lymphoma), but not in cases of DLBCL (HG lymphoma). Results of some studies indicate that t(11;18)(q21;q21) may be closely associated with colonic MALT lymphoma, but not with gastric MALT lymphoma [69]. Niino et al. (2010) reported that of the 8 cases of rectal MALT lymphoma analyzed with FISH for *MALT1* translocation, two demonstrated *MALT1* genetic abnormality. These cases were resistant to antibiotic treatment [37].

In specific subtypes of non-Hodgkin's BCL particular oncogene rearrangements related to chromosomal translocations have been determined. The t(11;14)(q13;q32) translocation is one of such fusions specific for MCL, which involves the *BCL1/cyclin D1* gene on chromosome 11. The t(14;18)(q32;q21) translocation that leads to overexpression of the *BCL2* gene has been found in 80–90% of FL cases. The *c-MYC* gene (8q24.1) is known to be rearranged in BL, in association with t(8;14)(q32;q32) translocation. In addition, the t(3;14)(q27;q32) is the most common translocation involving the *BCL6* gene (3q27.3) which results in deregulation of *BCL6* and is predominantly associated with DLBCL, rarely with FL [69].

Nakamura et al. (2000) believe that gastric MALT lymphoma can be rationally subdivided into 3 subtypes, MALT-A, MALT-B, and MALT-C. They suppose that MALT-A may represent a dysplasia or incipient neoplasm, MALT-B a neoplasm promoted by antigenic stimulation of *H. pylori*, and MALT-C a lymphoma independent of *H. pylori* infection. Polypoid lesions in MALT-C were associated with *c-IAP2-MALT1/MLT* gene alteration resulting from t(11;18)(q21;q21) translocation [73].

Data of Wang et al. show that identification of a t(11;18)(q21;q21) by reverse transcription real-time PCR is highly specific for extranodal MZL of MALT and helps in the diagnosis of this type of lymphoma. This translocation correlates with morphological features of gastric extranodal MZL of MALT and frequently shows monocytoid morphology, less often small lymphocytic morphology and not purely plasmacytoid morphology [76].

Proto-oncogene *BCL6* encodes a transcriptional repressor necessary for the development of germinal centers (GCs) and is directly implicated in lymphomagenesis. Post-GC development of B-cells requires *BCL6* down-regulation, while its constitutive expression caused by chromosomal translocations leads to the development of DLBCL [77]. The *BCL6* gene, which functions as a transcription repressor, is the target of multiple chromosomal translocations in NHL. These translocations occur in the nontranslated region of the *BCL6* gene; the *BCL6* promoter region is thought to deregulate *BCL6* gene expression [78]. *BCL6* promoter region can also be altered as a result of somatic mutations [79]. Most B-cell NHL, including DLBCL and FL, arise from GC B-cells; a stage at which B cells undergo rounds of proliferation and edit their immunoglobulins [80]. Therefore, *BCL6* is frequently over-expressed in the majority of extranodal HG lymphomas caused by chromosomal

translocation leading to the development of lymphoma in various ways [79, 81]. Chromosomal translocations and mutations of the *BCL6* promoter region are associated with ~40% of DLBCL and ~10% of FL [77]. The levels of expression of the *BCL6* gene and protein have been shown to predict the clinical outcome of DLBCLs [78, 79]. It has remained unclear whether DLBCL (gastric DLBCL is sometimes called HG gastric lymphoma) arises *de novo* or it transforms from LG gastric MALT lymphoma [82].

C. jejuni is considered an agent promoting lymphoid cell proliferation in the wall of the small intestine. *C. jejuni* has been revealed to persist in Peyer's patches and mesenteric LNs, and is capable of inducing a strong mucosal response in the small intestine as a B-cell proliferation that results in the production of IgA of the same type seen in IPSID [25].

MCL as a rule has been known to be an aggressive and incurable small BCL that is derived from naïve B-cells of the pregerminal center. Two types of clinically indolent variants are now identified reflecting that MCL might develop along 2 very different pathways [12]. Classical MCL is consisting of *IGH*-unmutated (in 20–30% of the cases) or minimally/borderline mutated (in 40–50% of the cases) B-cells that usually express SOX11 and characteristically involves LNs and extranodal sites. Acquisition of additional cytogenetic abnormalities targeting different oncogenic pathways can lead to the development of more aggressive variants (pleomorphic or blastoid) of MCL. Other MCLs are derived from *IGH*-mutated SOX11-negative B-cells which leads to leukemic non-nodal MCL, which commonly involves the peripheral blood, bone marrow and spleen [83]. These cases are commonly clinically indolent; however, secondary alterations involving *TP53* (17p13.1) may happen and subsequently result in the development of very aggressive disease [12, 83]. Therefore, *IGH*-mutational status can identify clinically distinct subtypes of MCL which are characterized by different biological behavior.

Genetics plays an essential role in the development of PGL. Patients with MALT lymphomas have a high prevalence of HLA-DQA1*0103, HLA-DQB1*0601 and R702W mutation in the *NOD2/CARD15* gene (16q12.1) [84, 85]. Cases of LG lymphoma are associated with the presence of TNF-857 T allele [59] probably due to fact that tumor necrosis factor- α (TNF- α) plays a crucial role in *H. pylori*-associated inflammation. Positive associations have been found also between variant alleles in *TNF*-308G > A and *IL10*-3575 T > A genes and risk of DLBCL. In the genetic susceptibility of PGL plays a substantial role the rare allele (TLR4 Asp299Gly) of the Toll-like receptor 4 [86] which belongs to the family of pattern recognition receptors and recognizes conserved microbial components. According to the results of some studies genetics associated with homozygous haplotypes for the rare allele G (rs12969413) of SNP3 (single nucleotide polymorphism) covering the *MALT1* locus protect the people against gastric HG lymphomas, but not of LG [87].

It should be noted that the list of genetic aberrations that are present in NHL and that are useful either for diagnosis or for understanding the pathogenesis of different diseases has been growing continuously [12].

5. Pathological characteristics

Although lymphoma can involve any part of the GIT, the most frequent sites in order of its occurrence are the stomach followed by the small intestine and the ileo-caecal region as mentioned earlier. Visually PGIL appears as a polyp, mass, ulcer or infiltration depending on the pathological subtypes of lymphoma and the involved sites. Sometimes PGIL can be multifocal. Multifocality has been reported particularly in MALT lymphoma and FL [4]. Multiple lymphomatous polyposis (MLP) is a

rare and particular clinical type of GI lymphoma characterized by the development of multiple polyps. Polypoid lesions of MLP are commonly encountered in several sites of the GIT including the esophagus, stomach, duodenum, and bowel. This is classified as B-cell centrocytic NHL; most of the cases of MLP pathohistologically tend to be classified as MCL, rarely as MALT lymphoma [23] and a few cases of FL or TCL have been reported [88, 89].

According to 2016 revised WHO classification there are around 40 different subtypes of NHL, each with characteristics and peculiar clinical behavior. Although the goals of the WHO classification are to identify well-defined entities and to facilitate the recognition of uncommon subtypes that require further clarification, as they move forward some challenges in the classification continue. The borders between some of the disease entities remain ill-defined for example nodular lymphocyte predominant HL with diffuse growth pattern versus T-cell/histiocyte rich large BCL [12].

Some discoveries have been rapidly incorporated into daily diagnostic practice such as IHC for SOX11 or BRAF used to help in the diagnosis of MCL or hairy cell leukemia (HCL), respectively. Molecular detection of the recurrent *MYD88* (3p22.2) and *RHOA* (3p21.31) or *IDH2* (15q26.1) mutations are helping to delineate the morphological spectrum of lymphoplasmocytic lymphoma and angioimmunoblastic T-cell lymphoma, respectively [12].

Theoretically, with the possible exception of a few subtypes, any lymphoma entities listed in the last WHO classification of lymphoid malignancies may arise in the GIT. There are various inflammatory and reactive conditions in the GIT that can give rise to, mimic, or mask lymphomas. As mentioned earlier, the GIT is home to various lymphoid neoplasms, most of which are of B-cell lineage, including the most common DLBCL subtype. Not frequently TCLs also are encountered in GIT, however, some of them are related to underlying GI disorders or treatment. Some subtypes of GI lymphoma are characterized by aggressive clinical behavior, but others are indolent and may not require treatment. Identifying these entities can provide adequate treatment and, equally importantly, avoiding of overtreatment when aggressive therapy is not needed. The 2016 revised WHO classification has introduced some important changes to the schema used to categorize lymphomas that affect the GIT, and several TCL and NK-cell lymphomas have been reclassified and/or introduced [90].

DLBCL is the most common pathological type of lymphomas in essentially all sites of the GIT, although recently the frequency of other forms has also increased in certain regions of the world. Histopathologically, almost 90% of the PGIL are of B-cell lineage with very few TCLs and HL [4, 8].

The majority of PELs are the DLBCL type of NHL. Only a few cases of MALT lymphoma, MCL, TCL involving the esophagus have been reported [91–93]. HL of the esophagus is extremely rare. FL affecting the esophagus is a part of the multifocal presentation in the GIT [4].

PGL is the most common extranodal NHL and represents a wide spectrum of diseases, ranging from indolent extranodal MZL of MALT to aggressive DLBCL [11]. Although all histological types of nodal lymphoma can arise from the stomach, the majority of them are of B-cell origin, and MALT lymphoma and DLBCL account for over 90%. Gastric DLBCL occurs in 59% while the extranodal MZL of the MALT occurs in 38% of the PGL cases. Approximately one-fourth of the cases of DLBCL is encountered with the MALT component. MCL is seen in 1% of the cases, FL in 0.5%. Peripheral TCL accounts for 1.5% of PGL [94]. It should be noted that small BCLs are composed mainly of small lymphocytes and are often referred to as “LG” BCLs. The WHO classification intentionally does not divide lymphomas by grade, and because they (“LG” BCLs) are not surely indolent, the preferred name used is

“small BCLs”. They include MALT lymphoma, FL, MCL, etc. In the literature, most of the authors use the terms “HG MALT lymphoma” and “LG MALT lymphoma” without reference to the official name in the classification. The use of such terminology is confusing, because, this leads to some tangles. So, the “MALT” descriptor implies that there is only one type of lymphoma with various grades that develops in organs with mucosa. In terms of biological behavior, however, there are two common subtypes of lymphoma that arise in mucosal locations, one indolent and the other aggressive. Therefore, the term “MALT” would comprise both subtypes and blur the border between them. This was the main ground why WHO classification chose the term “extranodal MZL” for the indolent entity—to distinguish it from DLBCL, the aggressive entity. The acronym “MALT” is fine for shorthand but should not be used without reference to the official name for the indolent neoplasm “extranodal MZL” [83] as it is specified in the 2008 WHO classification and 2016 revised WHO classification [95, 96].

PSIL that are more heterogeneous than those in the stomach includes MALT lymphoma, DLBCL, MCL, EATL, FL, IPSID [97], a variant of extranodal MZL of MALT, and BL. IPSID and EATL are the main histological subtypes of PSIL. TCL of the small intestine accounts for approximately 10–25% of all PILs primarily occurring as EATL [55, 56]. Lymphocytic lymphoma (chronic lymphocytic leukemia) rarely arises primarily from GIT [4].

PCRL is mostly (>90%) of the B-cell lineage as other sites of the GIT [37, 97]. The most common histological subtype of PCRL is DLBCL. Other histological subtypes include FL, BL, MALT lymphoma, MCL [60, 98] and TCL. MALT lymphoma is less common in the large bowel than in the small intestine (0.5–1% vs. 1–2% of total cases, respectively). MCL in the colorectum presents commonly in the setting of diffuse systemic diseases. Peripheral TCL is rare in Western countries but has an increasing incidence in many Asian countries, and is more aggressive than the other types of lymphoma. Perforation is a common feature of TCL, and its prognosis is poor [22, 98].

As mentioned earlier DLBCL is the most common histological subtype (up to 58%) of all PGILs [99] and is encountered in all sites of GIT more than 50% being seen in the stomach followed by the small intestine [18]. It originates from GC B-cells or post-germinal B-cells [100]. DLBCL is characterized by large lymphoid cells, with nuclei greater than twice the size of a small lymphocyte, and frequently larger than nuclei of tissue macrophage. The tumor cells contain round, oval, or slightly irregular nuclei with vesicular nuclear chromatin, prominent nucleoli, and ample amount of basophilic cytoplasm and have a diffuse growth pattern [15, 100, 101]. In most cases, the predominant cells resemble either large centroblasts or immunoblasts; nonetheless, a mixture of these two cell types is also commonly encountered. So cytologically, DLBCL is diverse and can be divided into the following morphologic variants: centroblastic, immunoblastic, T-cell/histiocyte rich and anaplastic. Histologically, there is an intense cellular infiltration of the lamina propria [15]. The tumor cells are CD45 positive and express the pan-B antigens (CD19, CD20, CD22 and CD79a) [4, 100, 101]. Variability has been observed in CD5 and CD10 expression [102]. CD10 is expressed in 30 to 60% of cases though CD5 is generally negative and only seen in *de novo* cases. MUM1/IRF4 is present in 35–65% of cases. Nuclear PAX-5 immunoreactivity is seen almost in all DLBCL cases and 70% of tumor cells may express bcl-6 protein [101]. CD10 expression is considered a marker of follicular-derived DLBCL. Immunohistochemical evaluation shows a moderate to high proliferative index with a Ki-67 [15, 100]. The most commonly seen translocations as mentioned earlier include t(14;18)(q32;q21), t(3;14)(p27;q32) and t(8;14)(q24;q32) with *BCL2*, *BCL6* and *MYC* rearrangement, respectively [4].

2008 WHO classification recognized GC B-cell-like (GCB) and activated B-cell-like (ABC) molecular “subgroups” of DLBCL based on gene expression profiling

(GEP). The GCB and ABC subgroups are distinct biologic entities and differed in their chromosomal alterations, activation of signaling pathways, and clinical outcome. The identification of the molecular characteristics of these 2 subgroups, however, has led to the investigation of more adequate treatment strategies to improve the worse outcome of the cases with ABC/non-GCB type DLBCL [83].

MALT lymphoma mainly involves the stomach and also can rarely be encountered in the small intestine and colorectum [103]. Gastric MALT lymphoma can involve any part of the organ, but more frequently it affects the antrum [32]. It is typically an LG neoplasm, characterized by a dense lymphoid infiltration that invades and destroys gastric glands and results in the so-called “lymphoepithelial lesion” which is pathognomonic for lymphoma [103]. It has been postulated that MALT lymphoma arises from post-germinal center memory B-cells with the capacity to differentiate into marginal zone cells and plasma cells [104]. MALT lymphomas do not have a specific antigenic profile, the B-cells share the immunophenotype with marginal zone B-cells present in the spleen, Peyer’s patches and LNs [4, 33]. So, the tumor B-cells can express the surface immunoglobulins (often IgM, not frequently IgA and IgG, rarely IgD) and pan-B antigens (CD19, CD20, CD22 and CD79a), the marginal zone-associated antigens (CD35 and CD21, and lack CD5, CD10, CD23) [4]. Therefore, gastric MALT lymphoma is CD20+, rarely CD5+; CD10-, CD23- and cyclin D1- [15, 32, 33]. *H. pylori*-negative MALT lymphoma tends to have a high positive rate for t(11;18)(q21;q21) translocation than *H. pylori*-positive MALT lymphoma [69]. The PCR for *IGH* gene rearrangement should be performed only when there is a lymphoid infiltrate morphologically suspicious of lymphoma, and MALT lymphoma should not be diagnosed in the absence of clear histological evidence [105].

B lymphocytes of the extranodal marginal zone are the lineage of MALT lymphoma and are characterized by the heterogeneous cellular population which is prevalently composed of small (monocytoid) lymphocytes and large cells (immunoblasts and centroblasts) [106]. The increase in the proportion of large cells in MALT lymphoma can lead pathologists to confusion, suggesting a conversion into DLBCL which is characterized by the presence of solid aggregates or sheet-like proliferation of large cells [107].

The question about whether all cases of primary gastric DLBCL are derived from previous LG MALT lymphomas or they develop *de novo* remains unsolved. It should be noted that the cytogenetic alterations observed in gastric MALT lymphomas are different from those of typical primary gastric DLBCL. Therefore, cytogenetics can differentiate the two variants in some cases [11]. MALT lymphomas have a nonspecific antigenic profile that can differentiate them from primary DLBCL which is characterized by different immunophenotypes, especially about CD45, CD5, and CD10 expression [102]. Moreover, both transformed MALT lymphomas and *de novo* DLBCLs show bcl-6 positivity; however, DLBCLs with a GC-like phenotype is frequently CD10 and bcl-2 positive, whereas transformed MALT lymphomas are CD10 and bcl-2 negative [108].

IPSID or alpha heavy chain disease (α HCD) is an extranodal BCL and represents a variant of MALT lymphoma, which involves mainly the proximal small intestine [24, 25]. This disorder is morphologically characterized by small bowel infiltration by a uniform population of lymphoplasmacytic cells associating with atypical lymphoid propagation to DLBCL. The centrocyte-like lymphocytes express CD20, and both atypical lymphocytic and plasmacytic populations will strongly stain with IgA heavy chain, with lack of light chain staining [25]. IPSID lymphomas reveal excessive plasma cell differentiation and produce truncated alpha heavy chain proteins lacking the light chains as well as the first constant domain. Cytogenetic studies demonstrated clonal rearrangements involving predominantly the heavy and light

chain genes, including t(9;14)(p13;q32) translocation with the involvement of the PAX5 gene [24].

BL, a type of non-Hodgkin BCL, displays a diffuse, monotonous infiltrate of medium-sized neoplastic lymphoid cells with round nuclei and little cytoplasm showing finely clumped and dispersed, with multiple basophilic nucleoli, presenting pathologically with a “starry sky” pattern [15, 29, 109]. It is most often found in the abdomen and the jaw, however, localization in the abdomen other than the ileocecal area is very rare [15, 109]. Mutations in the transcription factor 3 gene, *TCF3* (19p13.3) or in its negative regulator *ID3* (1p36.12) take place in about 70% of sporadic and immunodeficiency-related BL and less frequently (40%) in endemic cases. *TCF3* supports the proliferation and survival of lymphoid cells by activating the B-cell receptor/phosphatidylinositol 3-kinase signaling pathways and modulating the expression of *CCND3* (*cyclin D3*, 6p21.1), which also undergoes mutation in 30% of BL cases. One of the questions not fully settled is whether genuine BL without *MYC* arrangement exists in reality. A subset of lymphomas that resemble BL morphologically, to a great extent phenotypically and by GEP, surprisingly lack *MYC* rearrangements. Instead, they have an alteration in chromosome 11q which is characterized by telomeric losses and proximal gains. Compared with BL, these lymphomas have more complex karyotypes, weak *MYC* expression, a certain degree of cytological pleomorphism, sometimes a follicular pattern, and frequently a nodal presentation. Although the clinical course seems to be similar to BL this subtype of BL was classified as a new provisional entity designated as Burkitt-like lymphoma with 11q aberration in the 2016 revised WHO classification. In literature, the number of reported cases of this entity is still limited and more studies are needed to resolve the controversial issues [83]. Tumor cells express membrane immunoglobulins (IgM, Ig light chain), B-cell antigens (CD19, CD20, CD22), CD10, bcl-6, c-MYC while expressing negative results for CD5, CD23, and bcl-2. The most common cytogenetic change is t(8;14)(q24;q32) and t(8;22)(q24;q11) translocations that are characterized by overexpression of *c-MYC* oncogene and can be detected in 90% of cases by classical karyotyping or FISH. The proliferation index Ki-67 of BL is very high, usually over 95%, so it is not surprising because BL is the fastest growing human cancer [29, 109]. Cytogenetic analysis is recommended to allow a clear distinction between BL and other *c-MYC*-driven B-cell NHL, especially DLBCL [29].

The morphological distinction between BL and DLBCL has been problematic for pathologists [12, 109]. Distinguishing between these two lymphomas, however, is critical, especially in adults (BL is rare in adults and rarely found in the stomach and colon), as the two diseases are treated differently [109]. GEP studies have demonstrated that BL has a specific signature but that there are cases that resemble DLBCL and aggressive BCLs, and have a molecular signature similar to BL, hence fall into an intermediate category. 2008 WHO classification recognized this issue and added a provisional entity of BCL, unclassifiable, with characteristics intermediate between DLBCL and BL (BCLU) [12, 29].

MCL originates from small to medium-sized lymphocytes located in the mantle zone (inner layer) of follicular tissue. Extra nodal involvement is present in the majority of cases, with a peculiar tendency to invade the GIT in the form of MLP. MLP is one of the most common primary GI presentations of MCL and accounts for approximately about 9% of PGIL [110]. MLP most commonly occurs in the ascending colon and the small bowel (particularly in the ileum and ileocecal region) and gastric involvement are next common [110, 111]. Occasionally, however, numerous polyps are present throughout the entire GIT. Polyps may be sessile, polypoid or both. They range in size from 0.1 to 4–5 cm and present with ulceration [110]. MCL is now recognized as an aggressive BCL with various growth patterns (mantle zone, nodular, or diffuse) and a broad range of cytological features [112, 113].

The prototype MCL is positive for pan B-cell antigens, although few cases of CD5-negative MCL have been reported [24]. Most cases of MCL exhibit a characteristic phenotype (CD20+, CD5+, CD43+, CD3-, CD10-, CD23-) and have the t(11;14)(q13;q32) translocation with overexpression of the *CCND1* (*cyclin D1*) gene on chromosome 11q13 [112]. Neuronal transcription factor SOX11 nuclear expression is also characteristic of MCL and can help distinguish MCL from other BCLs. The current WHO guidelines for the diagnosis of MCL rely on morphologic examination and immunophenotyping, with the demonstration of cyclin D1 protein overexpression and/or the t(11; 14)(q13;q32) for confirmation [114]. Few cases of cyclin D1-negative MCL, however, have been reported with up-regulated cyclin D2 or D3 [112]. The existence of cyclin D1-negative MCL has been controversial and difficult to substantiate since cyclin D1 overexpression is believed to be essential in the pathogenesis of MCL [112].

Duodenal-type FL, formerly known as primary intestinal FL, is a variant of FL sharing many morphological and immunohistochemical characteristics with nodal FL [19] but is a distinct entity from nodal FL in terms of clinicopathological and molecular standpoints [115] and demonstrates almost universally LG cytology. Morphologically, the mucosa and submucosa are infiltrated with well-circumscribed round neoplastic follicles which form small nodules and polyps corresponding to the endoscopic manifestation. The neoplastic follicles are similar to those seen in nodal FL and are composed of monotypic centrocytes and rare centroblasts. Although the disease is not graded in the same manner as nodal FL, it corresponds to LG (grades 1–2) lymphoma. The lymphoma cells often infiltrate into the surrounding lamina propria [19]. The immunoprofile of the lymphoma cells demonstrate similarity to that of nodal FL, with the expression of CD20, CD10, bcl-2, and bcl-6. The proliferation marker Ki-67 demonstrates a low rate. In contrast with systemic FL, duodenal-type FL is not characterized by the expression of activation-induced cytidine deaminase (AID) [116]. The indolent biological behavior of duodenal-type FL may bring its neoplastic nature into question. But it harbors the same t(14;18)(q32;q21) translocation with *IGH/BCL2* rearrangement observed in conventional FL. Furthermore, the duodenal-type entity seems to have rarer additional genetic aberrations than conventional FL. In addition, some evidence suggest that its gene expression profile overlaps with that of extranodal MZLs of MALT [19]. Although FL is very rare, it expresses surface immunoglobulin (often IgM) and pan B-cell antigens. CD10 and bcl-2 are expressed in almost 90% of the cases. Duodenal-type FL does not express CD5 and cyclin D1 thereby can be differentiated from MCL. *IGH/BCL2* rearrangement related to t(14;18)(q32;q21) translocation can be found by FISH or PCR analysis in most of the cases [117].

MEITL differs from the “classic” form of EATL by characteristic morphologic and immunophenotypic features [19]. Recognizing these distinctions, 2016 revised WHO classification formally separated these 2 entities and now defines MEITL as a primary intestinal TCL not associated with celiac disease [118]. It is a rare and aggressive peripheral TCL deriving from intestinal intraepithelial T lymphocytes. The small intestine is affected most frequently, with rare cases involving the stomach and colon. The spreading pattern of MEITL is in contrast with EATL as well; the former often spreads diffusely within the intestinal mucosa with or without tumefactive lesions, since the latter is frequently associated with large and ulcerative tumors that may perforate the intestine. Ulceration may occur in cases of MEITL, and mesenteric LNs involvement is common [28]. No background villous atrophy in small intestinal mucosa associates the tumor. MEITL cells are positive for CD3, CD8, CD56, and MATK in most of the cases, but negative for CD4, CD5, CD30. Nearly 20% of the cases demonstrate aberrant expression of CD20, a feature that can potentially lead to diagnostic confusion with B-cell entities, such as DLBCL

or BL. By contrast, classic EATL is usually negative for CD8, CD56, and MATK, with CD4 negativity and variable CD30 positivity [19].

Intestinal TCL, not otherwise specified, does not represent a specific disease entity; it is a term used to denote a heterogenous group of TCLs developing in the GIT with insufficient evidence to be diagnosed as EATL or MEITL, due to incomplete clinical information, scarce biopsy specimens, or insufficient immunophenotypic data. Furthermore, a part of the cases may be peripheral TCL, not otherwise specified, with GI involvement [19]. No reported cases of this TCL subset with a history of celiac disease at initial diagnosis [119]. The morphologic and immunohistochemical characteristics are heterogenous, because this term likely encompasses multiple disease entities [19]. This subset of lymphoma has an aggressive clinical course, with several reported cases demonstrating widespread disease at initial diagnosis [119].

The EBV-positive MCU has been added as a newly recognized entity and is characterized by limited growth despite the aggressive morphological features, and good outcome with a conservative approach [12]. In the involved mucosal surfaces of GIT is encountered superficial ulceration with underlying dense infiltrate of atypical lymphoid cells, necrotic debris, and a rim of reactive T-cells around B-cell areas. Plasma cells are present to a varying degree; they may be prominent and maybe light chain-restricted. The background inflammatory infiltrate can contain histiocytes, eosinophils as well. A significant number of large atypical lymphocytes are found within the necrosis, sometimes in dense sheets. The atypical lymphocytes are large and various in appearance and can resemble those seen in DLBCL or classic HL. They have large pleomorphic nuclei and prominent nucleoli with often Hodgkin and Reed-Sternberg (HRS) cytology. In the setting of iatrogenic immunosuppression for a solid organ transplant, this is a type of post-transplantation lymphoproliferative disorder [120]. The distinction between DLBCL and EBV-positive MCU is important in the post-transplantation setting because EBV-positive MCU has an indolent course. The lesions are typically well-circumscribed at the base and surrounded by a rim of reactive lymphocytes, which are mainly T-cells [115]. The large, atypical lymphocytes are positive for PAX-5, OCT2, MUM1, CD30, EBER and LMP1, and negative for CD10. BOB1 and bcl-6 are frequently positive, with variable expression of CD15, CD20, CD45 and CD79a [42]. T-cells in the inflammatory background are EBER-negative and express normal pan-T-cell markers, including CD3 and CD8. It is particularly important to distinguish these cases from classical HL, which is extremely rare in the GIT [19].

Indolent T-cell lymphoproliferative disorder (ITLPD) of the GIT is a provisional entity in the updated WHO classification and is a nonaggressive, largely nonepitheliotropic small, mature T-cell disorder of the GIT with evidence of clonality by T-cell receptor gene rearrangement studies [19, 121, 122]. This disease is encountered in adulthood (it occurs in children occasionally) and can involve any part of the GIT with the small intestine and colon being the most commonly involved sites. However, because many of the histologic features may overlap with IBD, it is uncertain whether these patients truly have to precede IBD, or whether the lymphoproliferative disorder itself has been initially misdiagnosed as IBD. No cases have been reported in association with celiac disease [121]. Moreover, GI ITLPD may be misdiagnosed as EATL or MEITL and lead to aggressive therapy since the latter lymphoma subtypes are rare but aggressive lymphomas of the GIT. Microscopically, the lamina propria is expanded by a dense and monotonous lymphoid infiltrate. The mucosal crypts or glands are displaced and often distorted, but not destroyed. Cryptitis and crypt abscesses are absent, but granulomas may be focally present, potentially mimicking those seen in Crohn's disease. The lymphoid infiltrate is composed of small, mature lymphocytes with round nuclei and regular nuclear contours [19, 121, 122]. The lymphoma cells are mature T-cells that express

CD2, CD3, CD4, CD5, or CD8, and variably CD7. The absence of CD56 expression is particularly important for diagnosis, distinguishing this entity from MEITL. All reported cases have demonstrated TCR β expression, with no cases showing TCR γ expression. The proliferation marker Ki-67 rate is low (<10%) [121, 122]. Clonal rearrangements of TCR (either γ or β) have been observed in all cases, and all have been negative for EBV (EBER) by FISH, distinguishing this entity from extranodal NK/TCL of nasal type, which can involve the GIT [19].

5.1. Staging of PGIL

Accurate diagnosis and staging of PGIL are essential for the stratification of treatment in this heterogeneous group of malignancies [4]. In other words, tumor stage is one of the most important guidelines in the choice of local (surgery, radiotherapy) and systemic (chemotherapy—ChTh) management modalities. There is a lack of consensus regarding the best staging system for PGIL. Different subtypes of PGIL have a different dissemination pattern from their nodal counterparts, which limits the use of the conventional Ann Arbor staging system [101]. The Ann Arbor staging system, developed for and routinely used in nodal NHL, is not optimal for documentation of the specific relevant features of primary extranodal lymphoma in the GIT [123]. Various modifications have been proposed to aid the staging of PGILs, including those of Musshoff, Blackledge and the Lugano Workshop [101, 123, 124].

TNM staging for tumors of epithelial origin has also been proposed as an alternative in PGIL to describe to what extent the disease is localized or spread. The “T” part of this system pertains to the anatomical structure of the organs and sufficiently fulfills the requirements for the staging of the local extent of the disease. The European Gastro-Intestinal Lymphoma Study (EGILS) Group proposed a modified TNM staging system, named after the first venue of the group in Paris. The modified staging system adjusted to the PGIL, considering histopathological characteristics of extranodal B and T-cell lymphomas, and accordingly enroll: (1) depth of tumor infiltration along with the thickness of GIT; (2) extent of nodal involvement; (3) lymphoma spreading [123]. Paris staging system is valid for lymphomas originating from the gastro-esophageal junction to the anus [123] and has increasingly gained its significance [4].

Paris staging system classifies PGIL as follows:

- TX—lymphoma extent not specified
- T0—no evidence of lymphoma
- T1—lymphoma confined to the mucosa/submucosa
- T1m—lymphoma confined to mucosa
- T1sm—lymphoma confined to submucosa
- T2—lymphoma infiltrates muscularis propria or subserosa
- T3—lymphoma penetrates serosa (visceral peritoneum) without invasion of adjacent structures
- T4—lymphoma invades adjacent structures or organs
- NX—involvement of LNs not assessed
- N0—no evidence of LN involvement
- N1—involvement of regional LNs
- N2—involvement of intra-abdominal LNs beyond the regional area
- N3—spread to extra-abdominal LNs
- MX—dissemination of lymphoma not assessed
- M0—no evidence of extranodal dissemination
- M1—non-continuous involvement of separate site in GIT (e.g., stomach and rectum)

M2—non-continuous involvement of other tissues (e.g., peritoneum, pleura) or organs (e.g., tonsils, ocular adnexa, lung, liver, spleen, breast, etc.)

BX—involvement of bone marrow not assessed

B0—no evidence of bone marrow involvement

B1—lymphomatous infiltration of bone marrow

TNM—clinical staging: status of tumor, node, metastasis, bone marrow

pTNMB—histopathological staging: status of the tumor, node metastasis, bone marrow

pN—the histological examination will ordinarily include six or more LNs

According to the site of the PGIL “regional” LNs implies: (a) stomach: peri-gastric LNs and those located along the branches of the coeliac artery (left gastric artery, common hepatic artery, and splenic artery); (b) duodenum: pancreatoduodenal, suprapyloric and infrapyloric, hepatic LNs, and those located along superior mesenteric artery; (c) small intestine: mesenteric LNs; the ileocolic as well as the posterior caecal LNs for the terminal ileum only; (d) colorectum: pericolic and perirectal LNs and those located along the ileocolic, right, middle, and left colic, inferior mesenteric, superior rectal, and internal iliac arteries [123].

6. Clinical characteristics

PGIL is a relatively rare cancer that is easily misdiagnosed and indistinguishable from other benign and malignant conditions due to its unspecific symptoms attributable to the site of involvement [4, 11]. The clinical manifestation of PGIL is dependent on the involved site, pathological subtype and the stage of the tumor. The age of presentation varies with the histological subtypes of lymphoma [97].

Although PEL is often asymptomatic, the common symptoms of symptomatic patients include dysphagia, odynophagia, weight loss, chest pain or symptoms developed as a result of complications such as hemorrhage, obstruction or perforation [4, 125, 126]. Constitutional B symptoms (fever, night sweats) are not typically present and are seen rarely [4]. Some researchers suppose that the diagnosis of GI lymphoma, including PEL (despite its rare incidence) should be considered in any HIV-infected patient presenting with unexplained GI symptoms [44, 93].

Clinical manifestation of PGL is nonspecific and indistinguishable from other benign and malignant conditions. The most common complaints of patients with PGL are epigastric pain, nausea and vomiting (due to pyloric stenosis or reflex), iron-deficiency anemia due to chronic gastric bleeding, and weight loss. Occasionally, an abdominal mass is palpable. Severe complications such as perforation and life-threatening haemorrhage are seen rarely (4%) [127]. Lymphadenopathy is rare and such patients often have no physical signs [4]. Unlike nodal lymphoma, B constitutional symptoms are not common. Gastric MALT lymphoma is often an indolent, multifocal disease and in 10% of the cases, it can have synchronous involvement of intestinal and extraintestinal sites [128] with appropriate clinical signs.

The clinical presentation of PSIL is nonspecific and the patients have symptoms, such as colicky abdominal pain, nausea, vomiting, weight loss and rarely acute obstructive symptoms, intussusceptions, perforation or diarrhea [97]. However, the typical clinical features of IPSID, a subtype of MALT lymphoma, are different because the dominant region for IPSID is the duodenum and upper jejunum, and present diarrhea, malabsorption syndrome or protein-losing enteropathy [23, 24]. Intussusception is a common clinical finding in ileocecal lymphomas, occurring mainly in patients with the fungating type of the lesion [129]. In general, the most commonly affected region with PSIL is the ileum followed by the jejunum and duodenum (6–8%) [100].

PCRL presents with abdominal pain, altered bowel habit, palpable abdominal mass, lower GI bleeding and weight loss [22, 101, 130, 131]. Obstruction and perforation are relatively rare in patients with PCRL [131]. Primary colorectal TCLs are characterized by multifocal ulcerative lesions in relatively young patients and a high rate of hematochezia, fever or perforation, and aggressive clinical course even for cases of localized disease [22]. The caecum is the most common site of involvement because of the abundance of lymphatic tissue [101].

Some features of some PILs should be peculiarly noted. MCL, FL and MALT lymphoma of the small intestine rarely present with multiple polyps called MLP [20, 110, 132]. In one-third of the cases, MLP is due to MCL. MLP can present with symptoms such as abdominal pain, diarrhea, bleeding, and less frequently, protein-losing enteropathy, intestinal malabsorption, intestinal obstruction or chylous ascites. MLP polyps usually occur in the ileocecal region and one-third of cases present as a mass [110].

7. Diagnostics

During diagnostics, the clinician verifies the lymphoma, determines its site and stage, and detects possible relationship of some lymphoma subtypes with some infections and disorders, and inherited conditions. Comprehensive history taking and physical examination may provide a very important clues for reaching the goal promptly. The first objective examination tool depends on the patient's complaints and the result of the physical examination.

Endoscopy is the firstly used diagnostic modality for visualization of the lesion and for getting biopsy samples depending on the involved site. The histological examination of biopsy samples taken during endoscopy is the "gold standard" for the diagnosis of PGIL. The endoscopy by itself cannot identify lymphoma or differ it from the more common GI carcinomas [127]. The injury patterns of PGIL (ulceration, diffuse infiltration, polypoid mass, etc.) are characteristic also of GI carcinomas. However, the most common endoscopic appearances of PGIL are ulcerative and massive [8]. One of the main difficulties for accurate visual diagnosis of PGIL is the variation in endoscopic abnormalities, which varies from minimal mucosal irregularities to bigger ulcerations [18].

Endoscopic findings in PEL vary greatly and are nonspecific, which poses diagnostic challenges when it is differentiated from other benign and malignant lesions. The morphological features of PEL seen at endoscopy are nodular, polypoid, ulcerated or stenotic [92]. Multiple biopsies should be obtained from the stomach, gastroesophageal junction, duodenum, and from lesions in cases of PGL since gastroduodenal lymphomas (MALT lymphoma, duodenal-type FL, etc.) can occasionally present as a multifocal disease with involvement of tissue that appears to be unaffected on endoscopic visualization [133]. Endoscopic findings may vary from subtle mucosal changes (mucosal edema, friability, patchy redness, irregular patchy gray or whitish granularity, contact bleeding, superficial irregular erosions and ulcerations) to gross lesions (ulceration, diffuse infiltration, and a polypoid mass) [124] that are characteristic also for early gastric carcinoma and gastric carcinoma respectively and are not diagnostic (**Figure 1A**). The extension of a gastric lesion across the pylorus into the duodenum is highly suggestive of lymphoma, not of carcinoma, but is not pathognomonic. Endoscopy, however, is an indispensable tool for the initial diagnosis, for obtaining biopsy samples and as well as for follow-up of the cases. Conventional pinch biopsy results may be false-negative (up to 8%) owing to submucosal localization [127] without involving the mucosa. Repeated endoscopic biopsies are mandatory in case of clinical suspicion and negative or

Figure 1.

Endoscopic (A) and CT (B) views of gastric DLBCL in H. pylori-positive 63-year-old man who complained of anorexia, epigastric discomfort and vomiting. The diagnosis of DLBCL was confirmed pathohistologically and immunohistochemically. The lesion involved the proximal third of the stomach. Perigastric, regional, paraaortic and mesenteric LNs were enlarged on CT.

inconclusive histology [124] EUS-guided fine-needle aspiration biopsy can help to increase the yield in some cases. The presence of *H. pylori* in tissue samples obtained by esophagogastrosocopy must also be tested in all cases through immunohistochemistry (IHC) [11]. In the last years, magnifying endoscopy has improved endoscopic diagnosis of PGL by detection of destructed gastric pits, irregular pit size or distribution [62].

The duodenum and the terminal ileum can be investigated by conventional endoscopy which is home to special subtypes of PGIL. Detection and assessment of PSIL have been revolutionized since the introduction of capsule endoscopy and double-balloon enteroscopy (push-and-pull enteroscopy) which is capable of providing biopsy samples, thereby limiting major surgical interventions. PSIL is presented as a polyp, bulky lesion, or ulcer on capsule endoscopy which cannot be visually differentiated from other lesions [134]. Unlike the other endoscopic approaches, capsule endoscopy does not permit tissue sampling. Primary ileocolonic lymphoma and PCRL can be classified endoscopically into fungating, ulcerative, infiltrative and mixed types. Among these, fungating and ulcerofungating are the most frequent [129]. Total colonoscopy with tissue sampling is crucial for accurate diagnosis in cases of suspicion of PCRL.

As mentioned earlier MCL, FL and MALT lymphoma of the small intestine rarely present with multiple polyps called MLP [20, 110, 132]. Upper GI endoscopy, enteroscopy and colonoscopy are important tools in diagnosing MLP to assess the locations of the polyps and obtain tissue biopsies. Differentiating MLP from adenomatous or hamartomatous polyposis by endoscopic or radiological evaluation alone is impossible and tissue diagnosis is required [110].

MALT lymphoma of the large intestine is manifested as multiple mucosal nodularities [22, 135]. IPSID tends to affect proximally with a disseminated nodular pattern leading to mucosal fold thickening, irregularity and speculation [136]. Extranodal BL is frequently seen but GIT involvement varies among the three clinical subtypes, with the sporadic variant usually presenting as a bulky mass, commonly in the terminal ileum and caecum [15, 29].

About 10% of all FL is of GI origin and the GIT is the most frequently involved site [115]. Primary FL of the GIT is very rare and constitute <7% of all GI NHL lymphomas [20]. Many cases (43–77%) of GI FL are asymptomatic and sometimes

accidentally found by endoscopic examination [115]. Cases of GI FL often present as an incidental whitish polypoid lesion described as small polypoid nodules, multiple polypoid lesions, multiple small polyps, multiple nodules, or multiple granules in patients undergoing upper endoscopy for other unrelated reasons, such as dyspepsia or suspected gastroesophageal reflux [19, 137]. Other macroscopic features are infrequent, but they can present as erosions or ulcers [137]. The disease is usually found in the proximal part of the small intestine [19, 20, 115, 137–139] most often with duodenal involvement in the second portion [19, 115, 137]. Gastric and colorectal FL have been occasionally reported [137]. Multiple sites of small intestinal involvement are seen in 56–80% of cases [20, 139]. The most reliable way to distinguish primary GI FL from GI involvement of conventional FL, is to rule out intestinal involvement by mesenteric/retroperitoneal disease and/or systemic diseases by imaging and bone marrow biopsy [19].

PTCL preferentially involves the jejunum with an increased tendency to perforate [130]. EATL, usually proximal or diffuse, shows nodules, ulcers or strictures [136]. PTCL of the large intestine presents as a diffuse or focal segmental lesion with extensive mucosal ulceration similar to that observed in granulomatous conditions as Crohn's disease or tuberculosis [22, 135]. The GIT EBV-positive MCU usually presents with sharply circumscribed ulcers in the oral mucosa, esophagus, colon, rectum, and/or perianal area. It is usually a localized (albeit potentially locally aggressive) process, and lymphadenopathy, bone marrow involvement, and disseminated disease are exceedingly rare [41, 42]. In cases of ITLPD, the affected GI mucosa (the disease most often localizes in the small intestine and colon; however, all sites in the GIT may be involved) is viewed thickened with prominent folds, nodularity, and/or polyps. The surface can be hyperemic with superficial erosions [121].

It is recommended that biopsy specimens should undergo histological, immunohistochemical and genotyping studies to make the diagnosis [124]. It should be noted that on histological examination Reed-Sternberg-like cells can be seen in LG BCLs [140] including extranodal MZL, FL, IPSID that can be confused with HL. Histological assessment is currently considered the “gold standard” also for the assessment of treatment response in gastric lymphoma [5].

The different procedures employed for the pre-treatment staging include computed tomography (CT), magnetic resonance imaging (MRI), EUS, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). Contrast-enhanced techniques and functional imaging such as perfusion CT can also help the monitoring, assessment, and prediction of response [4, 11].

Radiographic patterns of PEL, described in the literature, are nonspecific and not diagnostic and include thickening of the wall mimicking other tumors, stricture, ulcerated mass, multiple submucosal nodules, varicoid pattern, achalasia-like pattern, progressive aneurysmal dilatation, and tracheoesophageal fistula formation, and none of them is specific and diagnostic [91, 141]. CT, however, is valuable for the evaluation of the mediastinal extension of PEL, fistula formation, and status of LNs, thus playing a role in staging disease, assisting in stratification of available treatment modalities, evaluating treatment responses, monitoring disease progression, and detecting relapses [141]. CT scan of the chest, abdomen and pelvis is should be employed to stage PGIL irrespective of the involved site.

Radiographic patterns of PGL observed in double-contrast upper GI studies include ulcers, thickened fold, polypoid mass, mucosal nodularities or infiltrating lesions, which are not conclusive, thus posing a diagnostic challenge while differentiating from other malignant and benign lesions, hence requiring pathological confirmation [142]. The radiological findings usually do not correlate to its pathological subtypes [4]. Conservation of pliability and distensibility of the gastric wall

despite the substantial gastric fold thickening and extensive infiltration of the gastric wall is a finding very suggestive of lymphoma. Gastric wall thickening is much more severe in HG lymphoma compared to LG lymphoma on CT images, and abdominal lymphadenopathy is more common in cases of HG lymphoma (**Figure 1B**) [142]. The patterns of gastric involvement can be as localized polypoid mass or segmental/diffuse infiltrative lesion. Tumor infiltration is usually homogeneous, however, areas of low attenuation may be observed in larger tumors. Segmental infiltration and diffuse infiltration involving more than 50% of the stomach are the most common hallmarks of gastric NHL on CT images [143]. Preservation of the fat plane which is an indirect sign that there is no invasion into surrounding anatomical structures may be suggestive of lymphoma as well, however, it is nonspecific. Transpyloric extension of the PGL with involvement of the duodenal wall and presence of bulky LNs, notably below the renal hilum is more suggestive of lymphoma than carcinoma [142].

The radiologic appearances of PCRL are variable and significantly overlapped with other benign and malignant conditions of the colorectal region. The imaging findings during double-contrast barium enema can be divided into focal and diffuse lesions. The observed focal lesions include mucosal nodularity, mucosal fold thickening, polypoid mass, circumferential infiltration with smooth mucosal surface or extensive ulceration, cavitory mass. Diffuse lesions encompass diffuse ulcerative and nodular lesions [22, 135].

The MRI characteristics of PGIL include exophytic tumor mass, irregularly thickened mucosal folds with submucosal infiltration, a circular infiltrating lesion which narrows the lumen, mesenteric or/and retroperitoneal lymphadenopathy. The lymphomas are mostly homogeneous on T1-weighted images and have intermediate signal intensity. Heterogeneously increased signal intensities are observed on T2-weighted images. The enhancement is commonly mild-moderate after intravenous administration of gadolinium-based contrast agents [144].

In routine clinical practice, EUS is being employed widely for assessment of the primary lesion and clinical staging because it is able accurately to depict the neoplastic disease in the wall of the GIT organs, extent of the lesion and depth of invasion. EUS findings, however, are not pathognomonic, because PGILs can be presented as anechoic, hypoechoic or even rarely hyperechoic masses [5, 93, 127]. Infiltrative carcinoma tends to grow vertically along the gastric wall, while PGL demonstrates mostly horizontal growth. Moreover, the involvement of perigastric LNs is most common in PGL cases [5]. EUS is highly accurate in detecting the depth of infiltration of tumor and the presence of perigastric LNs, which are essential for adequate treatment planning. It should be noted that EUS can provide significant information to distinguish lymphoma from carcinoma regardless of the stage of the mentioned tumors [124].

EUS has become an integral tool in the diagnosis, locoregional staging, and monitoring response of PGIL to treatment. EUS is superior to CT scan for the T- and N-staging by providing vivid details for any invasion within and beyond the gastric wall. The significance of EUS and CT, however, is a matter of debate in the follow-up of patients, since it has been well studied that histological remission is confirmed earlier than the disappearance of the wall changes in cases of PGIL. It eliminates the necessity for endoscopic biopsy follow-up in the relevant patients. Gastric MALT lymphoma, often requires a more meticulous staging procedure despite its indolent clinical behavior since it is not infrequently multifocal, can be transformed into DLBCL, and is difficult to diagnose due to normal endoscopic appearance in many cases. Therefore, endoscopic biopsy samples should be taken from multiple sites of the stomach and duodenum encompassing the areas with normal and abnormal appearance [145]. Some authors suppose that EUS seems sufficient for the routine follow-up of patients with PGL without using gastroscopy with biopsy [5].

Recently, the incorporation of PET-CT has emerged as an indispensable tool in staging the disease and following up the patients with extranodal involvement of HL and NHL, with increased sensitivity and specificity. The intensity of FDG uptake in lymphoma is influenced by various intrinsic tumor factors such as histological features and grade, as well as various extrinsic factors [144]. Application of 18F-FDG PET-CT in the diagnosis of PGL is challenging due to the physiologic FDG activity in the stomach and variability in the degree of uptake in various histologic subtypes [146]. FDG-PET has a significant advantage in the staging of DLBCL independent of the affected anatomic site, and MCL, although it has no added benefit for MALT lymphomas due to their indolent behavior [11, 147]. PET-scanning has no sufficient sensitivity (<50%) and is not reliable to diagnose the intestinal FL [137]. Currently, for PGL, PET CT is a standard initial imaging study in DLBCL histology but not recommended in cases of gastric MALT lymphoma [11] and intestinal FL because aggressive PGILs have more intense uptake than LG MALT lymphoma and GI FL [137, 146]. GI DLBCL is manifested as circumferential thickening of the wall, with diffuse increased FDG uptake. FDG PET-CT can also detect indolent lesions that are undetectable on conventional cross-sectional imaging [147]. New promising techniques using recent PET tracers like 18F-fluoro-thymidine may significantly benefit the overall management of lymphomas [4].

In some cases, the diagnosis of PGIL cannot be made by traditional methods and novel diagnostic methods and surgery is needed. Chen et al. report that 48.4% (201/415) of their patients with PGIL were diagnosed by surgery. Reasons for that surgery became a method of diagnosis were as follows: (1) the lesions of PGIL mainly locate submucosally, which increase the difficulty of diagnosis through endoscopic biopsy; (2) when the diagnosis of a visualized malignant lesion after repeating endoscopic biopsy still cannot be confirmed, surgery can be the choice; (3) part of PGIL patients came to the hospital because of acute abdomen, especially patients of TCL and in those cases diagnosis could only be verified after an emergency operation. They report that in their study, 37 (18.4%) of the 201 patients diagnosed by surgery underwent emergency operations. It makes suggests that surgery is an essential way for diagnosis of PGIL, particularly in the cases of TCL because of their high frequency of acute abdomen [8].

The other laboratory analyses conducted encompass a complete haemogram, hepatic and renal function panels, measurement of blood glucose, serum lactate dehydrogenase, uric acid, potassium, calcium, and phosphorus levels. Bone marrow aspirate with a biopsy is fulfilled for assessment of lymphoma dissemination and monitoring of treatment response. In certain types of lymphoma serum protein electrophoresis and identification of paraproteins can be performed as well. For recognition of etiological factors, appropriate serological tests are frequently conducted in various types of lymphoma [145].

8. Treatment strategies

The optimal treatment of PGIL is a matter of debate. The treatment strategy of PGIL depends on multiple factors; involved site, pathological variants, stage of the tumor, the existence of bacterial or viral associations and chromosomal translocations. Accurate staging is necessary for the important therapeutic implications. If the disease affects beyond the organ and regional nodes, treatment strategies can no longer be focused on local control and systemic aggressive ChTh must be the mandatory option.

Surgery was the main treatment modality in the past, but now, in uncomplicated cases, it is replaced by the combination of anthracycline-containing ChTh

and rituximab, a chimeric monoclonal antibody against the protein CD20 [13]. Treatment of PGIL is largely ChTh based, augmented with surgical and radiation therapy in many cases. The length and type of chemotherapeutic interventions depend on the extent of the disease but generally systemic therapy, as well as intrathecal delivery of agents, is required to prevent or treat involvement in the cerebrospinal fluid. Surgical resection is controversial and generally considered when complete resection is possible rather than debulking unless indicated by obstruction or perforation. Consolidation therapy with radiation is recommended in patients with localized disease [18]. So, the global therapeutic approach to the cure of primary GI NHL has completely changed over the last 10 years: innovative, conservative options to reduce treatment toxicity, therefore preventing systemic relapses, have made their appearance and are on the rise [16].

The discovery of a causative link between *H. pylori* and the development of gastric MALT lymphoma has revolutionized treatment options [5]. The literature has reported that approximately 60–100% of *H. pylori*-positive localized gastric MALT lymphoma without t(11;18)(q21;q21) chromosomal translocation obtain complete remission after the eradication of this bacteria [4]. Based on this recently, treatment to eradicate *H. pylori* has become standard management for primary gastric MALT lymphoma [148, 149]. Histological evaluation of tumor response to treatment, however, requires serial follow-up and needs standardization. The GELA histological evaluation system of residual disease in gastric biopsy samples following treatment is commonly used at certain centers. It has been reported that monoclonal B-cells persist in up to 50% of the cases with confirmed endoscopic and histological remission following treatment with antibiotics [150]. Patients with negative *H. pylori* infection and those with failure to eradication therapy should benefit from alternative therapeutic regimens that include radiation therapy or ChTh [32]. Gastric MALT lymphoma-specific chromosomal translocation t(11;18)(q21;q21) has been discovered to be a negative predictive parameter for regression following *H. pylori* eradication [73].

No definite guidelines have been advocated for the treatment of advanced or *H. pylori*-negative gastric MALT lymphoma. Although surgery has been used as its initial treatment, recent studies showed that moderate-dose radiotherapy alone can achieve a remission rate of 93–100%. Before antibiotic therapy, radiotherapy was the first-line therapy for gastric MALT lymphomas [32]. Thus, “involved-field” (stomach and perigastric LNs) irradiation at the total dose of 30 Gy for over 4 weeks has become the treatment of choice for stages I and II MALT lymphoma without *H. pylori* or with persistent lymphoma following therapy. Surgery is, at present, no longer a curative first-line treatment for gastric MALT lymphoma and reserved only for refractory cases to nonsurgical approaches and for those with complications such as perforation, hemorrhage or obstruction that cannot be treated with other alternative therapies [11, 151]. Systemic therapy must be taken into consideration in patients with advanced stages [151]. Patients with localized disease, who did not respond to antibiotic therapy or radiation therapy, should be considered for systemic ChTh [59]. Treatment options include ChTh and the use of monoclonal antibodies. ChTh using the CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) regimen is highly effective in the treatment of patients with localized primary HG PGL [18]. Thus ChTh and rituximab immunotherapy could be used in all stages of gastric MALT lymphoma alone or combination of both [11, 32].

Surgery traditionally was the standard procedure or an indispensable component of combined treatment strategy in primary GI DLBCL. The arguments in favor of the surgery include removal of the primary tumor, availability of precise histological assessment and tumor staging, as well as avoidance of life-threatening complications (perforation, hemorrhage) that may emerge during radiotherapy and ChTh. In recent decades, opinions have increasingly shifted away toward conservative

treatment even for patients with the resectable disease [152]. Gastric DLBCL is treated with aggressive poly-ChTh, which is usually combined with rituximab. Thus, gastric DLBCL should be treated with the front-line ChTh (CHOP) or chemoimmunotherapy with R-CHOP (CHOP with rituximab). Frontline chemoimmunotherapy with 3–4 cycles of standard R-CHOP followed by “involved-field” radiotherapy could be considered as a standard option for localized stages. Complete remission can be achieved in advanced gastric DLBCL patients after 6–8 cycles of R-CHOP as their nodal counterparts [4, 11, 16, 152]. In other words in the case of gastric DLBCL, either arising *de novo* or the following transformation from MALT lymphoma, conservative approaches demonstrate excellent results, as gastric DLBCL appears to be a highly chemosensitive disease [151]. A higher cost of rituximab was the prohibitive factor for cure in these patients [18]. Therefore, radical intent surgery might be proposed for the patients unfit for rituximab treatment [152] as rituximab use has raised concerns about a higher incidence of neutropenic infections [100].

If the patient has the progressive disease (according to PET CT), the consideration for second-line treatment (salvage ChTh) for DLBCL with a regimen, such as rituximab, ifosfamide, carboplatin, and etoposide or Gemcitabine, dexamethasone, cisplatin and rituximab, followed by autologous stem cell transplantation (SCT) should be considered [11].

Various recent studies have demonstrated a significant rate (50%) of complete regression (analogous to MALT lymphomas) in localized gastric DLBCL following anti-*H. pylori* therapy. These results exhibit that eradication, keeping chemoradiotherapy for unresponsive patients, is a fair strategy for patients with limited-stage gastric DLBCL [153]. This suggests that a subset of gastric DLBCL might still contain an antigenic drive, though antibiotics could be paired with ChTh at the clinician’s discretion (**Figure 2**). Nevertheless, these results need to be valid in larger prospective studies before broad usage [11].

Lymphomas originating from the duodenal bulbs might have similar characteristics with gastric MALT lymphomas. Unfortunately, the lesions observed over the descending portion might be less associated with *H. pylori* infection, indicating that *H. pylori* eradication therapy cannot be expected to be effective [23]. Nevertheless, various reports are showing that the eradication of *H. pylori* is effective for duodenal and even rectal MALT lymphomas [37, 154].

Figure 2. Endoscopic (A) and CT (B) views of the patient with a history of gastric DLBCL (described in **Figure 1**) following *H. Pylori* eradication therapy and 6 cycles of ChTh with CHOP regimen. According to gastroscopy and CT scan, a complete response was achieved after treatment. The patient lived 6 years without the signs of recurrence confirmed by regular endoscopy and CT scan performed annually and died of unrelated disease.

The treatment outcome of PIL is relatively poorer than that of PGL depending on their histological subtypes. Lymphoma primarily located in the small bowel usually warrants laparotomy with the affected segment removed both for its diagnosis and its treatment. LG BCL of the small intestine (stage IE) only requires surgical resection. A multi-agent chemotherapeutic strategy is warranted for advanced stage PIL with multifocal cases of lymphoma. Systemic treatment with anthracycline-based ChTh followed by radiotherapy is proposed for advanced PIL which cannot be removed [4]. No guidelines exist for the treatment of small intestinal DLBCL. Historically, in HIV patients ChTh combined with antiretroviral therapy remains the first step in the management of aggressive lymphomas [100].

IPSID in the early stage responds to antibiotics such as tetracycline or combined metronidazole and ampicillin, with remission occurring within 6–12 months. Patients without substantial regression following a 6-month course of antibiotic therapy or complete remission within 12 months should be administered ChTh with CHOP. ChTh is also recommended up-front combined with antibiotics for patients with intermediate or advanced stage of the disease at initial diagnosis. Surgery plays a limited role in the majority of cases due to diffuse involvement, although it may be required for accurate diagnosis [4, 24]. Most untreated IPSID patients progress to lymphoplasmacytic and immunoblastic lymphoma invading the intestinal wall and mesenteric LNs, and may metastasize to a distant organ [24].

No optimized therapeutic guideline is available for BL which usually requires an aggressive approach. High-intensity chemotherapeutic agents for a short duration, such as cyclophosphamide, vincristine, doxorubicin, methotrexate and cytarabine, can significantly improve the treatment outcome [4]. The risks of emerging tumor lysis syndrome (TLS) and CNS dissemination of the disease are also important issues that should be taken into consideration at the first presentation of patients with BL. To reduce the risk of TLS, many regimens use relatively low doses of ChTh drugs (especially cyclophosphamide) and administration of prednisone. High-dose intravenous (as well as intrathecal) methotrexate and cytarabine, both of which have CNS penetration, are commonly administered to reduce CNS dissemination of the disease [155].

CODOX-M/IVAC, Magrath regimen (CODOX-M, cyclophosphamide, vincristine, doxorubicin, methotrexate; /IVAC, ifosfamide, cytarabine, and etoposide) is commonly used for the treatment of BL. Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with methotrexate and cytarabine is another effective strategy in BL. Most adults with BL can favor the Magrath or modified Magrath regimens (depending on risk group) with the addition of rituximab. The benefit of administering rituximab in front-line BL therapy has been demonstrated in both adults and children, and it is a standard treatment in both cases. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) is an intermediate-intensity strategy, which was tested in BL because of its high efficacy in DLBCL and its hypothetical ability to overcome high tumor proliferation. Studies testing this strategy in patients with sporadic and immunodeficiency-associated BL demonstrated a progression-free rate > 90%, with low toxicity and low rates of TLS. A randomized trial comparing DA-EPOCH-R (dose-adjusted EPOCH-R) with R-CODOX-M/RIVAC (CODOX-M/IVAC with rituximab) is currently being conducted in several European countries for its comparative effect [155]. Rituximab exhibits sufficient promising results to recommend its adjunction to ChTh and it may even erase the prognostic difference between young and elderly patients. However, its administration is avoided during the debulking phase given the high risk of TLS [29].

Involved-field radiotherapy should not be considered in BL, except for patients with CNS involvement. In case of initial CNS invasion, the number of intrathecal

ChTh administrations is increased. SCT should not be recommended for patients with complete responses. This approach must be employed for cases of partial response or patients with chemosensitive recurrence. Due to the high proliferative ability of BL, graft-versus-tumor effects that appeared following allogeneic SCT are too sluggish to be manifested. Therefore, this type of transplant should not be employed [29]. It should be noted that because modern ChTh may be curative for the majority of BL patients and up to 90% of adolescents and young adults, the interest in hematopoietic cell transplantation has now considerably diminished [156].

MCL is an aggressive and incurable type of B-cell NHL [110, 113]. Conventional therapeutic regimens are not effective in MCL cases and are associated with poor survival [4, 110]. Current combinations of multi-drug ChTh and monoclonal antibodies have conferred significant improvement in response rates of MCL. Overall response rates comprise 80–95% and complete response rates of 30–50% are not being achieved. Other ChTh regimens such as R-Hyper-CVAD (Rituximab with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) have demonstrated good results. However, it is a more aggressive regimen associated with increased toxicity. The R-CHOP regimen can be used in patients with poor performance status as a less toxic regimen [110]. Those who are eligible for grafting are previously induced with R-CHOP. ChTh regimen, consisting of rituximab alone or purine nucleoside analogs with rituximab, can be applied to those ineligible for SCT [4, 157].

Compared with nodal FL, GI FL usually presents with localized disease [115] and shows indolent clinical course [4, 20, 117, 158, 159], with excellent long-term survival, even when the disease recurs in the intestine until they are symptomatic or show evidence of its progression [4, 117, 158, 159]. A small subset of patients (<10%) progress to nodal disease [158, 159]. Surgical resection might be curative for patients with GI FL who, after thorough evaluation, are considered to have disease confined to one segment of the bowel. However, given the multifocal nature of GI FL, the role of surgery is generally limited to establishing a diagnosis and treating actual or imminent complications [139]. Therefore, there is no consensus in the management strategy and some clinical problems are yet to be solved [115]. A variety of therapies have been used, but treatment is not likely to be necessary for most patients and a “watch-and-wait” approach is reasonable [4, 115] because unlike nodal FL, GI FL is known to be indolent [115]. Symptomatic cases, or advanced disease of FL necessitates surgery and ChTh (CHOP). Although rituximab is beneficial for FL, its true value has not been well ascertained [4].

No guidelines are available for the management of EATL although anthracycline-based ChTh is a mainstay treatment modality. ChTh as the first-line therapy is more effective in GI BCL when compared with the T-cell subtype. In cases of serious comorbidities and complications attributed to ChTh, such as perforation, and profuse bleeding multimodal approaches including debulking or radical intent surgery should be performed to remove the gross EATL before ChTh, if the patients can tolerate it. It was reported that two-thirds of the patients with EATL undergone surgical resection followed by combination ChTh and autologous SCT can obtain a sustained complete response [4].

Most patients with EBV-positive MCU have a favorable clinical course, with nearly all reported cases showing resolution following a reduction of immunosuppressive therapy [41, 42]. Other interventions, such as local radiation or ChTh, may be necessary for those patients in whom the immunosuppression cannot be reversed, such as in the elderly [19].

GI ITLPD usually presents as an indolent neoplasm with no progression to aggressive TCLs. These cases are often misdiagnosed as TCL with little or no response to

ChTh. Radiotherapy may be a more effective option compared with ChTh. But there are not enough clinical observations to confirm it [160].

Since the introduction of highly active antiretroviral therapy (HAART) in the treatment of AIDS patients, a decrease in the incidence of GI lymphoma among AIDS patients and improved survival rates for relevant lymphoma patients have been achieved. Therefore, therapeutic strategies including ChTh, immunotherapy and HAART can be able to demonstrate promising results in response and survival rates [43].

9. Prognosis

The clinical course and prognosis of PGIL are dependent on histopathological subtype and stage at the time of initial diagnosis [11]. The best overall survival (OS) and progression-free survival (PFS) were observed in MALT lymphoma and FL, followed by DLBCL, and the poorest in EATL and other lymphomas of T-cell lineage [8]. Overall survival rates remain poor also in MCL [110].

Gastric MALT lymphoma is commonly an indolent, multifocal disease and because of that, it has a high rate of relapse after surgery. In 10% of cases, it can have synchronous involvement of intestinal and extraintestinal sites [91]. In the early stages, the disease may completely resolve following antibiotic therapy; however, transformation to DLBCL is not uncommon [25].

There are many prognostic systems for prognostication of DLBCL of which the International Prognostic Index (IPI) is the most valuable and main clinical tool widely employed [101]. GEP is a new evolving approach to diagnose, classify and prognosticate DLBCL. According to GEP two prognostically significant types of DLBCL have been identified [12, 83, 101, 161]. The molecular subgroups include GCB and ABC, which are associated with different chromosomal aberrations. GCB group has a better prognosis than the ABC group [101]. GEP is considered the “gold standard” to identify the molecular subtypes of DLBCL, however, is not available in routine diagnostics due to its cost-ineffectiveness. Several studies have attempted to define the molecular subtypes (GCB and non-GCB) by IHC using a limited panel of available antibodies [12]. The Hans algorithm which used antibodies to CD10, BCL6, and IRF4/MUM1 has been the most widely used in clinical trials [83] with nearly 80% concordance with the GEP [161]. According to the results of most of the relevant studies, IHC algorithms can predict the prognosis in DLBCL, however, all researchers believe that these methods cannot perfectly substitute GEP. Taking into consideration of the possible prognostic significance of cell lineage and the incremental efforts to adjust the treatment strategy based on molecular characteristics, 2016 revised WHO classification recommends distinguishing the above-mentioned molecular subtypes of DLBCL. Therefore, the application of IHC algorithms is now considered an acceptable and effective tool by many experts [12].

BL, a type of non-Hodgkin BCL, is a substantially aggressive mature B cell neoplasm and the fastest growing human cancer that is seen mainly in children and young adults [15, 109]. Despite very aggressive biology most of the cases of BL can be cured by modern ChTh [156]. BL comprises up to 20% of HIV-associated lymphomas and is usually associated with higher median CD4 counts when compared with many other lymphoma types. In a recently presented multicenter study, there were no differences in survival between HIV-negative and HIV-positive counterparts [155].

Primary GI MCL is highly aggressive and survival is poor compared to nodal MCL involving the GIT. Patients respond poorly to CHOP chemotherapy [157].

Despite the improved response rate of ChTh for MCL, current overall survival rates remain poor because of the advanced stage in most of the cases and the early relapse. Median survival with standard treatment for MCL patients remains between 1.5 and 4 years [110, 113]. For risk prediction, the MCL International Prognostic Index (MIPI) that include also pretreatment Ki-67 proliferation rate, an important determinant of risk, is employed [157]. MIPI might be helpful to allow individualized, risk-adapted treatment decisions in patients with MCL.

GI FL has poorer outcomes than previously suggested [138]. Anatomical location within the GIT may have prognostic implications, with primary duodenal and small intestinal disease having a significantly higher progression-free survival rate than non-duodenal presentations [138, 139]. For risk stratification of FL patients, FLIPI (FL International Prognostic Index) and FLIPI2 have been developed as prognostic indexes. Despite the usefulness of these risk assessment criteria in nodal cases, no studies have been conducted on intestinal FL patients [115, 137]. Most of the GI FL cases are assessed as low risk or intermediate risk, but it is not confirmed by larger studies if these criteria are suitable for GI cases [115].

MLP may be one of the GI lymphomas with a poor prognosis, even though several regimens of systemic ChTh have been adapted for its treatment [23].

EATL and MEITL is clinically aggressive disease, with frequent early dissemination and a median survival of several months [28, 162].

EBV-positive MCU has an indolent clinical course and may spontaneously regress in some cases [41, 42].

ITLDP is a nonaggressive disease and its clinical course is chronic and relapsing, with rarely reported disseminated disease, including bone marrow and peripheral blood involvement, usually after many years [121, 122].

10. Summary and conclusions

GIT is the most common extranodal site involved in lymphoma. Histopathologically, almost 90% of PGILs are of B-cell lineage. PGILs represent a heterogeneous group of malignant neoplasms which are different entities in terms of cancerogenesis, cell lineage, pathological characteristics, immunoprofile, biological behavior, response to modern treatment approaches and prognosis. In most cases, pathogenesis of primary PGIL is associated with infectious agents such as *H. pylori*, *C. jejuni*, EBV, HIV, HBV and HTLV-1. Immunodepressive (congenital and acquired) and autoimmune conditions are the second most significant disorders associated with PGIL. Regardless of the etiologic factors in the pathogenesis of PGIL play a great role in chromosomal translocation that lead to overexpression or down-expression of some genes that promote uncontrolled lymphoid cell proliferation. Some specific gene rearrangements take place in the pathogenesis of different subtypes of PGIL. After the introduction of GEP some lymphoma subtypes, such as DLBCL and BL were further subdivided into distinct entities, hence some new provisional entities were added in the 2008 WHO classification and revised 2016 WHO classifications. Pathologically and immunohistochemically distinct subtypes of PGIL represent different entities that have characteristic hallmarks and molecular signatures. The distinction is also observed in the predominance of involved sites for different subtypes of lymphoma. The clinical course can range from indolence to very aggressive behavior depending on the lymphoma subtypes and concomitant gene rearrangements. In most cases, diagnosis of PGIL can be made endoscopically, however, few cases of intestinal lymphoma are being detected during surgery performed for its complications. Treatment of PGIL is largely ChTh based and

anthracycline-containing ChTh and rituximab is the mainstay treatment modality. Despite this, some PGIL subtypes (especially MCL) remain to be resistant to modern therapeutic approaches and associated with poor survival rates.

Conflict of interest

The authors declare no conflict of interest.

IntechOpen

IntechOpen

Author details

Ramiz Bayramov* and Ramila Abdullayeva
Department of Oncology, Azerbaijan Medical University, Baku, Azerbaijan

*Address all correspondence to: ramizbayramov@gmail.com

IntechOpen

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Groves F, Linet M, Travis L, Devesa S. Cancer surveillance series: Non-Hodgkin's lymphoma incidence by histologic subtype in the united states from 1978 through 1995. *Journal of the National Cancer Institute*. 2000;**92**(15):1240-1251. DOI: 10.1093/jnci/92.15.1240
- [2] Chiu B, Weisenburger D. An update of the epidemiology of non-Hodgkin's lymphoma. *Clinical Lymphoma*. 2003;**4**(3):161-168. DOI: 10.3816/clm.2003.n.025
- [3] Devesa S, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. *Cancer Research*. 1992;**52**(Suppl. 19):5432s-5440s
- [4] Ghimire P, Wu G-Y, Zhu L. Primary gastrointestinal lymphoma. *World Journal of Gastroenterology*. 2011;**17**(6): 697-707. DOI: 10.3748/wjg.v17.i6.697
- [5] Püspök A, Raderer M, Chott A, et al. Endoscopic ultrasound in the follow up and response assessment of patients with primary gastric lymphoma. *Gut*. 2002;**51**:691-694. DOI: 10.1136/gut.51.5.691
- [6] Nakamura S, Matsumoto T. Gastrointestinal lymphoma: Recent advances in diagnosis and treatment. *Digestion*. 2013;**87**:182-188. DOI: 10.1159/000350051
- [7] Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. *The British Journal of Surgery*. 1961;**49**:80-89. DOI: 10.1002/bjs.18004921319
- [8] Chen Y, Chen Y, Chen S, et al. Primary gastrointestinal lymphoma: Aretrospective multicenter clinical study of 415 cases in Chinese province of Guangdong and a systematic review containing 5075 Chinese patients. *Medicine (Baltimore)*. 2015; **94**(47):e2119. DOI: 10.1097/MD.0000000000002119
- [9] Herrmann R, Panahon AM, Barcos MP, et al. Gastrointestinal involvement in non-Hodgkin's lymphoma. *Cancer*. 1980;**46**(1): 215-222. DOI: 10.1002/1097-0142(19800701)46:1<215::aid-cncr2820460136>3.0.co;2-6
- [10] Rizvi MA, Evens AM, Tallman MS, et al. T-cell non-Hodgkin lymphoma. *Blood*. 2006;**107**:1255-1264. DOI: 10.1182/blood-2005-03-1306
- [11] Juárez-Salcedo LM, Sokol L, Chavez JC, Dalia S. Primary gastric lymphoma, epidemiology, clinical diagnosis, and treatment. *Cancer Control*. 2018;**25**(1):1-12. DOI: 10.1177/1073274818778256
- [12] Quintanilla-Martinez L. The 2016 updated WHO classification of lymphoid neoplasias. *Hematol Oncology*. 2017;**35**(S1):37-45. DOI: 10.1002/hon.2399
- [13] Papaxoinis G, Papageorgiou S, Rontogianni D, et al. Primary gastrointestinal non-Hodgkin's lymphoma: A clinicopathologic study of 128 cases in Greece. A Hellenic Cooperative Oncology Group study (HeCOG). *Leukemia & Lymphoma*. 2006;**47**(10):2140-2146. DOI: 10.1080/10428190600709226
- [14] Dionigi G, Annoni M, Rovera F, et al. Primary colorectal lymphomas: Review of the literature. *Surgical Oncology*. 2007;**16**(Suppl. 1):S169-S171. DOI: 10.1016/j.suronc.2007.10.021
- [15] Bautista-Quach MA, Ake CD, Chen M, Wang J. Gastrointestinal lymphomas: Morphology, immunophenotype and molecular features. *Journal of Gastrointestinal*

Oncology. 2012;**3**(3):209-225. DOI: 10.3978/j.issn.2078-6891.2012.024

[16] Ferrucci PF, Zucca E. Primary gastric lymphoma pathogenesis and treatment: What has changed over the past 10 years? *British Journal of Haematology*. 2007;**136**:521-538. DOI: 10.1111/j.1365-2141.2006.06444.x

[17] Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*. 2006;**107**(1):265-276. DOI: 10.1182/blood-2005-06-2508

[18] Suresh B, Asati V, Lakshmaiah KC, et al. Primary gastrointestinal diffuse large B-cell lymphoma: A prospective study from South India. *South Asian Journal of Cancer*. 2019;**8**(1):57-59. DOI: 10.4103/sajc.sajc_52_18

[19] Weindorf SC, Smith LB, Owens SR. Update on gastrointestinal lymphomas. *Archives of Pathology & Laboratory Medicine*. 2018;**142**:1347-1351. DOI: 10.5858/arpa.2018-0275-RA

[20] Damaj G, Verkarre V, Delmer A, et al. Primary follicular lymphoma of the gastrointestinal tract: A study of 25 cases and a literature review. *Annals of Oncology*. 2003;**14**(4):623-629. DOI: 10.1093/annonc/mdg168

[21] Kitamura K, Yamaguchi T, Okamoto K, et al. Early gastric lymphoma: A clinicopathologic study of ten patients, literature review, and comparison with early gastric adenocarcinoma. *Cancer*. 1996;**77**(5): 850-857. DOI: 10.1002/(sici)1097-0142(19960301)77:5<850::aid-cnrc7>3.0.co;2-i

[22] Kim YH, Lee JH, Yang SK, et al. Primary colon lymphoma in Korea: A KASID (Korean Association for the Study of Intestinal Diseases) study. *Digestive Diseases and Sciences*. 2005;**50**:2243-2247. DOI: 10.1007/s10620-005-3041-7

[23] Hirata N, Tominaga K, Ohta K, et al. A case of mucosa-associated lymphoid

tissue lymphoma forming multiple lymphomatous polyposis in the small intestine. *World Journal of Gastroenterology*. 2007;**13**:1453-1457. DOI: 10.3748/wjg.v13.i9.1453

[24] Al-Saleem T, Al-Mondhiry H. Immunoproliferative small intestinal disease (IPSID): A model for mature B-cell neoplasms. *Blood*. 2005;**105**(6): 2274-2280. DOI: 10.1182/blood-2004-07-2755

[25] Lecuit M, Abachin E, Martin A, et al. Immunoproliferative Small Intestinal Disease Associated with *Campylobacter jejuni*. *The New England Journal of Medicine*. 2004;**350**(3):239-248. DOI: 10.1056/nejmoa031887

[26] Biko DM, Anupindi SA, Hernandez A, et al. Childhood Burkitt lymphoma: Abdominal and pelvic imaging findings. *American Journal of Roentgenology*. 2009;**192**(5):1304-1315. DOI: 10.2214/AJR.08.1476

[27] Ge Z, Liu Z, Hu X. Anatomic distribution, clinical features, and survival data of 87 cases primary gastrointestinal lymphoma. *World Journal of Surgical Oncology*. 2016;**14**(1):1-7. DOI: 10.1186/s12957-016-0821-9

[28] Tse E, Gill H, Loong F, et al. Type II enteropathy-associated T-cell lymphoma: A multicenter analysis from the Asia Lymphoma Study Group. *American Journal of Hematology*. 2012;**87**(7): 663-668. DOI: 10.1002/ajh.23213

[29] Bonnet C, Janssens A, Wu KL, et al. BHS Guidelines for the treatment of Burkitt's lymphoma. *Belgian Journal of Hematology*. 2015;**6**(2):61-69

[30] Engels EA. Infectious agents as causes of non-Hodgkin lymphoma. *Cancer Epidemiology, Biomarkers & Prevention*. 2007;**16**(3):401-404. DOI: 10.1158/1055-9965.epi-06-1056

[31] Wang F, Meng W, Wang B, Qiao L. *Helicobacter pylori*-induced gastric

- inflammation and gastric cancer. *Cancer Letters*. 2014;**345**(2):196-202. DOI: 10.1016/j.canlet.2013.08.016
- [32] Filip PV, Cuciureanu D, Diaconu LS, et al. MALT lymphoma: Epidemiology, clinical diagnosis and treatment. *Journal of Medicine and Life*. 2018;**11**(3):187-193. DOI: 10.25122/jml-2018-0035
- [33] Zullo A, Cerro P, Chios A, et al. A very unusual cause of dysphagia: Mantle cell lymphoma. *Annals of Gastroenterology*. 2016;**29**(3):383-385
- [34] Mulalic E, Delibegovic S. An Aggressive Form of MALT Lymphoma of the Stomach with Pancreas Infiltration. *Medical Archives*. 2016;**70**(3):235-237. DOI: 10.5455/medarh.2016.70.235-237
- [35] Hussell T, Isaacson PG, Crabtree JE, Spencer J. Helicobacter pylori-specific tumour-infiltrating T cells provide contact dependent help for the growth of malignant B cells in low-grade gastric lymphoma of mucosa-associated lymphoid tissue. *The Journal of Pathology*. 1996;**178**:122-127. DOI: 10.1002/(SICI)1096-9896(199602)178:2<122::AID-PATH486>3.0.CO;2-D
- [36] Tsai HF, Hsu PN. Interplay between Helicobacter pylori and immune cells in immune pathogenesis of gastric inflammation and mucosal pathology. *Cellular & Molecular Immunology*. 2010;**7**(4):255-259. DOI: 10.1038/cmi.2010.2
- [37] Niino D, Yamamoto K, Tsuruta O, et al. Regression of rectal mucosa-associated lymphoid tissue (MALT) lymphoma after antibiotic treatments. *Pathology International*. 2010;**60**:438-442. DOI: 10.1111/j.1440-1827.2010.02538.x
- [38] Wang F, Xu RH, Han B, et al. High incidence of hepatitis B virus infection in B-cell subtype non-Hodgkin lymphoma compared with other cancers. *Cancer*. 2007;**109**:1360-1364. DOI: 10.1002/cncr.22549
- [39] Hui PK, Tokunaga M, Chan WY, et al. Epstein-Barr virus-associated gastric lymphoma in Hong Kong Chinese. *Human Pathology*. 1994;**25**(9):947-952. DOI: 10.1016/0046-8177(94)90017-5
- [40] Stefan DC, Lutchman R. Burkitt lymphoma: Epidemiological features and survival in a South African centre. *Infectious Agents and Cancer*. 2014;**9**:19. DOI: 10.1186/1750-9378-9-19
- [41] Bunn B, van Heerden W. EBV-positive mucocutaneous ulcer of the oral cavity associated with HIV/AIDS. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*. 2015;**120**(6):725-732. DOI: 10.1016/j.oooo.2015.06.02
- [42] Dojcinov SD, Venkataraman G, Raffel M, et al. EBV-positive mucocutaneous ulcer—A study of 26 cases associated with various sources of immunosuppression. *The American Journal of Surgical Pathology*. 2010;**34**(3):405-417. DOI: 10.1097/pas.0b013e3181cf8622
- [43] Heise W. GI-lymphomas in immunosuppressed patients (organ transplantation; HIV). *Best Practice & Research. Clinical Gastroenterology*. 2010;**24**(1):57-69. DOI: 10.1016/j.bpg.2010.01.001
- [44] Powitz F, Bogner JR, Sandor P, et al. Gastrointestinal lymphomas in patients with AIDS. *Zeitschrift für Gastroenterologie*. 1997;**35**(3):179-185
- [45] Andhavarapu S, Tolentino AM, Jha C, et al. Diffuse large B-cell lymphoma presenting as multiple lymphomatous polyposis of the gastrointestinal tract. *Clinical Lymphoma & Myeloma*. 2008;**8**:179-183. DOI: 10.3816/CLM.2008.n.023
- [46] Dal Maso L, Franceschi S. Epidemiology of non-Hodgkin lymphomas and other haemolymphopoietic neoplasms in

- people with AIDS. *The Lancet Oncology*. 2003;**4**(2):110-119. DOI: 10.1016/S1470-2045(03)00983-5
- [47] Coté TR, Biggar RJ, Rosenberg PS, et al. Non-Hodgkin's lymphoma among people with AIDS: Incidence, presentation and public health burden. AIDS/Cancer Study Group. *International Journal of Cancer*. 1997;**73**(5):645-650. DOI: 10.1002/(sici)1097-0215(19971127)73:5<645::aid-ijc6>3.0.co;2-x
- [48] Omar FE. Childhood lymphomas—A brief overview. *CME*. 2010;**27**(7):332-336
- [49] Biggar RJ, Engels EA, Frisch M, et al. Risk of T-cell lymphomas in persons with AIDS. *Journal of Acquired Immune Deficiency Syndromes*. 2001;**26**(4):371-376. DOI: 10.1097/00042560-200104010-00015
- [50] Deng L, Song Y, Young KH, et al. Hepatitis B virus-associated diffuse large B-cell lymphoma: Unique clinical features, poor outcome, and hepatitis B surface antigen-driven origin. *Oncotarget*. 2015;**6**(28):25061-25073. DOI: 10.18632/oncotarget.4677
- [51] Sugita S, Iijima T, Furuya S, et al. Gastric T-cell lymphoma with cytotoxic phenotype. *Pathology International*. 2007;**57**:108-114. DOI: 10.1111/j.1440-1827.2006.02065.x
- [52] Weeratunge CN, Bolivar HH, Anstead GM, Lu DH. Primary esophageal lymphoma: A diagnostic challenge in acquired immunodeficiency syndrome--two case reports and review. *Southern Medical Journal*. 2004;**97**:383-387. DOI: 10.1097/01.SMJ.0000100120.49153.3F
- [53] Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: A meta-analysis. *Archives of Internal Medicine*. 2005;**165**(20):2337-2344. DOI: 10.1001/archinte.165.20.2337
- [54] Royer B, Cazals-Hatem D, Sibilia J, et al. Lymphomas in patients with Sjögren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. *Blood*. 1997;**90**(2):766-775. DOI: 10.1182/blood.V90.2.766
- [55] Garrido A, Luque A, Vázquez A, et al. Primary small bowel neoplasms as a complication of celiac disease. *Gastroenterología y Hepatología*. 2009;**32**:618-621. DOI: 10.1016/j.gastrohep.2009.05.003
- [56] Ko YH, Karnan S, Kim KM, et al. Enteropathy-associated T-cell lymphoma--a clinicopathologic and array comparative genomic hybridization study. *Human Pathology*. 2010;**41**(9):1231-1237. DOI: 10.1016/j.humpath.2009.11.020
- [57] Craig VJ, Arnold I, Gerke C, et al. Gastric MALT lymphoma B cells express polyreactive, somatically mutated immunoglobulins. *Blood*. 2010;**115**(3):581-591. DOI: 10.1182/blood-2009-06-228015
- [58] Greiner A, Knörr C, Qin Y, et al. Low-grade B cell lymphomas of mucosa-associated lymphoid tissue (MALT-type) require CD40-mediated signaling and Th2-type cytokines for in vitro growth and differentiation. *The American Journal of Pathology*. 1997;**150**(5):1583-1593
- [59] Kuo SH, Yeh KH, et al. *Helicobacter pylori*-related diffuse large B-cell lymphoma of the stomach: A distinct entity with lower aggressiveness and higher chemosensitivity. *Blood Cancer Journal*. 2014;**4**(6):e220. DOI: 10.1038/bcj.2014.40
- [60] Ruland J, Duncan GS, Elia A, et al. Bcl10 is a positive regulator of antigen receptor-induced activation of

- NF-kappaB and neural tube closure. *Cell*. 2001;**104**(1):33-42. DOI: 10.1016/S0092-8674(01)00189-1
- [61] Ruskoné-Fourmestiaux A, Fischbach W, Aleman BMP, et al. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. *Gut*. 2011;**60**(6):747-758. DOI: 10.1136/gut.2010.224949
- [62] Zullo A, Hassan C, et al. Gastric MALT lymphoma: Old and new insights. *Annals of Gastroenterology*. 2014;**27**(1): 27-33
- [63] Sagaert X, De Wolf-Peeters C, Noels H, Baens M. The pathogenesis of MALT lymphomas: Where do we stand? *Leukemia*. 2007;**21**(3):389-396. DOI: 10.1038/sj.leu.2404517
- [64] Zhang Q, Siebert R, Yan M, et al. Inactivating mutations and overexpression of BCL10, a caspase recruitment domain containing gene, in MALT lymphoma with t(1,14) (p22;q32). *Nature Genetics*. 1999;**22**(1):63-68. DOI: 10.1038/8767
- [65] Willis TG, Jadayel DM, Du MQ, et al. Bcl10 is involved in t(1, 14) (p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. *Cell*. 1999;**96**(1):35-45. DOI: 10.1016/S0092-8674(00)80957-5
- [66] Yeh KH, Kuo SH, Chen LT, et al. Nuclear expression of BCL10 or nuclear factor kappa B helps predict *Helicobacter pylori*-independent status of low-grade gastric mucosa-associated lymphoid tissue lymphomas with or without t(11,18) (q21;q21). *Blood*. 2005;**106**(3):1037-1041. DOI: 10.1182/blood-2005-01-0004
- [67] Wlodarska I, Veyt E, De Paepe P, et al. FOXP1, a gene highly expressed in a subset of diffuse large B-cell lymphoma, is recurrently targeted by genomic aberrations. *Leukemia*. 2005;**19**(8):1299-1305. DOI: 10.1038/sj.leu.2403813
- [68] Sagaert X, de Paepe P, Libbrecht L, et al. Forkhead box protein P1 expression in mucosa-associated lymphoid tissue lymphomas predicts poor prognosis and transformation to diffuse large B-cell lymphoma. *Journal of Clinical Oncology*. 2006;**24**(16):2490-2497. DOI: 10.1200/jco.2006.05.6150
- [69] Nakamura S, Matsumoto T, Nakamura S, et al. Chromosomal translocation t(11,18)(q21;q21) in gastrointestinal mucosa associated lymphoid tissue lymphoma. *Journal of Clinical Pathology*. 2003;**56**:36-42. DOI: 10.1136/jcp.56.1.36
- [70] Dierlamm J, Baens M, Wlodarska I, et al. The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in the t(11,18) (q21;q21) associated with mucosa-associated lymphoid tissue lymphomas. *Blood*. 1999;**93**(11):3601-3609. DOI: 10.1182/blood.v93.11.3601
- [71] Yonezumi M, Suzuki R, Suzuki H, et al. Detection of AP12-MALT1 chimaeric gene in extranodal and nodal marginal zone B-cell lymphoma by reverse transcription polymerase chain reaction (PCR) and genomic long and accurate PCR analyses. *British Journal of Haematology*. 2001;**115**(3):588-594. DOI: 10.1046/j.1365-2141.2001.03158.x
- [72] Streubel B, Seitz G, et al. MALT lymphoma associated genetic aberrations occur at different frequencies in primary and secondary intestinal MALT lymphomas. *Gut*. 2006;**55**(11):1581-1585. DOI: 10.1136/gut.2005.090076
- [73] Nakamura T, Nakamura S, Yonezumi M, et al. *Helicobacter pylori* and the t(11,18)(q21;q21) translocation in gastric low-grade B-cell lymphoma of mucosa-associated lymphoid tissue type. *Japanese Journal of Cancer Research*.

2000;**91**:301-309. DOI: 10.1111/j.1349-7006.2000.tb00945.x

[74] Liu H, Ye H, Ruskone-Fourmestraux A, et al. t(11,18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. *Gastroenterology*. 2002;**122**:1286-1294. DOI: 10.1053/gast.2002.33047

[75] Ye H, Liu H, Raderer M, et al. High incidence of t(11,18)(q21;q21) in *Helicobacter pylori*-negative gastric MALT lymphomas. *Blood*. 2003;**101**(7):2547-2550. DOI: 10.1182/blood-2002-10-3167

[76] Wang G, Auerbach A, Wei M, et al. t(11,18)(q21;q21) in extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue in stomach: A study of 48 cases. *Modern Pathology*. 2009;**22**:79-86. DOI: 10.1038/modpathol.2008.155

[77] Saito M, Gao J, Basso K, et al. Signaling Pathway mediating downregulation of BCL6 in germinal center B cells is blocked by BCL6 gene alterations in B cell lymphoma. *Cancer Cell*. 2007;**12**(3):280-292. DOI: 10.1016/j.ccr.2007.08.011

[78] Lossos I, Akasaka T, Martinez-Climent J, et al. The BCL6 gene in B-cell lymphomas with 3q27 translocations is expressed mainly from the rearranged allele irrespective of the partner gene. *Leukemia*. 2003;**17**:1390-1397. DOI: 10.1038/sj.leu.2402997

[79] Offit K, Lococo F, Louie DC, et al. Rearrangement of the bcl-6 gene as prognostic marker in diffuse large cell lymphoma. *The New England Journal of Medicine*. 1994;**331**(2):74-80. DOI: 10.1056/nejm199407143310202

[80] Yang H, Green MR. Epigenetic Programming of B-Cell Lymphoma by BCL6 and Its Genetic Deregulation. *Frontiers in Cell and Development*

Biology. 2019;**7**:272. DOI: 10.3389/fcell.2019.00272

[81] Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature*. 2010;**463**:88-92. DOI: 10.1038/nature08638

[82] Foster LH, Portell CA. The role of infectious agents, antibiotics, and antiviral therapy in the treatment of extranodal marginal zone lymphoma and other low-grade lymphomas. *Current Treatment Options in Oncology*. 2015;**16**(6):28. DOI: 10.1007/s11864-015-0344-6

[83] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;**127**(20):2375-2390. DOI: 10.1182/blood-2016-01-643569

[84] Zullo A, Hassan C, et al. Effects of *Helicobacter pylori* eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. *Clinical Gastroenterology and Hepatology*. 2010;**8**(2):105-110. DOI: 10.1016/j.cgh.2009.07.017

[85] Rosenstiel P, Hellmig S, Hampe J, et al. Influence of polymorphisms in the NOD1/CARD4 and NOD2/CARD15 genes on the clinical outcome of *Helicobacter pylori* infection. *Cellular Microbiology*. 2006;**8**(7):1188-1198. DOI: 10.1111/j.1462-5822.2006.00701.x

[86] Ronchi A, Montella M, Panarese I, et al. Malt gastric lymphoma:an pathogenetic features. *WCRJ*. 2016;**3**(2):e715

[87] Hellmig S, Bartscht T, Fischbach W, et al. Germline variations of the MALT1 gene as risk factors in the development of primary gastric B-cell lymphoma. *European Journal of Cancer*. 2009;**45**(10):1865-1870. DOI: 10.1016/j.ejca.2009.03.010

[88] Tomita S, Kojima M, Imura J, et al. Extranodal diffuse follicular center

lymphoma mimicking mantle cell lymphoma of the intestine. *American Journal of Hematology*. 2003;**74**(4): 287-289. DOI: 10.1002/ajh.10437

[89] Isomoto H, Maeda T, Akashi T, et al. Multiple lymphomatous polyposis of the colon originating from T-cells: A case report. *Digestive and Liver Disease*. 2004;**36**(3):218-221. DOI: 10.1016/j.dld.2003.09.019

[90] Swerdlow SH, Campo E, Harris NL, et al. 2017 Revised WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2017

[91] Coppens E, El Nakadi I, Nagy N, Zalcman M. Primary Hodgkin's lymphoma of the esophagus. *American Journal of Roentgenology*. 2003;**180**: 1335-1337. DOI: 10.2214/ajr.180.5.1801335

[92] Zhu Q, Xu B, Xu K, et al. Primary non-Hodgkin's lymphoma in the esophagus. *Journal of Digestive Diseases*. 2008;**9**:241-244. DOI: 10.1111/j.1751-2980.2008.00354.x

[93] Kalogeropoulos IV, Chalazonitis AN, Tsolaki S, et al. A case of primary isolated non-Hodgkin's lymphoma of the esophagus in an immunocompetent patient. *World Journal of Gastroenterology*. 2009;**15**:1901-1903. DOI: 10.3748/wjg.15.1901

[94] Koch P. Treatment results in localized primary gastric lymphoma: Data of patients registered within the German multicenter study (GIT NHL 02/96). *Journal of Clinical Oncology*. 2005;**23**(28):7050-7059. DOI: 10.1200/jco.2005.04.031

[95] Ely S. Distinction between "high grade MALT" and diffuse large B cell lymphoma. *Gut*. 2002;**51**(6):893-894. DOI: 10.1136/gut.51.6.893

[96] Jaffe ES. The 2008 WHO classification of lymphomas:

Implications for clinical practice and translational research. *Hematology. American Society of Hematology. Education Program*. 2009;**1**:523-531. DOI: 10.1182/asheducation-2009.1.523

[97] Li B, Shi YK, He XH, et al. Primary non-Hodgkin lymphomas in the small and large intestine: Clinicopathological characteristics and management of 40 patients. *International Journal of Hematology*. 2008;**87**:375-381. DOI: 10.1007/s12185-008-0068-5

[98] Said J, Pinter-Brown L. Clinical and pathological diagnosis of peripheral T-cell lymphoma and emerging treatment options: A case-based discussion. *Clinical Advances in Hematology & Oncology*. 2009;**7**(11):S1. S4-13, quiz S15

[99] Ding W, Zhao S, Wang J, et al. Gastrointestinal lymphoma in Southwest China: Subtype distribution of 1,010 cases using the WHO (2008) classification in a single institution. *Acta Haematologica*. 2016;**135**:21-28. DOI: 10.1159/000437130

[100] Lodhi HT, Sadat I, Qulsoom H, et al. Primary small bowel diffuse large B-cell lymphoma: Excellent endoscopic appearance. *The American Journal of Gastroenterology*. 2018;**113**:S1422-S1423. DOI: 10.14309/00000434-201810001-02554

[101] Barbaryan A, Ali AM, Kwatra SG, et al. Primary diffuse large B-cell lymphoma of the ascending colon. *Rare Tumors*. 2013;**5**(2):85-88. DOI: 10.4081/rt.2013.e23

[102] Ponzoni M, Ferreri AJ, Pruneri G, et al. Prognostic value of bcl-6, CD10 and CD38 immunoreactivity in stage I-II gastric lymphomas: Identification of a subset of CD10+ large B-cell lymphomas with a favorable outcome. *International Journal of Cancer*. 2003;**106**:288-291. DOI: 10.1002/ijc.11179

[103] Foon KA, Lichtman MA. General Considerations of Lymphoma:

Epidemiology, Etiology, Heterogeneity, and Primary Extranodal Disease. In: Kaushansky K, Lichtman MA, Beutler E et al., editors. Williams Hematology 8th ed. McGraw-Hill; 2010. pp. 1-39

[104] Novak U, Basso K, Pasqualucci L, et al. Genomic analysis of non-splenic marginal zone lymphomas (MZL) indicates similarities between nodal and extranodal MZL and supports their derivation from memory B-cells. *British Journal of Haematology*. 2011;**155**(3): 362-365. DOI: 10.1111/j.1365-2141.2011.08841.x

[105] Bacon CM, Du MQ, Dogan A. Mucosa-associated lymphoid tissue (MALT) lymphoma: A practical guide for pathologists. *Journal of Clinical Pathology*. 2007;**60**(4):361-372. DOI: 10.1136/jcp.2005.031146

[106] Zucca E, Roggero E, Pileri S. B-cell lymphoma of MALT type: A review with special emphasis on diagnostic and management problems of low-grade gastric tumours. *British Journal of Haematology*. 1998;**100**(1):3-14. DOI: 10.1046/j.1365-2141.1998.00513.x

[107] Isaacson P, Muller-Hermelink H, Piris M, et al. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2001. pp. 157-160

[108] Ferreri AJ, Montalbán C. Primary diffuse large B-cell lymphoma of the stomach. *Critical Reviews in Oncology/Hematology*. 2007;**63**(1):65-71. DOI: 10.1016/j.critrevonc.2007.01.003

[109] Čubranić A, Golčić M, Fučkar-Čupić D, et al. Burkitt lymphoma in gastrointestinal tract: A report of two cases. *Acta Clinica Croatica*. 2019;**58**:386-390. DOI: 10.20471/acc.2019.58.02.25

[110] Kella VKN, Constantine R, Parikh NS, et al. Mantle cell lymphoma of the gastrointestinal tract presenting with multiple intussusceptions—Case report and review of literature. *World Journal of Surgical Oncology*. 2009;**7**:60. DOI: 10.1186/1477-7819-7-60

[111] Bajpai S, Narang J, Narang S, et al. Mantle Cell Lymphoma: Incidence of gastrointestinal involvement and correlation with overall response-retrospective review of multiple multicenter trials. *Blood*. 2020;**136** (Suppl. 1):33-34. DOI: 10.1182/blood-2020-137657

[112] Fu K, Weisenburger DD, Greiner TC, et al. Cyclin D1-negative mantle cell lymphoma: A clinicopathologic study based on gene expression profiling. *Blood*. 2005; **106**(13):4315-4321. DOI: 10.1182/blood-2005-04-1753

[113] Vose JM. Mantle cell lymphoma: 2012 update on diagnosis, risk-stratification, and clinical management. *American Journal of Hematology*. 2012;**87**(6):604-609. DOI: 10.1002/ajh.23176

[114] Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. *World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2001

[115] Takata K, Miyata-Takata T, Sato Y, et al. Gastrointestinal follicular lymphoma: Current knowledge and future challenges. *Pathol Intl*. 2018;**68**(1):1-6. DOI: 10.1111/pin.12621

[116] Foukas PG, de Leval L. Recent advances in intestinal lymphomas. *Histopathology*. 2015;**66**(1):112-136. DOI: 10.1111/his.12596

[117] Yamamoto S, Nakase H, Yamashita K, et al. Gastrointestinal follicular lymphoma: Review of the literature. *Journal of Gastroenterology*.

2010;**45**(4):370-388. DOI: 10.1007/s00535-009-0182-z

[118] Swerdlow SH, Jaffe ES, Brousset P, et al. Cytotoxic T-cell and NK-cell lymphomas: Current questions and controversies. *The American Journal of Surgical Pathology*. 2014;**38**(10):e60-e71. DOI: 10.1097/pas.0000000000000295

[119] Attygally AD, Cabeçadas J, Gaulard P, et al. Peripheral T-cell and NK-cell lymphomas and their mimics; taking a step forward—Report on the lymphoma workshop of the XVIth meeting of the European Association for Haematopathology and the Society for Hematopathology. *Histopathology*. 2014;**64**(2):171-199. DOI: 10.1111/his.12251

[120] Hart M, Thakral B, Yohe S, et al. EBV-positive mucocutaneous ulcer in organ transplant recipients: A localized indolent posttransplant lymphoproliferative disorder. *The American Journal of Surgical Pathology*. 2014;**38**(11):1522-1529. DOI: 10.1097/pas.0000000000000282

[121] Perry AM, Warnke RA, Hu Q, et al. Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. *Blood*. 2013;**122**(22):3599-3606. DOI: 10.1182/blood-2013-07-512830

[122] Carbonnel F, d'Almagne H, Lavergne A, et al. The clinicopathological features of extensive small intestinal CD4 T cell infiltration. *Gut*. 1999;**45**(5):662-667. DOI: 10.1136/gut.45.5.662

[123] Ruskoné-Fourmestiaux A, Dragosics B, Morgner A, et al. Paris staging system for primary gastrointestinal lymphomas. *Gut*. 2003;**52**:912-916. DOI: 10.1136/gut.52.6.912

[124] Al-Akwaa AM, Siddiqui N, Al-Mofleh IA. Primary gastric lymphoma. *World Journal of Gastroenterology*. 2004;**10**:5-11. DOI: 10.3748/wjg.v10.i1.5

[125] George MK, Ramachandran V, Ramanan SG, Sagar TG. Primary esophageal T-cell non-Hodgkin's lymphoma. *Indian Journal of Gastroenterology*. 2005;**24**(3):119-120

[126] Gaskin CM, Low VH, Ho LM. Isolated primary non-hodgkin's lymphoma of the esophagus. *American Journal of Roentgenology*. 2001;**176**:551-552. DOI: 10.2214/ajr.176.2.1760551

[127] Taal BG, Burgers JM. Primary non-Hodgkin's lymphoma of the stomach: Endoscopic diagnosis and the role of surgery. *Scandinavian Journal of Gastroenterology. Supplement*. 1991;**188**:33-37. DOI: 10.3109/00365529109111227

[128] Zinzani PL, Broccoli A. Marginal zone B-cell lymphomas. In: Press OW, Lichtman MA, Leonard JP, editors. *Williams Hematology Malignant Lymphoid Diseases*. McGraw Hill; 2017. pp. 1-14

[129] Myung SJ, Joo KR, Yang SK, et al. Clinicopathologic features of ileocolonic malignant lymphoma: Analysis according to colonoscopic classification. *Gastrointestinal Endoscopy*. 2003;**57**:343-347. DOI: 10.1067/mge.2003.135

[130] Byun JH, Ha HK, Kim AY, et al. CT findings in peripheral T-cell lymphoma involving the gastrointestinal tract. *Radiology*. 2003;**227**:59-67. DOI: 10.1111/j.1440-1827.2010.02538.x

[131] Gonzalez QH, Heslin MJ, Dávila-Cervantes A, et al. Primary colonic lymphoma. *The American Surgeon*. 2008;**74**:214-216. DOI: 10.1177/000313480807400306

[132] Chung HH, Kim YH, Kim JH, et al. Imaging findings of mantle cell lymphoma involving gastrointestinal tract. *Yonsei Medical Journal*. 2003;**44**:49-57. DOI: 10.3349/ymj.2003.44.1.49

[133] Tomizawa Y, Seki M, Mori M. Unusual presentation of localized gastric mucosa-associated lymphoid tissue

- lymphoma mimicking poorly differentiated gastric adenocarcinoma. *Case Reports in Gastroenterology*. 2012;**6**(1):47-51. DOI: 10.1159/000336322
- [134] Pennazio M. Small-intestinal pathology on capsule endoscopy: Spectrum of vascular lesions. *Endoscopy*. 2005;**37**(9):864-869. DOI: 10.1055/s-2005-870212
- [135] Lee HJ, Han JK, Kim TK, et al. Primary colorectal lymphoma: Spectrum of imaging findings with pathologic correlation. *European Radiology*. 2002;**12**:2242-2249. DOI: 10.1007/s00330-002-1307-4
- [136] Gollub MJ. Imaging of gastrointestinal lymphoma. *Radiologic Clinics of North America*. 2008;**46**(2): 287-312. DOI: 10.1016/j.rcl.2008.03.002
- [137] Iwamuro M, Kondo E, Takata K, et al. Diagnosis of follicular lymphoma of the gastrointestinal tract: A better initial diagnostic workup. *World Journal of Gastroenterology*. 2016;**22**(4):1674-1683. DOI: 10.3748/wjg.v22.i4.1674
- [138] Chouhan J, Batra S, Gupta S, Guha S. Gastrointestinal follicular lymphoma: Using primary site as a predictor of survival. *Cancer Medicine*. 2016;**5**(10):2669-2677. DOI: 10.1002/cam4.763
- [139] Wirth A, Ritchie D. The management of gastrointestinal follicular lymphoma: Some observations on a rare disease. *Leukemia & Lymphoma*. 2013;**54**:9-10. DOI: 10.3109/10428194.2012.713952
- [140] Ahuja S, Bharati V, Gupta A, et al. Reed Sternberg-Like Cells in an Aggressive Lymphoma: Report of a Rare Case and Review of Literature. *EMJ Hematology US*. 2020;**1**(1):65-69
- [141] Ghimire P, Wu GY, Zhu L. Primary esophageal lymphoma in immunocompetent patients: Two case reports and literature review. *World Journal of Radiology*. 2010;**2**:334-338. DOI: 10.4329/wjrv.v2.i8.334
- [142] Ghai S, Pattison J, Ghai S, O'Malley ME, Khalili K, Stephens M. Primary gastrointestinal lymphoma: Spectrum of imaging findings with pathologic correlation. *Radiographics*. 2007;**27**(5):1371-1388. DOI: 10.1148/rg.275065151
- [143] Lupescu IG, Grasu M, Goldis G, et al. Computer tomographic evaluation of digestive tract non-Hodgkin lymphomas. *Journal of Gastrointestinal and Liver Diseases*. 2007;**16**:315-319
- [144] Chou CK, Chen LT, Sheu RS, et al. MRI manifestations of gastrointestinal lymphoma. *Abdominal Imaging*. 1994;**19**:495-500. DOI: 10.1007/BF00198248
- [145] Boot H. Diagnosis and staging in gastrointestinal lymphoma. *Best Practice & Research. Clinical Gastroenterology*. 2010;**24**:3-12. DOI: 10.1016/j.bpg.2009.12.003
- [146] Radan L, Fischer D, Bar-Shalom R, et al. FDG avidity and PET/CT patterns in primary gastric lymphoma. *European Journal of Nuclear Medicine and Molecular Imaging*. 2008;**35**:1424-1430. DOI: 10.1007/s00259-008-0771-8
- [147] Paes FM, Kalkanis DG, Sideras PA, Serafini AN. FDG PET/CT of extranodal involvement in non-Hodgkin lymphoma and Hodgkin disease. *Radiographics*. 2010;**30**:269-291. DOI: 10.1148/rg.301095088
- [148] Ahmad A, Govil Y, Frank BB. Gastric mucosa-associated lymphoid tissue lymphoma. *The American Journal of Gastroenterology*. 2003;**98**(5):975-986. DOI: 10.1111/j.1572-0241.2003.07424.x
- [149] Stolte M, Bayerdörffer E, Morgner A, et al. Helicobacter and gastric MALT

lymphoma. *Gut*. 2002;**50**(Suppl. 3):
iii19-iii24. DOI: 10.1136/gut.50.
suppl_3.iii19

[150] Stathis A, Chini C, Bertoni F, et al. Long-term outcome following *Helicobacter pylori* eradication in a retrospective study of 105 patients with localized gastric marginal zone B-cell lymphoma of MALT type. *Annals of Oncology*. 2009;**20**:1086-1093. DOI: 10.1093/annonc/mdn760

[151] Raderer M, Valencak J, Österreicher C, et al. Chemotherapy for the treatment of patients with primary high grade gastric B-cell lymphoma of modified Ann Arbor Stages IE and IIE. *Cancer*. 2000;**88**:1979-1985. DOI: 10.1002/(sici)1097-0142(20000501)88:9<1979::aid-cncr1>3.0.co;2-l

[152] Zhang S, Wang L, Yu D, et al. Localized primary gastrointestinal diffuse large B cell lymphoma received a surgical approach: An analysis of prognostic factors and comparison of staging systems in 101 patients from a single institution. *World Journal of Surgical Oncology*. 2015;**13**(1):246. DOI: 10.1186/s12957-015-0668-5

[153] Ferreri AJ, Govi S, Raderer M, et al. *Helicobacter pylori* eradication as exclusive treatment for limited-stage gastric diffuse large B-cell lymphoma: Results of a multicenter phase 2 trial. *Blood*. 2012;**120**(18):3858-3860. DOI: 10.1182/blood-2012-06-438424

[154] Nagashima R, Takeda H, Maeda K, et al. Regression of duodenal mucosa-associated lymphoid tissue lymphoma after eradication of *Helicobacter pylori*. *Gastroenterology*. 1996;**111**(6):1674-1678. DOI: 10.1016/s0016-5085(96)70032-x

[155] Dunleavy K. Approach to the diagnosis and treatment of adult Burkitt's lymphoma. *Journal of Oncology Practice/ American Society of Clinical Oncology*. 2018;**14**(11):665-672. DOI: 10.1200/JOP.18.00148

[156] Dozzo M, Carobolante F, Donisi PM, et al. Burkitt lymphoma in adolescents and young adults: Management challenges. *Adolescent Health, Medicine and Therapeutics*. 2017;**8**:11-29. DOI: 10.2147/AHMT.S94170

[157] Dasappa L, Babu MCS, Sirsath NT, et al. Primary gastrointestinal mantle cell lymphoma: A retrospective study. *Journal of Gastrointestinal Cancer*. 2014;**45**(4):481-486. DOI: 10.1007/s12029-014-9655-2

[158] Ganapathi KA, Pittaluga S, Odejide OO, et al. Early lymphoid lesions: Conceptual, diagnostic, and clinical challenges. *Haematologica*. 2014;**99**(9):1421-1432. DOI: 10.3324/haematol.2014.107938

[159] Tari A, Asaoku H, Takata K, et al. The role of "watch and wait" in intestinal follicular lymphoma in Rituximab era. *Scandinavian Journal of Gastroenterology*. 2016;**51**(3):321-328. DOI: 10.3109/00365521.2015.1087589

[160] Küçük C, Wei L, You H. Indolent T-cell lymphoproliferative disease of the GI tract: Insights for better diagnosis, prognosis, and appropriate therapy. *Frontiers in Oncology*. 2020;**10**:1276. DOI: 10.3389/fonc.2020.01276

[161] Choi WWL, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. *Clinical Cancer Research*. 2009;**15**(17):5494-5502. DOI: 10.1158/1078-0432.CCR-09-0113

[162] Nijeboer P, de Baaij LR, Visser O, et al. Treatment response in enteropathy associated T-cell lymphoma; survival in a large multicenter cohort. *American Journal of Hematology*. 2015;**90**(6):493-498. DOI: 10.1002/ajh.23992