

Rare gastrointestinal lymphomas: The endoscopic investigation

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Author contributions: Vetro C is the primary author of the study and was involved in literature search and data collection and wrote the paper; Bonanno G and Giulietti G provided the figures, were content experts and involved in editing the manuscript; Vetro C, Romano A, Conticello C, Chiarenza A, Spina P, Coppolino F and Cunsolo R were content experts and involved in editing the manuscript; Vetro C and Di Raimondo F analyzed the data and were involved in editing the manuscript; Di Raimondo F was the principal investigator, content expert and involved in editing the manuscript.

Conflict-of-interest statement: No conflicts of interest.

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Received: March 12, 2015
Peer-review started: March 13, 2015
First decision: April 23, 2015
Revised: June 1, 2015
Accepted: July 8, 2015
Article in press: July 9, 2015
Published online: August 10, 2015

Abstract

Gastrointestinal lymphomas represent up to 10% of gastrointestinal malignancies and about one third of non-Hodgkin lymphomas. The most prominent histologies are mucosa-associated lymphoid tissue lymphoma and diffuse large B-cell lymphoma. However, the gastrointestinal tract can be the site of rarer lymphoma subtypes as a primary or secondary localization. Due to their rarity and the multifaceted histology, an endoscopic classification has not been validated yet. This review aims to analyze the endoscopic presentation of rare gastrointestinal lymphomas from disease diagnosis to follow-up, according to the involved site and lymphoma subtype. Existing, new and emerging endoscopic technologies have been examined. In particular, we investigated the diagnostic, prognostic and follow-up endoscopic features of T-cell and natural killer lymphomas, lymphomatous polyposis and mantle cell lymphoma, follicular lymphoma, plasma cell related disease, gastrointestinal lymphomas in immunodeficiency and Hodgkin's lymphoma of the gastrointestinal tract. Contrarily to more frequent gastrointestinal lymphomas, data about rare lymphomas are mostly extracted from case series and case reports. Due to the data paucity, a synergism between gastroenterologists and hematologists is required in

order to better manage the disease. Indeed, clinical and prognostic features are different from nodal and extranodal or the bone marrow (in case of plasma cell disease) counterpart. Therefore, the approach should be based on the knowledge of the peculiar behavior and natural history of disease.

Key words: Endoscopy; Lymphoma; Endosonography; Stomach; Intestine

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Core tip: The gastrointestinal tract can be the site of rare lymphomas as a primary or secondary localization. Their endoscopic behavior has been scantily evaluated but is emerging as a useful tool with prognostic and therapeutic implications. T-cell lymphomas present mainly with ulcerative lesions, while B-cell lymphomas (follicular or mantle cell lymphomas) present as a duodenal mass or multiple polyposis. Plasma cell-related disorders localize to the gastrointestinal tract, either as a neoplastic mass or as an amyloid deposition. Immunodeficits (primary or secondary) can lead to gastrointestinal localization of rare and seldom fatal high-grade lymphomas. More rarely, Hodgkin's lymphoma localizes to the gastrointestinal tract with an uncertain impact on prognosis.

Vetro C, Bonanno G, Giulietti G, Romano A, Conticello C, Chiarenza A, Spina P, Coppolino F, Cunsolo R, Di Raimondo F. Rare gastrointestinal lymphomas: The endoscopic investigation. *World J Gastrointest Endosc* 2015; 7(10): 928-949 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v7/i10/928.htm> DOI: <http://dx.doi.org/10.4253/wjge.v7.i10.928>

INTRODUCTION AND MAIN SECTION OF THE WORK

Gastrointestinal (GI) lymphomas represent 5%-10% of primary GI malignancies and almost two third of extranodal non Hodgkin's lymphomas (NHL), that in turn account for 24%-49% of all NHL^[1,2]. The most common lymphomas are mucosa-associated lymphoid tissue (MALT) and diffuse large B-cell lymphoma (DLBCL), accounting for 70%-95% of GI lymphomas^[3,4]. Apart from MALT and DLBCL, the GI tract can be the site of other lymphomas, either as a primary or secondary localization^[5], and these lymphomas will be the subject of this report. The knowledge of their clinical and echo-endoscopic features would help in addressing clinical questions^[3,6-8], sparing inappropriate evaluations^[9-13]. Nonetheless, histology, together with immunohistochemistry and molecular biology, are mandatory for diagnosis^[14].

While the endoscopic classification for MALT and DLBCL has been already validated^[15,16], such an analysis

Table 1 Endoscopic features of rare gastrointestinal lymphomas according to two classification systems

Ref.	Wang <i>et al.</i> ^[18]		Myung <i>et al.</i> ^[17]	
No. of patients	13		32	
Endoscopic pattern	Mucosal - ulcerative	30.7%	Fungating	39%
	Mucosal - erosive	15.3%	Ulcerative	6%
	Polypoid	23%	Infiltrative	14%
	Massive	31%	Ulcerofungating	31%
			Ulceroinfiltrative	11%

on rare GI lymphomas is still under debate. In 2001 and 2003, the Taiwanese^[17] and the South Korean group^[18] respectively published a 3/5 item classification of ileocolonic GI lymphomas. Table 1 shows patterns analyzed in both classifications. Basically, the endoscopic appearance is classified according to the presence and depth of ulcerations and of fungating lesions. To date, these were the only attempts to classify rare GI lymphomas. After that, Kim *et al.*^[19] investigated the endoscopic differences between B- and T-cell lymphomas of the colon and they observed that B-cell lymphomas occur more often as fungating or ulcerofungating lesions, while T-cell lymphomas more frequently have an ulcerative or ulceroinfiltrative pattern (Figure 1). Notwithstanding, a clear prognostic implication based on the endoscopic pattern has not been validated yet.

Newer techniques, *i.e.*, capsule endoscopy (CE) and double-balloon enteroscopy (DBE), are emerging as useful tools in detecting small bowel tumors (15% of them represented by lymphomas)^[3,20-22]. Surely both techniques can augment the endoscopic diagnostic field (especially for follicular lymphomas^[21]). Moreover, spiral enteroscopy has been also evaluated as a tool for revealing GI lymphomas of the small intestine. Boudiaf *et al.*^[23] reported that 4 out of 14 patients affected by refractory celiac sprue developed a small bowel mass that was confirmed to be an enteropathy-associated T-cell lymphoma (EATL) by histological evaluation. Although less widespread, single-balloon enteroscopy has been used in the definition of small bowel lesions and recently it has been implemented with the water exchange method in order to improve the visualization of the lumen to better define and sample the lesion^[24]. However, such deep diagnostic tools have not been validated for routine use in GI lymphoma staging and follow-up since they do not induce a treatment change. Thus, their application in gastric or colonic lymphomas has not been fully validated^[25]. Differently, faced with T-cell lymphomas with a jejunal tropism, DBE can lead to a definitive diagnosis coupling the endoscopic investigation with the bioptic evaluation^[26,27]. However, not many publications related to the usage of these techniques are available to date.

A particular consideration should be given to the role of endoscopic ultrasonography (EUS). Its role has gained more and more importance in MALT lymphomas since the locoregional staging of the disease has a great

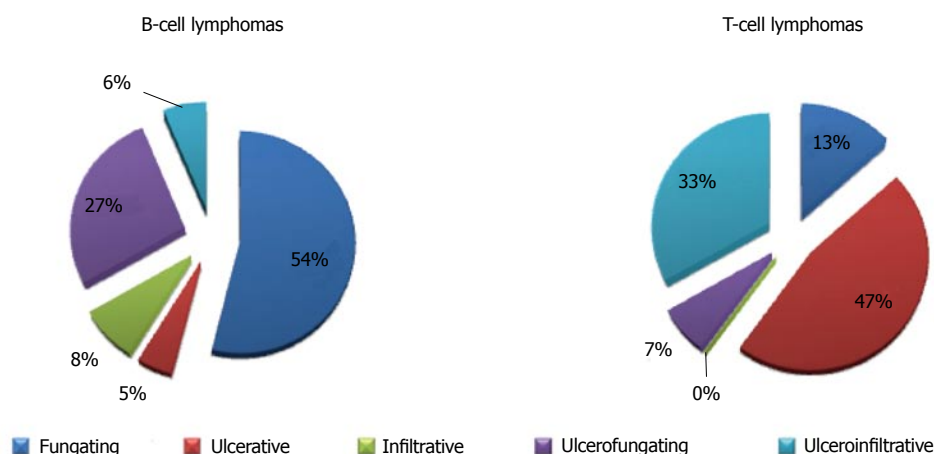


Figure 1 Differences in endoscopic pattern between B-cell and T-cell lymphomas of the gastrointestinal tract. Data extrapolated from Kim *et al*^[19] 2005.

impact on the treatment approach^[6]. Regarding DLBCL, the locoregional extension has significant prognostic implications, although its role in treatment definition is still under discussion^[3]. In contrast, few data are available in rare GI lymphomas. In particular, they are more frequently regarded as general diseases so that the locoregional extension is not always evaluated, with some reports indicating just the EUS pattern without any clinical implication. Exceptional cases have indicated the role of EUS in defining the limited extension of the disease, thus leading to an endoscopic resection of the mass [see the paragraph "Extramedullary Plasmacytoma (EMP) and Plasma Cell-related Diseases"]. That notwithstanding, EUS information is gathered only for describing the behavior of these lesions in most cases without any significant clinical impact.

Definitively, a proper staging for GI lymphomas will include^[28]: (1) physical examination: evaluation of superficial lymph nodes and Waldeyer ring inspection; abdomen palpation in order to detect liver enlargement, splenomegaly and abdominal masses; (2) endoscopic ultrasonography that is the golden standard in defining the locoregional GI involvement since it is able to distinguish the involvement of a specific layer and also of regional lymph nodes. However, as stated above, its role is under study and it is not strictly recommended in this setting; (3) computed tomography of the neck, chest and abdomen in order to detect involvement of nodes above and below the diaphragm and also other extranodal involvement not pertaining to the GI tract. In some cases, computed tomography can be of great help in defining the extension of a large bulky mass departing from the GI tract but exteriorizing outside the GI tract (see the paragraph "Plasma-cell related diseases"); (4) positron emission tomography is not generally indicated as a staging procedure, especially in MALT lymphomas, but it retains a role in defining the pre-treatment lymphomatous involvement and response to treatment; and (5) bone marrow biopsy: notwithstanding the low-grade, indolent diseases that tend to remain localized at the GI tract, bone marrow biopsy should be performed in order to exclude a

marrow involvement that could influence treatment and follow-up management. However, the level of evidence on its utility is poor. A recent update of the staging recommendation in nodal lymphomas does not encourage the performance of bone marrow biopsy facing diffuse large B-cell lymphoma and Hodgkin's lymphoma, but this strategy has not been evaluated specifically for GI lymphomas^[29].

However, these are general guidelines adopted from MALT lymphoma since in more rare GI lymphomas these guidelines have not been fully validated.

The aim of the present review is to highlight macroscopic features of rare GI lymphomas using endoscopy and related techniques. In particular, we will focus on T-cell lymphomas, lymphomatous polyposis (LP) and mantle cell lymphoma (MCL), follicular lymphoma (FL), plasma cell-related diseases, gastrointestinal lymphomas in immunodeficiency and Hodgkin's lymphoma (HL). An outline on the endoscopic presentation will be given for the diagnostic aspect and follow-up assessment. As a whole, Table 2 summarizes the clinical and molecular characteristics and prognostic features of these lymphomas.

T-cell and natural killer lymphomas

GI T-cell lymphomas are rare, representing about 5% of GI lymphomas^[14,30,31]. However, the incidence varies according to the geographical zones. European studies reported that 1.3% of primary GI lymphomas are of T-cell origin^[32], while groups from eastern countries reported 7%-15%^[33,34], reaching 41% in other series of intestinal lymphomas^[35].

Ulcerated lesions are the main endoscopic features^[30,36-38]. The first definition of this disease was "ulcerative jejunitis" by Isaacson and Du, given the always present ulcerative pattern^[14]. Usually, symptoms are related to malabsorption^[14], although perforation^[39] or intestinal bleeding^[40] can occur. Incidentally, GI perforation or bleeding can occur in cases of nodal T-cell lymphomas independently from GI localization and are an infective etiology, reflecting the immune impairment that characterizes these lymphomas^[41,42].

Table 2 Table listing gastro-intestinal lymphoma with main gastro-intestinal organ involvement, typical presenting characteristics, typical immunophenotype and genotype and prognosis

Lymphoma histotype		Presenting characteristics	Main GI involvement	Main endoscopic pattern	Typical immunophenotype	Typical genotype	Prognosis
T and NK lymphomas	EATL	Celiac patients with abdominal pain and small intestine obstruction/perforation	Duodenum and jejunum	Multiple erosions and ulcers	CD3 ⁺ , CD4 ⁺ , CD8 ^{+/−} , CD7 ⁺ , CD5 ⁺ , CD2 ⁺ , TIA ⁺ , GrBPer ⁺ , CD30 ^{+/+} , CD25 ^{+/+} , CD56 ^{+/+} , CD16 ⁺ , CD57 ⁺ , BCL6 ⁺ , CD10 ⁺ , EBV ⁺ , EMA ^{+/+}	TRB and TRG clonally rearranged +9q31.3 -16q12.1 +1q32.2-q41 +5q34-q35.2 +8q24 (MYC)	Poor
	PTCL	Poor performance status	Stomach and duodenum	Ulcerative	CD3 ⁺ , CD4 ⁺ , CD8 ⁺ , CD7 ⁺ , CD5 ⁺ , CD2 ⁺ , TIA ⁺ , GrBPer ⁺ , CD30 ^{+/+} , CD25 ⁺ , CD56 ⁺ , CD16 ⁺ , CD57 ⁺ , BCL6 ⁺ , CD10 ⁺ , EBV ⁺ , EMA [−]	¹ TCR clonally rearranged +7q/+8q/+17q/+22q/-4q -5q/-6q/-9p/-10q/-12q/-13q	54% survival at five year Poor in case of high IPI score and stage III-IV disease
	Extranodal NK/T-cell lymphoma	Gastrointestinal bleeding and B symptoms	Small intestine	Multiple erosions and ulcers	cyCD3 ⁺ , CD4 ⁺ , CD8 ^{+/+} , CD7 ⁺ , CD5 ⁺ , CD2 ⁺ , TIA ⁺ , GrBPer ⁺ , CD30 ⁺ , CD25 ⁺ , CD56 ⁺ , CD16 ⁺ , CD57 ⁺ , BCL6 ⁺ , CD10 ⁺ , EBV ⁺ , EMA [−]	TCR in germinal configuration No specific cytogenetic studies on this specific subtype	Poor especially if perforation occurs
	Adult T-cell leukemia/lymphoma	Abdominal pain, diarrhea, general fatigue, weight loss	No site preferences	Ulcers	CD3 ⁺ , CD4 ⁺ , CD8 ⁺ , CD7 ⁺ , CD5 ⁺ , CD2 ⁺ , TIA ⁺ , GrBPer ⁺ , CD30 ^{+/+} , CD25 ⁺⁺ , CD56 ⁺ , CD16 ⁺ , CD57 ⁺ , BCL6 ⁺ , CD10 ⁺ , EBV ⁺ , EMA [−]	TCR clonally rearranged Monoclonal integration of HTLV-1	Poor ² Good ³
	Indolent lympho-proliferative diseases of GI tract	Dyspepsia and mild diarrhea	Small intestine and colon	Unremarkable/friable or erythematous mucosa	CD3 ⁺ , CD4 ⁺ , CD8 ⁺ , CD7 ^{+/−} , CD5 ^{+/−} , CD2 ⁺ , TIA ^{+/−} , GrBPer ^{+/+} , CD30 ⁺ , CD56 ⁺ , EBV [−]	TCR-γ monoclonal	Indolent course
	NK-cell enteropathy	Vague symptoms (dyspepsia)	Stomach and small intestine	Lesions exhibit superficial ulceration, flat elevations with central depression and are associated with edema and local hemorrhage	cCD3 ⁺ , CD4 ⁺ , CD8 ⁺ , CD7 ⁺ , CD5 ⁺ , TIA ⁺ , GrBPer ⁺ , CD56 ⁺ , EBV [−]	TRC polyclonal or oligoclonal	Indolent course
Mantle cell lymphoma		Vague symptoms (dyspepsia)	Colon	Multiple polyposis, seldom with ulcerations	CD19 ⁺ , CD20 ⁺ , CD5 ⁺ , CD10 ⁺ , CD43 ⁺ , sIg ⁺ , BCL6 ⁺ , IRF4/MUM1 ⁺ , Cyclin D1 ⁺	BCR rearranged t(11;14)(q13;q32)	Negative impact on prognosis
Follicular lymphoma		Vague symptoms (dyspepsia)	Second part of duodenum	Whitish polyps	CD19 ⁺ , CD20 ⁺ , CD5 ⁺ , CD10 ⁺ , CD43 ⁺ , sIg ⁺ , BCL6 ⁺ , IRF4/MUM1 ^{+/+} , Cyclin D1, α4β7 ⁺	BCR rearranged t(14;18)(q32;q21)	Good
Extramedullary plasmacytoma		Alarm symptoms and obstruction	Stomach	Infiltrating mass	Plasmacells expressing CD79a ⁺ , CD38 ⁺ , CD19 ⁺ , CD138 ⁺ , CD56 ⁺ , usually CD20 [−]	BCR rearranged t(11;14)(q32;q13)	Poor
PTLD		Alarm symptoms	Colon	Rubbery erythematous or ulcerated	Similar to DLBCL and Burkitt's lymphoma CD19 ⁺ , CD20 ⁺ , CD5 ^{+/−} , CD10 ^{+/+} , CD43 ^{+/+} , sIg ^{+/−} , BCL6 ^{+/+} , IRF4/MUM1 ^{+/+} , Cyclin D1 ⁺	Monoclonal BCR	Poor median survival 6 mo
Plasmablastic lymphoma		Alarm symptoms	Stomach	Large masses and exophitic processes	CD79a ⁺ , CD138 ⁺ , CD38 ⁺ , IRF4/MUM1, CD45 ⁺ , CD20 ⁺ , PAX5 ⁺ , CD56 [−]	Clonal IgH chain gene rearrangement	Poor
Hodgkin's lymphoma		Obstruction	Colon	Protruding mass	CD30 ⁺ , CD15 ⁺ , CD45 ⁺ , CD20 [−] , CD79a [−] , PAX5 ⁺ , Ig [−] , OCT2 [−] , BOB1 [−] , CD3 [−] , CD2 [−] , CD5 [−] , ALK [−]	Clonal immunoglobulin gene rearrangement	Prognostic impact not known

¹Estrapolated from nodal counterpart but not explored in Primary GI lymphoma; ²ATLL acute and lymphoma types; ³ATLL chronic and smoldering types. TCR: T-cell receptor; BCR: B-cell receptor; EATL: Enteropathy-associated T-cell lymphoma; PTCL: Perypheral T-cell lymphoma; T-LPD: T-cell lymph-proliferative disease; NK: Natural killer; DLBCL: Diffuse Large B-cell lymphoma; PTLD: Post-transplantation lymph-proliferative disease; GI: Gastro-intestinal.

Guidelines suggest that diagnostic work-up and follow-up should be done in synergism between hematologists and gastroenterologists in order to better define the staging and the treatment needed and to ensure the best nutritional guidance (evidence level III grade B)^[43].

In a study from the German group, the most frequent histotype of intestinal lymphoma was T-cell lymphomas^[44]. The most commonly involved organs are the duodenum and jejunum, followed by the ileum and colon. Less frequent is the involvement of the stomach^[45], also as part of composite lymphoma^[46], *i.e.*, lymphoma with B- and T-cells origin. Regarding gastric involvement, in 30% of cases there is localization in the upper part of the stomach, in 20% the localization is in the middle part and diffuse in 40% of cases^[47]. Due to the fact that the prognosis and treatment strategy depends on the lymphoma histotype, biptic evaluation is a mandatory step. In addition, each subtype presents peculiar endoscopic behaviors that can drive diagnosis and treatment. GI T-cell lymphomas typically have a mature phenotype, while acute types of T-cell neoplasms do not classically involve the GI tract^[48].

According to the 2008 WHO classification of hematological malignancies, the most prevalent histotypes are^[48,49]: (1) enteropathy-associated T-cell lymphomas (EATL) (distinguished in type I and II); (2) peripheral T-cell lymphomas and extranodal natural killer (NK)/T-cell lymphoma; and (3) adult T-cell leukemia/lymphoma (ATLL).

In addition, very rare cases have been reported (mostly as singular events) of colorectal T-cell polymorphous leukemia/lymphoma^[50] or anaplastic T-cell lymphoma (ALCL) ALK⁺^[51] or ALK⁻^[52]. Distinct entities not described in the WHO classification are indolent T-cell/NK diseases that will also be taken into account.

Although EUS findings are not usually reported except in peculiar cases, submucosal hypoechoic lesions destroying the involved layer would be the main pattern^[53]. Another proof of the sub-mucosal origin of the tumor is given by narrow band imaging that is able to show intact gastric pits elevated from the underlying mass^[51]. Very rare and unusual is the GI involvement in Sezary syndrome where, despite unremarkable gastric mucosa, EUS can show the hyperechoic submucosa layer at giant fold level^[54].

Enteropathy-associated T-cell lymphoma

EATL can be divided into two forms^[14]. The first variant is characterized by features of celiac disease with abdominal pain and small intestine obstruction/perforation. Usually there is a large mass with massive necrosis, while the neighboring mucosa shows villous atrophy and crypt hyperplasia as in typical enteropathy. Type II exhibits villous atrophy in the context of tumor mass with normal intestinal mucosa in uninvolved sites. Contrarily to type I EATL, type II EATL does not progress from undiagnosed or refractory celiac disease^[14,55]. Prognosis is poor with a median overall survival of 7-10

mo^[56].

The exact incidence and lymphoma risk in celiac patients is still a debated issue^[57]. Some studies indicate a 200-fold increased risk of developing EATL compared to the general population^[58,59]. According to other studies, the risk of developing non-Hodgkin's lymphomas in celiac patients appears to be 6-fold higher than in the general population and this risk assumes a downward trend over years^[60]. Nonetheless, it appears clear that the occurrence of complications in celiac patients, although infrequent, is an event that negatively impacts on patient survival^[61]. In fact, the occurrence of intestinal perforation in a patient affected by celiac disease should lead to suspicion of lymphoma.

Usually, EATL patients tend to have a poorer performance status than B-cell lymphomas (even though tends to be localized), independent of the stage. Fever and diarrhea are the most frequent symptoms^[44]. The duodenum and jejunum are the most involved sites, with secondary involvement of the gross intestine in 14% of cases^[44]. The diagnosis of the disease in some cases is difficult since neoplastic lymphocytes can be present in a context of an inflammatory background.

Endoscopic features are aspecific, with multiple erosions and ulcers^[31]. Nodularity and thickened folds can be seen at DBE^[26,27]. Strictures and masses are less common^[62]. In some cases, macroscopic findings together with the occurrence of an intense inflammatory reaction can lead to a mistaken diagnosis of Crohn's disease (CD)^[31,63]. However, although it is not a general rule, CD ulcers are transversal, while, in the presence of T-cell lymphoma, ulcers are longitudinal^[63].

Peripheral T-cell lymphomas and extranodal NK/T-cell lymphoma

Peripheral T-cell lymphomas (PTCL) and NK lymphomas are more frequent in South America and Asia. These entities are distinct from other GI T-cell lymphomas by morphological and immunohistochemistry criteria^[62] and should be diagnosed when other more frequent T-cell lymphomas are excluded^[48]. Korean and Japanese series indicated that these are the most frequent GI T-cell lymphoma subtype, accounting for 40% of primary T-cell GI lymphomas HTLV-1 negative^[64]. PTCL arises frequently in extranodal sites, especially at the skin. However, the involvement of the gastrointestinal tract is a severe prognostic factor^[65,66]. The stomach and duodenum accounts for 60% of GI localizations^[52]. The most frequent findings are ulcerative (46% of cases), infiltrative (9%), ulceroinfiltrative (18%), ulcerofungating (18%) and erosive (9%)^[52]. Multiple polyposis can also be detected^[67]. In the literature, there are two reports indicating the involvement by T-cell lymphomas in the ileocolonic anastomosis for a previously resected right colon, presenting with polypoid lesions^[68] or ulcerative lesions^[69].

Extranodal NK/T-cell lymphoma usually arises in nasal cavities and rarely affects the GI tract. A strict relationship exists between ENKTCL and EBV infection,

with almost 70% of cases positive for Epstein–Barr virus-encoded small RNAs (EBER) detection^[70]. The small intestine is the most involved organ, while the stomach is rarely involved^[71]. The endoscopic pattern in the majority of cases is given by multifocal ulcers^[72–75] and infiltrative lesions^[52]. Sometimes the ulceration leads to intestine perforation and acute peritonitis (60% of the total complications)^[52]. Additionally, perforation is more frequent in the infiltrative pattern compared to the non-infiltrative. Fungating lesions are not usually reported^[76]. The most involved organ is the small intestine^[77,78] and/or colon^[72,76] (depending on the case series), followed by the small intestine, rectum and stomach^[72]. However, the location at the GI tract does not seem to affect the prognosis^[77]. Interestingly, since the perforation usually leads to the development of peritonitis, the Lugano staging system has been applied, resulting in the advanced stage of the disease being a prognostic factor at multivariate analysis^[72]. Due to the high risk of perforation, many patients undergo surgery as a pre-emptive or curative strategy, rarely for diagnosis^[79]. However, according to Kim *et al.*^[77], patients undergoing surgery followed by chemo/radiotherapy would show a better OS. However, as the authors themselves stated, this benefit would be ascribed to the fact that patients undergoing surgery had a better performance status and more limited disease which would have affected the outcome. Similarly, as Hong *et al.*^[78] reported in a multivariate analysis, surgery ensures a better survival compared to chemotherapy. Therefore, an appropriate locoregional staging is also useful to tailor treatment.

Adult T-cell leukemia/lymphoma

As for EATL, ATLL tends to present with ulcers with aggressive behavior. This is a specific variant of peripheral T-cell lymphoma that recognizes the HTLV-1 virus as an etiological agent^[48]. This variant is mainly found in endemic areas of Japan^[64]. In about one third of ATLL cases, GI involvement is secondary to a systemic disease^[49]. According to the first data by Suzumiya, the stomach is involved in 40% of cases and the small and large intestine in 38% and 34% respectively^[80]. Although four types of ATLL have been depicted (*i.e.*, smoldering, chronic, lymphoma, acute), no endoscopic pattern has been related to a peculiar histotype. HTLV-1 infection has no role in determining the macroscopic features^[47]. Noteworthy, the detection of GI involvement has a prognostic impact^[49], representing the aggressiveness of the disease^[43]. In fact, smoldering or chronic ATLL subtypes do not typically show GI involvement^[81]. However, primary GI smoldering ATLL have been described and show long term disease-free survival after chemotherapy^[82]. Gastric involvement can be enhanced by *Helicobacter pylori* infection that creates an inflammatory state able to lead lymphocytes (also malignant) to migrate into gastric wall through the expression of specific adhesion molecules^[83].

An ulcerative pattern is present in more than half

of cases of gastric involvement^[47]. Single or multiple yellow-whitish polyposis of the first or second loop are more frequent in the duodenum^[49] and multiple polyposis is the recurrent lesion in cases of colon involvement^[84]. Although a single or multiple polyps are the most frequent lesions, flat ulcerations/erosions can also be present^[84]. Red flat or elevated lesions in the rectum have been also documented^[85,86]. Rarely, there is the involvement of the ileum, where polyps are the main features^[87]. It should be underlined that GI lesions are not always monotone but can be variegated. For examples, case reports indicate the occurrence of protruding masses with normal or eroded mucosa at the stomach and the occurrence of flat granular, friable lesions that bled on contact with mucosa at the colon^[88] or reddish irregular flat lesions at the esophagus^[89].

Narrow band imaging is able to document irregular microvascular architecture, dilated and destroyed gastric pits and dense aggregations between the pits with variegated irregular nuclei without interglandular infiltration (reflecting the absence of lymphoepithelial lesions)^[90].

Indolent lymph-proliferative diseases of the GI tract

A new category of T-cell GI lymphoproliferative disease, namely T-cell lymphoproliferative disease (T-LPD), has been recently introduced^[91]. The indolent course is the main clinical hallmark while this entity has been previously treated and managed as PTCL. Noteworthy, the etiology of the disease is unknown, although many patients present with a history of inflammatory bowel disease (IBD). Basically, the clinical picture is dyspepsia and mild diarrhea, while endoscopic features can vary from unremarkable mucosa to erythema. The small intestine and colon are the most frequently involved sites, followed by the oral cavity, stomach and esophagus. Usually, the gastric mucosa is normal despite a disease localization, while the duodenum can show thickened folds and an irregular pattern. In the colon, the occurrence of friable mucosa, erythematous mucosa and small polyps can be seen. Ulcerations are not described. At immunohistochemistry, lymphoid cells have a cytotoxic phenotype (CD8⁺; CD4⁻; TIA⁺), clonal T-cell receptor (TCR) gene rearrangements, do not form masses, do not invade the intestinal crypts and do not cover the full thickness of the bowel^[91]. Additionally, the lymphoid infiltrate is limited to the mucosa and sub-mucosa. The molecular study for TCR can show a monoclonal rearrangement of TCR- γ chain^[91]. The recognition of this disease has many therapeutic implications since aggressive chemotherapy is excessive and an immunosuppressive treatment is virtually sufficient.

Indolent CD4⁺ T-cell lymphoma has also been described and shows a good outcome and survival despite a persistence after immunomodulatory drug-based treatment^[92]. Rarely, gastric mucosa can show multiple nodularities^[93]. However, a clinical and endoscopic follow-up of these lesions is always

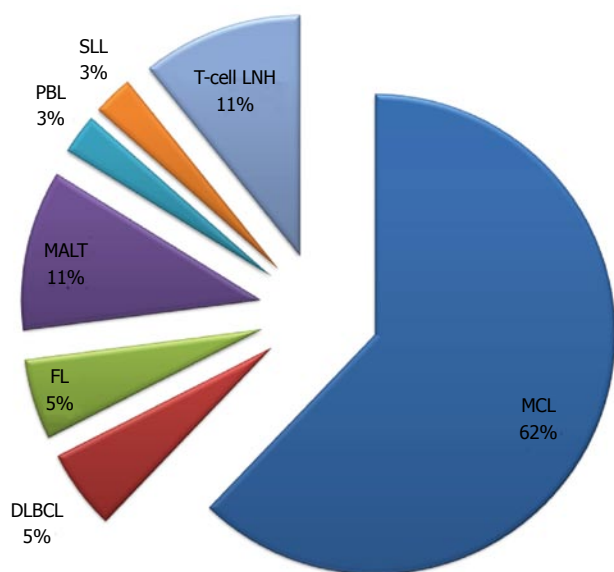


Figure 2 Pie chart describing the distribution of lymphomatous polyposis as a presenting gastrointestinal feature in gastrointestinal non-Hodgkin's lymphomas according to histotype. SLL: Small lymphocytic lymphoma; PBL: Plasmablastic B-cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; MCL: Mantle cell lymphoma.

advisable^[93], also for the risk of progression in the long term^[92].

Similarly to T-LPD, NK cells can also give rise to an indolent form of lymphoid infiltrate in the context of the GI tract, *i.e.*, NK-cell enteropathy^[94]. Usually the symptoms are vague and the GI lesions can be present in the stomach (more frequently), duodenum, small intestine and colon. At endoscopy, these lesions exhibit superficial ulceration, flat elevations with central depression and are associated with edema and local hemorrhage. Usually these ulcers are 1 cm in diameter and the surrounding mucosa is not abnormal. This disease is distinct from ENKTL since gastric involvement in the latter is really infrequent (and if present, the localization is not limited to the stomach) and EBER is positive. In addition, in the presence of NK-enteropathy, the epithelium can be invaded, showing a lymphoepithelial-like lesion^[95]. Moreover, contrarily to T-LPD, the TCR rearrangement is polyclonal or oligoclonal^[94].

Lymphomatous polyposis and mantle cell lymphoma

The pioneering study by Cornes *et al*^[96] in 1961 first reported the term "lymphomatous polyposis (LP)". It is defined as the presence of diffuse proliferation of monotonous small-to-intermediate sized lymphocytes presenting as multiple polypoid tumors from 2 mm to several centimeters in different GI sites. Although the preferred site is the small intestine^[14], other sites can be involved alone or at the same time^[97-104]. Actually, LP is present in 4%-9% of all GI lymphomas^[14], more frequently in western than eastern countries^[105]. B-cell lymphomas are more frequent than T-cell lymphomas and this is due to the fact that histologically these polyps

originate from the mantle zone of the lymphoid follicle of the mucosa-associated lymphoid tissue^[106]. Additionally, this fact justifies the augmented frequency in the small intestine (rich in lymphatic tissue) compared to other GI tract sites. Additionally, multiple tumors or different kinds of lymphomas can be simultaneously present in a context of LP^[107]. Therefore, the biopsy of more than one polyp and of different types of lesions is always advisable^[108,109]. Additionally, it must be underlined that although the occurrence of multiple polyposis in a patient with nodal lymphoma is not a criterion to absolutely define the involvement of the GI tract, the histological evaluation is always mandatory^[110].

Typical lymphoma presenting with LP is MCL^[14,111], although other tumors can show this feature^[98-100,112-114]. Among 37 case reports of LP since 2000^[67,84,98-100,103,112-142], MCL was indeed the most frequent disease (more than 50% of cases) (Figure 2). The most involved site was the colon (Figure 3). In the case series by Saito *et al*^[143], regarding patients affected by MALT lymphomas or MCL at the ileal site, it was underlined that LP was the most frequent presentation of MCL and the least common lesion in MALT lymphomas (Figure 4).

MCL can locate at the GI tract secondary to the generalized disease^[102] and, although only 25% of patients with nodal mantle cell lymphoma suffer GI symptoms, 77%-88% have a localization at the gross intestine and 43%-77% in the upper GI tract, also in the absence of macroscopic lesions^[14] (Figure 5). LP is the most frequent endoscopic pattern although other endoscopic features can be present^[144], for example, a granular pattern associated with polyps (Figure 6) or ulcerated polyps^[145] or masses^[146]. In addition, the endoscopic pattern varies according to the part of the GI tract involved (Figure 7). EUS has been applied in this setting, giving the possibility of identifying submucosal lesions^[115]. MCL appears echo-poor, usually departing from the second layer and remaining confined to the GI wall (Figure 8)^[115,147,148]. In some cases, the diagnosis of MCL could be incidental during the endoscopic definition of gastric bleeding caused by gastric ulcers^[149].

Contrarily to GI follicular lymphoma (discussed below), the GI tract involvement by MCL assumes a great prognostic implication and is useful to monitor patients after the treatment^[14,101]. Indeed, the occurrence of LP designates a median survival of 3-4 years^[14,101]. Due to the fact that the small intestine can be also involved by the tumor, the performance of CE or DBE would be advisable in order to correctly stage the patient and assess the follow-up evaluations^[116,117].

Although the disease presentation has been well studied, there are no data about the management of LP during follow-up assessment. Our opinion is that endoscopic evaluation with mapping biopsies should be performed in these patients since in some cases the presence of aspecific abnormalities during follow-up can lead to the finding of lymphoma reappearance^[146], sometimes many years after complete remission^[103,119].

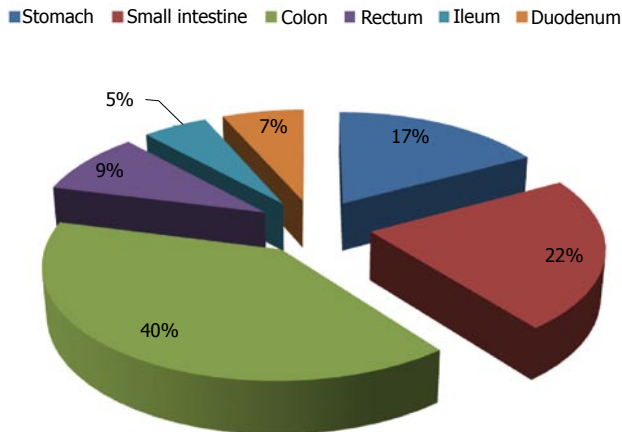


Figure 3 Pie chart describing the most involved gastrointestinal site in lymphomatous polyposis.

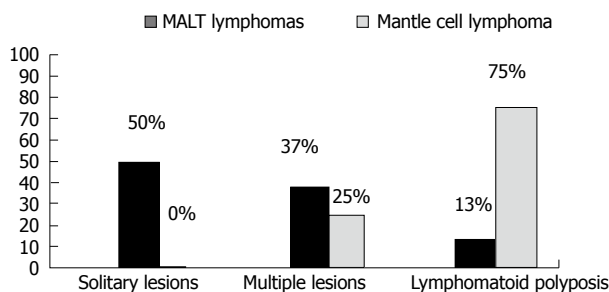


Figure 4 Frequency of lymphomatous polyposis at ileum in mucosa-associated lymphoid tissue lymphoma and mantle cell lymphoma. Adapted from Saito *et al*^[143], 2005.

Follicular Lymphoma

GI FL is a rare entity, representing up to 3.6% of all GI NHL^[150,151]. Primary GI FL was recognized as an histological variant of FL in the 2008 WHO classification of hematopoietic tumors^[152]. Sites most frequently involved are the duodenum (55.6% of cases)^[101], in particular the second part^[152], and the terminal ileum (33.3% of cases)^[151,153]. Since positron emission tomography and computed tomography have low sensitivity and specificity^[154] in catching small intestine involvement, CE and DBE have acquired more and more importance^[155,156]. Indeed, these techniques have shown that the small bowel can be involved in 70%-83% of cases^[157,158], even in cases of duodenal lymphoma^[152].

To date, a clear endoscopic classification of GI-FL has not been done, as for GI MALT lymphomas. However, Yamamoto *et al*^[151], reviewing 249 GI-FL cases, reported a reliable endoscopic classification of the disease. Whitish polyps usually up to 2 mm^[151,153] and/or white granules-nodular aggregates, with or without ulceration of the mucosa layer (Figure 9), are the typical endoscopic pattern^[150,159,160]. This can be unifocal or multifocal and is mainly present in intestinal FL. A large mass with or without ulceration is less frequent and in half of cases can be associated with multifocal whitish polyps. The latter is the most frequent endoscopic pattern of primary gastric FL. Multiple lymphomatous polyposis can also be

Vetro C *et al*. Endoscopy in rare GI lymphomas

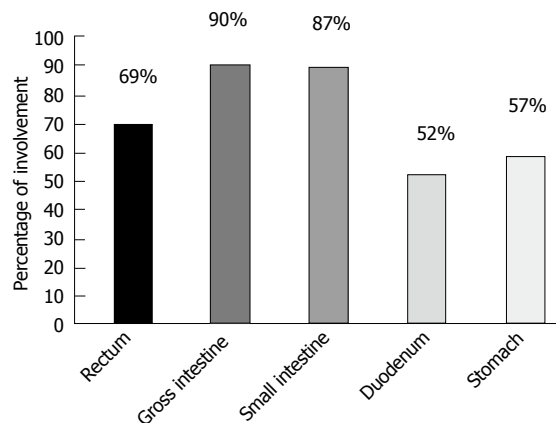


Figure 5 Frequency of the sites involved in mantle cell lymphoma. Adapted from Ruskoné-Fourmestreaux *et al*^[101], 2010.

found^[30,101,150,158,161,162]. Interestingly, in the series of 48 patients with GI FL reported by Yanai *et al*^[163], it was found that the LP was the most frequent endoscopic feature (more than 50% of cases), followed by polypoid or ulcerative lesions (Figure 10).

Recently, high-definition endoscopy, as well as magnifying endoscopy (ME), has been used to describe the surface microstructures of GI FL, such as enlarged whitish villi and tiny whitish depositions and an irregular microvascular pattern^[164,165]. This fact indicates that the tumor is of non-epithelial origin and usually reflects the formation of lymphoid follicles^[164,166-169]. EUS has not been widely applied. A few reports have indicated that the echoendoscopic pattern is given by second and third layer thickening, dotted by hypoechoic nodules^[170].

Capsule endoscopy and double-balloon enteroscopy are useful in the definition of small intestine involvement in a non-invasive way. The typical picture is a whitish submucosal elevation presenting as nodules or polyps^[21], usually multifocal^[171,172]. However, the limitation is the inability to perform a biopsy that is postponed until the enteroscopy and the risk of retention in cases of stenosis (unusual in cases of GI-FL).

Nodal spread is rare and GI FL tends to be localized in the gastrointestinal tract (stage IE according to Ann Arbor staging system)^[173] and to have an indolent course^[152,174]. However, transformation to aggressive lymphoma has been documented^[175]. Different from other form of lymphomas, the GI involvement is not an adverse prognostic factor^[176]. Lymphoma grading is low in the majority of cases, while in the nodal counterpart grade I-II FL is documented in 1 case out of 10^[173]. Furthermore, in contrast to nodal FL, these cells do not acquire additional mutations and this justifies the absence of grade 3 GI FL and the very low rate of transformation^[173,175].

Treatment strategies are not uniform, although GI FL are treated more frequently compared to the nodal counterpart^[177]. Different case series have demonstrated that a watch and wait approach is as useful as the pharmacological approach, except for relieving clinical symptoms^[163,178-180]. However, case series differ greatly

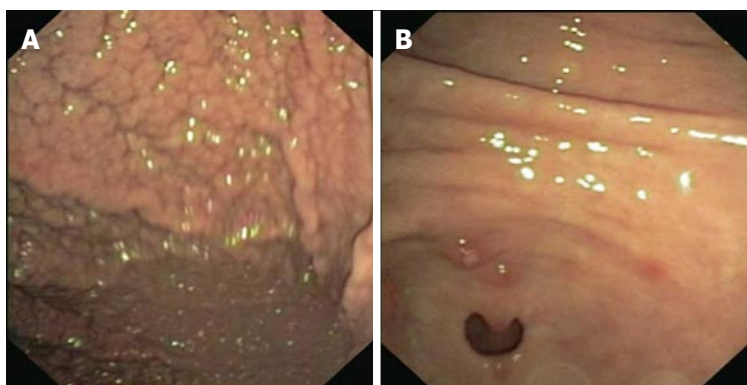


Figure 6 Endoscopy stomach: Granular pattern of the fundus and body of the stomach (A) and polyps in the antrum (B).

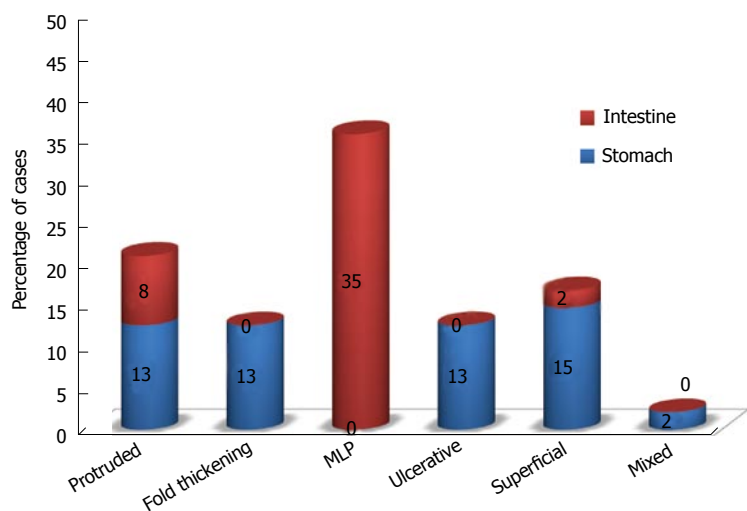


Figure 7 Endoscopic lesions in mantle cell lymphomas according to the gastric and intestinal localization. Adapted from Iwamuro *et al.*^[144], 2010.



Figure 8 Endoscopic ultrasonography (radial scanning): Marked thickening of the muscularis propria and increased wall thickness (12 mm) in the angulus (A); antrum (B); body (C).

in identifying the correct treatment approach to be applied. Surgical resection is not recommended and chemoimmunotherapy is preferred^[151,171]. It must also be considered that the introduction of anti CD20 antibodies has augmented the survival rate and in some series localized/low-grade GI FL have been treated with anti CD20 monoclonal antibody alone, without chemotherapy^[151].

It is debatable whether CE and/or DBE are truly useful. Indeed, no studies have demonstrated that the detection of small bowel involvement (especially if duodenal lymphoma is present) would have changed the treatment needed. Surely, these procedures would change the treatment strategy in cases of radiation or surgical treatment and are needed in cases of obscure gastrointestinal bleeding^[172,181]. Apart from these occ-

urrences, the effectiveness of chemoimmunotherapy or immunotherapy alone would render these procedures less practical in patient management. However, since no clear data exists regarding survival and quality of life in dependence of small bowel involvement, clinician choice is the only way to proceed.

That notwithstanding, the diagnostic suspicion based on the endoscopic features, together with the patient history, is fundamental in addressing the pathological diagnosis. Indeed, in almost 20% of cases, FL can be misdiagnosed by endoscopic biopsy evaluation^[182]. Therefore, multiple biopsies would be necessary. In particular, biopsies of the peripheral mucosa would be more informative than biopsies from the erosion/ulceration since the probability of catching necrotic tissue decreases significantly.

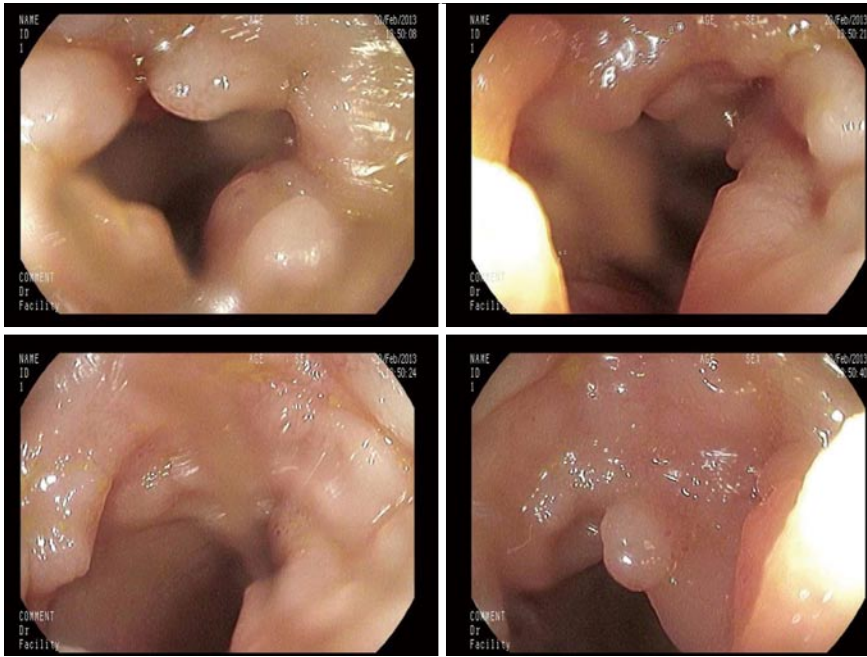


Figure 9 Ileoscopy revealing the presence of hyperemic mucosa with whitish polypoid nodularity. The subsequent diagnosis was a grade 2A follicular lymphoma.

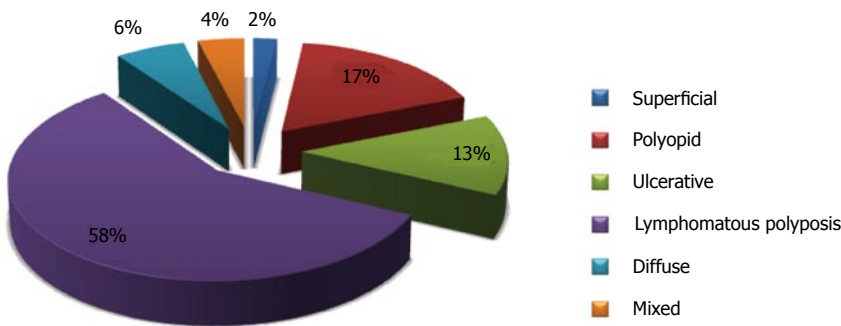


Figure 10 Endoscopic features of follicular gastrointestinal lymphomas. Adapted from Yanai *et al*^[163], 2011.

EMP and plasma cell-related diseases

EMP belongs to a precise type of lymphoid malignancies, *i.e.*, plasma cell neoplasms, representing 3%-4% of cases^[183]. It is important to distinguish this subtype from lymphomas with plasmacytic differentiation, particularly MALT lymphomas^[48]. The upper respiratory tract is the most involved organ (almost 80% of cases), while GI localization is rare^[48]. Among these cases, the stomach is the most involved site, followed by the liver, colon and the small intestine (duodenum, jejunum and ileum)^[184].

Usually, gastric localization is secondary to a plasma cell myeloma (PCM) and often emerges through a clone selection process. Indeed, multiple myeloma treatment itself can select a particular chemoresistant PC clone able to migrate at extra-nodal organs. In these cases, an accurate endoscopic investigation is critical for the diagnostic assessment and disease monitoring^[185]. Due to the strict relationship with plasma cell myeloma, the clinical course is poor. The most frequent endoscopic finding consists of an infiltrating mass or masses in the stomach and/or the duodenum^[186,187] or well-

demarcated, flat, yellow-whitish mucosal changes^[188] or nodular lesion with central umbilication^[189]. Endoscopic appearance as diffusely thickened mucosal folds simulating linitis plastica is rare^[190]. Sometimes, large ulcerations can be seen^[191,192]. However, the gastric mucosa can appear normal, while the extramural growth is incredibly vast (Figure 11). EUS could be of great help in defining the disease extension that appears as a large echo-poor mass infiltrating surrounding organs^[186]. However, sometimes EUS can be useful to detect limited gastric wall involvement and in these cases, an endoscopic resection of the mass can be performed, resulting in safety for the patient and effective in the treatment of the disease^[188,193,194]. Alternatively, patients with localized disease can be treated with radiation treatment^[190,195].

Small intestine involvement is generally primary with a benign course. These lesions can be explored by enteroscopy and/or capsule endoscopy^[196], paying attention to the cases in which obstructions or retention are expected. Differential diagnosis is other cases of

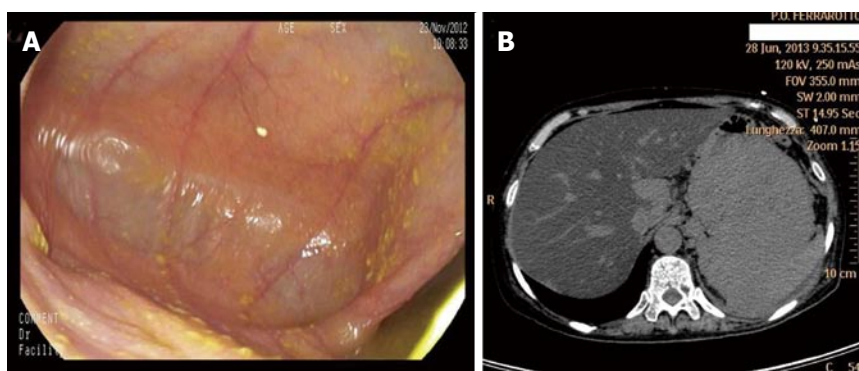


Figure 11 Extra-mucullary plasmacytoma with gastric localization arising after treatment for multiple myeloma. A: Gastroscopy resulted negative for tumor detection; B: CT scan analysis of the upper abdomen showing a bulky mass departing from the stomach.

sub-mucosal masses in the small intestine, as reported by Lopes da Silva^[196]. Colon involvement appears more frequently as stricture^[197,198], in some cases difficult to differentiate from colon adenocarcinoma^[199], returning to the differential diagnosis of sub-mucosal tumors^[193]. Rarely it can determine rectal bleeding^[200]. The localization at the rectum appears as a mild granularity as well as a reddish, protruded lesion^[201]. Usually these lesions disappear after treatment and this is a confirmation of treatment efficacy^[186], although mucosal atrophy and non-specific inflammation can be reinstated^[195].

Apart from EMP, other plasma cell-related disorders can involve the GI tract. This is due to the production of amyloid protein in AL amyloidosis (light chain amyloidosis)^[187]. The most involved organ is the small intestine. In some cases the amyloid deposition is synchronous with EMP^[187,193,195] or other GI lymphomas^[202]. Usually, the amyloid protein in AL amyloidosis involves the submucosa and the muscularis mucosae, resulting in thickened folds and valvulae conniventes and polypoid lesions in the GI tract. The typical deposition of AL amyloid proteins result in pseudo-obstruction, constipation and mechanical obstruction as the main symptoms^[203]. Intestinal bleeding can also occur^[204] and if this event occurs in a patient with multiple myeloma, the occurrence of aspecific elevated lesions at the endoscopic evaluations should lead to suspicion of systemic amyloidosis. More rarely, submucosal hematoma, ulcers and hemorrhagic bullous colitis can be seen^[205]. On the other hand, nodularity, fine granular appearance and mucosal friability are more frequent in other types of amyloidosis, *i.e.*, AA amyloidosis (amyloidosis secondary to systemic disorders). This is due to the deposit of amyloid proteins into the lamina propria with impaired absorption and subsequent diarrhea^[203].

Immunodeficiency and GI lymphomas

Immunodeficiency is defined as a state of impaired function of the immune system that can be congenital, acquired or iatrogenic. The reduced immune-surveillance can determine an augmented rate of lymphomas. Two

conditions mainly determine the arising of lymphomas: human immunodeficiency virus (HIV) infection with the correlated acquired immunodeficiency syndrome (AIDS) and post-transplant immunosuppression. In both conditions, the GI tract is the most involved site^[206]. Apart from HIV and PTLT, common variable immunodeficiency (CVID) has been associated with the development of gastrointestinal NHL, although this is a very rare finding^[207,208].

In HIV patients, the rate of GI lymphomas was higher in the pre-HAART era before 1996^[209] and the risk of gastric NHL was 353-fold compared with normal subjects, with aggressive lymphomas the most prevalent feature^[59]. In cases of AIDS-related lymphoma, the GI tract is involved in 20% to 50% of cases^[206,210]. However, the decrease of GI lymphoma incidence has not been as high as in central nervous system lymphomas^[209]. A recent analysis of 243 HIV patients performed at the University of Sao Paulo revealed an incidence of gastric NHL of 2.5%^[211]. Co-infection with EBV and/or CMV would complicate the prognosis^[212], although the occurrence of viral infection is less pathogenetically important compared to PTLT^[206]. The main histologies are B-cell lymphomas (67%) (DLBCL, Burkitt lymphoma, MALT lymphoma)^[213], while T-cell lymphomas are less frequent (33%)^[209] and other types of hematological malignancies are anecdotal^[214,215]. In 5%-10% of cases, cMyc rearrangement is present and confers a poor prognosis^[212]. Additionally, the prompt recognition of this lymphoma subtype has a great impact in patient management since the presenting symptoms are usually alarm symptoms in about half of patients. However, in the majority of patients, the lymphoma is diagnosed at Ann Arbor stage III-IV^[206]. The most frequent endoscopic features are multifocal ulcerations, followed by polypoid or a bulky mass together with bloody spots^[206,212]. The most involved sites are the stomach and duodenum^[216], followed by the small bowel and colon-rectum (Figure 12)^[211]. However, unusual presentations can be seen more commonly than in immunocompetent patients^[206]. At narrow-band, a honeycomb-like pattern is present without irregularity in the microvasculature^[212]. The localization can also be perirectal and in these cases,

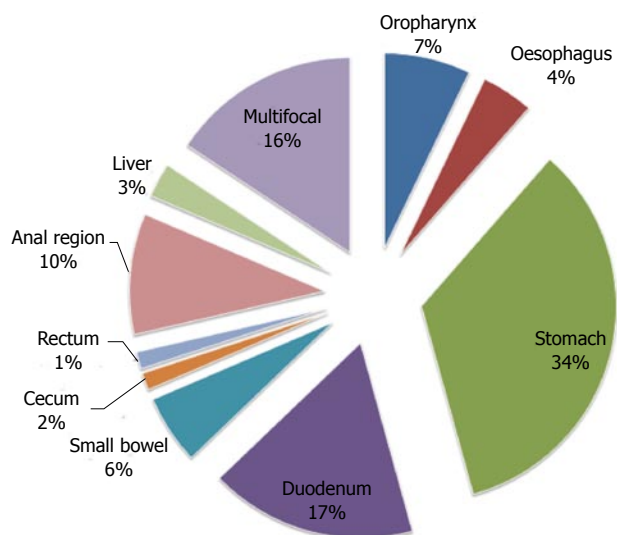


Figure 12 Frequency of the involved gastrointestinal tract in human immunodeficiency virus-related gastrointestinal lymphomas. Adapted from Heise^[206], 2010.

EUS-guided fine needle biopsy would be a valid tool for diagnosis given the high grade nature of this kind of lymphomas^[217]. Noteworthy, EUS appearance is of a hypoechoic poorly defined mass^[217] and is important for the locoregional staging^[206]. Prognosis is poor with a median survival of 6 mo and a rate of complete remission less than 40%^[211]. Prognosis is also impaired by the occurrence of opportunistic infections^[210]. Extremely suggestive is the development of EBV-related DLBCL in patients suffering other types of lymphomas that induce a state of immunosuppression, such as AITL^[218]. In these peculiar cases, the outcome is really poor and alarm symptoms and perforation can occur with fatal implications^[218].

GI lymphomas are also more frequent in solid organ transplant recipients, particularly after renal, heart and small bowel transplantation, encompassing the spectrum of PTLD (Table 3). The pathogenetic events seem to be different compared to HIV-related lymphomas since in this kind of lymphomas, Epstein-Barr virus reactivation due to immunosuppressants plays a pivotal role^[219]. Apart from negative EBV serology prior to transplantation, length of immunosuppression is an overt risk factor^[220,221]. EBV-positive lymphomas arise earlier than EBV-negative lymphomas^[221]. In adults, the majority of cases arises over 12 mo from transplantation^[222], at a median of 36 mo^[223]. A second peak is after 5-10 years^[206]. Median overall survival is 8 years and the principal histotype is B-cell lymphoma, although lymphomas of T-cell origin can also be present. Noteworthy, the GI tract is involved in one third of cases. Endoscopy is of great help in establishing the diagnosis. Especially in small bowel transplantation, endoscopic follow-up has gained a pivotal role in defining the transplant-related complications, including the onset of PTLD^[224]. Typically, lesions are raised, rubbery, erythematous or ulcerated^[222,225,226]. The most

Table 3 Prevalence of gastrointestinal lymphomas among transplant recipients according to transplanted organ

Transplant	Prevalence
Bone marrow	0.50%
Liver	1%-2%
Kidney	0.7%-4%
Heart	2%-10%
Small bowel	up to 30%

The data extracted from Heise^[206], 2010.

involved organ is the colon, followed by the small intestine and stomach^[223]. However, the recognition of symptoms together with the patient history is of great help in driving the diagnosis. Additionally, endoscopic procedures are essential in order to follow the course of disease^[225], also valid in the long-term^[226]. Interestingly, early stage PTLD can be safely removed endoscopically and this would be a valid approach in the treatment of localized PTLD^[224].

Plasmablastic lymphoma (PBL) is a rare and aggressive type of lymphoma characterized at histological evaluation by the presence of large immunoblasts with plasmacytic differentiation with an high replication index^[227]. Usually, this lymphoma arises in the oral cavity in HIV-infected patients and in the literature there are few cases of GI localization (Table 4)^[228-237]. The stomach is the most involved site (about 50% of cases), followed by the small intestine, anal region, cecum, colon and esophagus^[237]. Large masses and exophytic processes are the main endoscopic appearance in the stomach and anal region. Intestinal localization is extremely rare and when present, the endoscopic appearance is of multiple nodularity^[227]. Moreover, PBL can also arise in immunocompetent patients with ulcerated lesions at the stomach^[236]. These patients are normally older than HIV⁺ patients, tend to present with GI localizations more than HIV⁺ patients and have a worse overall survival^[236,237].

Additionally, CD has also been linked to the development of lymphomas of the gastrointestinal tract. Most of them are of B origin, comprising DLBCL and HL, although T-cell lymphomas can also arise. In the recent report by Kappelman *et al.*^[238], patients with CD showed a greater risk of developing hematological malignancies compared to the general population. This study confirmed the previous report by Askling *et al.*^[239], also showing an augmented rate of hematological malignancies compared to the general population and 10% of developed lymphomas were T-type. Probably, it would be related to the state of immunosuppression leading to infection of lymphotropic and oncogenic viruses, but the specific mechanism is still to be clarified. This predisposition seems to be unrelated to immunosuppressive treatment. In this setting, anti-TNF α treatment has been related to development of hepatosplenic T-cell lymphoma^[240]. However, two years later, a meta-analysis by Siegel *et al.*^[241] indicated that



Figure 13 Exophytic erythematous circumferential non-ulcerated mass determining a stenosis of the ileocecal region. The mass arises from the deep layer and the mucosa presents reddish areas suggestive for lymphomatous infiltration of the cecum (A, B, C).

Table 4 Reports of gastrointestinal plasmablastic lymphoma from 1998				
Manuscript	Year	localization	Endoscopic appearance	HIV
Pruneri <i>et al</i> ^[230]	1998	Stomach	Large polypoid mass	-
Colomo <i>et al</i> ^[231]	2004	Anal region	Mass	+
Dong <i>et al</i> ^[232]	2005	GI tract	Not reported	+
		Small Intestine	Not reported	+
Tavora <i>et al</i> ^[228]	2006	Anal region	Not reported	+
		Anal region	Exophytic mass	+
Taddesse-Heath <i>et al</i> ^[233]	2010	Small intestine/colon (2 cases)	Not reported	+
Brahmania <i>et al</i> ^[234]	2011	Ano-rectal junction	Hypervascular cauliflower-like mass	-
Mihaljevic <i>et al</i> ^[235]	2012	Stomach	Not reported	-
Hashimoto <i>et al</i> ^[236]	2012	Stomach	Not reported	-
Chapman-Fredricks <i>et al</i> ^[229]	2012	Stomach	Not reported	+
Luria <i>et al</i> ^[237]	2014	Anal region	Mass	+
		Sigma	Mass	-
		Small bowel	Not reported	-
		Ileum	Not reported	-

HIV: Human immunodeficiency virus; GI: Gastrointestinal.

immunosuppressive treatment is not a risk factor for the development of NHL in CD patients. However, it is still a matter of discussion since the augmented incidence of GI lymphomas in these patients is related to the more intensive examinations. Moreover, the histological evaluation is a crucial point since the inflammatory background can lead to a false positive result. That notwithstanding, anti-TNF α treatment seems to be safe regarding the incidence of NHL and should not be regarded as a risk factor. Therefore, more epidemiological studies will be needed in order to better define the link between CD and GI lymphomas.

Hodgkin's lymphoma

Lymphomatous GI involvement in HL appears as a stricture (Figure 13) or ulceration^[242-245]. The abundant lymphoid tissue present at this site renders it one of the most involved regions^[246]. HL rarely presents as a colonic localization (almost 1%-3% of extra-nodal HL cases^[247] and less than 5% of gastrointestinal lymphomas^[243]) and the prognostic impact is still obscure. Mixed-cellularity subtype is the most common feature^[248]. As for the nodal counterpart, the inflammatory background is a key feature of HL^[249]. In some cases, the endoscopic and

histological presentation can resemble IBD, that in turn is seldom associated with colonic HL^[244,250]. Additionally, immunodeficiency is a risk factor^[251], although this type of lymphoma can also arise in immunocompetent patients^[247].

Recently, a new entity has been proposed, *i.e.*, "EBV-associated mucocutaneous ulcer" (EBVMCU)^[252]. This disease subtype resembles HL but there are peculiar clinical and histological differences. Indeed, the presence of "plasmacytoid" apoptotic cells and the confinement to mucosa and sub-mucosal layers are the histological hallmark that can lead to a differential diagnosis from cHL. However, EBV infection is always present, as in GI-HL.

CONCLUSION

Endoscopic features of GI lymphomas are variegated encompassing ulcers, erosions, polyps and so on. It is a fascinating matter of study for both hematologists and gastroenterologists. As stated in guidelines, a synergism between these two figures is fundamental. This is due to the lack of data and the fact that information regarding rare GI lymphomas are extrapolated from case series or

case reports. Actually, the scientific community is gaining more and more knowledge about the recognition and management of these lymphomas, with the creation of proper guidelines for specific lymphoma subtypes. In this setting, the collection of different case series and their analysis will assume a pivotal role in drawing general guidance on disease characterization. Certainly, as has emerged in the manuscript, the management of these lymphomas is different from the nodal or medullary counterparts and a proper understanding of the endoscopic features together with clinical and histological characteristics is crucial for better management of patients, with the ultimate goal of improving clinical outcome and quality of life for patients.

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