Gastrointestinal lymphoma: the new mimic

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To cite: Shirwaikar Thomas A, Schwartz M, Quigley E. Gastrointestinal lymphoma: the new mimic. *BMJ Open Gastro* 2019;6:e000320. doi:10.1136/bmjgast-2019-000320

The material in the paper was previously presented as an abstract at the WCG meeting in Orlando in 2017.

Received 11 June 2019

Revised 21 August 2019

Accepted 27 August 2019

ABSTRACT

Background Gastrointestinal (GI) lymphomas comprise a group of distinct clinicopathological entities of B- or T- cell type, with primary gastrointestinal Hodgkin lymphoma being extremely uncommon. The GI tract is the predominant site of extranodal non-Hodgkin lymphoma accounting for 30–40% of all extranodal lymphomas. In the Western world, the stomach is the most commonly involved site followed by the small bowel. Several chronic inflammatory and immune-mediated disorders which predispose to accelerated cell turnover may lead to the malignant transformation of gut lymphocytes and ultimately manifest as GI lymphoma. The challenge for the clinical gastroenterologist is that these tumors may have varied presentations, ranging from nonspecific symptoms such as dyspepsia or bloating to abdominal pain, nausea, vomiting, GI bleeding, diarrhea, weight loss or bowel obstruction.

Objective We illustrate the range of presentations of GI lymphoma with examples based on consecutive cases evaluated at our institution over a 6-month period. These cases demonstrate how appropriately directed endoscopic evaluation with biopsies has the potential to provide a definitive diagnosis and allow the patient to proceed to definitive therapy.

Conclusions The GI tract is the most commonly involved site for extranodal lymphoma with the stomach being most frequently involved organ. Chronic *Helicobacter pylori* infection, celiac disease, inflammatory bowel disease and autoimmune disorders may predispose to GI lymphoma. This heterogeneous group of diseases has varied presentations that may mimic several other GI clinicopathologic entities. GI lymphomas may be diagnosed with appropriately directed endoscopic evaluation coupled with generous tissue sampling and expert pathologic assessment. Management may range from antibiotic therapy, in the case of *Helicobacter pylori*-associated gastric MALT lymphoma, to chemotherapy with or without radiation and, in rare instances, surgery. There are presently no guidelines to direct endoscopic surveillance of GI lymphomas following treatment.

INTRODUCTION

The gastrointestinal (GI) mucosal surface functions as a variably permeable barrier subserving its roles in secretion and absorption along the length of the gut. Its surface area is greatly increased through various anatomical and ultrastructural features

(folds, villi and microvilli). This facilitates its access to the products of digestion as well as exposure to a significant antigenic load from microorganisms and ingested materials in the lumen. The mucus layer on the mucosal surface, together with the epithelium (gut barrier), serves as the first line of defence against pathogens and other potentially injurious invaders. More specific immunological responses are generated by the gut or mucosa-associated lymphoid tissue (MALT) in the epithelium and lamina propria. These lymphoid cells are produced in the bone marrow and thymus and migrate to the gut to form one of the largest collections of immune cells in the body.¹ MALT, through its unique immunophysiological characteristics, serves to maintain immune homeostasis in the intestine. The most distinctive and visible aggregation of lymphoid tissue in the GI tract is found in the Peyer's patches in the terminal ileum; the remainder is diffusely distributed in the form of lymphoid aggregates in the lamina propria throughout the entire GI tract.^{1 2} Repetitive inflammation and antigenic stimulation in response to autoimmune and inflammatory disorders can lead to monoclonal proliferation and the development of extranodal GI lymphomas over time. For example, chronic *Helicobacter pylori* infection in the gastric mucosa, typically devoid of MALT, may lead to lymphoid cell proliferation.³ Malignant transformation of this acquired gastric MALT results in an indolent MALT lymphoma which may be treated simply by eradication of the underlying chronic infection.⁴ Among those with a hereditary sensitivity to gluten, that is, coeliac disease, gluten peptides presented by HLA-DQ2 and HLA-DQ8-positive antigen presenting cells elicit an immune response leading to destruction of the intestinal epithelium by intraepithelial T-cell lymphocytes.⁵ Malignant transformation of these cells can lead to an aggressive enteropathy-associated T-cell lymphoma (EATL) of the small bowel.⁶ Autoimmune disorders such as systemic lupus

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erythematosus have been associated with the development of GI lymphoma; immunosuppression, rather than the disease process itself, confers this risk in this patient population. Additionally, congenital syndrome as well as AIDS predisposes to the development of lymphomas.⁷ Thiopurines and anti-tumour necrosis factor therapies, such as those employed in the management of patients with inflammatory bowel disease (IBD), also increase the risk of developing lymphoma.^{8–10} Young males under the age of 35 on thiopurine therapy for IBD seem to be especially at risk for the development of hepatosplenic T-cell lymphoma.¹¹

Epidemiology

The WHO broadly classifies lymphoid neoplasms as precursor lymphoid neoplasms, mature B-cell neoplasms, mature T-cell and natural killer cell neoplasms, and Hodgkin’s lymphomas based on distinctive pathological and genetic features.¹² Extranodal Hodgkin’s lymphoma is exceedingly rare. Extranodal GI B-cell lymphomas are more common (contributing 80% of the total) than T-cell lymphomas, are more responsive to chemotherapy and have a better overall prognosis.¹³ Most lymphomas demonstrate fairly typical architectural features and specific cytogenetic abnormalities which aid in pathological diagnosis.

GI lymphomas constitute 1%–4% of all GI malignancies, 10%–15% of all non-Hodgkin’s lymphomas (NHL), and 30%–40% of all extranodal NHLs, making the GI tract the most common site for extranodal lymphoma.¹⁴ In terms of anatomical location the most common site

is the stomach, followed by small bowel and colorectum; oesophageal lymphoma is exceptionally rare.^{15 16} In one large study of primary GI NHLs, the anatomical distribution was as follows: gastric—74.8%, small bowel—8.6% and ileocaecal—7.0%. Multiple locations were noted in 6.5%.¹⁷

Typically, GI lymphomas present in the sixth decade of life and are slightly more common in males.¹⁸ The challenge for the clinical gastroenterologist is that these tumours may present in very varied ways, ranging from non-specific symptoms such as dyspepsia or bloating to abdominal pain, nausea, emesis, GI bleeding, diarrhoea, weight loss or bowel obstruction. Appropriately directed endoscopic evaluation with biopsies has the potential to provide a definitive diagnosis and allow the patient to proceed to definitive therapy. Routine histology, immunohistochemistry, flow cytometry, in situ hybridisation, and fluorescent in situ hybridisation can all be performed on biopsies to provide the detailed information needed for optimal therapy.

METHODS

To exemplify the range of presentations of GI lymphoma and to illustrate the important role of the gastroenterologist in its assessment, we present a series of cases of GI lymphomas seen at our institution between January and June 2017 (table 1). We identified 16 individual cases that were diagnosed by various gastroenterologists during this time period. Illustrative clinical and endoscopic features are provided.

Table 1 Demographics, presenting features and clinical findings in 16 consecutive cases of gastrointestinal lymphoma			
Case	Gender	Clinical presentation	Endoscopy
1	Female	Dyspepsia	Antral ‘gastritis’, duodenitis
2	Male	Chronic diarrhoea	Multiple colonic polyps
3	Male	Positive stool DNA testing	Ulcerated mass at splenic flexure and ascending colon
4	Male	Food impaction, dysphagia	Clean-based gastric ulcers
5	Male	Melena	Fungating, ulcerated circumferential mass in the gastric fundus
6	Male	Gastric outlet obstruction	Fungating, infiltrative, ulcerated circumferential mass in gastric body
7	Female	Haematemesis	Large cratered necrotic duodenal ulcer
8	Male	Intussusception at terminal ileum (TI)	Partially obstructing mass at the ileocaecal valve
9	Male	Abdominal pain	Fungating, partially obstructing mass in ascending colon and caecum
10	Female	Epigastric pain	Patchy mild erythema in duodenum
11	Male	Haematochezia	3 cm ulcerated non-obstructing polypoid mass in the terminal ileum
12	Female	Abdominal pain	Partially obstructing tumour in the caecum
13	Male	Abnormal abdominal imaging, anaemia	Partially obstructing mass at the ileocaecal valve
14	Female	Profound hypoalbuminaemia (malnutrition), anasarca	Mucosal changes in jejunum
15	Male	Severe anaemia, abdominal pain	Non-obstructing, circumferential, polypoid mass in the terminal ileum
16	Female	Iron deficiency anaemia	Large, ulcerated, non-obstructing mass at ileocaecal valve

Figure 1 (A) Partially obstructing mass at ileocecal valve. (B) High grade B cell lymphoma

Illustrative clinical presentations

Abdominal pain

Approximately 45%–65% of all cases of GI lymphomas present clinically with abdominal pain due to a mass or bowel obstruction, as illustrated by the following three patients.^{15–18}

- ▶ A man presented with abdominal pain for several weeks and imaging findings of intussusception due to a caecal mass. Colonoscopy showed a partially obstructing mass at the ileocaecal valve (**figure 1A**). Biopsies demonstrated a high-grade B-cell lymphoma (**figure 1B**).
- ▶ A man on therapy for *H. pylori*-associated chronic gastritis was evaluated for progressive severe right lower quadrant pain. CT of the abdomen showed focal thickening in the terminal ileum with associated mesenteric lymphadenopathy. Colonoscopic evaluation demonstrated a multilobulated ulcerated polypoid lesion at the ileocaecal valve (**figure 2A**) as well as a large fungating, polypoid, ulcerated, non-obstructing mass in the distal ileum (**figure 2B**). Biopsies of both lesions showed large B-cell lymphoma.
- ▶ A woman with a history of anal cancer treated by chemoradiation and complicated by an anal stricture was hospitalised with progressive right lower abdominal pain. Abdominal imaging with CT revealed the presence of a caecal mass with adjacent lymphadenopathy (**figure 3A**). Colonoscopic evaluation demonstrated a malignant appearing partially obstructing tumour in the caecum (**figure 3B**) and biopsies showed Epstein-Barr virus-positive Burkitt lymphoma (**figure 3C**).

Figure 2 (A) Multilobulated ulcerated polypoid lesion at the ileocaecal valve. (B) A large fungating, polypoid, ulcerated, non-obstructing mass in the distal ileum

Figure 3 (A) A caecal mass with adjacent lymphadenopathy on contrasted abdominal imaging. (B) Malignant appearing partially obstructing cecal tumor. (C) EBV positive Burkitt Lymphoma.

Diarrhoea

- ▶ A man with hemochromatosis complicated with portopulmonary hypertension and common variable immunodeficiency syndrome on intravenous immunoglobulin replacement and idiopathic thrombocytopenia on high-dose steroids was evaluated for chronic non-bloody diarrhoea and weight loss for 3 months. Colonoscopy showed several polyps in the transverse colon, hepatic flexure, ascending colon and caecum that were biopsied (**figure 4A,B**). Biopsies from the hepatic flexure polyp demonstrated marginal zone lymphoma with focal transformation to diffuse large B-cell lymphoma (DLBL).

GI haemorrhage

- ▶ A woman presented with massive haematemesis. Oesophagogastroduodenoscopy (EGD) was remarkable for a large cratered necrotic duodenal ulcer (**figure 5A**, arrowed) and CT of the abdomen revealed marked thickening of the duodenal wall (**figure 5B**, arrowed). Biopsies demonstrated large B-cell lymphoma (**figure 5C**).

Figure 4 Benign appearing colon polyps.

Figure 5 (A) Large cratered necrotic duodenal ulcer. (B) Marked duodenal wall thickening on contrasted abdominal imaging. (C) Large B- cell lymphoma.

- A man was admitted with overt melena and progressive symptomatic anaemia for a week; evaluation by upper endoscopy showed a large, fungating, infiltrative and ulcerated circumferential mass in the gastric fundus (also seen on imaging of the abdomen—figure 6A) in addition to congested, granular, nodular and ulcerated mucosa of the entire stomach (figure 6B); biopsies demonstrated DLBL (figure 6C).

Non-specific upper GI symptoms

- A woman was evaluated with upper endoscopy (EGD) for dyspepsia. Findings included non-specific erythema and erosions in the stomach and duodenal bulb (figure 7A,B). Antral biopsies demonstrated low-grade B-cell lymphoma.

Figure 6 (A) Mass in the gastric fundus on contrasted abdominal imaging. (B) Large, fungating, infiltrative mass in fundus. (C) Diffuse large B cell lymphoma.

Figure 7 Non specific gastric erosions and duodenal bulb erythema.

- A man with a remote history of treated *H. pylori*-associated peptic ulcer disease was admitted with early satiety accompanied by nausea, emesis and significant weight loss. CT of the abdomen showed a large gastric mass with direct invasion into the left lobe of the liver suspicious for malignancy (figure 8A); an upper endoscopy showed a large fungating, infiltrative and ulcerated circumferential mass in the body of the stomach (figure 8B); biopsies demonstrated DLBL (*H. pylori* negative).

Gastric ulceration

- A man presented with a food impaction; EGD showed a non-obstructive Schatzki's ring, erythematous gastric mucosa and multiple clean-based ulcers in the stomach and duodenum (figure 9A,B). Biopsies demonstrated *H. pylori*-associated chronic active gastritis and extranodal marginal zone lymphoma of mucosal associated lymphoid tissue (MALT lymphoma) (figure 9C). He completed a course of treatment for *H. pylori* with complete resolution of the lymphoma on repeat endoscopic evaluation.

DISCUSSION

Clinical features by anatomical location

Oesophageal lymphoma

Primary oesophageal lymphoma is very rare comprising less than 1% of all primary GI lymphomas. Oesophageal involvement is usually secondary to spread from cervical or mediastinal lymph nodes.¹⁹ Clinically, patients may present with dysphagia, weight loss, dyspepsia or upper GI bleeding. Endoscopically, these tumours may have a

Figure 8 (A) Large gastric mass with direct invasion into left lobe of liver on contrasted abdominal imaging. (B) Fungating, ulcerated mass in gastric body. (C) Diffuse large B cell lymphoma.

Figure 9 (A, B) Clean based antral and duodenal bulb ulcers. (C) MALT lymphoma.

nodular, polypoidal, ulcerated or stenotic appearance. Endoscopic ultrasound may be employed to assess the depth of tumour invasion.²⁰

Gastric lymphoma

The stomach is the most frequently involved GI site among GI lymphomas. MALT lymphoma is the most common subtype followed by DLBL.²¹ A small proportion of patients with *H. pylori* infection may develop MALT lymphoma. The bacterial infection may trigger activation of CD4 T cells and indirectly stimulate B cells and, thereby, lead to the development of a malignancy.²² Additionally, it has been noted that individuals with the t(11;18)(q21;q21) translocation appear to have a higher predisposition to develop MALT lymphoma.²³ Clinically, these patients may report abdominal pain, nausea, vomiting or present with upper GI bleeding.^{21 24} The endoscopic appearance of MALT lymphomas is variable ranging from an exophytic ulcerated mass to hypertrophic and enlarged gastric folds or hyperaemic changes in gastric mucosa,^{24 25} as illustrated by case 9.

Though less common than MALT lymphoma, gastric DLBL has also been observed to be associated with *H. pylori* infection and reported to express CD19, CD20, CD22 and CD79.^{26 27} They may present with symptoms similar to MALT lymphoma. Endoscopically, they are often located in the gastric body/fundus and may appear as an ulcerated lesion or a polypoid mass or diffuse/focal thickening of the gastric wall (cases 5, 6, 8)²⁶

Intestinal lymphoma

The small bowel and large bowel are the second most commonly affected sites, with the ileum most often involved. Various lymphoma subtypes found in the intestines include MALT, DLBL, mantle cell lymphoma (MCL), follicular lymphoma (FL) and intestinal T-cell lymphoma.^{14-18 28 29} Patients may present with fever, abdominal pain, diarrhoea, haematochezia and weight loss (cases 1, 3, 4). CT of the abdomen may display

bowel wall thickening, obstruction or mucosal ulceration.^{14-18 28-30} Capsule endoscopy and colonoscopy are used to detect these tumours which may appear as ulcerated lesions or diffuse mucosal thickening with coarse or fine granular appearance.³¹ The latter is especially useful due to the predilection of lymphoma to the distal ileum and ileocaecal areas.³¹

Lymphoma of gall bladder, biliary tree, pancreas and liver

While our focus has been on lymphoma involving the oesophagus, stomach, small intestine and colon we should note that other components of the digestive system may also give rise to primary lymphomas. Primary lymphoma of the gall bladder, most commonly a MALT lymphoma or DLBL, is very rare and typically present as right upper quadrant pain.³²⁻³⁵ MALT lymphomas arising in the bile duct at the hilum have also been described as having extremely rare instances of B-cell lymphoma, follicular lymphoma and lymphoblastic lymphoma. Clinically, cholangiocarcinoma, primary sclerosing cholangitis or pancreatitis is the initial diagnosis with the true nature of the pathology being discovered at surgery.^{35 36} Primary pancreatic lymphomas account for less than 0.5% of all malignant pancreatic neoplasms and are usually diffuse B cell in morphology and most commonly present as a mass in the pancreatic head.³⁷ While secondary involvement of the liver by lymphoma is common, primary hepatic lymphomas comprise 0.016% of all instances of NHL. Righty upper quadrant pain, fever and weight loss are common presenting symptoms, and hepatomegaly, rather than jaundice the main physical sign. Again B-cell morphology dominates.³⁸

Management

Various strategies and modalities of treatment are employed in the management of GI lymphomas based on the area of involvement, histological type and clinical staging.^{12 39 40} For example, early-stage follicular lymphoma follows an indolent course and may be followed clinically with a 'watch and wait' policy.⁴¹ Indeed, a retrospective study by Young and colleagues noted a similar overall 7.5-year survival rate among those with follicular lymphoma that underwent watchful waiting or aggressive combined modality treatment.⁴²

More than 70% of patients with early-stage (Ann Arbor Classification Stages I-II₁) MALT lymphomas associated with *H. pylori* infection can achieve remission with triple or quadruple eradication therapy alone,^{43 44} with a tumour location, patient ethnicity, depth of invasion and molecular feature all influencing response rates.²⁴ Radiation therapy and chemotherapy are reserved for advanced tumours and non-responders. Surgery should prove necessary only in instances of perforation or where haemorrhage cannot be controlled endoscopically.⁴⁵ With regard to follow-up, it is recommended that endoscopy with careful inspection and biopsy of the previously affected area is recommended at six monthly intervals for the first 6 months and yearly thereafter.⁴⁵ For non-*H.*

pylori-associated MALT lymphomas, there is currently a lack of consensus on optimal initial therapeutic mode with both radiation therapy and chemotherapy being employed.⁴⁶

For DLBLs of the stomach and intestine the consensus is that chemotherapy incorporating rituximab-cyclophosphamide-oncovin-prednisolone should be the standard regimen.^{45–49} Here again, surgery is restricted to the management of complications such as perforation and haemorrhage.⁴⁵ In the past, surgical resection was widely employed in the management of patients with GI lymphoma⁵⁰; greater accuracy in preoperative diagnosis should minimise the need for surgical intervention nowadays, even in instances of intestinal obstruction, as illustrated by our case 1, where chemotherapy induced complete resolution of an obstructing tumour.

The prognosis for intestinal T-cell lymphomas, in general, and for EATL type I (ie, that associated with coeliac disease) and monomorphic epitheliotropic intestinal T-cell lymphoma (formerly referred to as EATL type II), in particular, is poor and management strategies for these and other rare forms of GI lymphoma vary according to presentation, location, stage and histological type and may involve chemotherapy, radiation therapy, immunotherapy, surgery and autologous stem cell transplantation.^{51–53} In one study which included a variety of peripheral T-cell lymphomas the response rate to cyclophosphamide-oncovin-prednisolone at a median follow-up of 27 months was 62%.⁵⁴

One complication of chemotherapy that the gastroenterologist should be aware of is intestinal perforation. In one series of 1062 patients with histologically proven GI lymphoma 9% developed a perforation with just over one-half of these occurring after commencement of chemotherapy. The median time to perforation following initiation of chemotherapy was 46 days, most commonly involved the small intestine; aggressive B-cell histology was an important risk factor.⁵⁵

With the exception of the surveillance strategy outlined above for following patients with *H. pylori*-associated T-cell lymphoma there are no guidelines for the endoscopic surveillance of patients following successful treatment of other gastric, small intestinal or colonic lymphomas. The role of endoscopic ultrasound in the follow-up of gastric lymphoma is yet to be defined.⁵⁶ Nor are there guidelines for surveillance of at-risk individuals such as those with disorders associated with an increased risk for lymphoma, such as coeliac disease⁵⁷ or nodular lymphoid hyperplasia.^{58–59}

Contributors AST and EQ conceived the idea for the study and planned the study. AST collated the clinical and endoscopic data. MS collated and reviewed all pathology. AST drafted the manuscript which EQ and MS edited. All three authors reviewed and approved the final manuscript.

Funding This study was supported in part by a bequest to the Lynda K and David M Underwood Center for Digestive Disorders and the Josephine Hughes Sterling Foundation.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There are no data in this work.

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