

Case Report

Gastric lymphoma

Sravani Padala*, Jian Bing Zhu, Li Yu

Department of Medical and Imaging, the Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, PR China

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***Correspondence:**

Dr. Sravani Padala,

E-mail: sravani.0228@gmail.com

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ABSTRACT

Gastrointestinal lymphomas represent 5-20% of extra nodal lymphomas and mainly occur in the stomach and small intestine. Clinical findings are not specific, thus often determining a delay in the diagnosis. Imaging features at conventional and cross-sectional imaging must be known by the radiologist since he/she plays a pivotal role in the diagnosis and disease assessment, thus assisting in the choice of the optimal treatment to patients. This review focuses on the wide variety of imaging presentation of esophageal, gastric, and small and large bowel lymphoma presenting their main imaging appearances at conventional and cross-sectional imaging, mainly focusing on computed tomography and magnetic resonance, helping in the choice of the best imaging technique for the disease characterization and assessment and the recognition of potential complications. Gastrointestinal tract is the most common extra nodal site involved by lymphoma. Although lymphoma can involve any part of the gastrointestinal tract. The most frequent sites in order of its occurrence are the stomach followed by small intestine and ileocecal region. Gastrointestinal tract lymphoma is usually secondary to the widespread nodal diseases and primary gastrointestinal tract lymphoma is relatively rare.

Keywords: *H.pylori*, Gastric lymphoma, B cell and T cell lymphoma, Endoscopic and radiological findings

INTRODUCTION

Gastrointestinal tract is the most common extra nodal site involved by lymphoma accounting for 5-20% of the cases.¹ Primary gastrointestinal lymphoma however is very rare, constituting only about 1-4% of all gastrointestinal malignancies. Gastrointestinal lymphoma is usually secondary to the widespread nodal diseases. Although virtually lymphoma can arise from any region of the gastrointestinal tract, the most commonly involved sites in term of its occurrence are the Stomach followed by small intestine and ileocecal region and rectum.²

Gastric Lymphoma accounts for 3%-5% of all malignant tumors of the stomach. Malignant lymphomas affect the stomach as a primary tumor or as part of more wide spread disease process, which is more common. Generally lymphomas are considered as "primary" in the

gastrointestinal tract when the initial symptoms of the disease are in the abdomen indicating a disturbance of the gastrointestinal function, or when the bulk of the disease is in the stomach. Non-Hodgkin's lymphoma (NHL) is the most frequent gastric tumor after adenocarcinoma while Hodgkin's lymphomas (HL) are uncommon in stomach, whether primary or secondary. Most gastric lymphomas are thought to arise in the mucosa or submucosa from the so-called mucosa-associated lymphoid tissues (MALT), which usually develop after chronic inflammation induced, by *Helicobacter pylori* infection. Although all histological kinds of nodal lymphoma can arise from the stomach, the majority of them are of the B-cell origin, and mucosa associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma (DLBCL) account for over 90%. MALT lymphoma comprises up to 50% of all primary lymphomas involving the stomach. Primary gastric

lymphomas (PGLs) are generally seen in elderly age group (above 50 years).

Table 1: Different types of lymphoma and their relative frequency of occurrence.

Type of lymphoma	Relative frequency (%)
B cell	
DLBCL	38-57
ENMZL	23-48
Mantle cell lymphoma	<1-13
Follicular lymphoma	2-12
Burkitt lymphoma	1-5
Hodgkin lymphoma	<1
T cell	
EATL	3

CASE REPORT

Epidemiology

Stomach is the most commonly involved site (60%-75%) in gastrointestinal tract followed by small bowel, ileocecal region and rectum.³ Gastric lymphoma accounts for 3%-5% of all malignant tumors of the stomach.⁴ Although the incidence of gastric carcinoma has been reduced. The incidence of primary gastric lymphoma is increasing.⁵ *H.pylori* play a role in the development of most MALT lymphomas. However, its exact mechanism has not been fully understood, although a chronic inflammation may enhance the probability of malignant transformation via B cell proliferation in response to *H. pylori* mediated by tumor-infiltrating T cells.⁶ *H. pylori* may play a similar role in development of DLBCL and few studies have shown complete remission after eradication therapy alone.⁶ It has been shown that individuals with positive HBsAg have an increased risk of developing NHL.⁷ It was reported that HBV plays a role in the development of B-cell NHL.⁸ In contrast, primary gastric lymphoma with a T-cell phenotype is relatively rare, accounting for only 7% of primary gastric lymphomas in HTLV-1 infected endemic areas and a relatively large number of such cases are secondary gastric involvement of adult T-cell leukemia. Primary gastric T-cell lymphoma without HTLV-1 infection is rare, and sporadic cases have been reported.⁹ The age of most gastric lymphoma patients is over 50 years with a relative predilection in males.

Clinical features

Clinical symptoms of gastric lymphoma are nonspecific and indistinguishable from other benign and malignant conditions. The most common complaints of gastric lymphoma patients are epigastric pain, weight loss, nausea and vomiting. Occasionally, an abdominal mass is palpable. Lymphadenopathy is rare and its patients often have no physical signs. Perforation, bleeding, or obstruction is very uncommon.

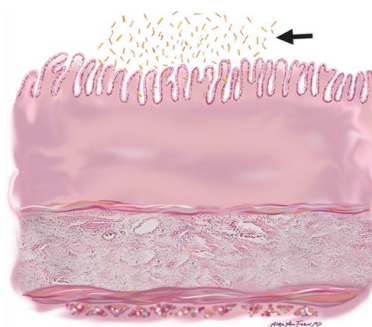


Figure 1: *H. pylori* bacteria (arrow) colonize the normal gastric wall, which lacks organized, native lymphoid tissue.



Figure 2: A 31 year old man with abdominal pain, postprandial vomiting, weight loss, and a history of celiac disease. Photograph of the sectioned gross specimen shows diffuse mucosal and sub-mucosal involvement and thickening.

Histopathology

Although all histological kinds of nodal lymphoma can arise from the stomach, the majority of them are of the B-cell origin, and MALT lymphoma and DLBCL account for over 90%. MALT lymphoma comprises up to 50% of all primary lymphomas involving the stomach. Histologically, the most significant finding is the presence of a variable number of lymphoepithelial lesions defined by evident invasion and partial destruction of mucosal glands by the tumor cells. MALT lymphoma shows the immunophenotype of B cells in the normal marginal zone of spleen, Peyer’s patches and lymph nodes. The tumor B-cells can express the surface immunoglobulin and pan-B antigens (CD19, CD 20, and CD79a), the marginal zone-associated antigens (CD35 and CD21, and lack CD5, CD10, CD23) and cyclin D1. MALT lymphoma can be divided into *H. pylori* positive or negative based on the presence of *H. pylori*. *H. pylori* negative MALT lymphoma tends to have a higher positive rate for t (11:18) (q21;q21) translocation than *H. pylori* positive MALT lymphoma.¹⁰ DLBCL, a heterogeneous group of tumors which are clinically, histologically, immunophenotypically, cytogenetically variable, can be divided into 3 subgroups, namely germinal-center B-cell-like, activated B-cell-like, and primary mediastinal DLBCL according to the gene

expression patterns with each having a different prognostication. The most commonly seen translocations as mentioned earlier include t (14:18) (q32:q21) with BCL2-rearrangement, t (3:14) (p27:q32) with BCL6-rearrangement and t (8:14) (q24:q32) with MYC rearrangement, respectively. Variability has been observed in CD45, CD5 and CD10 expression, with the CD10 expression in particular referred as a prognostic indicator.¹¹

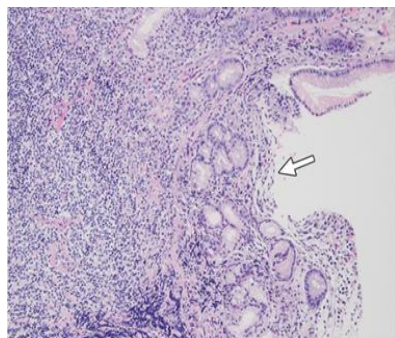


Figure 3: A 67-year-old man with a 4-day history of chest and epigastric pain. Photomicrograph (original magnification, $\times 20$; hematoxylin - eosin [H-E] stain) shows erosion of the epithelium (arrow) and a heterogeneous infiltrate of small cells within the gastric mucosa.

Diagnosis

Endoscopy

Endoscopy cannot distinguish gastric lymphoma from the more common gastric carcinoma. The three main patterns that can be recognized at endoscopy include ulceration, diffuse infiltration, and polypoid mass, which are, however, not specific.¹² Endoscopy, however, is an indispensable tool for the initial diagnosis and follow-up of cases as well as for obtaining biopsy specimens. EUS can assess the extent of lesion and its invasion. Lesions are usually hypoechoic although few hyperechoic cases have been reported.¹² Infiltrative carcinoma tends to have a vertical growth in gastric wall, while lymphoma tends to show mainly a horizontal extension and more involvement of perigastric lymph nodes.¹³ EUS is highly accurate in detecting the depth of lymphomatous infiltration and the presence of perigastric lymph nodes, thus providing additional information for treatment planning, and can differentiate lymphoma from carcinoma both in early stage and in advanced stage.¹⁴

Imaging

The main imaging appearance of GI lymphoma may be summarized as follows:

- Diffuse infiltrative form, which is characterized by a circumferential wall thickening of the involved GI wall, leading to destruction of the muscularis propria

and autonomic plexus and subsequent dilatation of the involved segment.

- Focal GI involvement, which may appear as a solitary or multiple nodular involvement.

Ulcerative form

The most common radiological signs on barium meal vary from normal to bull's eye appearance due to central ulceration, filling defects, thickened gastric mucosal folds, and linitis plastica.



Figure 4: A 67-year-old man with a 4-day history of chest and epigastric pain. Photograph from upper endoscopy shows an ulcerated mass (arrow).

Radiographic patterns of gastric lymphoma observed in double-contrast UGI studies include ulcers, polypoid mass, thickened fold, 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. Preservation of gastric distensibility and pliability, despite the extensive infiltration with gastric fold thickening, is a finding more suggestive of lymphoma. Gastric wall thickening is much less severe in low-grade lymphoma than in high-grade lymphoma on CT images, and abdominal lymphadenopathy is less common in low-grade lymphoma. Preservation of the fat plane with no invasion of surrounding structures may be suggestive of lymphoma, although it is, however, not specific. Transpyloric spread and extension of lymphadenopathy below the renal hilum and the presence of bulky lymph nodes are more suggestive of lymphoma than carcinoma.¹⁵ The patterns of gastric involvement observed can be segmental or diffuse infiltration, or localized polypoid. Tumor infiltration is usually homogeneous although areas of low attenuation may be present in larger tumors. Diffuse infiltration involving more than 50% of the stomach and segmental infiltration are the most common features of gastric NHL on CT images.¹⁶ The MRI features include irregularly thickened mucosal folds, irregular submucosal infiltration, annular constricting lesion, exophytic tumor growth, mesenteric masses and mesenteric/retroperitoneal lymphadenopathy. The tumors are usually homogeneous and intermediate in signal intensity on T1-weighted images. Heterogeneously increased signal intensities are noted on

T2-weighted images. The enhancement is usually mild-moderate after intravenous administration of gadolinium dimeglumine.¹⁷ Application of 18F-FDG PET/CT in diagnosis of gastric lymphoma is challenging due to the physiologic FDG activity in the stomach and variability in the degree of uptake in various histologic subtypes. It was reported that aggressive gastric lymphoma has more intense uptake than low grade MALT lymphoma.¹⁸

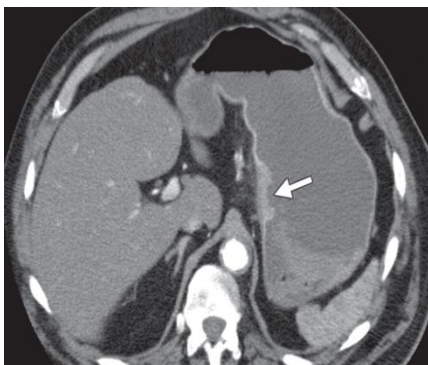


Figure 5: A 67-year-old man with a 4-day history of chest and epigastric pain. Axial computed tomographic (CT) image with intravenous contrast material shows focal, mild wall thickening with central ulceration (arrow) in the region of the gastric cardia.

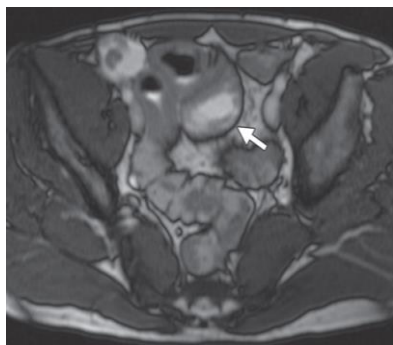


Figure 6: A 31-year-old man with abdominal pain, postprandial vomiting, weight loss, and a history of celiac disease. Axial T1-weighted fat-suppressed MR image with intravenous contrast material shows moderate homogeneous enhancement of the thickened bowel wall (arrow).

Treatment

The treatment strategy for gastrointestinal lymphoma is dependent on the age of patients, clinical scenario, histological subtype, extent and burden of the disease, and co-morbidity, besides other factors. Surgery, chemotherapy, radiotherapy and radio immunotherapy are the different modalities for its management and can be applied in different combinations. Diffuse large B-cell lymphomas of the stomach are primarily treated with chemotherapy with cyclophosphamide, doxorubicine, vincristine, prednisone with or without rituximab being a

usual first choice. Antibiotic treatment to eradicate *H. pylori* is indicated as first line therapy for MALT lymphomas. About 60% of MALT lymphomas completely regress with eradication therapy. Radiation treatment for *H. pylori* negative gastric malt lymphoma has a high success rate, 90% or better after 5 years. Second line therapy for MALT lymphomas is usually chemotherapy with a single agent, and complete response rates of greater than 70% have been reported.

Subtotal gastrectomy, with post-operative chemotherapy is undertaken in refractory cases, or in the setting of complications, including gastric outlet obstruction.

Gastric lymphoma

Treatment strategies for gastric lymphoma have changed dramatically over the last two decades. However, they are still very controversial. The most widely recommended strategy for the management of early stage *H. pylori* positive MALT type of gastric lymphoma is to eradicate *H. pylori* with antibiotics and proton pump inhibitors. Antibiotic therapy can achieve a long-term remission in 60%-100% patients with localized *H. pylori*-positive MALT lymphoma without t (11:18) chromosomal translocation. Histological assessment of treatment response, however, faces the problem of standardization, thus mandating serial follow-up. The GELA histologic evaluation system is commonly employed at certain centers. It has been shown that monoclonal B-cells still exist in almost half of the patients despite histological and endoscopic remission following antibiotic therapy [19].

No definite guidelines have been advocated for the treatment of advanced or *H. pylori* negative MALT-type of gastric lymphoma. Although surgery has been used as its initial treatment, recent studies showed that radiotherapy alone can achieve a complete remission with a 5-year disease free period.⁴ Thus, “involved-field” 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, reserved only for those with complications such as perforation, hemorrhage or obstruction that cannot be treated with other alternative therapies. Systemic therapy similar to that for indolent and advanced lymphoma must be taken into consideration in patients with their disease spread. Treatment options include chemotherapy and use of monoclonal antibodies. Diffuse large B-cell lymphoma of the stomach is treated with aggressive poly-chemotherapy, which is usually combined with Rituximab. Thus, gastric lymphoma should be treated with the front-line chemo immunotherapy with 3-4 cycles of standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) followed by “involved-field” radiotherapy. A complete remission can

be achieved in advanced gastric lymphoma patients after 6-8 cycles of R-CHOP as their nodal counterparts. Recent studies have demonstrated that anti-H. Pylori therapy can achieve the remission of indolent lymphoma, *H. pylori* negative MALT lymphoma and DLBCL.^{4,20}

DISCUSSION

Gastrointestinal tract is the most common extra nodal site involved by lymphoma with the majority being non-Hodgkin type. Gastrointestinal lymphomas are usually not clinically specific and indistinguishable from other benign and malignant conditions. Diffuse large B-cell lymphoma is the most common pathological type of gastrointestinal lymphoma.

Almost 90% of the primary gastrointestinal lymphomas are of B cell lineage with very few T-cell lymphomas and Hodgkin lymphoma. Certain histological subtypes have been noted to have a relative predilection site as mucosa-associated lymphoid tissue (MALT) lymphoma in stomach, mantle cell lymphoma (MCL) in terminal ileum, jejunum and colon, as well as enteropathy-associated T-cell lymphoma (EATL) in jejunum, and follicular lymphoma (FL) in duodenum with a geographic variation in its distribution.²¹

Multifocality, however, has been noticed particularly in MALT lymphoma and follicular lymphoma. Certain risk factors have been implicated in the pathogenesis of gastrointestinal lymphoma including Helico-bacter pylori (*H. pylori*) infection, human immunodeficiency virus (HIV), celiac disease, *Campylobacter jejuni* (*C. jejuni*), Epstein-Barr virus (EBV), hepatitis B virus (HBV), human T-cell lymphotropic virus-1 (HTLV-1), inflammatory bowel disease and immunosuppression.^{22,23}

Dawson's criteria is used for the differentiation of primary gastro-intestinal lymphoma, it includes (1) absence of peripheral lymphadenopathy at the time of presentation; (2) lack of enlarged mediastinal lymph nodes; (3) normal total and differential white blood cell count; (4) predominance of bowel lesion at the time of laparotomy with only lymph nodes obviously affected in the immediate vicinity; and (5) no lymphomatous involvement of liver and spleen.²⁴

Ann Arbor staging with Musshoff modification is commonly employed to stage gastrointestinal lymphoma and the inter-national prognostic index has been used to define the prognostic subgroups and Paris staging has increasingly gained its significance. Accurate diagnosis and staging of gastrointestinal lymphoma are detrimental for the stratification of treatment in this heterogeneous group of malignancies.

The different procedures employed for the pre-treatment staging include endoscopic ultrasound (EUS), endoscopic biopsies, computed tomography (CT), magnetic resonance imaging (MRI), 18F-fluorodeoxyglucose

positron emission tomography (FDG-PET) or molecular markers.^{25,26} Contrast-enhanced techniques and functional imaging such as perfusion CT can also help the monitoring, assessment, and prediction of response. New promising techniques such as hybrid PET-CT imaging and new PET tracers like 18F-fluoro-thymidine may significantly benefit the overall management of lymphomas.²⁷

There has been a tremendous leap in the diagnosis, staging and management of gastrointestinal lymphoma in the last two decades. With a better insight into its etiology and molecular aspect, various critical signaling pathways provide an impetus with greater benefits. Identification of the cell surface antigens has led to the introduction of mono-clonal antibodies like Rituximab and radioimmunotherapy that can result in a more targeted approach with a significant impact for the overall management of lymphoma. A deep understanding of the role of monoclonal antibodies in the pathogenesis of gastrointestinal lymphoma has led to development of the second and third generations of anti CD-20 antibodies (ofatumumab, veltuzumab, ocrelizumab), anti CD-22 antibodies such as Epratuzumab, anti CD-30 antibodies such as SGN-30, anti CD-40 antibody SGN-40, and anti vascular endothelial growth factor (VEGF) antibody bevacizumab.²⁸ Furthermore, addition of cytokines and other immune modulators has a boon resulting from a better understanding of the antibody activities at targeted tissues. Agents targeting the Bcl-2, Syk and the PI3K/AKT/mTOR pathways have emerged as a more biologically focused management with further development in this field.²⁹

CONCLUSION

The epidemiology, clinical presentation, histopathology, as well as radiological presentation of gastric lymphomas are highlighted in this review, with emphasis laid on the need for accurate diagnosis, staging, and treatment of the disease with the promising novel techniques.

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