GASTROINTESTINAL LYMPHOMA.

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Abstract: In the gastrointestinal tract, lymphoid elements occur in the lamina propria and submucosa. The quantity of lymphoid tissue varies among segments, but either primary or secondary lymphomatous neoplasms may occur in any portion of the gastrointestinal tract. Gastrointestinal tract is the most common extranodal site involved. Advanced lymphomas arising in the gastrointestinal tract may eventually disseminate widely and be clinically, radiologically, and pathologically indistinguishable from secondary gastrointestinal lymphomas. A number of risk factors other than HIV infection have been identified in the pathogenesis of gastrointestinal lymphoma, namely, Helicobacter pylori infection, celiac disease, inflammatory bowel disease, and immunosuppression after solid organ transplantation. Most gastrointestinal lymphomas are of the B-cell type, although different series report large B-cell type and MALT type lymphomas as occurring most frequently. At ultrasonography (US), these tumors are hypoechoic and most commonly demonstrate circumferential wall thickening (Figs 14, 15), although other patterns may be seen, such as nodular or bulky tumours.

Key words: Lymphorna, B-cell type, Malt-type non Hodgkin'slympharia.

INTRODUCTION

Extranodal lymphomas may arise anywhere outside the lymph node region: from sites with primary lymphoid organs (eg, spleen, thymus, Waldeyer ring); from organs or tissues devoid of lymphoid tissue (eg, brain, soft tissue); or from organs with a significant lymphoid tissue component (eg, gastrointestinal tract). In the gastrointestinal tract, lymphoid elements occur in the lamina propria and submucosa. The quantity of lymphoid tissue varies among segments, but either primary or secondary lymphomatous neoplasms may occur in any portion of the gastrointestinal tract. Gastrointestinal tract is the most common extranodal site involved by non Hodgkin lymphoma accounting for 5%-20% of all cases[1,2]. Primary involvement of the gastrointestinal tract is exceedingly rare in Hodgkin disease, with only isolated case reports in the literature[3]. Primary gastrointestinal lymphoma, however, is very rare, constituting only about 1%-4% of all gastrointestinal malignancies. Secondary gastrointestinal involvement is common because of the frequent origination of lymphomas in the mesenteric or retroperitoneal nodes and the abundance of lymphoid tissue in the gastrointestinal tract, it is usually secondary to the widespread nodal diseases. Multiple sites are typically involved. On the other hand, primary lymphomas of the gastrointestinal tract usually involve only one site... Although virtually lymphoma can arise from any region of the gastrointestinal tract,

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the most commonly involved sites in term of its occurrence are the stomach followed by small intestine and ileocecal region[4].

Dawson et al (5) cited five criteria that must be met for the diagnosis of a primary gastrointestinal lymphoma to be made:

1. No palpable superficial lymph nodes are seen.
2. Chest radiographic findings are normal (ie, no adenopathy).
3. The white blood cell count (both total and differential) is normal.
4. At laparotomy, the alimentary lesion is predominantly involved, with lymph node involvement (if any) confined to the drainage area of the involved segment of gut.
5. There is no involvement of the liver and spleen.

Advanced lymphomas arising in the gastrointestinal tract may eventually disseminate widely and be clinically, radiologically, and pathologically indistinguishable from secondary gastrointestinal lymphomas [6].

The incidence of non-Hodgkin lymphoma has been increasing, primarily due to a variety of environmental and exogenous factors, particularly the increasing incidence of human immunodeficiency virus (HIV) infection[7,8]. The exact incidence of extranodal non-Hodgkin lymphoma is difficult to ascertain, but a world standardized incidence of 1.9 in 100,000 individuals per year has been estimated (8), giving an incidence of primary gastrointestinal non-Hodgkin lymphoma of approximately one in 100,000 individuals per year. There is a slight male predilection, with a male-female ratio of 3:2. Primary gastrointestinal non-Hodgkin lymphomas account for about 0.9% of all gastrointestinal tract tumors and occur predominantly in middle-aged persons (6th decade of life) of both sexes, but a double peak can be demonstrated: the first in patients under 10 years of age and the second in patients with a mean age of 53 years. Although these tumors are rare in childhood, they constitute the most common gastrointestinal tumor in children[9].

Etiology.

A number of risk factors other than HIV infection have been identified in the pathogenesis of gastrointestinal lymphoma, namely, Helicobacter pylori infection, celiac disease, inflammatory bowel disease, and immunosuppression after solid organ transplantation. Although normally there is no lymphoid tissue in the gastric mucosa, chronic H pylori infection is associated with the development of lymphoid tissue in the lamina propria. Most low-grade primary gastric lymphomas arise from this mucosa-associated lymphoid tissue (MALT) and are therefore classified as MALT lymphomas. It has also been suggested that high-grade lymphomas result from transformation of the low-grade tumor[10]. Immuno-proliferative small intestine disease, a special form of MALT lymphoma, is also suspected to have an infectious etiology [3]. Celiac disease has been noted as a risk factor for small bowel adenocarcinomas, esophageal cancer, melanoma, and non-Hodgkin lymphoma[11], although the degree of risk is unclear[12]. Celiac disease is often associated with enteropathy type T-cell lymphoma, but the latter is not the most common type of non-Hodgkin lymphoma associated with celiac disease[13]. A two- to threefold increase in lymphoma risk in inflammatory bowel disease has been cited, with a further increase in risk of approximately fivefold associated with immunosuppressive treatment of

patients with inflammatory bowel disease, although the risk is less than that associated with renal and hepatic transplant–related immunosuppression[14]. Patients with HIV-induced immunodeficiency are at high risk for developing a B-cell phenotype intestinal lymphoma with unusual morphologic features, a high grade of malignancy, and a poor prognosis[15].

Pathologic Features

Most gastrointestinal lymphomas are of the B-cell type, although different series report large B-cell type and MALT type lymphomas as occurring most frequently[16]. These lymphomas are most commonly encountered in the stomach. Less common are the T-cell type, usually seen in the small intestine and often associated with enteropathy; Burkitt lymphoma; and the slow-growing types, mantle cell and follicular lymphoma. In the Western world, the stomach is the most commonly involved site, followed (in decreasing order of frequency) by the small intestine, large intestine, and esophagus. However, with population migration and an increasing incidence of HIV infection, the incidence of small intestine involvement has increased in Western series.

CLINICAL/PATHOLOGICAL/IMAGING CHARACTERISTICS

Oropharyngeal lymphoma

The head and neck region is the second most common site for extra-nodal lymphoma accounting for 10%-15% of all cancers in this region. Approximately 2.5% of all malignant lymphomas originate from the oral and paraoral region, and the majority of them in the Waldeyer's ring include adenoids, palatine tonsils, base of tongue and oropharyngeal walls. Tonsil is the most frequently involved site (> 50%) of tumors, followed by nasopharynx and base of tongue[17]. Viral (EBV) and several other factors are known to increase the risk of oropharyngeal lymphoma. The affected patients are usually at the age of over 50 years with a predilection of males. The most common clinical presentations of oropharyngeal lymphoma include airway obstruction, hearing pain, progressive enlarging painless local mass, dysphagia and foreign body sensation in the throat. Cervical lymphadenopathy is present in over 50% patients with tonsillar lymphoma[18].

As far as pathological characteristics are concerned, more than 80%-90% of oropharyngeal lymphomas belong to the B-cell lineage of non-Hodgkin lymphoma (NHL)[19]. Diffuse large B-cell lymphoma (DLBCL) is the most common type of primary oral and paraoral NHL with a small percentage of thymic T-cell type. Histologically, DLBCL, composed of intermediate-large cells which may be noncleaved, cleaved and immunoblastic, shows B-cell lineage with expression of pan-B-cell antigens (CD19, CD20, CD22, CD79A, and PAX5/BSAP), and is less commonly positive for germinal centre cell markers (CD10 and BCL6) and negative for T-cell antigens. A small number of cases show a translocation between the BCL-2 gene on chromosome 18 and the IgH gene on chromosome 14, t (14;18)[20]. Other lymphomas involving the Waldeyer's ring include 15% B-cell lymphomas in extranodal marginal zone of MALT, 8% peripheral T-cell lymphomas, 6% follicular lymphomas, and 3% MCLs. Hodgkin lymphoma (HL) involving the oropharynx is very rare accounting for about 1%-5% of all Hodgkin diseases. The majority of oropharyngeal HL are of lymphocyte predominant and nodular sclerosis type on histopathology with a common immunophenotype of Reed

Sternberg cells positive for CD15, CD30 and negative for CD45, CD20, and EMA, which can rule out the diagnosis of NHL[21].

Radiologically, oropharyngeal lymphoma typically appears in barium studies as a lobular mass near the base of tongue in the palatine fossa with the overlying mucosa usually being nodular. The appearance of oropharyngeal lymphoma can be hard to differentiate from more common pharyngeal carcinomas. Because the signal intensity of lymphoma is similar to that of normal tissue, the MR signal characteristics cannot reliably show the early lymphomatous involvement at these sites. CT or PET with FDG and CT (PET/CT) has proved their usefulness both in diagnosis and staging of the disease and in assessment of its response to therapies[22]. Certain features that may favor the diagnosis of NHL on imaging are the short clinical history and a large homogeneous mass which displaces rather than invades local structures and large homogeneous non-necrotic cervical nodes[23].

Esophaus.

Esophageal lymphoma most frequently occurs secondary to cervical and mediastinal lymph node invasion or contiguous spread from gastric lymphoma. Primary lymphoma of the esophagus is a rare condition, accounting for only about 1% of primary gastrointestinal lymphomas, with only a few cases of Hodgkin or non-Hodgkin lymphoma reported in the literature. Primary esophageal lymphomas are predominantly B-cell type, with some more recent reports diagnosing MALT lymphomas[24]. The etiology of esophageal lymphoma is unknown and the role of EBV in its pathogenesis is controversial. It has been shown that esophageal lymphoma is most common in immunocompromised patients, with HIV infection as a probable risk factor[25]. The age of presentation is variable. The common symptoms of patients with esophageal lymphoma include dysphagia, odynophagia, weight loss, chest pain or present as a result of complications such as hemorrhage, obstruction or perforation with a tracheoesophageal fistula. Constitutional B symptoms (fever, night sweats) are not typically present.

Radiological and endoscopic findings in esophageal lymphoma vary greatly and are nonspecific, which poses diagnostic challenges when it is differentiated from other benign and malignant lesions. The predominant appearance is that of submucosal infiltration, but these tumors may also manifest with a polypoid mass (Fig 1), ulceration, stricture, nodularity, achalasia-like pattern, progressive aneurysmal dilatation, and tracheoesophageal fistula formation, and none of them is diagnostic. The morphological features seen at endoscopy are nodular, polypoidal, ulcerated or stenotic[26,27]. Esophageal lymphoma can be demonstrated at barium studies or CT. Barium studies better demonstrate subtle mucosal and submucosal abnormalities, whereas CT better defines the extent of local disease and the disease stage. Perforation , fistulization (Fig 1b) and status of lymph nodes may also be demonstrated. EUS has gained clinical acceptance for the assessment of lymphoma and preoperative staging, because it can accurately depict the structural abnormalities and depth of invasion of the lesions. EUS findings, however, are not pathognomonic, with presentation varied as anechoic, hypoechoic or even hyperechoic masses[28]

Recently, incorporation of PET/CT has

emerged as an indispensable tool in staging the disease and following up the patients with extranodal involvement of Hodgkin's and non-Hodgkin's lymphoma, with an increased sensitivity and specificity. Diffuse large B-cell non-Hodgkin lymphoma of the esophagus is manifested as circumferential thickening of the wall, with diffuse increased FDG uptake. However, the intensity of FDG uptake in lymphoma is influenced by various intrinsic tumor factors such as histological features and grade, as well as various extrinsic factors. FDG PET/CT can also detect the indolent lesions that are undetectable on conventional cross-sectional imaging[29].

Gastric lymphoma

Stomach is the most commonly involved site (60%-75%) in gastrointestinal tract followed by small bowel, ileocecal region and rectum[30]. Gastric lymphoma accounts for 3%-5% of all malignant tumors of the stomach[31]. Although the incidence of gastric carcinoma has been reduced, the incidence of primary gastric lymphoma is increasing[32]. 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[33]. H. pylori may play a similar role in development of DLBCL and few studies have shown complete remission after eradication therapy alone[33]. It has been shown that individuals with positive HBsAg have an increased risk of developing NHL[34]. It was reported that HBV plays a role in the development of B-cell NHL[35]. 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[36]. Primary gastric lymphoma often originates as a low-grade MALT lymphoma, which, it has been suggested, transforms into intermediate or high-grade large cell lymphoma if not diagnosed or treated in time[37]. Low-grade MALT lymphoma that is diagnosed at an early stage has a good prognosis, and, in some cases, eradication of H pylori with antibiotic therapy has resulted in regression of early-stage tumors[38]. Low-grade tumors are associated with a 5-year survival rate of 75%–91%, compared with a 5-year survival rate of less than 50% for patients with high-grade MALT lymphomas [37]. Therefore, early diagnosis is crucial, although detection of low-grade lymphoma is not easy because the clinical, endoscopic, and radiologic findings are often mistakenly thought to indicate gastritis and gastric carcinoma.

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. [39]

The age of most gastric lymphoma patients is over 50 years with a relative predilection in males. 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. Unlike nodal lymphoma, B constitutional symptom is not common.

The stomach may initially be imaged with barium studies, since they are often performed as part of the investigation of upper gastrointestinal symptoms (epigastric pain, dyspepsia) and may be the first to reveal gastrointestinal lymphoma. Double-contrast studies may reveal ulcerative, polypoid, or infiltrative patterns, which are essentially the same as those of gastric carcinomas. However, the diagnosis of lymphoma may be suggested by the presence of multiple polypoid tumors, especially with central ulceration ("bull'seye" appearance), giant cavitating lesions, or extensive infiltration with gastric fold thickening. The latter finding may be distinguished from linitis plastica on the basis of the preservation of gastric distensibility. A variety of findings have been described in both low- and high-grade MALT lymphomas at upper gastrointestinal examination, including single or multiple ulcers of varying size; single or multiple masses with or without an ulcer, along with thickened folds; rugal thickening, commonly converging to an ulcer or a mass; mucosal nodularity of varying size, either focal or diffuse; and coarse areae gastricae. Low-grade MALT lymphoma has a wider spectrum of appearances than does high-grade MALT lymphoma, in which a mass-forming lesion or severe fold thickening is present in most cases[38,40]. At CT, gastric wall thickening has been noted to be much less severe in low-grade lymphoma than in high-grade lymphoma, and abdominal lymphadenopathy is less common in low-grade lymphoma[40,41]. It has also been postulated that the absence of abnormality at CT is highly predictive of low-grade MALT lymphoma[41], and greater than minimal thickening should be considered as possibly indicating transformation to a higher grade[42]. Barium studies may demonstrate subtle lesions not seen at CT but do not demonstrate the true extraluminal extent of the disease and are of little value in staging.

Preservation of the perigastric fat planes at CT is more likely to be seen in lymphoma than in adenocarcinoma, particularly in the presence of a bulky tumor[43]. In addition, the stomach remains pliable even with extensive lymphomatous infiltration, and the lumen is preserved, making gastric outlet obstruction a rather uncommon feature[44]. However, non-Hodgkin gastric lymphoma should be recognized as another cause of linitis plastica, an appearance that results from dense infiltrates of lymphomatous tissue in the gastric wall without associated fibrosis[45]. Although transpyloric spread is more common in gastric lymphoma than in carcinoma, because of the higher incidence of carcinoma, transpyloric spread by itself should not be considered to suggest the diagnosis of lymphoma[46]. Adenopathy is seen with both adenocarcinoma and lymphoma, but if it extends below the renal hila or the lymph nodes are bulky, lymphoma is more likely[42,43]. Complications such as obstruction, perforation, or fistulization can occur as a result of the disease itself or of treatment and can be detected with CT and barium studies.

Small Bowel

Primary malignant tumors of the small intestine are very rare, accounting for less than 2% of all gastrointestinal malignancies. Lymphoma constitutes 15%-20% of all small intestine neoplasms and 20%-30% of all primary gastrointestinal lymphomas. Ileum is

the most common site (60%-65%) involving small intestine lymphoma followed by jejunum (20%-25%), duodenum (6%-8%) and other sites (8%-9%)[47]. The age of presentation varies with the histological subtype of lymphoma. The clinical presentation of small intestinal lymphoma is non specific and the patients have symptoms, such as colicky abdominal pain, nausea, vomiting, weight loss and rarely acute obstructive symptoms, intussusceptions, perforation or diarrhea[48].

Small bowel B-cell lymphoma may appear as a circumferential bulky mass in the intestinal wall, often associated with extension into the small bowel mesentery and regional lymph nodes (Fig 9). The tumor may involve a relatively long segment of bowel and may ulcerate and perforate into the adjacent mesentery, resulting in the formation of a confined, usually sterile abscess[49]. Aneurysmal dilatation of the lumen may be seen due to replacement of the muscularis propria and destruction of the autonomic nerve plexus by lymphoma. As in other sites of lymphomatous involvement, obstruction is uncommon in the small bowel, since the tumor does not elicit a desmoplastic response, although less commonly the radiologic appearance of lymphoma may mimic that of adenocarcinoma with bowel obstruction (Figs 10, 11) and infiltration into adjacent structures (Fig 12b). A focal, polypoid, homogeneous intraluminal mass without wall thickening or lymphadenopathy has also been described[50]. Barium studies may show single or multiple polypoid lesions (Fig 12a), diffuse or segmental ulcerative or infiltrative change, or diffuse or focal nodularity. Peritoneal lymphomatosis from primary gastrointestinal lymphoma is rare compared with carcinomatosis, and patterns of tumor involvement of the mesentery, omentum, and peritoneum are indistinguishable from those seen in peritoneal carcinomatosis (Fig 13) or tuberculous peritonitis[51].

At ultrasonography (US), these tumors are hypoechoic and most commonly demonstrate circumferential wall thickening (Figs 14, 15), although other patterns may be seen, such as nodular or bulky tumors. Aneurysmal dilatation of the lumen and intussusception may also be seen at US (Fig 16)[52]. Evaluation of the small intestinal lymphoma has been revolutionized since the introduction of capsule endoscopy (CE) and double-balloon technique of push-and-pull enteroscopy which is capable of enabling biopsies as well as performing interventions, and limiting major surgical interventions. Small intestine lymphoma appears as a mass, polyp and ulcer on CE which cannot be distinguished from other lesions[53]. Radiologic findings of small intestinal lymphoma are not specific, thus posing a difficulty in distinguishing it from other benign and malignant lesions. The common features of small intestine lymphoma seen in barium studies and CT include polypoid form, multiple nodules, infiltrative form, endoexoenteric form with excavation and fistulization, and mesenteric invasive form with an extraluminal mass.

The prevalence of malabsorption and intestinal recurrence is high in enteropathy-associated T-cell lymphoma. There have also been reports of non-enteropathy-associated intestinal T-cell lymphoma in the literature. Unlike lymphomas of B-cell origin, peripheral T-cell lymphoma is most frequently seen in the small intestine, particularly the jejunum (Fig 17). In addition, peripheral T-cell lymphoma has a higher prevalence of multifocal involvement and bowel perforation. Also, the degree of wall thickening in peripheral

T-cell lymphoma is usually mild to moderate, as opposed to the marked thickening that is often seen in B-cell lymphomas[54].

Large Bowel Lymphoma.

Colorectal lymphoma constitutes 6%-12% of all gastrointestinal lymphomas. Most colorectal lymphomas are secondary involvement of the wide spread diseases. Primary colorectal lymphoma is very rare, constituting only 0.2% of all malignant tumors arising from the colorectal region with caecum, ascending colon and rectum more often affected[55]. The disease predominantly affects males in the fifth-seventh decade of life with abdominal pain, loss of weight, palpable abdominal mass or lower gastrointestinal bleeding. Obstruction and perforation are relatively rare in patients with colorectal lymphoma[56].

Lymphoma of the colorectal region is mostly the B-cell lineage as other sites of the gastrointestinal tract. Primary colorectal lymphoma comprises low grade B-cell lymphoma arising from MALT, MCL and T-cell lymphoma besides large B cell lymphoma. The role of H. pylori in the pathogenesis of colorectal lymphoma has not been fully established[57]. Colorectal MALT-lymphoma is less common in colon and rectum than in small intestine. MCL in the colorectal region presents usually in the setting of diffuse systemic diseases. Peripheral T-cell lymphoma is rare in Western countries with an increasing frequency in many Asian countries, and is more aggressive in nature than other types with perforation as its common feature, and its prognosis is poor[58].

Endoscopically, lymphoma appears to be fungating, ulcerative, infiltrative, ulcerofungating, and ulceroinfiltrative types, with fungating and ulcerofungating types being more common[59]. The radiologic appearances of colorectal lymphoma are variable and significantly overlapped with other benign and malignant condition of the colorectal region. The imaging findings during double-contrast barium enema can be divided into focal and diffuse lesions. The observed focal lesions include polypoid mass, circumferential infiltration with smooth mucosal surface or extensive ulceration, cavitary mass, mucosal nodularity, and mucosal fold thickening. Diffuse lesions encompass diffuse ulcerative and nodular lesions. Peripheral T-cell lymphoma presents as a diffuse or focal segmental lesion with extensive mucosal ulceration similar to that observed in granulomatous conditions as Crohn's disease or tuberculosis. MALT lymphoma is manifested as multiple mucosal nodularity[60,61].

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