From the Radiologic Pathology Archives[1]

Gastrointestinal Lymphoma: Radiologic and Pathologic Findings[2]

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Abbreviations: DLBCL = diffuse large B-cell lymphoma, EATL = enteropathy-associated T-cell lymphoma, EBV = Epstein-Barr virus, ENMZL = extranodal marginal zone B-cell lymphoma, FDG = fluorine 18 fluorodeoxyglucose, GI = gastrointestinal, H-E = hematoxylin-eosin, HIV = human immunodeficiency virus, HRS = Hodgkin and Reed-Sternberg, IPSID = immunoproliferative small intestinal disease, NHL = non-Hodgkin lymphoma, NK = natural killer, RCD = refractory celiac disease, 3D = three-dimensional, 2D = two-dimensional

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TEACHING POINTS

See last page

Gastrointestinal (GI) lymphoma encompasses a heterogeneous group of neoplasms that have a common lymphoid origin but variable pathologic and imaging features. Extranodal marginal zone B-cell lymphoma (ENMZL) and diffuse large B-cell lymphoma (DLBCL) are the most common. ENMZL usually occurs in the stomach, where it is associated with chronic infection by *Helicobacter pylori*, and is typically a superficial spreading lesion that causes mucosal nodularity or ulceration and mild wall thickening. DLBCL may arise de novo or from transformation of ENMZL or other low-grade lymphomas. This form of lymphoma produces extensive wall thickening or a bulky mass, but obstruction is uncommon. Mantle cell lymphoma is the classic cause of lymphomatous polyposis, but multiple polyps or nodules can also be seen with ENMZL and follicular lymphoma. Burkitt lymphoma is usually characterized by an ileocecal mass or wall thickening in the terminal ileum in young children, often in the setting of widespread disease. Primary GI Hodgkin lymphoma, which is rare, may be manifested by a variety of findings, though stenosis is more common than with non-Hodgkin lymphoma. Enteropathy-associated T-cell lymphoma is frequently associated with celiac disease and is characterized by wall thickening, ulceration, and even perforation of the jejunum. Accurate radiologic diagnosis of GI lymphoma requires a multifactorial approach based on the clinical findings, site of involvement, imaging findings, and associated complications.

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- List the major types of lymphoma that commonly involve the GI tract.
- Describe the imaging features of each of these types of GI lymphoma.
- Identify important clinical, pathologic, and imaging features that enable differentiation of these various types of GI lymphoma.

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Introduction

The lymphoid tissue associated with the gastrointestinal (GI) tract constitutes the largest immunologic organ in the body and the most common extranodal site of lymphoma (1). Some patients have primary GI lymphoma, whereas others have generalized lymphoma

Classification of GI Lymphomas

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

Source.—References 9–13, 67.

involving the GI tract. Primary GI non-Hodgkin lymphoma (NHL) accounts for 10%–15% of NHLs and 30%–40% of extranodal lymphomas affecting the stomach, small bowel, and colon, in decreasing order of frequency (2). GI involvement by generalized lymphoma also is surprisingly common and is found in up to 50% of lymphomas at autopsy, although this GI involvement is usually associated with subclinical disease (1).

In the classic description of primary GI lymphoma by Dawson et al (3), the bowel is involved by lymphoma (with or without regional lymph node disease) at surgery, but there is no palpable lymphadenopathy, no mediastinal lymph node enlargement on chest radiographs, no hepatic or splenic involvement, and a normal white blood cell count. By these criteria, patients therefore have primary GI lymphoma only when their disease is confined to the GI tract. A more liberal definition of primary GI lymphoma includes all cases in which GI involvement is the dominant clinical component, even in the setting of widespread disease, as these tumors are assumed to have arisen in the GI tract (4).

This article reviews the most common primary GI lymphomas, as well as disseminated lymphomas (eg, mantle cell lymphoma and Burkitt lymphoma) that come to clinical attention because of GI disease. Lymphomas are a heterogeneous group of neoplasms with varying GI sites of involvement and varying gross and histologic features that account for the wide spectrum of imaging findings. Instead of using the usual organ approach for describing the radiologic features of GI lymphoma, this article focuses on radiologic and pathologic findings for each type of lymphoma involving the GI tract, including extranodal marginal zone B-cell lymphoma (ENMZL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, follicular lymphoma, Burkitt lymphoma, Hodgkin lymphoma, and enteropathy-associated T-cell lymphoma (EATL). A detailed discussion of imaging techniques for GI neoplasms is beyond the scope of this article and is available elsewhere (5–7).

Teaching Point

Classification of GI Lymphoma

The most recent classification of lymphoid neoplasms by the World Health Organization broadly categorizes lymphoma into a B-cell lineage (which includes Hodgkin lymphoma) and a T-cell or natural killer (NK)–cell lineage (8). B and T/NK cells pass through multiple stages of development, as they differentiate from progenitor cells in the bone marrow to mature peripheral cells. Lymphoma can arise during any of these stages, and pathologists employ a multifactorial approach for the diagnosis of lymphoma based on histologic features, immunohistochemical profile, and, in some cases, genetic evaluation. Most lymphomas are mature B-cell neoplasms, with DLBCL and ENMZL accounting for the majority of primary GI NHLs. The most common lymphomas involving the GI tract and their frequencies are shown in the Table, although there is considerable geographic variation.

B-Cell Lymphoma

Extranodal Marginal Zone B-Cell Lymphoma

ENMZL, formerly known as marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), is a low-grade lymphoma involving cells that arise from the marginal zone surrounding lymphoid follicles. This form of lymphoma represents 23%–48% of all primary GI NHLs, second only to DLBCL in most series (9–13). There is a slight male predominance, with a male-to-female ratio of 1.2:1, and most patients are over 50 years of age (2,9,10).

ENMZL is found predominantly in the stomach, despite the usual absence of native lymphoid tissue in this organ. In as many as 90% of patients, the explanation for this apparent paradox is a gram-negative bacterial organism known as *Helicobacter pylori* (2). Infection of the stomach by *H pylori* produces a chronic form of gastritis associated with the formation of reactive lymphoid follicles in the gastric mucosa (Fig 1). The interplay of persistent antigenic stimulation, activated *H pylori*–specific T cells, and genetic risk factors can then lead to the development of ENMZL (14). Removal of this antigenic stimulus by eradication of *H pylori* (using a combination of antibiotics and proton pump

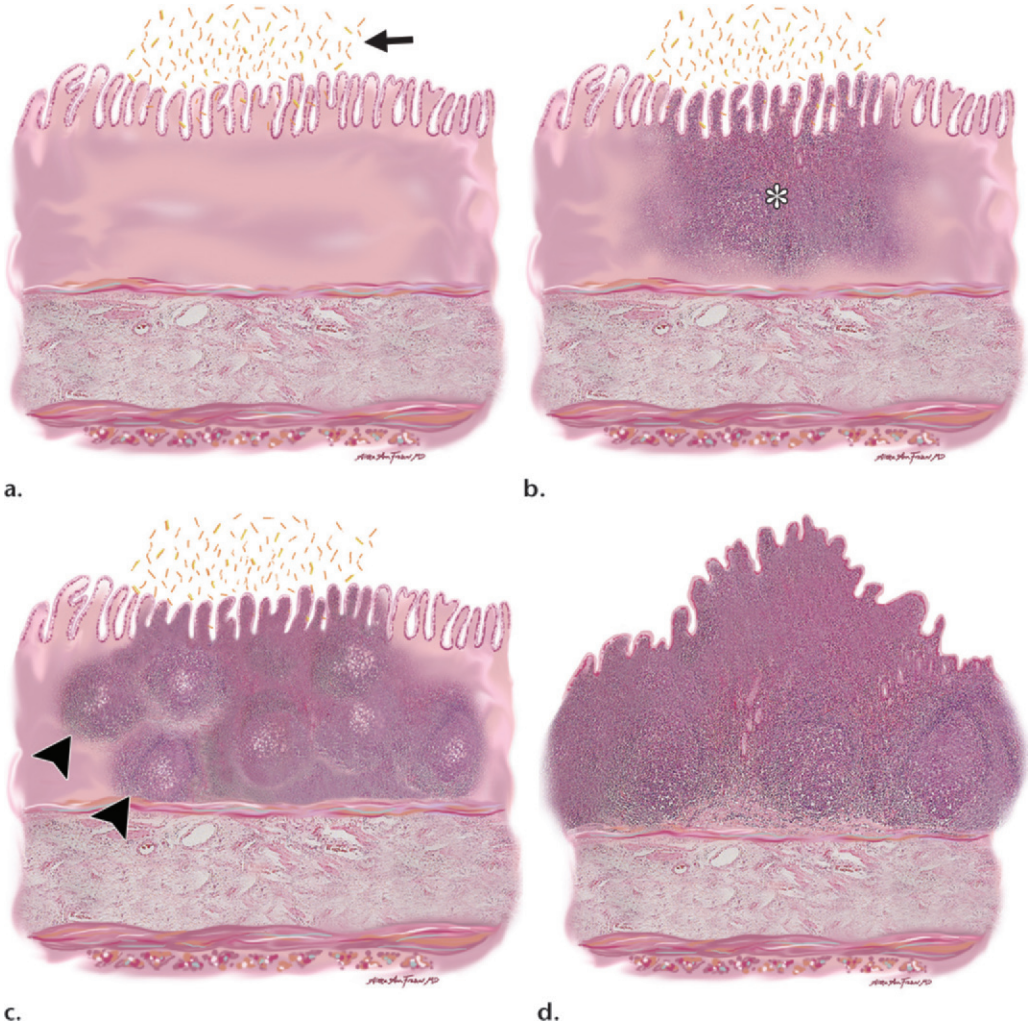


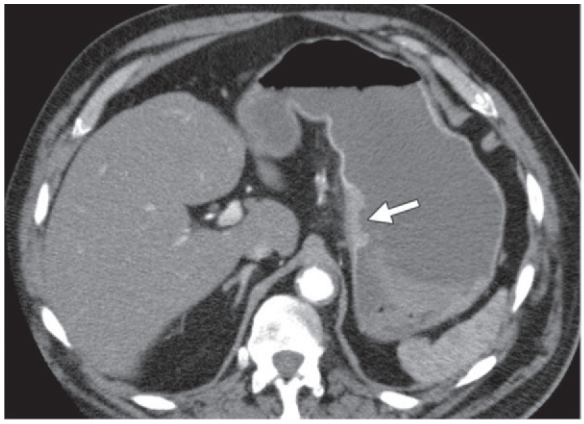
Figure 1. Stages of development of ENMZL. **(a)** *H pylori* bacteria (arrow) colonize the normal gastric wall, which lacks organized, native lymphoid tissue. **(b)** *H pylori* infection induces acute gastritis (*), with infiltration of neutrophils and macrophages into the epithelium and lamina propria. **(c)** Acute gastritis develops into chronic gastritis, characterized by infiltration of lymphocytes and plasma cells and formation of lymphoid follicles (arrowheads). **(d)** A malignant clone of marginal zone–like cells surrounds and replaces the reactive follicles and becomes autonomous as a result of chronic *H pylori* stimulation. (Courtesy of Aletta Ann Frazier, MD.)

inhibitors) induces complete remission of gastric ENMZL in about 75% of patients, although combination therapy is not usually effective in patients who do not have *H pylori* infection and in patients whose lymphoma cells harbor the translocation t(11;18)(q21;q21) (15).

ENMZL accounts for 10%–14% of primary NHLs of the small bowel and colon in North America, but is extremely rare in the esophagus (9,10). Immunoproliferative small intestinal disease (IPSID), also known as α heavy chain disease or Mediterranean lymphoma, is a type of ENMZL found in the small bowel. IPSID affects young adults in the Middle East, where it represents nearly one-third of GI lymphomas (2). Like ENMZL involving the stomach, IPSID most likely develops as a result of a combination of genetic risk factors and chronic small-bowel infection (possibly by *Campylobacter jejuni*), so early-stage disease may respond to antibiotic therapy (16).

Pathologic Features.—Gastric ENMZL is usually a superficial spreading lesion confined to the mucosa and submucosa. It occurs anywhere in the stomach and is commonly multifocal (14,17). The diseased mucosa may be granular, nodular, or ulcerated (Fig 2). In the small bowel, ENMZL is typically manifested by annular lesions in the distal ileum (Fig 3), whereas IPSID is characterized by thickened, nodular folds in the jejunum (16). Less frequently, ENMZL may be manifested by a diffusely infiltrating gastric mass (which is more common with DLBCL) or by multiple polyps (which are more common with mantle cell lymphoma or follicular lymphoma).

Teaching Point



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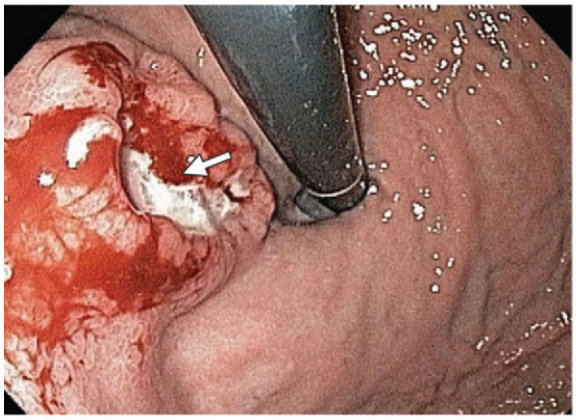

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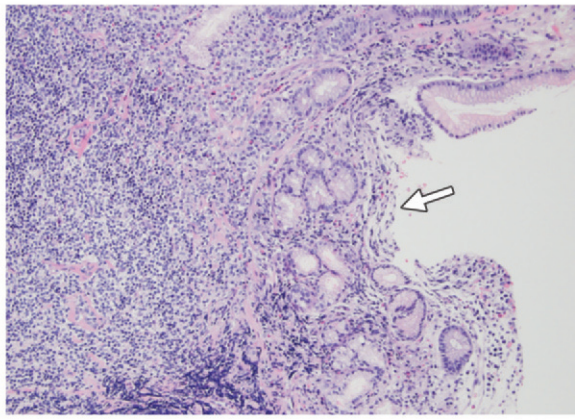

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Figure 2. ENMZL in a 67-year-old man with a 4-day history of chest and epigastric pain. **(a)** Axial computed tomographic (CT) image with intravenous contrast material shows focal, mild wall thickening with central ulceration (arrow) in the region of the gastric cardia. **(b)** Photograph from upper endoscopy shows an ulcerated mass (arrow). **(c)** Photomicrograph (original magnification, ×20; hematoxylin-eosin [H-E] stain) shows erosion of the epithelium (arrow) and a heterogeneous infiltrate of small cells within the gastric mucosa.

The lymphoma cells of ENMZL usually appear as small to intermediate-sized cells with irregular cleaved nuclei and a moderate amount of clear cytoplasm, so these cells phenotypically and immunologically resemble the post–germinal center memory B cells found in lymphoid follicle marginal zones (18). ENMZLs are heterogeneous lymphomas, often containing monocytoid-like cells, plasma cells, and scattered large cells intermixed with marginal zone cells. The lymphomatous cells initially surround reactive follicles, then infiltrate and invade the follicles, disrupting the glandular epithelium of the stomach, at which time they are called lymphoepithelial lesions (19). The presence of these lymphoepithelial lesions enables differentiation of ENMZL from reactive gastritis (15).

Imaging Features.—The imaging features of gastric ENMZL reflect its superficial location. Mucosal nodularity and ulceration are the most common findings at barium studies, occurring in 30%–52% and 39%–50% of patients, respectively (20–22). Affected individuals have small (<1 cm in diameter), rounded, often confluent nodules, most likely resulting from focal enlargement of the lamina propria (21,23). When ulcers are present, they tend to be shallow and may be associated with thickened folds or a focal mass.

In a retrospective review of CT findings in patients with proven gastric ENMZLs, Choi et al (24) found no imaging abnormalities in nearly 50% of patients. The most common CT finding was gastric wall thickening, which tended to be mild (with a wall thickness of only 5–10 mm) and segmental (involving 50% or less of the stomach) (Fig 2) (24). Contrast material–enhanced CT typically reveals a homogeneous wall that is equal or lower in attenuation than the normal gastric wall (25). Ulceration of ENMZLs is more difficult to detect at CT (Fig 2) than at barium studies, which are better for evaluating the gastric mucosa. Abdominal lymphadenopathy is found at CT in only 14%–24% of patients with ENMZLs versus 67%–75% of patients with DLBCLs (20,24).

With the exception of IPSID, there is a dearth of radiology literature about the imaging findings of ENMZL in the small bowel or colon. IPSID typically affects the duodenum and jejunum, producing multiple small nodules and thickened folds (26,27). In contrast, intestinal ENMZL may be manifested at CT by circumferential wall thickening (Fig 3) or by a polypoid mass (Fig 4), most often in the ileocecal region (25,28).

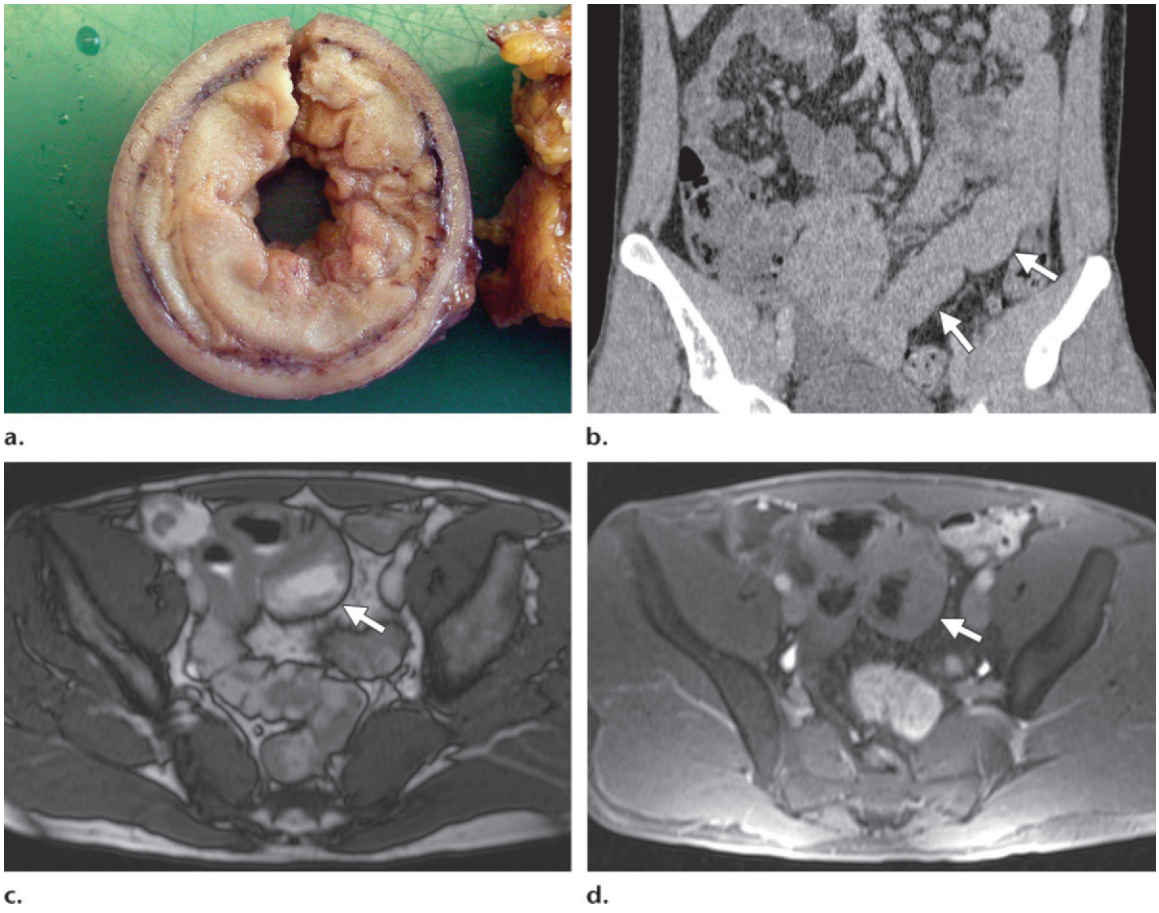


Figure 3. ENMZL in a 31-year-old man with abdominal pain, postprandial vomiting, weight loss, and a history of celiac disease. **(a)** Photograph of the sectioned gross specimen shows diffuse mucosal and submucosal involvement and thickening. **(b)** Coronal CT image with intravenous contrast material shows a long segment of moderate bowel wall thickening (arrows) in the proximal to mid ileum without evidence of obstruction. **(c)** Axial T2-weighted magnetic resonance (MR) image shows small-bowel wall thickening with heterogeneous high T2 signal intensity (arrow). **(d)** Axial T1-weighted fat-suppressed MR image with intravenous contrast material shows moderate homogeneous enhancement of the thickened bowel wall (arrow).

There are few articles describing the MR imaging features of GI lymphomas, and most of these articles do not characterize the MR imaging findings of the various pathologic types. In general, GI lymphomas are manifested at MR imaging by heterogeneous increased T2 signal intensity, homogeneous intermediate T1 signal intensity, and mild to moderate enhancement (Fig 3) (29). GI lymphoma is usually characterized by wall thickening at conventional MR imaging, MR enterography, and MR enteroclysis, but one or more polypoid or ulcerated lesions can also be seen (29–32). Gastric lymphomas are reported to have increased signal intensity at diffusion-weighted imaging with higher apparent diffusion coefficient values than gastric carcinoma (33).

Although fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) and FDG PET/CT are often performed for staging and follow-up of lymphoma, this examination has a limited role in evaluating GI ENMZL because of this tumor's indolent growth pattern and background GI accumulation of FDG (34). In one study of PET/CT for evaluation of primary gastric lymphoma, FDG uptake in the stomach was 71% for patients with ENMZL versus 100% for patients with aggressive NHL and 63% for control patients (35).

Diffuse Large B-Cell Lymphoma

DLBCL makes up 38%–57% of primary GI lymphomas and is the most common type of GI lymphoma in adults (9–13). As in patients with ENMZL, DLBCL most frequently affects the stomach, presumably as a result of chronic *H pylori* gastritis and the development of ENMZL, which subsequently undergoes transformation to DLBCL because of accumulated genetic alterations (14). In fact, concomitant ENMZL has been reported in more than one-third of patients with gastric DLBCL, and 50% of these tumors undergo remission after eradication of *H pylori* from the stomach (19).

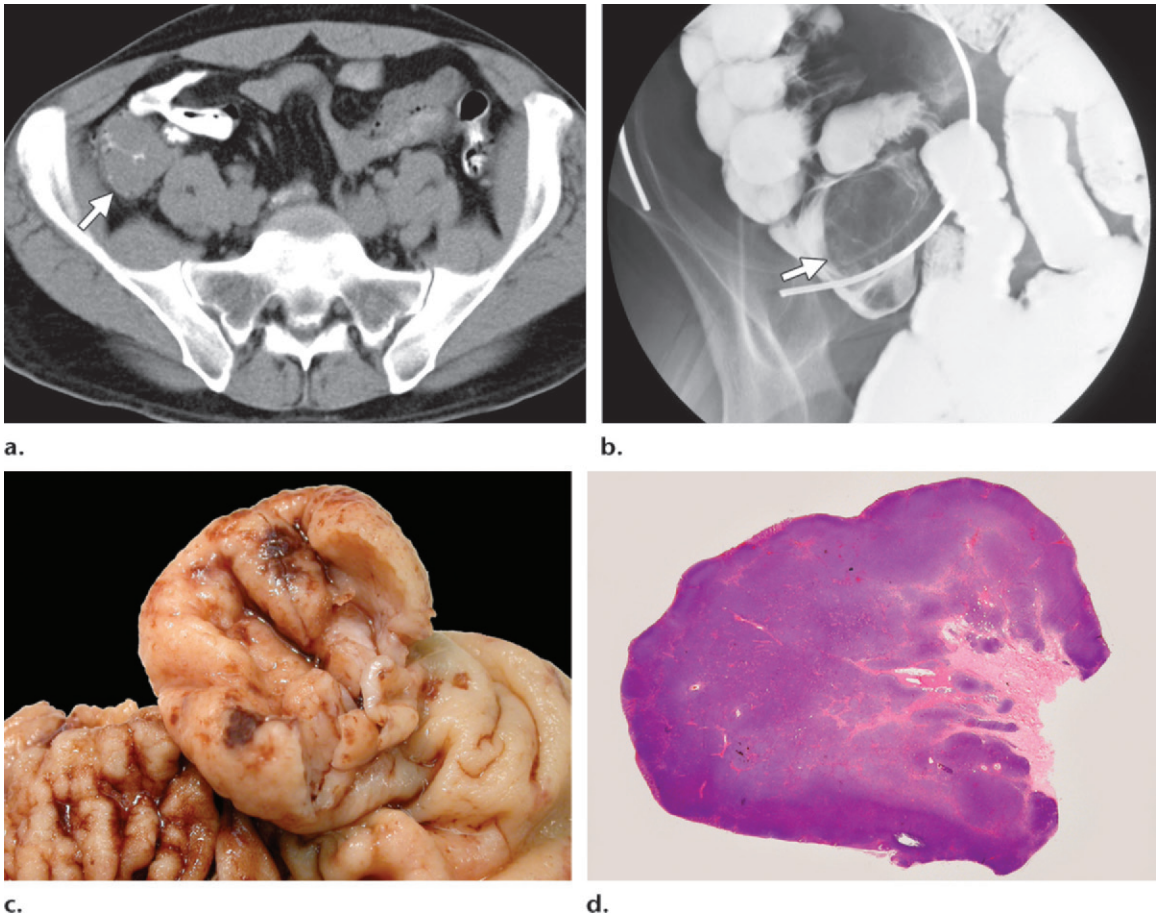


Figure 4. ENMZL in a 43-year-old man who underwent surveillance imaging because of a history of NHL. **(a)** Axial CT image with oral contrast material shows focal homogeneous wall thickening in the cecum (arrow). **(b)** Spot image from a small-bowel follow-through study shows a smoothly marginated mass in the cecum (arrow). **(c)** Photograph of the sectioned gross specimen confirms the presence of a polypoid mass. **(d)** Photomicrograph (scanning magnification; H-E stain) shows diffuse infiltration of the mucosa and submucosa by tumor.

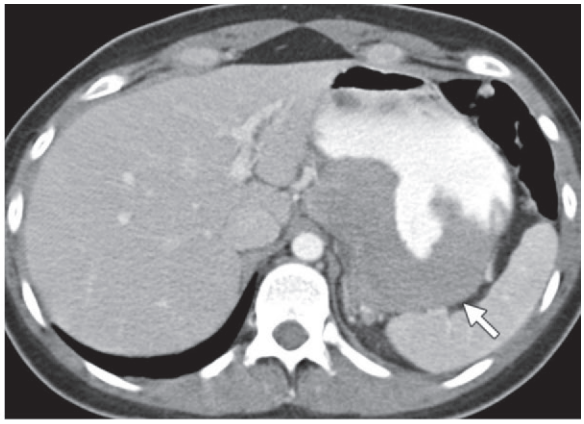
DLBCL may also arise de novo or from transformation of other types of low-grade lymphoma. Additional risk factors include immunodeficiency states, chronic inflammatory bowel disease, and the Epstein-Barr virus (EBV) (2). As in patients with ENMZL, there is a male predominance of 1.3–1.6:1 and a median age in the early 60s (9–11). Overall 5-year-survival rates range from 60% to 90% (19).

Teaching Point

Pathologic Features.—Primary GI DLBCLs are most commonly found in the stomach, followed by the ileum. These lymphomas are characterized by diffusely infiltrative and nodular lesions with extensive ulceration (19). The lymphomatous cells involve the bowel wall from the submucosa to the serosa (Fig 5) and may directly invade adjacent structures. These tumors have exophytic, annular, and occasionally, intraluminal growth patterns, and full-thickness bowel wall involvement may lead to GI perforation because of the absence of a desmoplastic response (Fig 6) (36).

Microscopically, diffuse sheets of large lymphoid cells infiltrate the lamina propria and submucosa, with frequent obliteration of the muscularis propria and ulceration of the overlying mucosa. The lymphomatous cells contain irregular nuclei, prominent nucleoli, and basophilic cytoplasm and are more than twice as large as normal lymphocytes. Immunohistochemical studies may be performed to confirm the B-cell origin of these tumors and to determine whether they arose de novo or from transformation of preexisting ENMZLs (2).

Imaging Features.—Gastric DLBCL is most commonly manifested at barium studies by diffusely thickened folds or bulky masses, often containing deep areas of ulceration (24). Gastric wall thickening is more extensive than in patients with ENMZL, usually involving more than 50% of the stomach. CT may reveal a gastric wall thickness greater than 1 cm and, occasionally, a wall thickness up to 8 cm (Figs 5, 6) (20,24). A bulky submucosal mass with delayed



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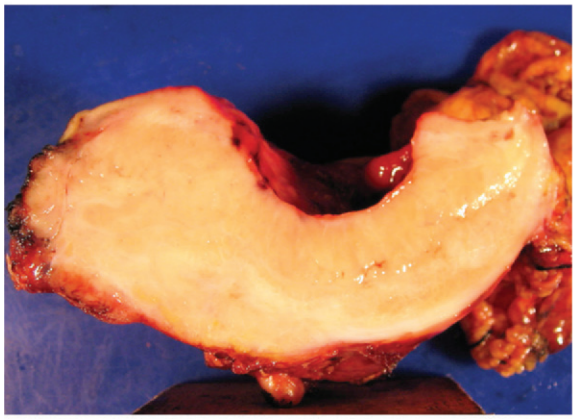

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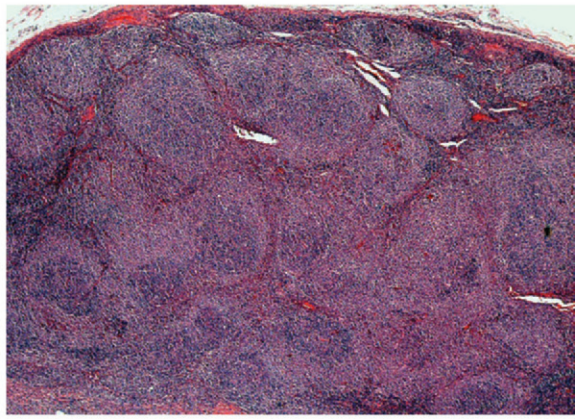

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Figure 5. DLBCL in a 35-year-old woman with a 2-week history of abdominal pain. **(a)** Axial CT image with intravenous and oral contrast material shows marked homogeneous wall thickening in the region of the gastric cardia and posterior wall of the proximal stomach (arrow). **(b)** Photograph of the sectioned gross specimen shows a uniform tan intramural mass measuring up to 4 cm in thickness. **(c)** Photomicrograph (original magnification, ×10; H-E stain) shows a diffuse nodular infiltrate extending to the serosal surface of the gastric wall.

enhancement of the lesion and a thin band of early arterial enhancement of the overlying mucosa may be seen at contrast-enhanced CT (37). Tumoral enhancement is usually homogeneous, but low-attenuation areas of necrosis may occasionally be seen (24,38). Unlike patients with ENMZL, the majority of patients with DLBCL have abdominal lymphadenopathy at CT. FDG avidity has been reported in 97% of primary gastric DLBCLs, and PET/CT may also provide a more accurate assessment of lymph node involvement (Fig 6) (39).

In other portions of the GI tract, DLBCL produces variable segments of circumferential wall thickening, most commonly in the distal ileum. Ulceration, cavitation, or perforation can occur. Even when considerable luminal narrowing is present, obstruction is uncommon, as these tumors rarely incite a desmoplastic reaction (1). Aneurysmal dilatation (characterized by a luminal diameter > 4 cm in segments of bowel wall thickening) has been reported in 31% of patients with small-bowel disease (Fig 7) (40). This finding is thought to result from the weakening of the muscularis propria and the destruction of the autonomic nerve plexus by tumor (1).

The differential diagnosis for gastric involvement by DLBCL includes other malignant tumors (particularly adenocarcinoma), as well as inflammatory or infectious conditions involving the stomach. Preservation of wall stratification is a helpful CT criterion for differentiating benign from malignant processes in the gastric wall (37). Findings that favor DLBCL over adenocarcinoma include more pronounced wall thickening, the lack of obstruction, preserved perigastric fat planes, longer or multifocal involvement, and bulky abdominal lymphadenopathy (38,41,42). Although a characteristic feature of DLBCL, aneurysmal dilatation of the small bowel can be seen with a GI stromal tumor, metastatic disease, and rarely, adenocarcinoma (43).

Mantle Cell Lymphoma

Mantle cell lymphoma is an aggressive form of lymphoma that is usually associated with nodal and extranodal involvement at the time of clinical presentation. This tumor constitutes up to 9%–13% of primary GI lymphomas and is typically characterized by multiple polyps throughout the GI tract, a condition known as lymphomatous polyposis (9,44). Microscopic GI involvement is found in 88%–92% of patients with peripheral mantle cell lymphoma (45,46). Most patients with mantle cell lymphoma are middle-aged to elderly men, with a mean age of 62 years (44,46).

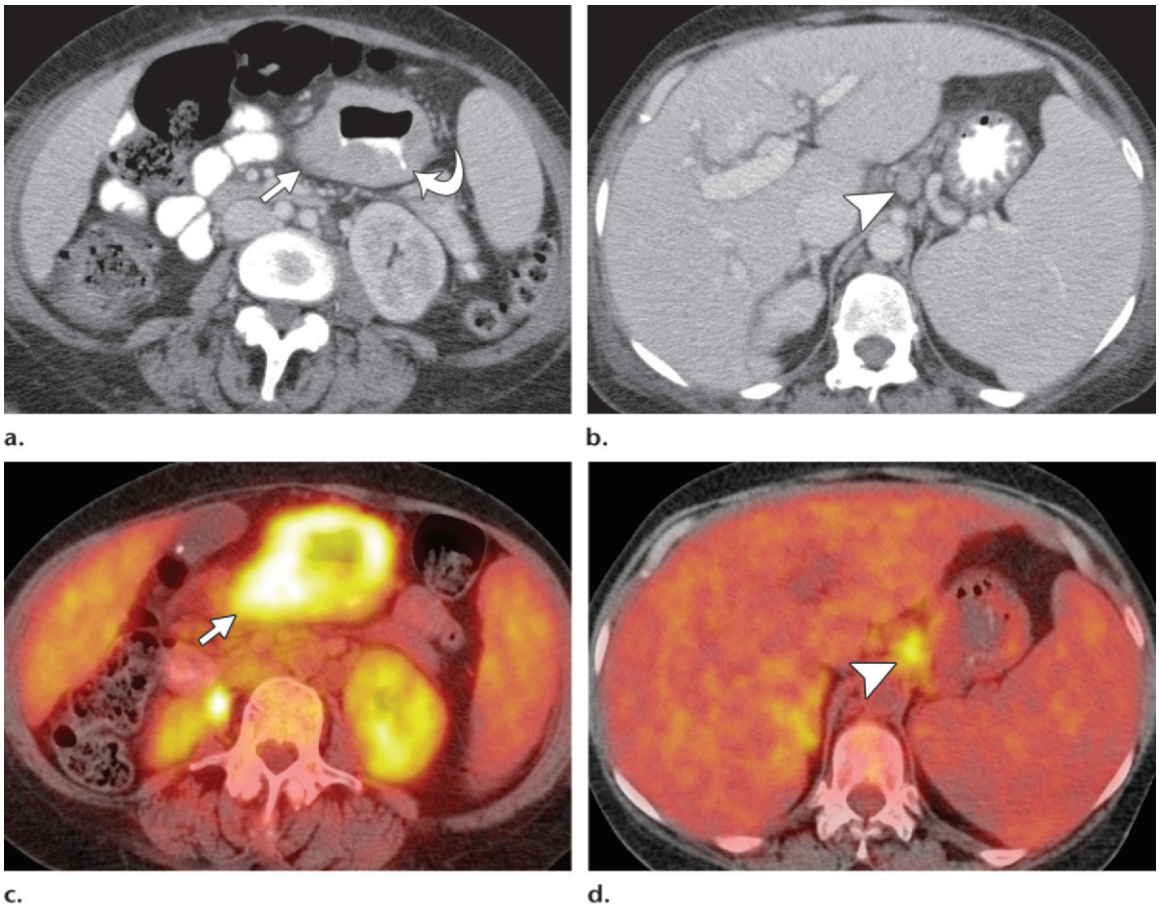


Figure 6. DLBCL in a 51-year-old woman with acute abdominal pain. **(a, b)** Axial CT images with intravenous and oral contrast material show marked gastric wall thickening (straight arrow), with focal ulceration (curved arrow) and an enlarged celiac lymph node (arrowhead). Also note the pneumoperitoneum in **a** and splenomegaly in **b**. **(c, d)** Axial fused PET/CT images show FDG uptake in the primary gastric tumor (arrow) and a celiac lymph node (arrowhead). **(e)** Photograph of the sectioned gross specimen shows a diffusely thickened gastric wall (arrow) containing an area of perforation (*).

These patients traditionally have had a poor prognosis, with a median survival of only 3–4 years, but outcomes have improved substantially with the use of autologous stem cell transplantation (44).

Teaching Point

Pathologic Features.—The most common macroscopic form of mantle cell lymphoma is lymphomatous polyposis, in which numerous small polyps or nodules (ranging from several millimeters to several centimeters in diameter) are found in one or more portions of the GI tract (Fig 8). This appearance is not specific for mantle cell lymphoma, as it can also be seen in patients with ENMZL and follicular lymphoma (47).

The nodular proliferations of mantle cell lymphoma contain uniform small to medium-sized cells with irregularly-shaped nuclei and scant cytoplasm (Fig 8). The lymphomatous cells are a pre–germinal center type that arises from the inner mantle zone of lymphoid follicles. Subsequent invasion of the germinal center is thought to be responsible for the nodular pattern of disease in these patients (48). Mantle cell lymphoma expresses B-cell antigens, but the most useful immunohistochemical marker is cyclin D1. Overexpression of cyclin D1 (Fig 8) results from the translocation t(11;14)(q13;q32), which is believed to be the primary genetic alteration in mantle cell lymphoma (48).

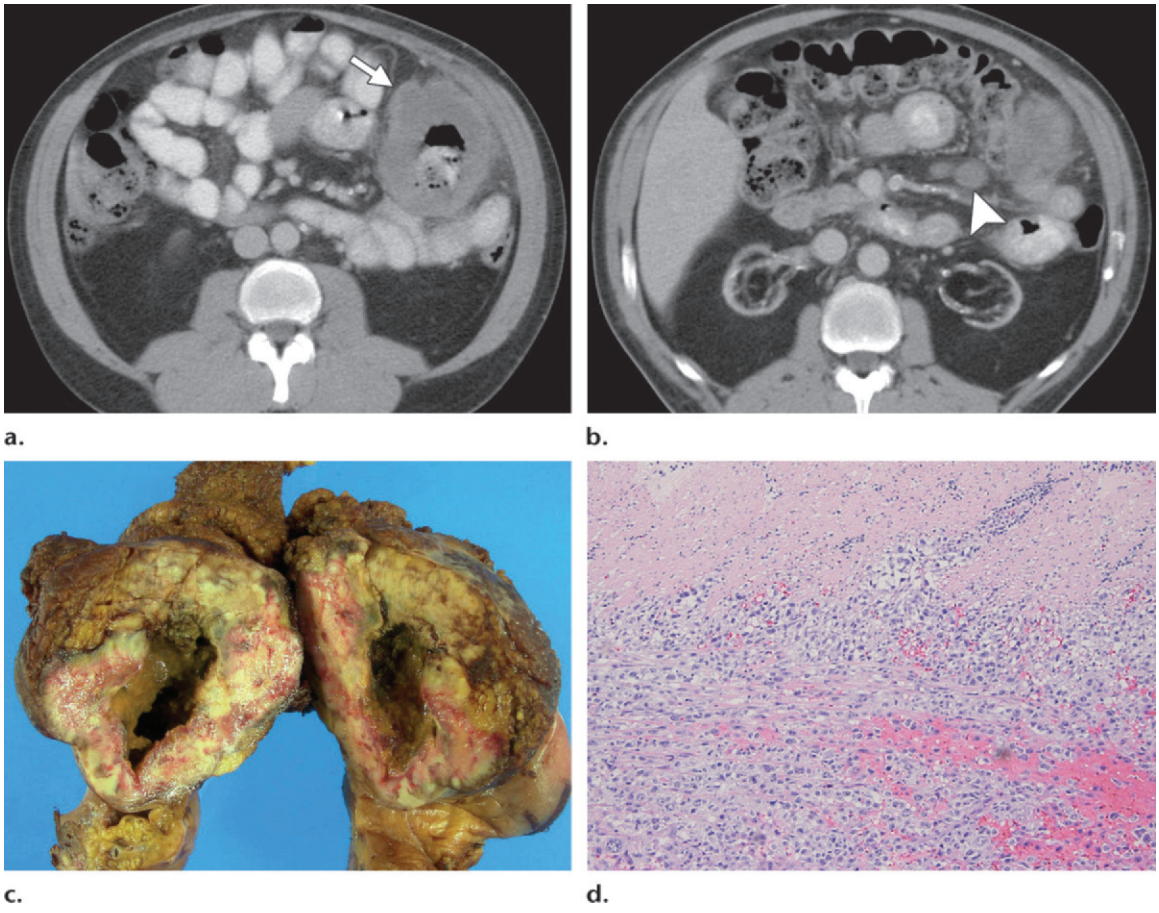


Figure 7. DLBCL in a 45-year-old man undergoing immunosuppression for pancreas and renal transplantation with acute left-sided abdominal pain. **(a, b)** Axial CT images with intravenous and oral contrast material show hypoattenuating circumferential thickening of the jejunal wall (arrow) with aneurysmal dilatation and infiltration of the adjacent fat. Also note the enlargement of draining mesenteric lymph nodes (arrowhead). **(c)** Photograph of the sectioned gross specimen shows bulky circumferential jejunal infiltration and a widened lumen. **(d)** Photomicrograph (original magnification, ×20; H-E stain) shows invasion and destruction of the muscularis propria.

Imaging Features.—Mantle cell lymphomas are manifested at barium studies by innumerable nodular or polypoid lesions up to 4 cm in size throughout the GI tract (Figs 8, 9) (49,50). The small bowel and colon are both affected, with the ileum, ascending colon, and rectum the most frequent sites of involvement (49). The polypoid nature of the nodules may not be apparent at CT, at which nonobstructive bowel wall thickening and mass formation are the most common findings (49). Most patients also have abdominal lymphadenopathy (Fig 8) as well as extra-abdominal involvement by this disease. FDG-PET may reveal intense uptake in involved bowel and lymph nodes, with curvilinear foci corresponding to affected loops of bowel (Fig 9) (50).

The inherited polyposis syndromes are a more common cause of multiple GI polyps than mantle cell lymphoma (49). A family history of one of the polyposis syndromes is extremely helpful for distinguishing these conditions, but because of incomplete penetrance or spontaneous mutations, such a history is not always present. A polyposis syndrome should also be suspected in patients who present during childhood or early adulthood and in patients who have characteristic extraintestinal findings such as mucocutaneous pigmentation in Peutz-Jeghers syndrome and fibromatosis, osteomas, and dental anomalies in Gardner syndrome. Multiple GI masses may also be found in patients with blood-borne metastases, most commonly from breast or lung cancer and malignant melanoma, as well as other types of GI lymphoma, particularly follicular lymphoma and ENMZL. However, hematogenous metastases to the GI tract tend to be larger and more sporadic and usually appear as submucosal masses or as centrally ulcerated bull's-eye or target lesions.

Follicular Lymphoma

Despite being the most common nodal lymphoma in Western countries, follicular lymphoma

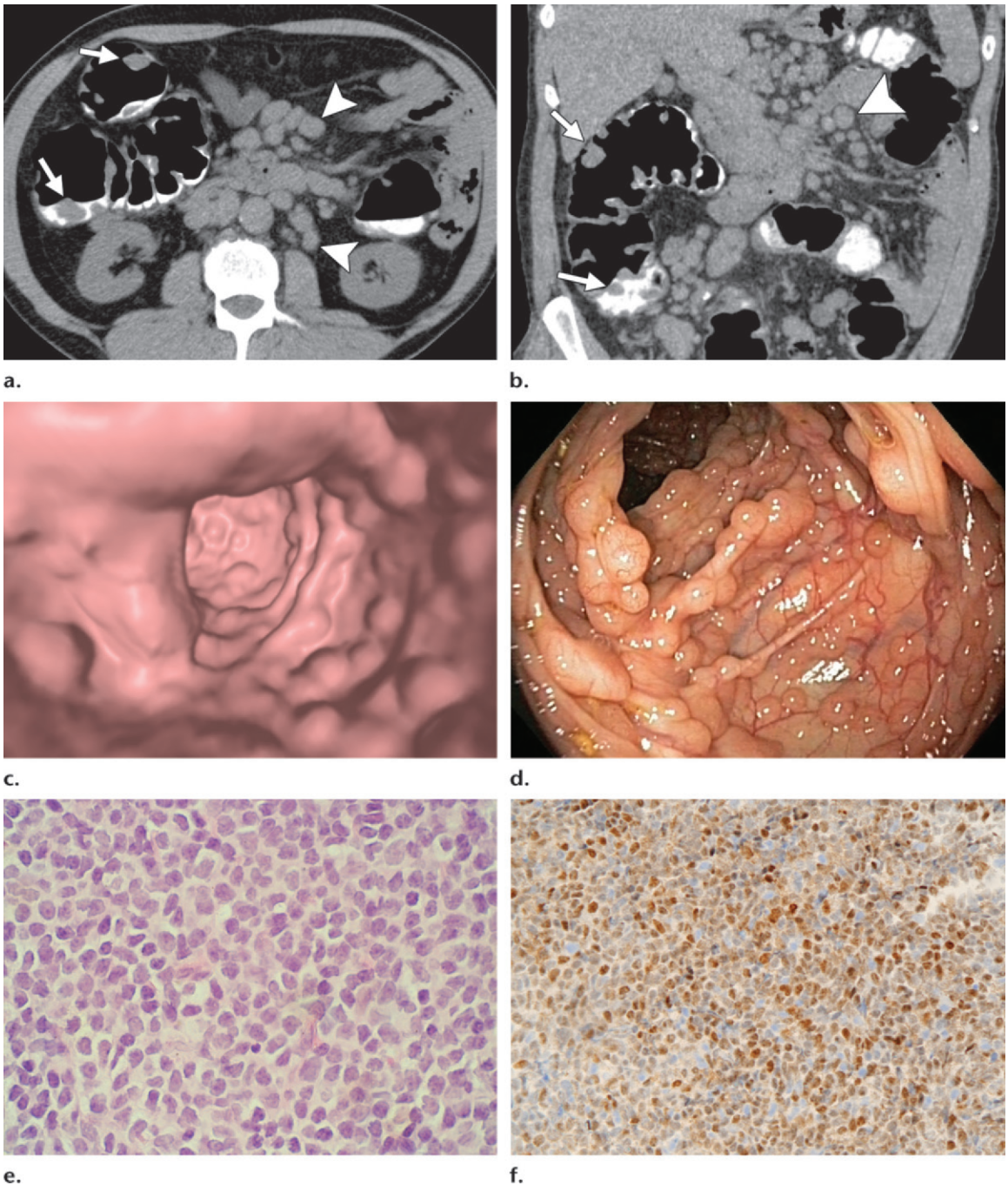


Figure 8. Mantle cell lymphoma in an asymptomatic 63-year-old man who underwent screening CT colonography. **(a, b)** Axial **(a)** and coronal **(b)** two-dimensional (2D) images with oral contrast material from CT colonography show multiple polyps (arrows) in the ascending colon and hepatic flexure as well as mesenteric and retroperitoneal lymphadenopathy (arrowheads). **(c, d)** Endoluminal three-dimensional (3D) image from CT colonography **(c)** and photograph from optical colonoscopy **(d)** show numerous subcentimeter polyps in the colon. **(e)** Photomicrograph (original magnification, ×40; H-E stain) shows uniform small to medium cells with irregular nuclear contours and scant cytoplasm. **(f)** Photomicrograph (original magnification, ×20; cyclin D1 stain) shows strong expression of cyclin D1.

represents only 2%–12% of primary GI NHLs (9–12). In a review of 249 patients with primary GI follicular lymphoma, the median age at presentation was 56 years, with a range of 26–81 years and an equal sex distribution (51). GI follicular lymphomas are usually low-grade, indolent tumors that do not require treatment, although some lesions may progress to DLBCL. Median relapse-free survival is 98 months (51).

Pathologic Features.—GI follicular lymphomas are usually characterized by multiple scattered

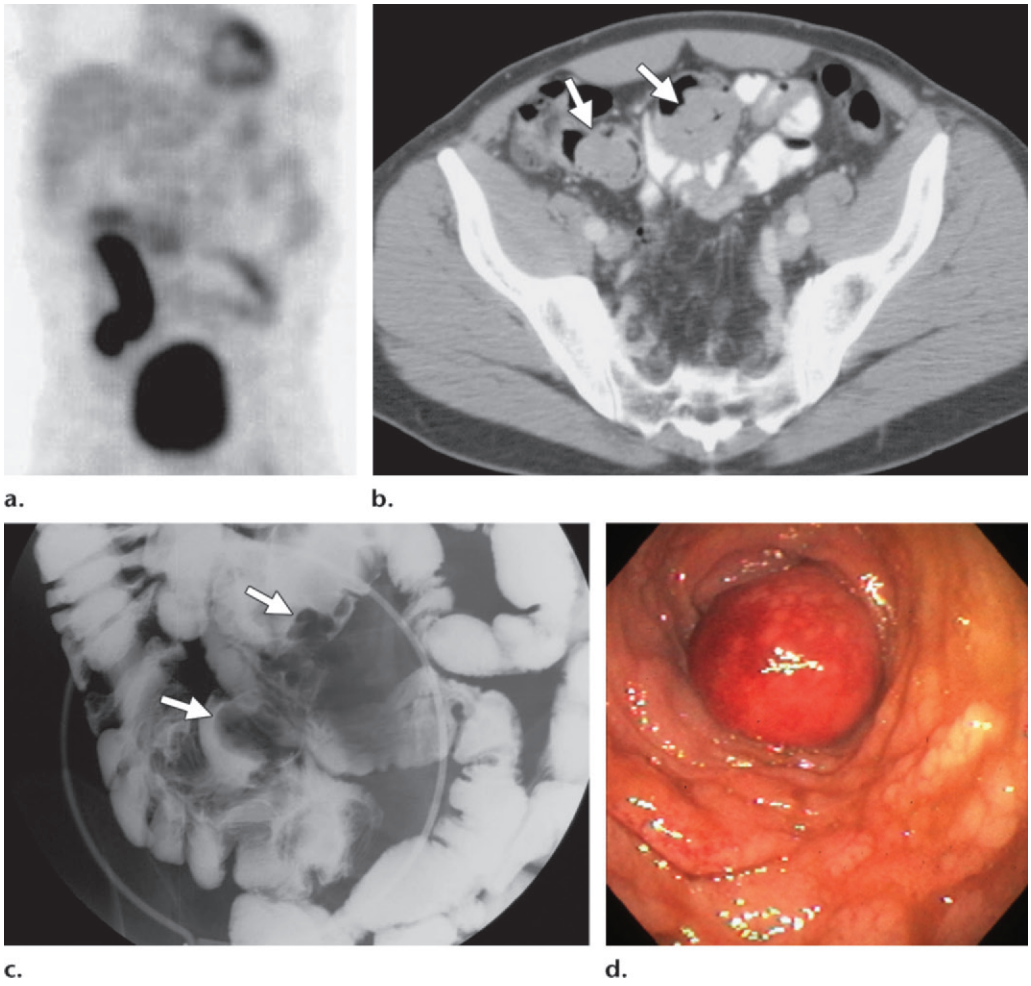


Figure 9. Recurrent mantle cell lymphoma in a 55-year-old man during routine surveillance. **(a)** FDG PET image shows curvilinear uptake in the right lower quadrant. **(b)** Axial CT image with intravenous and oral contrast material shows multiple intraluminal polypoid masses in the distal ileum (arrows). **(c)** Spot image from small-bowel follow-through study shows several polypoid masses in the terminal ileum (arrows). **(d)** Photograph from optical colonoscopy confirms the presence of a polypoid lesion in the distal ileum.

or confluent nodules or polyps primarily involving the duodenum and jejunum (Fig 10), although some patients have diffuse GI involvement (51,52). The nodules consist of villi that are enlarged by aggregates of follicles in the lamina propria (Fig 10) (51). As in nodal follicular lymphoma, the follicles are composed of monotonous, small lymphoid cells with cleaved nuclei. GI follicular lymphomas express CD10, enabling differentiation from other causes of lymphomatous polyposis, such as ENMZL and mantle cell lymphoma, which are CD10 negative (51). As many as 90% of follicular lymphomas have the translocation t(14;18)(q32;21), resulting in the overexpression of anti-apoptotic proteins (2).

Imaging Features.—GI follicular lymphomas are manifested at barium studies and CT by multiple small-bowel nodules of varying size (53). In one retrospective study, however, Iwamuro (54) found that only 15% of patients with GI involvement by follicular lymphoma had abnormal GI findings at CT, with a thickened bowel wall in all cases (Fig 10). The frequent absence of CT findings may be explained by the small size of the lesions. FDG PET also is not a reliable imaging tool, with a sensitivity of 46% for detecting GI follicular lymphoma (54). This high false-negative rate is likely related to the small size of the GI lesions, as well as the lower avidity of GI follicular lymphoma at FDG PET compared with more aggressive forms of lymphoma (54).

Burkitt Lymphoma

Burkitt lymphoma is an aggressive B-cell lymphoma that is usually found in children or immunocompromised adults. It is considered to be the fastest growing of all malignant tumors, with a doubling time of only 24 hours (53,55). It is the most frequent subtype of NHL in children, rep-

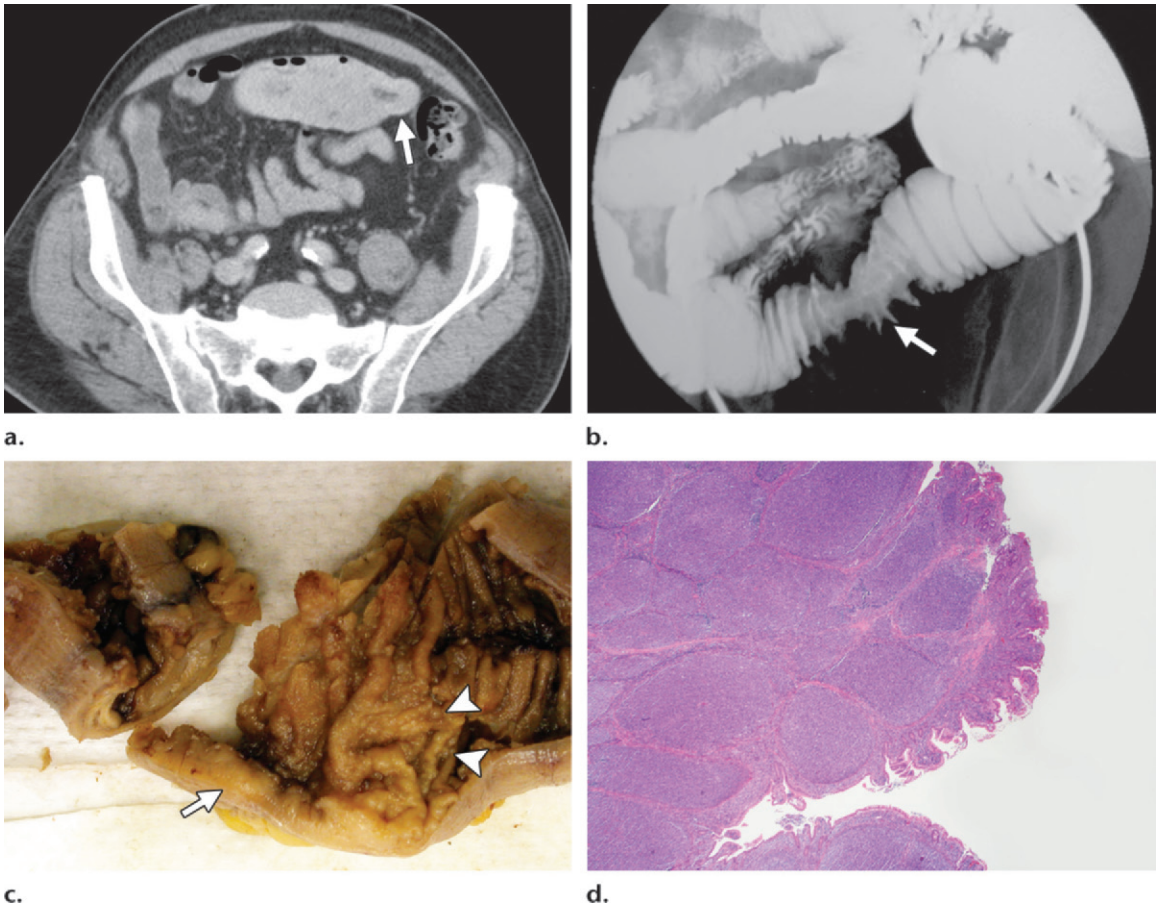


Figure 10. Follicular lymphoma in a 79-year-old man with a 2-week history of abdominal pain, vomiting, and decreased appetite. **(a)** Axial CT image with intravenous contrast material shows a focal segment of wall thickening in the jejunum (arrow). **(b)** Spot image from a small-bowel follow-through study shows a short segment of small bowel with thickened, irregular folds (arrow). **(c)** Photograph of the sectioned gross specimen shows an area of wall thickening (arrow) with prominent folds and numerous small nodules (arrowheads). **(d)** Photomicrograph (original magnification, ×10; H-E stain) shows nodular expansion of the mucosa by multiple lymphoid follicles.

resenting up to 40% of pediatric lymphomas in the United States and western Europe (55,56). In contrast, Burkitt lymphoma represents only 1%–2% of all NHLs and 1%–5% of primary GI NHLs in adults (9,10,12,56). Short-duration intensive chemotherapy has improved outcomes for Burkitt lymphoma, with an overall survival of 50%–70% in adults, 5-year survival rates of greater than 90% in children with localized disease, and 2-year disease-free survival rates of 75%–89% in children with advanced disease (56,57).

Endemic, sporadic, and immunodeficiency-associated variants of Burkitt lymphoma have been described. The endemic variant is associated with EBV infection and is found in Africa, where jaw lesions predominate, and in the Middle East, where intestinal lesions are common (58). In contrast, the sporadic variant is found worldwide and commonly involves the GI tract, but is not usually related to EBV infection. Both of these variants have a male predilection. Finally, the immunodeficiency-associated variant primarily affects patients with human immunodeficiency virus (HIV); up to 40% of NHLs in HIV-positive patients are Burkitt lymphomas (56).

Pathologic Features.—Burkitt lymphoma affecting the GI tract usually involves the terminal ileum or ileocecal region. It spreads diffusely through the bowel wall, often producing a large mass or extensive bowel wall thickening (55,59). These tumors contain uniform medium-sized cells with multiple nucleoli, dispersed chromatin, basophilic cytoplasm, and numerous mitotic figures. A "starry sky" appearance is produced by scattered macrophages containing apoptotic cellular debris on a basophilic background (Fig 11) (2). The proliferation index is very high (typically 99% or higher), reflecting the rapid growth of these tumors (Fig 11). The hallmark molecular finding of Burkitt lymphoma is a translocation of the c-Myc oncogene with one

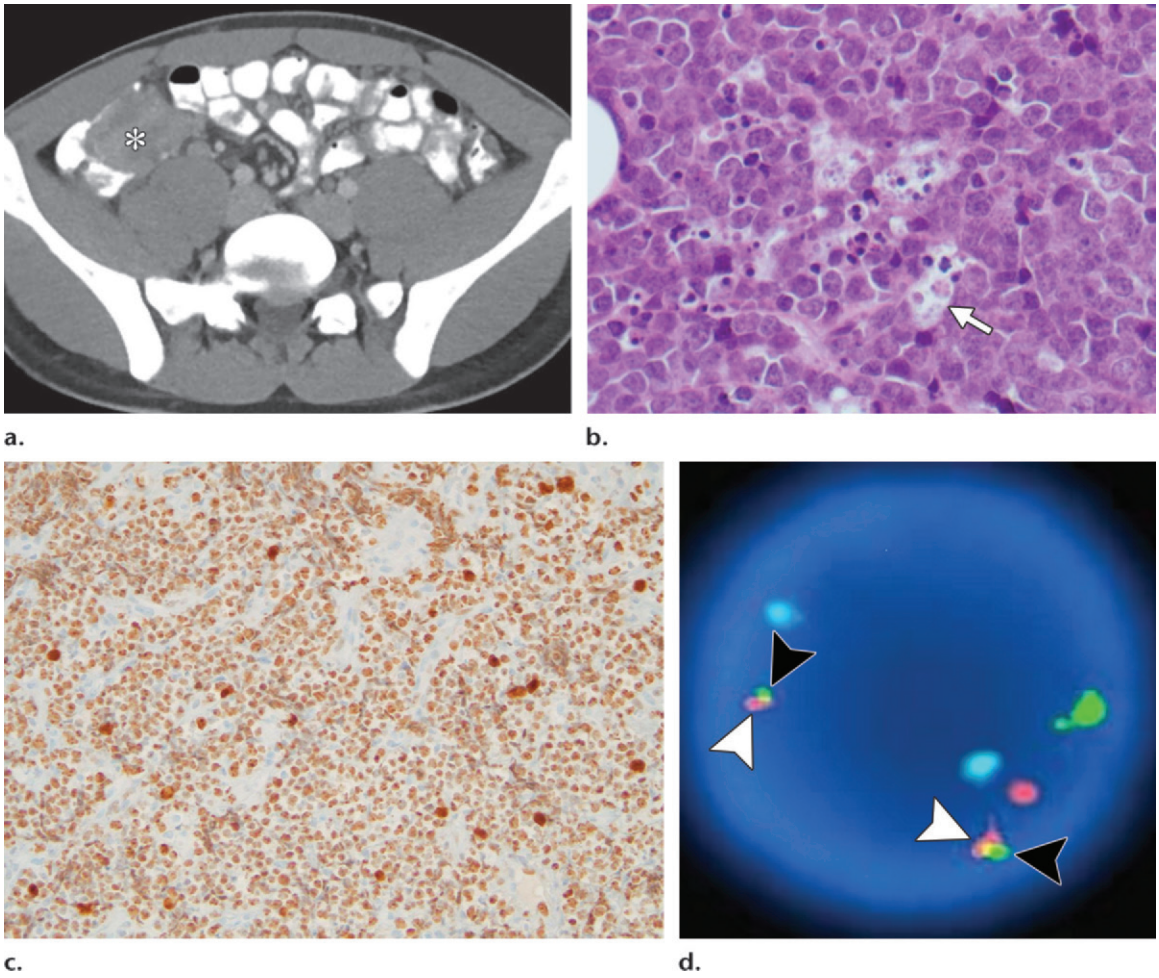
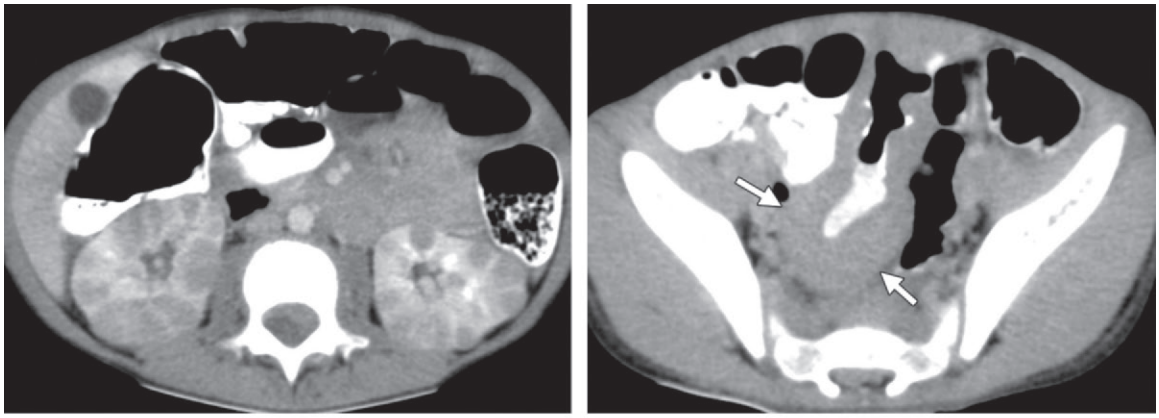


Figure 11. Burkitt lymphoma in a 16-year-old boy with a 5-day history of crampy periumbilical pain. **(a)** Axial CT image with intravenous and oral contrast material shows a nonobstructing mass (*) in the terminal ileum projecting into the cecum. **(b)** Photomicrograph (original magnification, ×40; H-E stain) shows medium-sized cells with dispersed chromatin and scant basophilic cytoplasm as well as multiple mitotic figures. A "starry sky" appearance results from scattered macrophages containing apoptotic cell debris (arrow). **(c)** Photomicrograph (original magnification, ×20; Ki-67 stain) shows a cellular proliferation index of greater than 95%. **(d)** Photograph from fluorescent in situ hybridization shows fusion of the c-Myc oncogene (white arrowheads) with the IgH gene (black arrowheads), compatible with the translocation t(8;14)(q24;q32).

of the immunoglobulin genes, most frequently t(8;14)(q24;q32) (Fig 11) (15).

Imaging Features.—Burkitt lymphoma is usually manifested at barium studies and CT by an ileocecal mass or thickened folds and narrowing in the distal ileum (Figs 11, 12) (55,60,61). Because these are aggressive lesions, malignant ascites and intraperitoneal seeding have been reported in 63% and 42% of patients with GI involvement, respectively (60). Other less-frequent findings include intussusception, aneurysmal dilatation, and perforation of the distal ileum or ileocecal region, which may occur at the time of presentation or during treatment (60–63). Burkitt lymphoma less commonly affects the stomach or colon. When it does, the tumor may be manifested by submucosal infiltration and thickening of the gastric or colonic wall at barium studies and CT (55,62–64).

Extraintestinal involvement by Burkitt lymphoma is common; 70% of patients present with widespread disease (Fig 12) (56). Affected individuals often have mesenteric and/or retroperitoneal lymphadenopathy, sometimes resulting in the development of large abdominal or pelvic masses (55,60,62). Multiple hypoechoic or hypoattenuating masses may be found in the kidneys, liver, or spleen at ultrasonography or CT (60,62,64). Skeletal, chest, soft-tissue, head and neck, and central nervous system involvement have also been described (56,60,65). Because Burkitt lymphoma has a high glycolytic rate, FDG PET and FDG PET/CT are sensitive tests for both initial diagnosis and follow-up of this disease (65,66).



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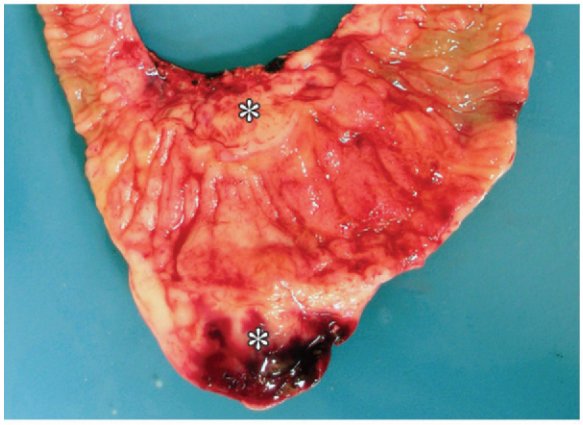


c.

Figure 12. Burkitt lymphoma in a 5-year-old boy with abdominal pain, weight loss, and fever. **(a, b)** Axial CT images with intravenous and oral contrast material show numerous bilateral low-attenuating masses in both kidneys and marked wall thickening in the distal ileum (arrows). **(c)** Photograph of the sectioned gross specimen shows a short segment of circumferential bowel wall thickening (*) with focal hemorrhage.

Hodgkin Lymphoma

Hodgkin lymphoma rarely affects the GI tract, and GI involvement is usually secondary to extension of tumor from adjacent lymph nodes involved by the disease (19). Primary GI Hodgkin lymphoma has primarily been described in anecdotal case reports and likely represents less than 1% of all primary gastric and small intestinal lymphomas (67,68). Nevertheless, the GI tract may be involved by all subtypes of Hodgkin lymphoma, including nodular sclerotic, mixed cellularity, and lymphocyte-rich and lymphocyte-depleted forms of this tumor (69,70).

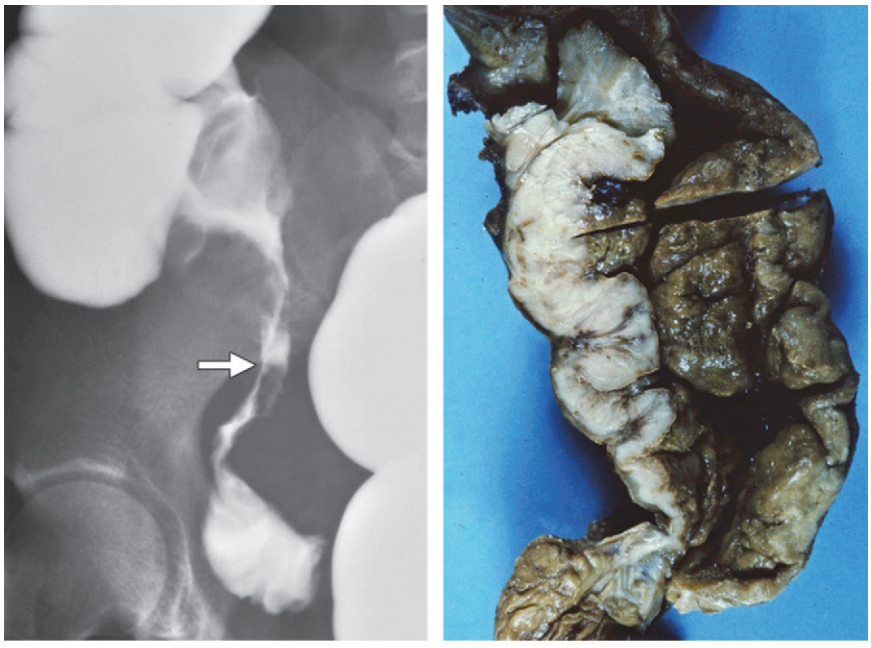
Pathologic Features.—Primary GI Hodgkin lymphoma mainly affects the stomach, followed by the small bowel, colon, and esophagus (2). An infiltrating pattern of growth is most common in the stomach, and ulcerated lesions have been reported (67,69,71,72). The characteristic Hodgkin and Reed-Sternberg (HRS) cells are binucleated cells with prominent nucleoli scattered in an infiltrate of inflammatory and accessory cells (Fig 13) (2). HRS-like cells can also be found in other types of lymphoma, necessitating a thorough immunohistochemical analysis for accurate diagnosis. HRS cells are positive for CD30 and CD15, as well as EBV, reflecting a known association between Hodgkin lymphoma and EBV infection (2).

Imaging Features.—GI Hodgkin lymphoma may be manifested at barium studies by diffuse fold thickening or an ulcerated mass in the stomach and irregular luminal narrowing and nodularity in the esophagus, small bowel, and colon (Fig 13) (70,73,74). CT usually reveals nonspecific concentric thickening of the affected bowel wall (40,73). Focal stenosis and obstruction are more common in GI Hodgkin lymphoma than in other types of lymphoma, most likely because of the greater degree of fibrosis generated by this tumor (70). Hodgkin lymphoma is FDG avid, with increased uptake of FDG reported in various sites of GI involvement by this form of lymphoma (75,76).

T-Cell Lymphoma

Enteropathy-associated T-Cell Lymphoma

T-cell lymphomas involve the GI tract much less frequently than their B-cell counterparts, constituting only about 3% of all primary GI NHLs (9,10). A variety of peripheral T-cell lymphomas have been implicated, but the most common is EATL, especially in northern Europe, where celiac disease is more prevalent. The World Health Organization classifies EATLs as type I EATL, which represents 80%–90% of cases and is strongly associated with celiac disease, and type II EATL (also referred to as monomorphic CD56+ intestinal lymphoma), which is not related to celiac disease,



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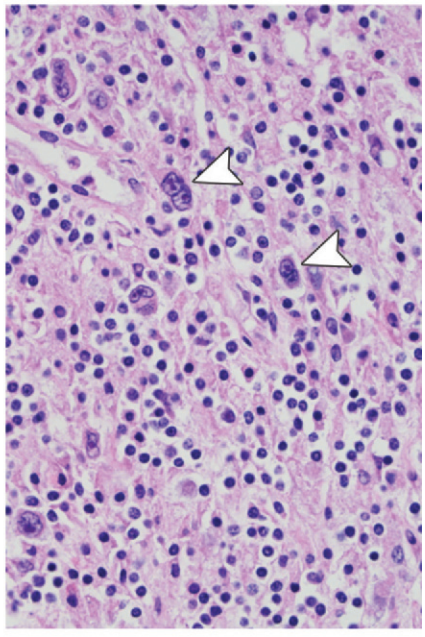

c.

Figure 13. Hodgkin lymphoma in a 29-year-old woman with a recent history of crampy right lower quadrant abdominal pain. **(a)** Spot image from barium enema examination shows an irregular stricture (arrow) in the terminal ileum. **(b)** Photograph of the sectioned gross specimen shows lobulated, full-thickness involvement of the wall of the terminal ileum by tumor. **(c)** Photomicrograph (original magnification, ×40, H-E stain) shows binucleated HRS cells (arrowheads) interspersed among inflammatory cells.

although enteropathy-like changes can be found histologically (77). Both types of EATL have similar clinical findings, with a male predominance, median age in the 50s, poor prognosis, and frequent complications, particularly intestinal perforation (78–80).

In an epidemiologic study from Sweden, the prevalence of NHL in patients with celiac disease was 6.6 times greater than in the general population (81). Most of the lymphomas were primary GI tract lymphomas, and the majority of these were T-cell lymphomas involving the small bowel, although patients with celiac disease also had an increased frequency of nodal and extranodal B-cell lymphomas (81). Lymphoma may develop any time during the course of celiac disease, including the time of initial diagnosis. Patients with refractory celiac disease (RCD) on a 12-months-gluten-free diet (RCD type I) and also having aberrant intraepithelial lymphocytes (RCD type II) are at particular risk for EATL; as many as 60% of patients with RCD type II develop EATL within 5 years (82).

Pathologic Features.—Type I EATL usually involves the jejunum or proximal ileum and is associated with the development of multiple ulcerated masses or nodules. Transmural invasion and necrosis are common, with a high perforation rate (2,82). Type II EATL may produce similar findings, but this form of lymphoma tends to involve the distal ileum, ileocecal region, or colon (77).

Type I and type II EATL have differing histologic, immunohistochemical, and genetic features. The lymphoma cells of type I EATL are predominantly large cells with abundant cytoplasm and angulated nuclei that are negative for CD56 and express the HLADQ2 or HLADQ8 genotypes

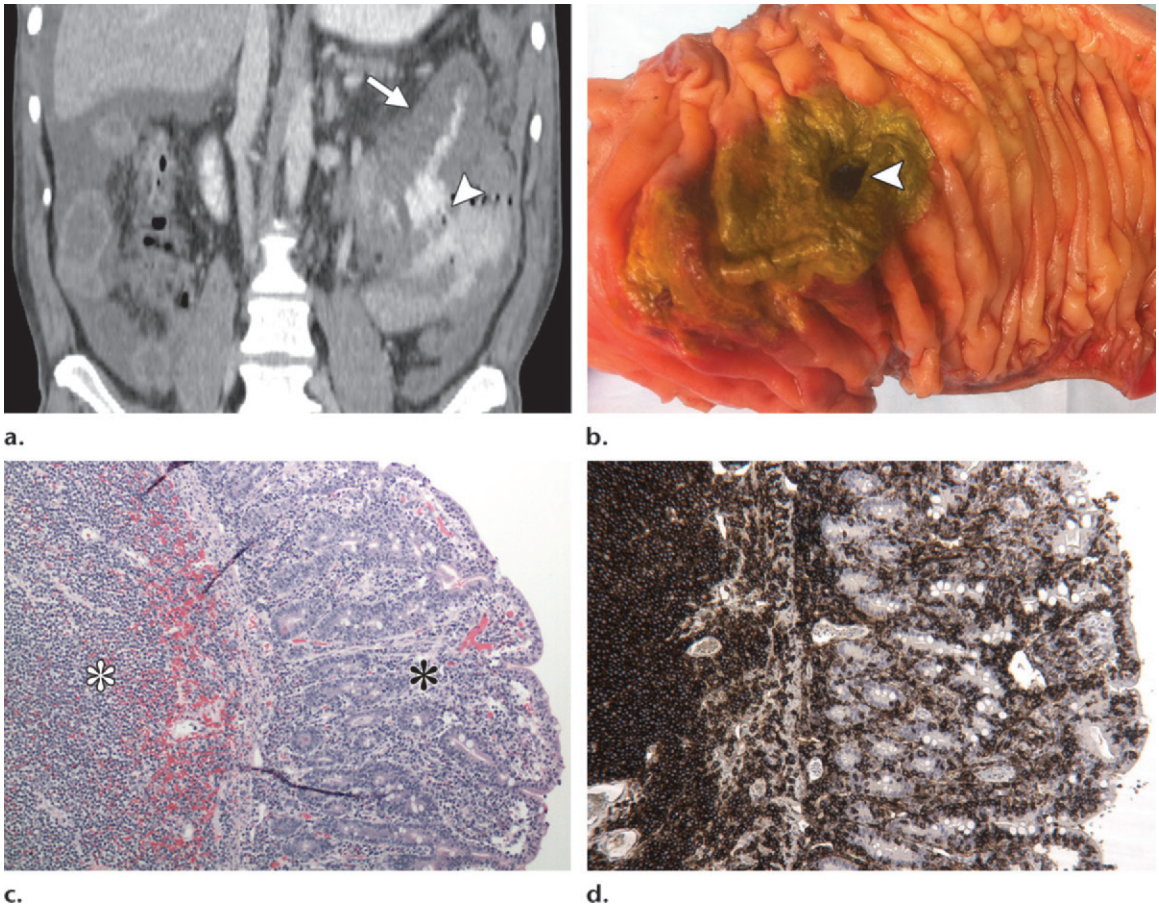

Figure 14. Intestinal EATL type II (monomorphic CD56+ intestinal T-cell lymphoma) in a 59-year-old man with a 3-month history of intermittent, generalized abdominal pain and 10-lb (4.5-kg) weight loss. **(a)** Coronal CT image with intravenous and oral contrast material shows marked wall thickening (arrow) in the proximal jejunum with focal perforation (arrowhead) and an adjacent extraluminal collection of contrast material. **(b)** Photograph of the sectioned gross specimen shows a brown area of ulceration of the mucosal surface with a focal perforation (arrowhead). **(c)** Photomicrograph (original magnification, ×20; H-E stain) shows submucosal (white ∗) and intraepithelial (black ∗) infiltration by monotonous lymphoid cells. Also note the villous atrophy and crypt hyperplasia from associated enteropathy. **(d)** Photomicrograph (original magnification, ×20; CD56 stain) shows diffuse positivity of both submucosal and intraepithelial lymphoid cells.

found in almost all patients with celiac disease (82). Patients with type I EATL also have the underlying enteropathy of celiac disease characterized by crypt hyperplasia, villous atrophy, and intraepithelial lymphocytosis. Although patients with type II EATL may also have an underlying enteropathy (Fig 14), the lymphoma cells are uniform, small, round cells with scant cytoplasm and hyperchromatic nuclei. These tumors are positive for CD56 (Fig 14), and the frequency of HLADQ2 or HLADQ8 is comparable to that in the general population.

Imaging Features.—Barium studies in patients with EATL may reveal thickened, nodular folds, ulcers, and strictures, particularly in the proximal small bowel (42,83,84). EATL is most commonly manifested at CT and MR imaging by circumferential wall thickening in the jejunum, ileum, or both (Figs 14, 15) (30,85). There may be accompanying lymphadenopathy and infiltration of the mesenteric fat. Perforation is found at the time of clinical presentation in 16% and 33% of patients with type I and type II EATL, respectively (Figs 14, 15) (79,86).

A decreased number of jejunal folds, small-bowel wall thickening, intussusception, infiltration of the mesenteric fat, lymphadenopathy, and splenic atrophy have all been reported to be more common findings at CT and MR imaging in RCD type II than in RCD type I or uncomplicated celiac disease (87,88). EATL can be differentiated from RCD by increased uptake at FDG PET, which occurs in 86%–100% of patients with this form of lymphoma (85,86).

While ulcerative jejunitis, another rare complication of celiac disease, has imaging features (ie, circumferential bowel wall thickening and ulceration) similar to those of EATL, some authors

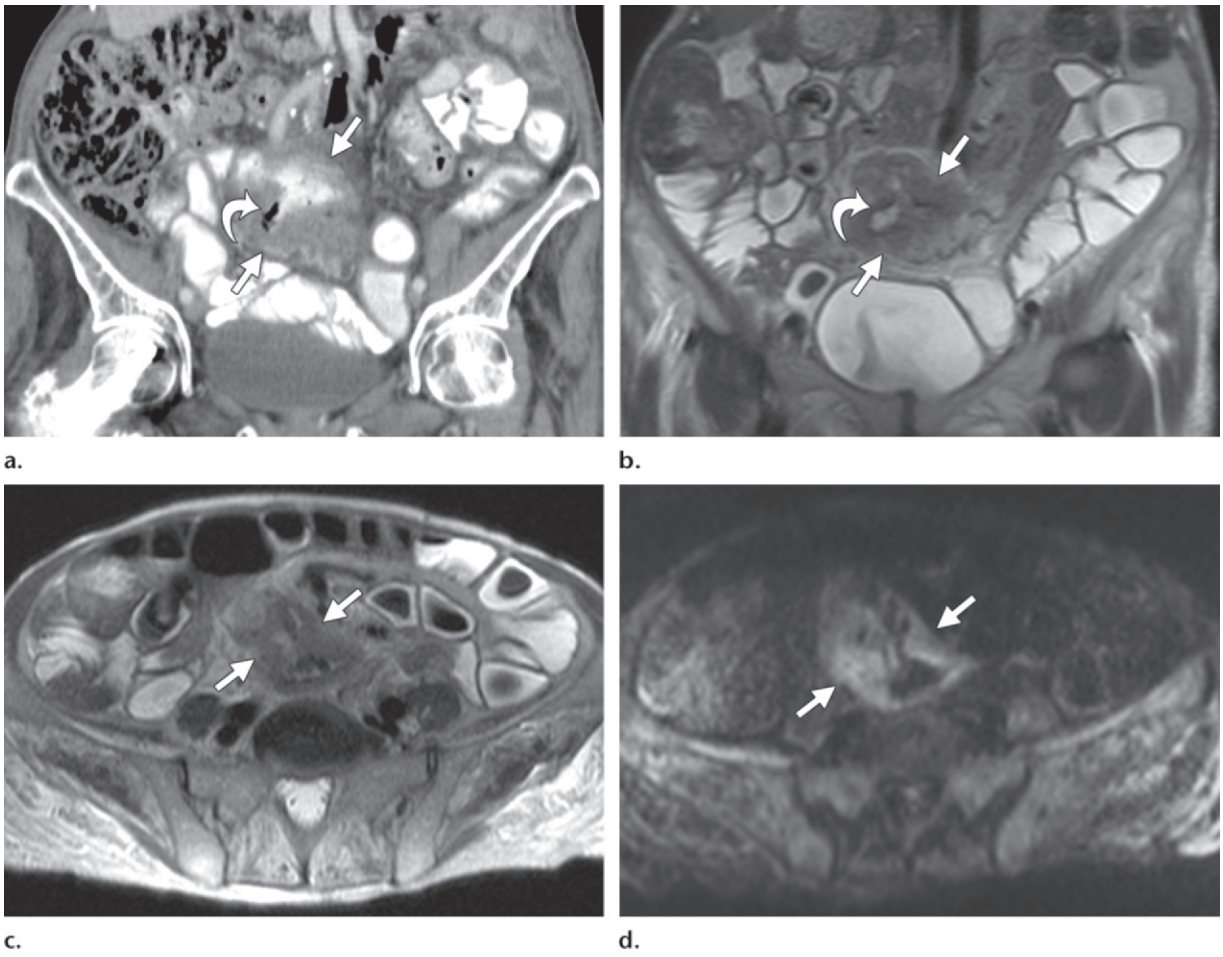

Figure 15. Intestinal EATL type I in a 71-year-old woman with 25-lb (11-kg) weight loss and fever. **(a, b)** Coronal CT image with intravenous and oral contrast material **(a)** and coronal T2-weighted MR image **(b)** show circumferential wall thickening of the mid ileum (straight arrows), with a focal area of ulceration and perforation (curved arrow). **(c, d)** Axial T2-weighted **(c)** and diffusion-weighted **(d)** MR images show wall thickening of the mid ileum with restricted diffusion (arrows).

Teaching Point

believe ulcerative jejunitis is actually a low-grade form of EATL (82). DLBCL should also be included in the differential diagnosis for EATL, but T-cell lymphoma more frequently involves the proximal small bowel and is more likely to be associated with multifocal disease and a higher frequency of perforation than B-cell lymphoma (89). Finally, patients with celiac disease are at increased risk for developing GI cancers, which may be manifested by focal masses or annular lesions, most commonly in the jejunum.

Conclusion

GI lymphomas comprise a heterogeneous group of entities that vary in cell lineage, stage of lymphoid cell development, and biologic behavior. These tumors have overlapping pathologic features, so pathologists use a multifactorial approach for the diagnosis of GI lymphoma by analyzing histologic, immunohistochemical, and genetic findings. Similarly, radiologists can narrow the differential diagnosis for the many types of GI lymphoma by analysis of the clinical information, site of involvement, fluoroscopic and cross-sectional imaging findings, and associated complications. The approach should help radiologists to not only suggest a diagnosis of GI lymphoma but also to identify the specific subtype of lymphoma in these patients.

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From the Radiologic Pathology Archives
Gastrointestinal Lymphoma: Radiologic and Pathologic Findings

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Page 1935
Lymphomas are a heterogeneous group of neoplasms with varying GI sites of involvement and varying gross and histologic features that account for the wide spectrum of imaging findings.

Page 1936
Gastric ENMZL is usually a superficial spreading lesion confined to the mucosa and submucosa. It occurs anywhere in the stomach and is commonly multifocal. The diseased mucosa may be granular, nodular, or ulcerated.

Page 1939
Primary GI DLBCLs are most commonly found in the stomach, followed by the ileum. These lymphomas are characterized by diffusely infiltrative and nodular lesions with extensive ulceration.

Page 1941
The most common macroscopic form of mantle cell lymphoma is lymphomatous polyposis, in which numerous small polyps or nodules (ranging from several millimeters to several centimeters in diameter) are found in one or more portions of the GI tract. This appearance is not specific for mantle cell lymphoma, as it can also be seen in patients with ENMZL and follicular lymphoma.

Page 1950
DLBCL should also be included in the differential diagnosis for EATL, but T-cell lymphoma more frequently involves the proximal small bowel and is more likely to be associated with multifocal disease and a higher frequency of perforation than B-cell lymphoma.