Upper Gastrointestinal Tract Involvement in Inflammatory Bowel Diseases: Histologic Clues and Pitfalls

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Abstract: The upper gastrointestinal (UGI) manifestations of inflammatory bowel diseases (IBDs) are frequently observed by classic ileal and colonic symptoms and are reported to involve only 0.5% to 4% of adult patients. However, because of the improvement of endoscopic techniques and the growing use of esophagogastroduodenoscopy with biopsy, both asymptomatic and clinically significant esophageal, gastric, and duodenal manifestations are increasingly recognized. The UGI involvement in IBD was historically synonymous with Crohn’s disease (CD), but the doctrine of ulcerative colitis (UC) being limited to the colon has been challenged, and UC-related gastroduodenal lesions have been reported. The diagnosis of UGI IBD should ideally rely on a combination of the clinical history, endoscopic picture, and histologic features. Although endoscopic changes such as aphthoid or longitudinal ulcers and bamboo-joint-like pattern are suggestive of CD, histologic evaluation increases the sensitivity of the IBD diagnosis since histologic alterations may be present in endoscopically unremarkable mucosa. Conversely, in many cases, the histologic findings are nonspecific, and the knowledge of clinical history is vital for reaching an accurate diagnosis. The presence of epithelioid granuloma is highly suggestive of CD but is present in a minority of CD cases; thus, pathologists should be aware of how to diagnose UGI IBD in the absence of granulomata. This article reviews the most important clinical, endoscopic, and histologic features of IBD-associated esophagitis, gastritis, and duodenitis, as well as the IBD-related manifestations in the biliary tract and the postcolecystectomy setting.

Key Words: inflammatory bowel disease, Crohn’s disease, ulcerative colitis, esophagus, stomach, duodenum, pouchitis, primary sclerosing cholangitis

Although upper gastrointestinal (UGI) involvement of Crohn’s disease (CD) and ulcerative colitis (UC) is typically obscured by the terminal ileal and colonic pathology, both asymptomatic and clinically significant esophageal, gastric, and duodenal manifestations are increasingly recognized, including complications with important management implications such as obstruction, fistulæ, and perforation. The reported prevalence of UGI involvement varies considerably because of the diversity of the applied definition of UGI involvement, methodology (endoscopy vs. histology), the type of inflammatory bowel disease (IBD) (ie, CD vs. UC), and patient populations (ie, pediatric vs. adult). A recent systematic review reported an overall prevalence of 34% in a total of 2511 CD patients.1 A recent study investigated the temporal trends of the frequency of UGI involvement. While the prevalence of esophagogastroduodenal involvement was 5.1% between 1955 and 1995, it increased significantly to 11.3% for patients diagnosed between 2009 and 2016.2 The increased detection rate can be ascribed to the improvement of endoscopic techniques and the growing use of esophagogastroduodenoscopy with histologic evaluation.

The diagnosis of UGI involvement of IBDs should ideally rely on a combination of clinical history, endoscopy, and histology. However, there is no consensus on whether UGI involvement should be histologically confirmed or can be established solely based on clinical or endoscopic features. Furthermore, there is no consensus on whether asymptomatic adult patients should undergo UGI evaluation to identify silent histologic inflammation. For example, the Montreal classification system recognized an independent category of UGI involvement in CD without specifying what methodology should be used to reach the diagnosis.3 Although endoscopic changes such as aphthoid or longitudinal ulcers and the presence of a bamboo-joint-like pattern may be suggestive of the disease, histologic evaluation increases the sensitivity of the IBD diagnosis since histologic alterations may be present in endoscopically unremarkable mucosa.4 Conversely, in many cases, the histologic findings are nonspecific. The presence of epithelioid granuloma is highly suggestive of CD, but it can only be recognized in a minority of cases. Therefore, in many patients, the diagnosis of UGI involvement of IBD cannot be established with certainty without proper clinical information and the cautious exclusion of other inflammatory diseases. Furthermore, some guidelines recommend upper endoscopy to be performed in patients with a preliminary diagnosis of IBD-unclassified to discriminate between CD and UC (eg, by recognizing strictures, fistulæ, or epithelioid granulomata).4,7 The majority of IBD patients with UGI involvement typically either show concurrent ileocolonic disease or were previously diagnosed with lower gastrointestinal (GI) IBD. Nevertheless, up to 13% of newly diagnosed adult and almost a third of pediatric patients have isolated UGI manifestations.2

It is widely accepted that esophagogastroduodenal manifestations of IBD are more common in children compared with adults. Symptomatic UGI involvement is
reported to be present in only ~5% of adult patients. However, since esophagogastroduodenoscopy is not recommended as part of the routine clinical diagnostic workup in the adult population,3–8 many cases with mild esophageal, gastric, and duodenal manifestations may remain undiagnosed. Conversely, most pediatric gastroenterology guidelines advise esophagogastroduodenoscopy at the time of the initial diagnosis with biopsy sampling from all segments of the examined GI tract, even in the absence of endoscopic alterations.9,10 Therefore, the presence of esophagogastroduodenal disease is understandably higher in the pediatric setting, with a prevalence reported in the 30% to 50% range.11 If esophagogastroduodenoscopy is regularly performed in asymptomatic adult patients, the rate of UGI manifestations increases to the same order of magnitude as in the pediatric populations.1,4 In conclusion, the discrepancy of prevalence between adult and pediatric upper GI tract CD is, at least in part, related to the differences in the standards of the diagnostic workup.

There is a conflicting body of literature concerning the prognostic value of UGI involvement in IBD. The previously detailed methodological variability of the UGI IBD diagnosis partially explains why the data regarding the prognostic value is heterogeneous. Earlier literature suggested that the diagnosis of UGI involvement might have an adverse prognostic value,12,13 however, recent publications failed to support the association with a worse outcome,2 and the clinical significance of the asymptomatic and endoscopically invisible lesions is contested.4 Whether upper GI manifestations at the time of the initial diagnosis may predict a complicated disease course has not yet been systematically and prospectively studied.

**CROHN'S DISEASE**

**Esophagus**

**Clinical Aspects**

The prevalence of esophageal CD ranges from 0.2% to 11% in the adult population and from 5% to 17% in pediatric patients.14–19 The vast majority of esophageal CD cases are associated with ileocolonic manifestations,20 and only a few cases of isolated esophageal CD have been reported.21,22 Patients with histologic evidence of esophageal CD may be asymptomatic or present with symptoms including dysphagia,odynophagia, heartburn, and chest or epigastric pain (Table 1).19

**Endoscopic Features**

The nonspecific endoscopic features include mucosal erythema, nodularity, friability, erosions, and aphthoid or punched-out (herpes virus-like) ulcers. In more advanced cases, mucosal cobblestoning, fistulas, wall stiffness, and stenosis may be noted.23,24 The mid (29%) and distal (29%) segments are the most common sites of involvement, while proximal and diffuse manifestations are less common (Table 1).19 Interestingly, Ramaswamy et al16 were unable to demonstrate a difference between the endoscopic findings of symptomatic and asymptomatic pediatric esophageal CD cases. In CD patients with concomitant eosinophilic or lymphocytic esophagitis, the endoscopic picture is similar to the non-IBD-associated counterparts of the respective diseases with frequent transverse ring formation, also known as trachealization.25

**Histologic Features**

Histology usually reveals nonspecific focal lymphoplasmacytic inflammation of the lamina propria (83%) that may extend transmurally, with various degrees of active inflammation and erosions/ulcerations (Table 1). The reported frequency of non-necrotizing epithelioid granulomas is rather diverse and varied greatly depending on the type of specimen (ie, biopsy vs. resection) and the workup protocol (ie, number of studied sections). Decker et al14 reviewed all 20 biopsy cases of esophageal CD diagnosed at Mayo Clinic Rochester between 1976 and 1998 and not a single case showed granulomata. De Matos et al18 evaluated biopsy specimens from esophagogastroduodenoscopies and ileocolonoscopies in a pediatric population and found granulomatous inflammation in the esophageal samples in only 2.7% of cases and identified the esophagus as the least common site for this histologic feature. Ammoury et al27 identified granulomata in 12% of children, suggesting that the frequency of granulomas may be higher in the pediatric population. However, according to a review of the literature by Rudolph and colleagues and the series of D’Haens and colleagues, granulomata may be present in up to 50% of adult cases (Fig. 1A).15,28 Nevertheless, to reach the diagnosis of esophageal CD, one should not depend on the recognition of granulomata, but rather interpret the frequently nonspecific histologic changes in the context of clinical history and endoscopic morphology.

Concurrent eosinophilic and lymphocytic esophagitis characterized by increased intraepithelial eosinophilia and lymphocytosis (ie, ≥15 eosinophils/high-power field and ≥20 lymphocytes/high-power field, respectively) has been described in patients with CD (Fig. 1B).29–33 Spongiosis resembling contact dermatitis and dyskeratosis are also frequently seen in these cases, while the absence of intraepithelial neutrophils is an important differentiating feature from other forms of esophagitis, including reflux esophagitis. Although an increased association of lymphocytic esophagitis and CD has been reported in pediatric patients,30 series of adult patients reported either a lower positive predictive value of a lymphocytic esophagitis diagnosis for coexisting IBD29,34 or failed to demonstrate a significant association between these 2 entities.35 The data regarding the co-occurrence of eosinophilic esophagitis and CD is even more conflicting, with some publications reporting a 5-fold increase in the occurrence of eosinophilic esophagitis among IBD patients,32,33 whereas a more recent population-based study demonstrated an inverse relationship.36 Differences regarding the demographics and frequencies of unrecognized diseases (ie, gastroesophageal reflux and Helicobacter pylori gastritis) in the control groups are believed to account for these differences and further studies are warranted to better understand the association between lymphocytic/eosinophilic esophagitis and IBD.36

**Differential Diagnosis**

The exclusion of other ulcerative (eg, gastroesophageal reflux, cytomegalovirus, herpes simplex virus, fungal, drug induced, and radiation esophagitis) and granulomatous (eg, foreign body reaction, immunologic disorders including sarcoidosis and immunodeficiencies, and infections, especially tuberculosis) conditions is an essential role of the microscopic examination. Regarding the lymphocytic and eosinophil esophagitis pattern, further diseases enter the differential diagnosis, including celiac disease and other autoimmune disorders (ie, Hashimoto thyroiditis), esophageal manifestations of
TABLE 1. Comparison of the Clinical, Endoscopic, and Histologic Features, and Most Relevant Differential Diagnostic Considerations of UGI Crohn’s Disease and Ulcerative Colitis

|                  | Crohn’s Disease | Ulcerative Colitis |
|------------------|-----------------|--------------------|
| **Clinical symptoms** |                 |                    |
| Esophagus        | Prevalence: adult: 0.2%-11%; pediatric: 5%-17% | Very rare (not more common than in control population) |
|                  | Presentation: asymptomatic or dysphagia, odynophagia, heartburn, chest/epigastric pain | |
| Stomach          | Prevalence: symptomatic: 0.5%-4%; histologic: ∼50% | Prevalence: symptomatic: 8%; histologic: ∼30% |
|                  | Presentation: nausea, vomiting, anorexia, postprandial fullness, epigastric pain, bleeding, iron-deficiency anemia, gastric outlet obstruction | Presentation: asymptomatic or associated with severe pancolitis/postcolectomy setting |
| Duodenum         | Prevalence: symptomatic: 2%-4%; histologic: 28%-48% | Prevalence: adult: 3%-10%; pediatric: up to 30% |
|                  | Presentation: asymptomatic or nausea, vomiting, bleeding, iron-deficiency anemia, delayed gastric emptying (“ram’s horn” sign); acute or chronic pancreatitis | Presentation: asymptomatic or associated with severe pancolitis/postcolectomy setting, frequently associated with pouchitis |
| **Endoscopic morphology** |                 |                    |
| Esophagus        | Distribution: middle and distal segments > proximal segment and diffuse | Nonspecific |
|                  | Features: erythema, nodularity, friability, aphthoid or punched-out erosions/ulcers, cobblestoning, fistulas, wall rigidity, stenosis | |
| Stomach          | Distribution: antral and pyloric > oxyntic | Erythema, mucosal friability, aphthous erosions and rarely bamboo-joint-like lesions |
|                  | Features: edema, superficial aphthoid or deep linear and serpentine erosions/ulcers, nodularity, bamboo-joint-like lesions (linear fissures and swollen longitudinal folds); wall rigidity, reduced peristalsis, antropyloric stricture, fistulas (usually secondary) | |
| Duodenum         | Distribution: bulbar (often with antropyloric gastritis) > distal duodenal (often with jejunitis) | Distribution: Panduodenitis |
|                  | Features: edema, hyperemia, friability, aphthoid, circular, or longitudinal erosions/ulcers, cobblestoning, notched Kerckring’s folds, stenosis with reduced distensibility, rosary-like protuberant lesions | Features: diffuse hyperemia, edema, friability, granularity, multifocal erosions |
| **Histomorphology** |                 |                    |
| Esophagus        | Features: nonspecific focal lymphoplasmacytic lamina propria infiltrate; may extend transmurally, various degrees of active inflammation and erosions/ulcerations Granuloma: up to 50% | Nonspecific |
|                  | Special presentations: eosinophilic esophagitis: (ie, ≥ 15 eosinophils/HPF) lymphocytic esophagitis: (20 lymphocytes/HPF) | |
| Stomach          | Active chronic *H. pylori*-negative gastritis or focally enhanced gastritis: diffusely distributed or focal lamina propria lymphoplasmacytic infiltrate, macrophages/epithelioid cells, various numbers of neutrophils and eosinophils | Focally enhanced gastritis, basal mixed inflammation, and active chronic superficial *H. pylori*-negative gastritis |
|                  | Immunohistochemistry: *H. pylori*-negative Granuloma: up to 80% | Immunohistochemistry: *H. pylori*-negative |
| Duodenum         | Features: focal cryptitis, various degrees of villous blunting and increased IEL, foveolar metaplasia | Diffuse mucosal lymphoplasmacytic infiltration with variable eosinophilic and neutrophilic infiltration in the lamina propria, cryptitis, crypt abscesses, architectural distortion, foveolar metaplasia, increased IEL |
|                  | Granuloma: 0%-49% | |
| **Differential diagnosis** |                 |                    |
| Esophagus        | Active ulcerative esophagitis: gastroesophageal reflux disease, CMV, HSV, fungal, drug-induced (eg, NSAIDs, iron-pill), radiation esophagitis Granulomatous esophagitis: foreign body reaction, infections (tuberculosis), and other immunologic disorders Lymphocytic and eosinophil esophagitis: autoimmune disorders (eg, celiac disease), lichenoid dermatologic disorders, allergic reactions (drugs and foods), systemic diseases with eosinophilic, motility disorders, neoplasms, diabetes | |

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lichenoid dermatologic disorders, allergic reactions including drugs and foods, systemic diseases with tissue eosinophilia, motility disorders, neoplastic lesions, and diabetes (Table 1).37,38 Ancillary techniques including silver and periodic acid–Schiff stains as well as immunostains against herpes viruses, polarized light, and pH monitoring may be used to identify infectious agents to detect birefringent pill fragments, or to verify gastroesophageal reflux, respectively. However, because of the nonspecific nature of the histologic changes and the frequent lack of detailed clinical history, in many cases, a specific diagnosis of esophageal CD cannot be established, and only a diagnosis of “compatible with esophageal CD” can be achieved.

TABLE 1. (continued)

| Crohn’s Disease | Ulcerative Colitis |
|-----------------|-------------------|
| **Stomach**     |                   |
| Active chronic *H. pylori*-negative gastritis or focally enhanced gastritis: undetected *H. pylori* organisms, other infections (eg, syphilitic, CMV), iatrogenic (eg, NSAIDs, iron-pill, immune checkpoint inhibitors, and GVHD) |                   |
| Granulomatous gastritis: infections (mycobacterial, syphilitic, fungal, or parasitic), immunologic (sarcoidosis, chronic granulomatous disease, granulomatous vasculitis), foreign body reaction |                   |
| **Duodenum**    |                   |
| Focally active duodenitis: peptic duodenitis in patients with *H. pylori* gastritis, as well as iatrogenic injury (eg, because of NSAIDs), celiac disease |                   |
| Granulomatous duodenitis: infections, immunologic disorders, and foreign body reaction |                   |

CMV indicates cytomegalovirus; GVHD, graft versus host disease; HPF, high-power field; HSV, herpes simplex virus; IEL, intraepithelial lymphocytes; NSAID, nonsteroidal anti-inflammatory drugs; UGI, upper gastrointestinal.

Stomach
Clinical Aspects
Clinically diagnosed gastric involvement in CD has been reported in 0.5% to 4% of CD patients.12,39 However, histologic changes (ie, focal inflammation) can be detected in approximately half of the patients if esophagogastroduodenoscopy with biopsy is automatically performed as part of the initial diagnostic workup, especially in children.1,4,40–42 Although gastritis is the most common UGI manifestation of CD, an isolated gastric CD is exceedingly rare,39,43 as gastric involvement typically develops in patients with a concurrent duodenal disease (ie, gastroduodenal CD). In the majority of cases, lower GI tract manifestations are also present.2,4 Most cases of gastric CD are paucisymptomatic, but some patients may present with nausea, vomiting, anorexia, postprandial fullness, abdominal pain, UGI bleeding, and chronic iron-deficiency anemia. Symptoms of gastric outlet obstruction may develop in cases with advanced antpyloric stenosis (Table 1).39

Endoscopic Features
Endoscopically, the antral and pyloric regions are the most frequently affected, whereas the body and fundus are less likely involved. Mucosal edema, erosions, ulcers (superficial and deep; aphthoid, linear, and serpentine), nodularity, and more specific changes such as the bamboo-joint-like appearance have been described. In contrast to other gross alterations, Bamboo-joint-like lesions are most common on the lesser curvature of the proximal stomach and are formed by linear fissures that traverse the swollen longitudinal folds. Japanese authors reported that these lesions have a specificity of ~95% and sensitivity of 40% for CD.44,45 In cases with more prominent transmural involvement, mucosal thickening, wall rigidity with reduced peristalsis, and antral or pyloric stricture may complicate the picture. Gastric perforation and fistulas are rare and usually result from adhesions to inflamed ileocolonic segments (Table 1).46 Given the discontinuous distribution of CD, multiple biopsy fragments from both the endoscopically affected and normal-looking areas should be sampled.

Histologic Features
Microscopically, CD usually causes a nonspecific active chronic *H. pylori*-negative gastritis (Fig. 2). *H. pylori*-negative gastritis has been detected in 26% of pediatric CD
patients, compared with just 2% in controls. Rare, particularly pediatric cases can present with an increased intraepithelial lymphocytosis (IEL) and lymphocytic gastritis-like picture. Focally enhanced gastritis (FEG), also known as focally active gastritis, is a special form of gastritis with a focal distribution (Fig. 3, Table 1). FEG has been identified in 43% to 55% of CD patients. The infiltrate primarily consists of lymphocytes and macrophages (sometimes with epithelioid morphology), admixed with various numbers of neutrophils and eosinophils. Although immunohistochemistry is not routinely applied for the study of inflammatory cell types, characteristic perifoveolar or periglandular accumulation of macrophages and T cells can be highlighted by CD68 and CD3 antibodies, respectively. Granulomata tend to be poorly formed and small, but expansive granulomata with giant cells may also be encountered. Yao et al demonstrated that microaggregates of macrophages and epithelioid cells are typical for CD and are not present in patients with UC. Furthermore, such microaggregates (54.5%) were more frequent than granulomas (18.2%) in this series. However, Magalhães-Costa et al reported that microaggregates of macrophages may also be found in patients with UC and in non-IBD controls, and their presence was almost exclusively associated with H. pylori infection. In addition, lymphoid aggregates, fibrosis, and epithelioid granulomas may also occur. Similar to esophageal involvement, the detection rate of granulomas shows a significant variability (0% to 80%) in the literature and depends on the type of specimen (resection vs. biopsy), methodology of sampling (eg, number of biopsy fragments), and tissue processing (eg, number of histologic sections, use of serial sectioning, or deeper levels). Regarding sampling, both grossly affected and unremarkable areas may contain granulomas. However, the frequency of granulomas correlates with the site and endoscopic type of lesion the biopsy targeted. Antral samples are more likely to contain granulomas than those from the body. According to publications largely based on Japanese population, targeting the bamboo-joint-like lesions may offer a relatively high yield of granuloma detection (14.3% to 45.5%), although other authors demonstrated contradicting results.

**Differential Diagnosis**

Regarding endoscopic wall rigidity in advanced cases, gastric syphilis, rheumatologic diseases, amyloidosis, as well as diffuse gastric cancer, and lymphomas may be considered. In addition to IBD-related cases, H. pylori-negative chronic active gastritis may represent a H. pylori gastritis in which the organisms remain undetected because of the masking effect of antibiotic and proton pump inhibitor therapy, inadequate sampling, or suboptimal staining. Consequently, immunohistochemistry is recommended to exclude the presence of rare H. pylori bacteria undetectable on hematoxylin and eosin stains. We should also keep in mind that gastric CD may also coexist with H. pylori gastritis. Alternatively, H. pylori-negative chronic active gastritis may be caused by etiologic factors unrelated to H. pylori organisms, including other infections (eg, syphilitic, fungal, and cytomegalovirus gastritis) and iatrogenic causes (eg, nonsteroidal anti-inflammatory drugs, immune checkpoint inhibitors, and graft vs. host disease). Similarly, while the FEG pattern has been
described in a high percentage of CD patients, it may develop in a myriad of other conditions (Table 1). In adults, the positive predictive value of FEG for IBD is only ~5%. Conversely, in the pediatric setting, the positive predictive value of FEG is ~30%. Therefore, when FEG is seen in the absence of *H. pylori* infection, the pathology report may include a comment about the possibility of IBD, especially when the presence of macrophage microaggregates or epithelioid cells has been noted and in the pediatric setting.

More than 50% of North American granulomatous gastritis cases are related to *H. pylori*. Among the other diseases that can present with gastric granuloma are mycobacterial, syphilitic, or fungal infections, parasites, sarcoidosis, chronic granulomatous disease, granulomatous vasculitis, and foreign body reaction. Gastrointestinal tuberculosis typically affects the ileocecal region, while gastric involvement is only reported in ~6% of cases. Similarly to CD, the prepyloric and antral regions are the most frequently affected. However, the endoscopic presentation is typically different, with most cases of gastric tuberculosis exhibiting a large, nonhealing ulcer or a submucosal mass. Unfortunately, the epithelioid granulomata do not always harbor the distinguishing histologic feature of caseous necrosis. Given its superior sensitivity, if available, polymerase chain reaction analysis should be preferred over the labor-intensive but frequently unrewarding examination of acid-fast stains.

**Duodenum**

**Clinical Aspects**

Duodenal manifestation of CD is uncommon, with ~2% to 4% of all adult CD patients diagnosed clinically with such a complication, while jejunal manifestations develop in 4% to 10% of patients. However, studies of pediatric patients that also included asymptomatic cases with endoscopically unremarkable duodenum have reported a high frequency (28% to 48%) of microscopic alterations with questionable clinical implications. Isolated involvement of the duodenum is unusual in CD, and typically, duodenal manifestations are part of a more extensive gastroduodenal or duodenojejunal CD. Most frequently (32%), the bulbular (proximal) duodenum is affected together with the antral and pyloric regions of the stomach. A smaller number of patients (18%) present with distal duodenal involvement that tends to be accompanied by jejunitis. A retrospective study of Nugent and colleagues reported that almost one-third of patients with duodenal CD had an already established history of IBD, while in more than half of the patients, the stomach manifestation was diagnosed synchronously with lower GI tract disease. Isolated (at the time of diagnosis) gastroduodenal disease was only identified in 17% of patients. Altogether ~90% of patients developed lower GI tract involvement during the study period. The clinical symptoms show considerable overlap with gastric CD. The rare complication of bulbular stenosis may lead to delayed gastric emptying and the so-called “rum’s horn” sign, while duodenopancreatic fistula and the fibrotic stenosis of the ampulla can cause refractory abdominal pain and acute or chronic pancreatitis (Table 1).

**Endoscopic Features**

Duodenoscopy may reveal focal mucosal edema, hyperemia, and friability, as well as aphthoid, circular, or longitudinal erosions and ulcers. Mucosal cobblestoning and notched appearance of the duodenal Kerckring’s folds are more distinctive of CD. The diagnostic specificity of the notched sign is 94%; however, the sensitivity is only 10% (vs. 1.5% in UC). In cases with transmural disease and fibrosis, there may also be signs of duodenal stenosis with reduced distensibility, rigidity, and luminal narrowing. Another relatively specific endoscopic feature is the presence of longitudinally arranged protruding lesions designated as “rosary-like protuberant lesions” (Table 1).

**Histologic Features**

Similar to other segments of the upper GI tract, the histologic findings of duodenal CD are frequently non-specific. Most cases show focal crypt inflammation with various degrees of villous blunting and increased IELs. Many cases with increased IEL show a retained villous architecture (Table 1). Although more than 15% of duodenal CD cases have been reported to show increased IEL, according to Patterson and colleagues, only 5% of patients with increased IEL have CD. In contrast to the de crescendo pattern of celiac disease, the intraepithelial T cells are usually evenly distributed from the top of the villi to the base of the crypts. In many cases, foveolar metaplasia is also detected. Foveolar metaplasia has long been documented in various forms of duodenitis, including peptic injury, while pseudopyloric metaplasia is used as a sign of chronic ileitis. However, recently it was recognized that foveolar metaplasia is not specific to the UGI tract, and both forms of gastric metaplasia may develop in ileal Crohn’s disease.

Epithelioid granulomas are present in approximately one-third of the cases (range: 0% to 49%) and are more distinctive of CD. The diagnostic specificity of the notched sign is 94%; however, the sensitivity is only 10% (vs. 1.5% in UC). In cases with transmural disease and fibrosis, there may also be signs of duodenal stenosis with reduced distensibility, rigidity, and luminal narrowing. Another relatively specific endoscopic feature is the presence of longitudinally arranged protruding lesions designated as “rosary-like protuberant lesions” (Table 1).

**Differential Diagnosis**

The differential diagnosis of duodenal CD includes other causes of active duodenitis, aphthous erosions, increased IEL, and villous blunting. Peptic duodenitis in patients with *H. pylori* gastritis, as well as iatrogenic injury [eg, because of nonsteroidal anti-inflammatory drugs (NSAIDs)], can also induce active duodenitis with limited villous blunting, foveolar metaplasia, and increased IEL (Table 1). Hardee and colleagues compared the histologic alterations of duodenal involvement in pediatric IBD to various other etiologic types of duodenitis and aimed to identify the microscopic features that are characteristic of duodenal CD. Excluding granulomas (that have a low sensitivity), focal active duodenitis with cryptitis was the most distinctive feature of IBD, whereas significant IELs, especially with severe villous blunting was significantly more common in celiac disease. Patients with CD may have positive tissue transglutaminase and deaminated gliadin peptide serology tests. This false-positive result, in combination with increased IELs, may be a possible diagnostic pitfall. However, these patients do not show susceptible HLA haplotypes. Similar to other UGI segments, the presence of granulomatous inflammation has its own differential diagnostic considerations. The typical CD-related granulomata are small and poorly formed, whereas large necrotizing granulomata are more characteristic for infectious etiologies, including GI tuberculosis.
interpreted to favor the diagnosis of CD in patients with indeterminate colitis. However, the classic doctrine of CD being able to affect any part of the gastrointestinal tract whereas UC being restricted to the colon has been challenged by an increasing body of literature reporting on gastroduodenal lesions in adult patients with UC. Nevertheless, our knowledge regarding the UGI manifestations of UC is still limited compared with CD (Table 1).

**Esophagus**

Most of our knowledge regarding esophageal manifestations of UC is based on studies of pediatric patients, but case reports of adult patients were also published. Unfortunately, these data are hard to interpret, given the nonspecific morphology of esophageal UC, the absence of granulomatous inflammation as a possible confirmatory tool, and the methodological issues concerning how other inflammatory disorders were excluded. Some publications reported that esopagitis is not more common in patients with UC compared with controls in adult populations.

**Stomach**

Gastritis is the most common manifestation of UGI UC, with endoscopic lesions detected in up to 8% and histologic changes in approximately a third of the patients. Most patients with gastric manifestations of UC are asymptomatic, while most symptomatic cases are associated with severe pancolitis or develop in a postcolectomy setting (see also in the section regarding Ileal Pouch-Anal Anastomosis-related diseases).

Endoscopically, the majority of UC-associated gastritis is characterized by nonspecific erythema and mucosal friability. Aphthous erosions and bamboo-joint-like structures are commonly regarded as specific features of gastric CD; however, these lesions can also be encountered in ~5% to 10% of UC cases.

According to Lin et al, there are 3 distinct patterns of gastritis that occur more frequently in UC patients than in controls, including FEG (UC: 29%; controls: 9%), basal mixed inflammation (UC: 22%; controls: 8%), and chronic superficial *H. pylori*-negative gastritis (UC: 20%; controls: 6%). Although the frequency of FEG in UC patients is estimated to be somewhat lower (~20% to 30%) than that of CD patients (~50%), the presence of FEG cannot be used to distinguish CD from UC. Ushiku and colleagues reported a series of 57 pediatric UC cases with upper and lower gastrointestinal biopsies, with 30% of the patients showing evidence of FEG compared with the 55% of the CD group and only 5% of controls. The total number of glands involved in each FEG focus was higher in UC than in CD cases. There was no correlation between FEG and other gastrointestinal findings of UC.

As all 3 patterns of UC-related gastritis are nonspecific, its diagnosis should always include correlation to the clinical and endoscopic presentation as well as the exclusion of alternative etiologic factors. Similar to CD, the association of FEG with previously, concurrently, or subsequently diagnosed classic lower GI tract disease is more common in the pediatric population compared with adults. In a case showing a FEG pattern, the clinical history is helpful to exclude iatrogenic causes such as graft versus host disease or immune checkpoint inhibitor therapy. The possibility of *H. pylori* gastritis should always be entertained, and exclusion by immunohistochemistry is recommended. Compared with gastric CD, the presence of granuloma is exceedingly rare.

**Duodenum**

The reported frequency of histologically detectable duodenitis is 3% to 10% in adult UC patients, but a higher prevalence (up to 29%) has been documented in the pediatric population. Similar to UC-related gastritis, the vast majority of patients with clinically detected UC-associated duodenitis have been previously diagnosed with severe colonic UC, usually with a pancolitis phenotype that required colectomy. Furthermore, diffuse chronic duodenitis in UC patients who have colectomy is suggested to be a strong predictor of pouchitis.

Endoscopy usually reveals mucosal hyperemia, edema, friability, granularity, and multifocal erosions with a predominantly diffuse pattern. Although considered a feature indicative of CD, luminal narrowing has also been reported in rare cases of UC-related duodenitis.

Histologically, UC-related duodenitis is characterized by diffuse mucosal lymphoplasmacytic infiltration with increased eosinophilic and variable neutrophilic infiltration in the lamina propria, cryptitis, crypt abscesses, and architectural distortion (Fig. 4). Foveolar metaplasia may also develop, albeit less frequently compared with duodenal CD. On the basis of the series of Lin et al, diffuse chronic duodenitis is the only unique UGI inflammatory pattern that occurred only in UC patients and not in controls. Increased IEL may also be detected, especially in pediatric patients, and it is significantly more common in UC-associated duodenitis compared with CD-related cases.

**FIGURE 4.** Diffuse active chronic duodenitis in a patient with ulcerative colitis. In contrast to the usually focal cryptitis associated with Crohn’s disease, the inflammatory infiltrate shows a diffuse distribution (A). Similar to colonic ulcerative colitis, crypt architectural distortion with various degrees of active inflammation, including cryptitis and crypt abscesses, are mainstay histologic features of the duodenal manifestation. Usually, numerous eosinophil granulocytes can also be noted (B). Please see this image in color online.
The diagnosis of duodenal UC should be primarily entertained in patients with a history of severe pancolitis, colectomy, and recurrent pouchitis. Otherwise, the diagnosis of UC-related duodenitis might prove extremely difficult because of the nonspecific nature of the morphological changes.

Inflammatory Bowel Disease in Patients With Ileal Pouch-Anal Anastomosis

Overview

IPAA surgery creates a unique anatomic situation that subsequently modifies many physiological processes of the gastrointestinal tract. IPAA procedure is an effective treatment for a variety of diseases, including inflammatory colitides and cancer predisposition syndromes (eg, familial adenomatous polyposis). UC is the most common indication (88%) for IPAA surgery\(^{95,96}\) and is mainly performed in 5 settings: (1) severe acute colitis unresponsive to medical treatment; (2) chronic disease refractory to medical therapy; (3) patients who fail to tolerate medical treatment; (4) dysplastic or carcinomatous transformation; and (5) in pediatric cases with failure to thrive.\(^{97,98}\) Although CD only accounts for a minority (1%) of IPAA procedures, the rate of pouch failure (10%) is not significantly different from that in UC\(^ {99,100}\) and IPAA is increasingly used in the setting of CD, indeterminate colitis, and IBD-U.\(^ {100,102}\) Nevertheless, in patients with CD undergoing intentional IPAA, the risk of developing recurrent CD of the pouch is high (41% to 64%), and long-term medical therapy and future surgical interventions are frequently needed.\(^ {97,98}\) Therefore, IPAA can only be offered for carefully selected CD patients without terminal ileal and perianal involvement, who are motivated to maintain intestinal continuity and can accept the risk of increased pouch-associated morbidity.\(^ {102}\)

Patients who underwent IPAA surgery can develop a range of distinctive inflammatory complications that can be classified according to the bowel segment that the process involves. Inflammation involving the ileum proximal to the pouch is labeled as prepouch ileitis. Pouchitis affects the small intestine-derived part of the pouch, while the involvement of the remnant rectal mucosa is designated as cuffitis (Fig. 5).

Pouchitis

Pouchitis can be clinically categorized as antibiotic-responsive, antibiotic-dependent, and antibiotic-refractory. The incidence of pouchitis is significantly higher in patients who undergo IPAA surgery for UC than that of patients with familial adenomatous polyposis. The estimated incidence of at least one pouchitis episode in post-IPAA UC patients is \(\sim 50\%\) \(^ {103}\) while up to \(\sim 5\%\) to \(\sim 10\%\) of these patients develop pouch failure and require pouch excision.\(^ {104,105}\) The etiology of pouchitis is enigmatic, with likely a combination of genetic factors, alterations in host immunologic function, and microbiota contributing to the pathogenesis.\(^ {106}\) The significantly higher rate of pouchitis in UC patients suggests that relapsing cases of pouchitis might represent the recurrence of UC in the pouch mucosa. Because of the frequent loss of specific small bowel histologic features, including villous atrophy and crypt hyperplasia, a theory of mucosal adaptation-related colonic transformation (ie, colonic metaplasia) was proposed.\(^ {107}\) Histochemical studies, including high iron diamine-alcian blue stain of pouch mucosal mucin, demonstrated a change from small intestinal mucin to colonic mucin.\(^ {108}\) This phenomenon suggests that a possible explanation regarding the pathogenesis of pouchitis is that it enables the recurrence of UC in the small intestinal mucosa because of its shift toward a colonic phenotype. In contrast, many cases of pouchitis respond to antibiotic treatment, which raises the possibility of infectious etiology, at least in some cases.\(^ {109,110}\) The manifestation of other specific diseases (eg, CD of the pouch, prolapse changes, and ischemic or drug-induced enteritis) in the pouch mucosa are not considered pouchitis.

Villous architecture abnormalities and increased lymphoplasmacytic inflammation are considered mainstay features of mucosal adaptation in the ileal pouch, and such changes should not be regarded as evidence for pouchitis. Pouchitis usually presents histologically as a chronic active inflammation with cryptitis, crypt abscesses, erosion, ulceration, crypt distortion, and basal plasmacytosis (Fig. 6A).\(^ {110}\) Occasionally, transmural inflammation, fissures, fistulas, strictures, and even granulomatous inflammation can occur in the pouch of patients with UC. Granulomatous transformation of lymphoid follicles and Peyer’s patches is a particularly common phenomenon (Fig. 6B). These histologic changes could raise the possibility of CD involving the pouch mucosa. In such cases, the histologic picture must be correlated to the previous biopsies and resection specimens in order to differentiate pouchitis with transmural inflammation or granulomata from CD. The reclassification of the IBD as CD is not recommended unless pathognomonic features of CD can be identified by reevaluating the prior colectomy and preoperative biopsy specimens. Granulomata in a patient without any evidence of CD may be related to diversion colitis in cases with a multistage pouch procedure, infectious agents, foreign material, or mucin extravasation.\(^ {111}\) Pseudopyloric metaplasia is another characteristic feature of CD that can also develop in the setting of pouchitis, and therefore it cannot be used as a distinctive feature.\(^ {112}\)

Prepouch Ileitis

Prepouch ileitis is defined as histologically confirmed inflammation of the afferent limb of the pouch that can extend proximally to affect the UGI tract.\(^ {113–115}\) Extensive cases have also been referred to as postcolectomy panenteritis, but the disease can sometimes also involve the duodenal and even the
Cuffitis

The clinical symptoms of cuffitis are similar to that of ulcerative proctitis. A cuff length ≥ 20 mm is a risk factor of cuffitis. Inflammation of the surgical cuff represents an etiologically heterogenous group of diseases with therapy responsive and refractory cases. Inflammation of the remnant rectal mucosa not removed at the time of colectomy (ie, cuffitis) may develop concordantly to pouchitis or in isolation.

In cases of isolated cuffitis, recurrent UC should be first considered. Cuffitis usually presents histologically with chronic active inflammation, cryptitis, crypt abscesses, crypt distortion, and basal plasmacytosis. Because of the frequent colonic transformation in pouchitis as well as the irregular surface with villiform change and Paneth cell metaplasia in the cuffitis, the distinction of the cuff and pouch mucosa can become difficult. Therefore, the cuff and pouch mucosa are recommended to be sampled and submitted for pathology examination in separate, labeled containers. Albeit less frequent, Crohn’s disease of the cuff mucosa, infectious conditions, and any miscellaneous form of colitis may develop in the cuff mucosa.

Primary Sclerosing Cholangitis in Patients With Inflammatory Bowel Disease

Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic liver disease affecting the intrahepatic and extrahepatic bile ducts, potentially leading to cirrhosis and liver failure that is associated with IBD in ∼60% to 70% of cases. Usually, the IBD diagnosis precedes that of PSC, although the high rate of asymptomatic patients in both colonic and liver disease may bias data regarding the temporal relationship of the 2 disease components. A recent large meta-analysis of more than 13,000 patients demonstrated a 3-fold increased risk of colorectal neoplasia and cancer among patients with PSC-IBD compared with IBD patients without liver disease. According to the most widely accepted theory, the increased neoplastic risk is related to cholestasis, which favors an altered intestinal bile acid metabolism, and increased production of carcinogenic secondary bile acids by microbiota. The higher rate of asymptomatic and therefore undiagnosed and untreated cases may also contribute to the increased neoplastic risk.

PSC-related IBD (PSC-IBD) is reported to show a usually UC-like but distinct IBD phenotype with an increased incidence of pancolitis (Fig. 7). An association with backwash ileitis and rectal sparing is also frequently but less consistently reported. Despite the higher frequency of

FIGURE 7. The specific phenotype of inflammatory bowel disease (IBD) in patients with primary sclerosing cholangitis (PSC-IBD). PSC-IBD presents more frequently as pancolitis, while the activity is usually not severe and shows a decreasing intensity aborally. Backwash ileitis and relative rectal sparing are also often reported. PSC-IBD patients have a 3-fold increased risk of developing colorectal neoplasm. Please see this image in color online.
pancolitis, the activity of colitis is usually milder and commonly only histologically detectable, with a higher rate of normal endoscopic picture.\textsuperscript{12} Nevertheless, the incidence of pouchitis in patients undergoing IPAA is higher in PSC-IBD compared with classic IBD patients. According to multiple series, the disease activity is typically the highest in the right colon and lowest toward the distal colon.\textsuperscript{12,18,129} Recently, various nonconventional IBD-associated dysplasia types were increasingly recognized, and a frequent association with hypermucinous, crypt cell, and goblet cell deficient dysplasia types has been reported (for more detail, see another review of this special issue: The Significance of Nonconventional Dysplastic Subtypes in Inflammatory Bowel Disease).

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