Clinical Aspects of Idiopathic Inflammatory Bowel Disease

A Review for Pathologists

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Context.—Idiopathic inflammatory bowel disease manifests with different clinical phenotypes showing varying behavior and risk for neoplasia. The clinical questions that are posed to pathologists differ depending on phase of the disease and the clinical circumstances. Understanding the clinical aspects of the dynamic disease process will enhance the role of pathology in optimizing the care of patients with inflammatory bowel disease.

Objective.—To review clinical and surgical aspects of inflammatory bowel disease that are relevant to practicing pathologists.

Data Sources.—The literature was reviewed.

Clinical and pathologic features of idiopathic inflammatory bowel disease (IBD), that is, Crohn disease (CD) and ulcerative colitis (UC), have been extensively studied for almost a century. Also, during the last decade, the incidence and prevalence of IBD has increased in Asian countries. Therefore, there is an increasing need for pathologists with expertise in IBD. Pathology plays an essential role in the clinical care and management of patients with IBD. This begins from the interpretation of the first set of diagnostic biopsies, monitoring the disease activity and detection of colorectal neoplasia on surveillance endoscopic biopsies, to the evaluation of surgical resection specimens. Moreover, histology still remains as the gold standard for IBD-related research. However, the histologic interpretation of these specimens by practicing pathologists requires in-depth knowledge of the clinical aspects of the diseases. Thus, this review seeks to provide the necessary information about the clinical and surgical aspects of IBD to practicing pathologists. It also includes a brief appraisal of IBD in Asian regions and IBD in patients with primary sclerosing cholangitis (PSC), 2 conditions that are not routinely reviewed in pathology literature.

BIOPSY INTERPRETATION

Knowledge regarding the indications and guidelines for endoscopy and tissue sampling will help pathologic interpretation. In this section, we also review the common pathologic findings in IBD as well as normal histology of small and large intestine and mimics of IBD. The concept of histologic mucosal healing, which may potentially serve as a new treatment target in the future, has gained renewed interest.

Endoscopy and Tissue Sampling

Endoscopy and tissue sampling is fundamental in the diagnosis and surveillance of IBD. For initial diagnostic biopsies from patients with possible IBD, at least 2 biopsies from 5 different sites, including terminal ileum and rectum and both diseased and normal-appearing mucosa, should be submitted in separate containers. Patients with chronic constipation or symptoms of dyschezia may show features of rectal prolapse mimicking IBD; therefore, biopsy from the anterior rectal wall is preferred in these patients. Sodium phosphate–based bowel preparations and nonsteroidal anti-inflammatory drugs may induce histologic changes mimicking IBD, and hence should be avoided. In surveillance colonoscopy and ileoscopy, all endoscopically visible lesions as well as each colonic segment are sampled. In pancolitis, 4-quadrant biopsies every 10 cm from the rectum should be taken.
the cecum to the rectum for a minimum of 33 biopsies are performed to screen for dysplasia. In nonpancolitis, the sampling can be limited to the endoscopically or histologically involved segments of greatest extent documented by any colonoscopy. For the distal colon, sampling every 5 cm may be considered because of a greater risk of colorectal cancer in this site.3 Fulminant colitis is a contraindication for colonoscopy; however, flexible sigmoidoscopy may be considered.4

If an upper gastrointestinal (GI) tract endoscopy is performed for suspected IBD, at least 2 biopsies from the esophagus, stomach, and duodenum are performed.3

Histology of Normal Small-Bowel and Colonic Biopsy

Normal small-bowel mucosal biopsies show slender and fingerlike villi. The villi are shorter and broader in the first portion or bulb of the duodenum, and are also shorter in the ileum. Scattered intraepithelial T lymphocytes (about 1 lymphocyte per every 5 epithelial cells) are normally seen in the villi. Paneth cells are situated in the base of the crypts of Lieberkühn. Although intraepithelial lymphocytes may be seen in the crypt and surface epithelium, intraepithelial neutrophils, either in the crypts or villi, are abnormal. The base of the crypt anchors on the muscularis mucosae without intervening inflammatory cells, unless there are lymphoid aggregates/Peyer patches. The lamina propria contains plasma cells, lymphocytes, eosinophils, histiocytes, and mast cells. Lymphoid nodules can be seen in any part of the small bowel. The mononuclear inflammatory cell density in the lamina propria is higher in the duodenum compared with the rest of the small bowel. Submucosal Brunner glands are present in the duodenum, but are absent in the rest of the small bowel. Peyer patches are prominent in the terminal ileum.5

In well-oriented colonic mucosa, the base of the crypt directly anchors on the upper edge of the muscularis mucosae, without intervening inflammatory cells (Figure 1, A), unless there are lymphoid aggregates. The crypts are regularly and evenly arranged without branching, distortion, or dropout. Rectal and sigmoid colon biopsies may show somewhat conspicuous baseline distortion compared with the right colon. For example, 1 to 2 bifurcated crypts are considered normal in these sites.6

Paneth cells are normal components of the small intestine up to the transverse colon. Descending colon, sigmoid colon, and rectum are devoid of Paneth cells.6–8 Pyloric-type mucous glands are absent in the colon.6–8 Surface intraepithelial lymphocytes can be seen, up to 20 per 100 epithelial cells, with a greater degree in the right colon. Lymphoid aggregates are common in colonic biopsies, and the mucosal surface overlying those areas may show marked intraepithelial lymphocytosis. Mononuclear inflammatory cells in the lamina propria are more prominent in the right colon compared with the left, whereas the proportion of goblet cells and muciphages in

Figure 1. A, Normal colonic mucosa. B, Crypt distortion (yellow arrow) and basal lymphoplasmacytosis (red arrow) in chronic active colitis. C, Paneth cell metaplasia (arrow) and unevenly spaced crypts in the left colon. D, Pyloric gland metaplasia (arrow) in the terminal ileal biopsy of Crohn disease (hematoxylin-eosin, original magnification ×100 [A through D]).
the lamina propria increases distally. Bowel preparation may induce mild neutrophilic inflammation in the surface epithelium or focal cryptitis.

**Activity and Chronicity**

Activity refers to neutrophil-induced crypt and/or surface epithelial injury, which includes erosion, superficial ulceration, cryptitis, and crypt abscess. Chronicity refers to histologic features indicative of longstanding mucosal injury and damage of tissue structure. In general, 4 histologic features are used to determine chronicity. First, crypt architectural distortion or crypt branching (Figure 1, B) is a relatively objective criterion with a caveat that crypts of the sigmoid colon and rectal biopsy may appear somewhat distorted and bifurcated in normal states. Also, the biopsy procedure itself may induce artifactual crypt distortion, especially at the base of the crypts near areas sampled without muscularis mucosae. Secondly, basal lymphoplasmacytosis, the separation of the base of the crypts and muscularis mucosa by lymphoplasmacytic inflammation in well-oriented sections, is a feature of chronicity (Figure 1, B). As the evaluation of this feature requires well-oriented sections with intact crypts, this may not always be appreciated in tangentially oriented biopsies or in ulcer beds. Third, the presence of Paneth cells distal to splenic flexure indicates a metaplastic process and suggests chronicity (Figure 1, C). Thus, this feature is useful in left colon biopsies. Lastly, the presence of pyloric-type mucous glands—pyloric gland metaplasia (PGM)—in the ileum or colon biopsy is abnormal and indicates chronic mucosal injury (Figure 1, D). Pyloric gland metaplasia is not specific for CD, but tends to be commonly observed in CD than in UC. Marked mononuclear cell infiltrate in the lamina propria can be seen in ulcer and fulminant colitis as well as in chronic mucosal injury. Therefore, it may be prudent to search for other evidence of chronicity when heavy plasma cell–rich lamina propria infiltrate is encountered. Some pathologists accept sheets of mononuclear cells in the lamina propria as a feature of chronicity. Again, however, it should be kept in mind that the right colon can have prominent lamina propria mononuclear inflammatory cells in the normal state. In the small bowel, unequivocal villous atrophy is a feature of chronicity.

**Lower GI Tract Biopsy of IBD**

When there are both activity and convincing histologic features of chronicity, a histologic diagnosis indicative of these findings, for example, chronic active colitis, is rendered. In CD and surveillance biopsies for UC after treatment, the activity may be focal and the chronicity may not be obvious. Well-controlled IBD biopsies may be unremarkable or show chronicity but no activity indicative of quiescent/inactive colitis. Ileal biopsies in CD may show activity and PGM indicative of chronic active enteritis/ileitis. In pediatric IBD patients, chronicity may not be evident until later in the disease course. Therefore, pediatric patients suspected of having IBD need to be closely followed despite the lack of chronicity in initial biopsies.

**Upper GI Tract Biopsy of IBD**

Crohn disease patients with upper GI involvement may show inflammation, erosion, ulceration, duodenal villous atrophy, mucosal edema, and granulomas. Especially in pediatric CD, esophageal biopsy may show marked intraepithelial lymphocytosis. Duodenal intraepithelial lymphocytosis with intact villous architecture can also be seen in CD. So-called “focal enhanced gastritis” pattern injury can be seen in but is not specific for CD. A subset of UC patients may show esophagitis, gastritis, duodenitis, and intraepithelial lymphocytosis.

**Histologic Differential Diagnosis of IBD**

Although all IBD biopsies demonstrate chronicity at some point of the disease course, not all chronicity equates to IBD. Colitis by other etiologies may show chronicity, mimicking IBD.

**Chronic Infectious Colitis/Enteritis.**—Usually self-limiting infectious colitis does not demonstrate chronicity, and is characterized by heavy neutrophilic infiltrates predominating in the lamina propria. However, indolent colitides caused by infectious agents, such as *Entamoeba histolytica* and intestinal tuberculosis (ITB), may resemble IBD by their well-developed chronicity and granuloma (in ITB). *Yersinia* is another histologic mimic of CD with frequent granulomas. The distinction is important because immunosuppressive therapy may be considered for IBD, whereas it is generally contraindicated in infection. The identification of organisms in the biopsy and isolation or cultivation of the pathogens in the stool specimens confirm the diagnosis. Alternatively, clinical correlation with serologic studies may help to arrive at a correct diagnosis.

**Medication-Induced Colitis.**—Colitis induced by drugs, such as by nonsteroidal anti-inflammatory drugs or mycophenolate mofetil in the posttransplant setting, can mimic IBD histologically. Although chronicity including crypt architectural distortion and Paneth cells in the left colon may be seen in mycophenolate mofetil–associated colitis, the additional pattern of injury, such as crypt apoptosis and isolated crypt damage, may be conspicuous compared with IBD. High index of suspicion and establishing a temporal relationship between the medication use and the onset of clinical symptom are crucial to arrive at a correct diagnosis.

**Chronic Ischemia.**—In chronic ischemia, finding a coexisting typical ischemic pattern of injury such as attenuated crypts in association with hyalinized lamina propria and surface injury may be helpful in differentiating chronic ischemia from IBD. In addition, the degree of active and chronic inflammation tends to be milder in chronic ischemia compared with typical IBD. Conversely, IBD patients are at increased risk for venous thromboembolism due to generalized hypercoagulability. Therefore, ischemic injury may be superimposed on preexisting injury due to IBD.

**Miscellaneous.**—Diverticular disease–associated colitis is another histologic mimic of IBD. In diverticular disease–associated colitis (Figure 2, A and B), the topographic distribution of colitis is in association with diverticular disease. The finding of rectal sparing may also be helpful. Microscopic colitis—lymphocytic/collagenous colitis—may demonstrate IBD-like features with crypt architectural distortion, Paneth cells in the left colon, and conspicuous neutrophilic crypt injury. However, these features tend to be focal. In addition, the predominant pattern of injury is lymphocytic or collagenous colitis with no significant endoscopic disease in microscopic colitis. Of note, IBD patients may display features of microscopic colitis at the onset of the disease or during the follow-up (Figure 2, C). Therefore, the histology needs to be interpreted in conjunction with clinical and endoscopic findings.
Prolapse may result in scarring of the lamina propria and distorted crypts and/or activity, mimicking IBD. Diversion colitis shows diverse histology; it may mimic chronic active UC with crypt architectural distortion and marked mononuclear cell infiltrate, or resemble CD with aphthous lesions and patchy cryptitis. Knowing that the sample is from a diverted segment of colon will be the most helpful. If observed, endoscopic mucosal nodularity may also be helpful in recognizing diversion colitis (Figure 2, D). Behcet disease is an important differential diagnosis before a diagnosis of CD is made, especially in Asia (see “CD in Asia” below).
Initial Diagnostic Biopsy Versus Surveillance Biopsy

The information that needs to be relayed to clinicians depends on the clinical circumstances. In initial diagnostic biopsies prior to treatment, documenting that chronic injury is present and the distribution of the inflammation (segmental versus diffuse) is relevant. Finding chronicity in the appropriate clinical setting favors IBD over other etiologies, especially infectious colitis. Therefore, in cases with subtle features of chronicity, additional level sections may aid in confirming the chronicity and arriving at a correct diagnosis. The presence or absence of granulomas, patchy inflammation indicative of skip lesions, and ileal involvement are especially informative in diagnosing CD. Accurate assessment of disease distribution prior to the initiation of medical therapy is crucial for the correct classification of CD versus UC. Therefore, it is of utmost importance that the endoscopist biopsy from the entire colon and terminal ileum according to current guidelines during the index endoscopy. On the other hand, the primary goal of surveillance biopsies in established IBD patients is to monitor disease activity and screen for dysplasia and malignancy. The presence or absence of granuloma and dysplasia is routinely documented in surveillance biopsies. In addition, unexpected histologic findings to account for clinical symptoms—for example, superimposed infection, ischemia, or microscopic colitis—may be seen, which may alter the management. One of the well-known causes of refractoriness to treatment in IBD is cytomegalovirus infection. Immunohistochemical stain for cytomegalovirus is more sensitive in detecting viral inclusions than routine hematoxylin-eosin stain, and hence may be indicated in such cases (Figure 2, E). Superimposed Clostridium difficile–associated colitis also not uncommonly complicates the clinical manifestation of IBD patients. Histologic examination may give clues as to the presence of C. difficile–associated colitis (Figure 2, F), and detection of C. difficile toxin gene by polymerase chain reaction in the stool confirms the diagnosis.

Documenting chronicity or distribution of the disease may not be as important in surveillance biopsies as in initial diagnostic biopsies. Chronicity may become inconspicuous, or the biopsy may even be unremarkable in well-controlled IBD biopsies. Furthermore, treatment may alter the distribution of the disease. For example, UC may manifest as skip lesions after treatment. In cases where clinicians request reclassification or confirmation of the diagnosis on mucosal biopsies in established IBD patients, a review of initial systematic diagnostic biopsies prior to treatment may be indicated.

Activity Score and Mucosal Healing

Comprehensive histologic grading schemes are available in the literature to assess the degree of activity, such as the Riley score and the Geboes score. Endoscopic activity grading schemes are also available: for example, Rutgeert score and Lemman score for CD and Mayo score and UC Endoscopic Index of Severity for UC. Endoscopic mild activity refers to the presence of erythema, decreased vascular pattern, and mild friability, and moderate activity refers to marked erythema, absent vascular pattern, friability, and erosions (Figure 3, A). In severe disease, spontaneous bleeding and ulceration may occur. A correlation study between the histologic and endoscopic grading schemes in UC showed that the histologic and endoscopic activity scores of inactive disease and disease with severe activity correlated well, whereas histologic activity was variable in endoscopically mildly to moderately active disease. The assessment of activity is used in monitoring the response to therapy and determining the endpoint—mucosal healing.

Mucosal healing is a known predictor of favorable long-term outcome in both UC and CD, and may potentially alter the disease course. Endoscopic mucosal healing is defined as an absence of friability, blood, erosions, and ulcers in all visualized segments (Figure 3, B), and it has been established as a treatment target in UC. However, histologic mucosal healing is yet to be defined, and its implication and application in clinical practice are to be determined. A recent study showed that histologic mucosal healing, when defined as crypt architectural changes without erosions, crypt abscesses, or neutrophilic infiltration, not only is distinct from endoscopic mucosal healing, but also is a better predictor of clinical outcome. In addition, the overall activity by histologic evaluation during the IBD course appears to be associated with the risk of colorectal neoplasia. Histologic mucosal healing may potentially become a part of outcome measurements of clinical management and clinical trials in IBD in the future.

UC: Clinical Aspects and Variants

The distribution and extent of UC at presentation are predictive of its biology and prognosis, and impact clinical care and surveillance. Pathology is crucial for recognizing atypical forms and proper evaluation of the surgical resection specimens.

UC: Phenotype

Ulcerative colitis is classified into subtypes depending on the extent and severity of the disease at diagnosis. By Montreal classification, E1 is inflammation limited to the rectum (proctitis), E2 is limited to the splenic flexure (left-sided colitis), and E3 is pancolitis. Also, S0 to S4 is assigned by the gastroenterologists depending on the clinical symptoms, including the number of stools per day, systemic symptoms, and serologic inflammatory markers. At diagnosis, 30% to 50% present as distal colitis (proctitis or involvement of the sigmoid colon), 20% to 30% as E2, and 20% as E3. The extent of disease may change; 25% to 50% of distal colitis at diagnosis eventually progress proximally (progressive flare). The extent of disease is also predictive of a likelihood of future colectomy and colorectal cancer.
UC: Cancer Risk and Surveillance

Colorectal cancer risk in UC is cumulative; a meta-analysis showed that the overall colorectal cancer risk is 2% after 10 years, 8% after 20 years, and 18% after 30 years of diagnosis.44 However, a recent population-based study showed that the risk of colorectal cancer in UC substantially decreased during the period of 1999–2008 (relative risk of 0.57) compared with 1979–1988 (relative risk of 1.34), with the overall relative risk of 1.07. The authors postulated that UC may no longer pose an increased risk for colorectal carcinoma as long as there are no additional adverse factors, such as concomitant PSC, long duration of disease, and a young age of onset.45

In general, the surveillance program for UC ensues 8 to 10 years after the diagnosis and every 1 to 3 years thereafter.46 The exceptions to this are UC restricted to the rectum or rectosigmoid colon and patients with coexisting PSC. Patients with proctitis and proctosigmoiditis have little or no increased risk of cancer compared with the general population; therefore, the usual screening program for colorectal cancer for the general population may suffice for these patients.46 The risk of colorectal carcinoma in UC patients with concomitant PSC is 4 times greater than in those without PSC; thus, these patients are subject to annual surveillance at the time of diagnosis.46

UC: Surgery and Pathologic Examination of Surgical Resection Specimen

The symptoms of UC differ depending on the severity of inflammation and the distribution of the disease. Patients with UC generally experience abdominal pain, diarrhea, and rectal bleeding with alternating periods of remission and relapse, and 20% to 30% of the patients eventually undergo colectomy within 10 years of diagnosis.47,48 Indication for surgery is divided into 3 categories. Emergent surgery is performed for life-threatening fulminant colitis unresponsive to medical treatment. Urgent surgery is performed for patients admitted to the hospital with severe UC that is not responsive to intensive treatment. Elective procedures are performed for patients who cannot tolerate maintenance treatment, are refractory to treatment, or have dysplasia or cancer.

Because of the high complication rate associated with pouch procedure during acute inflammation, the emergent and urgent procedures are performed in stages. The first stage is subtotal colectomy with a temporary ileostomy, without removing the rectal stump. After recovery from the first procedure, an ileal pouch–anal anastomosis is created and the ileostomy is closed.49 If the surgery is elective, total proctocolectomy is followed by creation of a pouch. This can be done as a 2- or 3-stage procedure to reduce the risk of pelvic complication.50 In selected patients, total colectomy with ileorectal anastomosis or colostomy with Hartmann procedure may be offered with continued surveillance of the rectum or Hartmann pouch, respectively.51

Typical UC is a mucosa-limited disease without submucosal fibrosis or mural scarring. Therefore, unlike CD colon, UC colon tends to lie flat on the grossing table when opened (Figure 4, A). The mucosal disease usually involves the rectum and extends proximally with sharp or inconspicuous demarcation between the diseased and uninvolved segments. Skip lesions with inflammatory involvement of the cecum or right colon in left-sided colitis, relative rectal sparing, ileal involvement, and deep fissuring ulcers may be seen in atypical forms of UC (see “UC: Atypical Features” below). The disease in typical UC is confined within the mucosa (Figure 4, B). The absence of characteristic histology for CD such as transmural inflammation with transmural lymphoid aggregates and granuloma in an otherwise mucosa-limited chronic active/inactive colitis, in conjunction with clinical history, supports the diagnosis of UC.

UC: Atypical Features

Typical UC involves the rectum and extends proximally continuously without skip lesion. However, several atypical features may lead to misdiagnosis as CD.

Skip Lesions and Rectal Sparing.—Treated UC patients may show patchy disease with rectal sparing and skip lesions. Similarly, left-sided or rectal UC may have a skip lesion involving the cecum—referred to as cecal patch, appendiceal orifice inflammation, or periappendiceal red patch—or have inflammation in the right colon, mimicking CD. The clinical features of UC with skip lesion do not differ from those of conventional UC without skip lesion.50,53 In resection specimens for UC, discontinuous appendiceal involvement as a skip lesion is identified in 12% to 86% of patients (Figure 4, C).54–56 Earlier studies suggested that appendiceal involvement as a skip lesion is indicative of active disease; however, the findings were not validated in subsequent studies.52,53 In the study of Glickman et al,12 22 of 73 pediatric UC patients (30%) presented with relative or complete rectal sparing in pretreatment biopsy, and patchy disease was seen in 15 patients (21%). Fulminant UC may show rectal sparing and linear deep ulcers, resembling CD.59,60

Granuloma.—It is well known that not all granulomas are indicative of CD. Typical Crohn granuloma is well formed and epithelioid, and is preferably situated away from injured epithelium. In UC, granulomas can be formed secondary to epithelial injury such as that seen next to a ruptured crypt or underneath erosion. These epithelial injury–associated granulomas are loosely formed in proximity to damaged crypts or eroded surface (Figure 4, D); mucin or neutrophils may be seen within the granuloma. Deeper levels may demonstrate direct association of epithelial injury with granuloma in equivocal cases.

Upper GI Tract Involvement.—Lin et al61 reported intense focal gastritis, mixed basal inflammation, and superficial plasmacytosis in 17 (29%), 13 (22%), and 12 (20%) of 59 gastric biopsies from UC patients, respectively, as well as duodenal involvement. Another study also reported focally enhanced gastritis in 6 of 27 UC patients (22%) without Helicobacter pylori.62 In the study of Lin et al,61 4 patients with diffuse chronic duodenitis developed pouchitis (see definition, see “Pouchitis” below). Some UC patients may show duodenal intraepithelial lymphocytosis without villous blunting, similar to that seen in CD.63

Backwash Ileitis.—Backwash ileitis refers to ileal involvement of UC secondary to incompetence of the ileocecal valve, usually in the context of pancolitis. The prevalence of backwash ileitis was reported to be 17% (34 of 200 UC patients).63 The major differential diagnosis of backwash ileitis is ileal CD. Although there are no standardized diagnostic criteria, the degree of inflammation and villous blunting tends to be milder in backwash ileitis of UC compared with that of CD.11,65,64 Conversely, if the length of involved ileum is more than 5 cm, with significant submucosal inflammation, granuloma, crypt architectural distortion, and fissure formation, it possibly represents CD involving the ileum. Backwash ileitis does not appear to
pose an increased risk for pouchitis after ileal pouch–anal anastomosis, dysplasia, or carcinoma.46,63,65

**CD: CLINICAL ASPECTS AND VARIANTS**

Accurate assessment of the distribution of CD at presentation prior to treatment is important for prognostication and management. Colonoscopic surveillance is recommended for a subset of patients with CD.

**CD: Phenotype**

In the Montreal modification of the Vienna classification, the phenotype of CD is classified per the age of onset (A1, ≤16 years; A2, 17–40 years; A3, >40 years), location (L1, terminal ileum; L2, colon; L3, ileocolon; L4, upper GI), and behavior (B1, nonstricturing, nonpenetrating; B2, stricturing; B3, penetrating), with a modifier p for perianal disease. The B2 and B3 classifications are considered complicated behavior.40

Recently, a large-scale population-based study was performed on 306 CD patients in a Midwest county in the United States.66 In this report, common phenotypes at diagnosis were A2 (56.2%; 172 patients) and L1 (45.1%; 138 patients), followed by L2 (32%; 98 patients) and L3 (19%; 57 patients). The most common behavior at diagnosis was B1 (81.4%; 249 patients). However, at 20 years after diagnosis, 50.8% of noncomplicated (B1) patients experienced complicated behaviors (stricturing or penetrating; B2 or B3). Presence of ileal disease and perianal disease at diagnosis appears to be a risk factor for intestinal complications.66,67

Similar studies on Swedish and European populations reported predominance of L2.68,69 Although the behavior frequently changes during the course of disease, the location remains relatively stable.67,70,71

**CD: Cancer Risk and Surveillance**

Unlike UC, in which the cancer risk is cumulative, colorectal cancer risk in CD is not well established, possibly because of confounding factors including variable anatomic involvement and chemoprevention.46,72 Nevertheless, colorectal cancer risk in CD appears to be comparable with that in UC, particularly when there is colonic involvement, with an estimated overall relative risk of 2.5. By meta-analysis, the relative risk is estimated to be 4.5 for colonic CD and 1.1 for ileal CD.46,72 There is substantial evidence that small-bowel CD poses an up to 27 times increased risk for small-bowel cancer. The risk was suggested to be higher for ileal CD.46,73 In addition, malignancy arising in association with perianal fistulas has been reported, of which 59% (36 of 61 cases) were adenocarcinoma and 31% (19 of 61 cases) squamous cell carcinoma.74
Although there are no randomized clinical trials showing benefit of surveillance in Crohn colitis, surveillance colonoscopy is recommended by many groups, usually for CD involving more than 1 segment of the colon and/or at least one-third of the colon.1,46

**CD: Surgery and Pathologic Examination of Surgical Resection Specimen**

The clinical course of CD is variable. A subset of patients experience intermittent attacks of mild or bloody diarrhea, fever, and abdominal pain similar to that seen in UC. Some may develop malabsorption, malnutrition, protein loss, and hypoalbuminemia secondary to small-bowel involvement. Crohn disease patients may develop intestinal complications requiring surgery; most of the patients undergo operation at least once, with variable indications including fistula formation, obstruction, mass/abscess formation, and medical intractability.75-79 Forty-four percent undergo surgery in the first year of diagnosis, indicative of the aggressive clinical course in the initial phase of CD. By 10 years after diagnosis, 71% to 83% of the patients have undergone surgical intervention.76-77 Ileal and ileocolonic CD and CD with perianal disease increase the probability for resection.75,78,79

About 70% and 30% of patients, respectively, experience endoscopic and clinical recurrence of CD 1 year after surgery, requiring reoperation in some patients.80-83 Smoking, age of onset, sex, family history of CD, location and duration of CD, genetic factors, and the presence of fistula or perianal disease influence the development of postoperative recurrence.75,83

Crohn disease is characterized by segmental submucosal and mural inflammation and fibrosis. Therefore, the gross specimen tends to be rigid and maintains a tubular structure on the grossing table when opened (Figure 5, A). The bowel wall is usually thickened. Creeping serosal fat, fistula, stricture, and mucosal longitudinal linear ulcer with transverse ulcer (cobblestone appearance) may be seen. Microscopically, CD demonstrates transmural plasma cell–rich inflammation, transmural lymphoid aggregates, scarring of the submucosa, and hypertrophy and fibrosis of the muscularis propria (Figure 5, B). Neural hypertrophy is a common finding. The overlying mucosa may show chronic active/inactive enteritis with PGM and deep fissuring ulcers (Figure 5, C). Granulomas are seen in 30% to 60% of the resections (Figure 5, D).84 The presence of characteristic histology in conjunction with clinical history is diagnostic of CD.

**CD: Variant**

Rarely, CD is clinically and/or serologically defined, but the histology resembles that of UC.85-88 This variant, so called UC-like CD, or superficial CD, may be initially
misclassified as UC and subsequently reclassified as CD after pouch complications. Fortunately, this variant is very rare, comprising only 1% of IBD. If unusual features for UC such as segmental disease, absolute skip lesions, granulomas in colectomy, or clinical perianal disease are noted in IBD that otherwise appears to be UC, this variant of CD needs to be suspected.88 James et al89 evaluated 17 proctocolectomy specimens from patients who were reclassified as having CD after pouch complications (UC-like CD) in comparison with proctocolectomy from 18 UC patients without pouch complications. Compared with UC patients without pouch complications, the patients with UC-like CD were 13 years younger and tended to show more severe proximal disease, active ileitis, and appendicitis, with conspicuous neutrophils in the lamina propria. Typical Crohn granulomas and transmural inflammation away from ulcer were not identified in either group. Compared with classic CD patients, UC-like CD patients were younger, and left-sided colitis was more common.86 Studies on pouch outcome in UC-like CD show conflicting results.86–88 This may in part be due to the different criteria used for the diagnosis of UC-like CD, necessitating further study and standardization of the diagnostic criteria.

INDETERMINATE COLITIS

Indeterminate colitis (IC) poses a challenge to clinicians and pathologists. When strict diagnostic criteria are applied, the natural history and outcome of IC appear to be akin to those of UC.

Definition and Incidence

Indeterminate colitis refers to IBD, of which definitive diagnosis cannot be established in the colectomy specimen.90 This is a provisional diagnosis for colectomy only. When mucosal biopsies with overlapping features of UC and CD are encountered, a diagnosis of IBD, unclassified, or of equivocal/nonspecific IBD is recommended.91 Indeterminate colitis comprises about 5% to 10% of IBD, and the most common scenario is fulminant colitis with CD-like features in IBD that otherwise appears to be UC, with severe ulcer, superficial fissure, transmural inflammation, and rarely lymphoid aggregates underneath the ulcer, and relative rectal sparing.

Most IC is classifiable if strict criteria are applied and atypical forms are recognized. Swan et al89 reviewed 95 resection cases of fulminant IC. Of 67 cases with clinical follow-up, 61 cases (91%) were reclassified as either UC or CD. The most helpful and specific histologic features of CD were granulomas and lymphoid aggregates away from the ulcer. In another series, IC had an 80% probability of being CD, whereas in UC, it was 8%.88,91 Several outcome studies suggested that most IC cases behave like UC.86,91 Furthermore, the overall pouch failure rate in IC (20%) is closer to UC (10%) than to CD (30%–60%). Conversely, many presumed IC cases with severe pouch complications turn out to be CD. Therefore, it is generally accepted that IC is probably UC; thus, patients with IC should not be denied a restorative procedure if there is no convincing evidence of CD.17,88,91 A recent microRNA study of IC provided direct molecular evidence that the mRNA profile of IC clustered with that of UC.94

DYSPLASIA AND NEOPLASIA IN IBD

There have been considerable controversies regarding terminology and management recommendations for IBD-related dysplasia. The Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations consensus statement85 endorsed updated recommendations in 2015. Recent studies on the natural history of low-grade dysplasia (LGD) and indefinite for dysplasia (IND) supported that these pathologic diagnoses may potentially serve as a biomarker for IBD progression.

Terminology

Dysplasia is the earliest visible biomarker for neoplastic progression in IBD. The classification system of Riddell et al96 is used for histologic grading of dysplasia in the United States. This system consists of 4 categories—negative for dysplasia, IND, LGD, and high-grade dysplasia—with an overall fair and modest interobserver agreement for negative for dysplasia and high-grade dysplasia, and poorer agreement (higher variability) for LGD and IND.97–99 The IND category is used when the epithelial changes cannot be classified as either negative or positive for dysplasia with certainty. For example, IND may be rendered when coexisting florid acute inflammation, lack of the surface epithelium for evaluation, or processing/technical issues preclude definitive assessment of the epithelial alterations.17 Dysplasia in IBD may be flat, depressed, or polypoid/elevated endoscopically. The endoscopic appearance of dysplasia is clinically relevant because it determines endoscopic resectability and further management. Visibility does not necessarily translate into resectability. For example, a flat dysplastic lesion may be visible or invisible endoscopically; this usually indicates that it may be unresectable endoscopically. Polypoid/elevated lesions are usually visible, but may be endoscopically unresectable depending on the size and boundaries. With recent advancements in endoscopic technologies, most dysplasia in IBD is visible.95

In previous clinical practice, the terms adenoma-like and non–adenoma-like were used to imply endoscopic resectability by endoscopists. Similarly, in pathology practice, the terms adenoma-like dysplasia-associated mass or lesion and non–adenoma-like dysplasia-associated mass or lesion have been used.46,100,101

In the 2015 Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) statement, these terms were abandoned and more descriptive terms were recommend- ed (Table). In the statement, the term endoscopically resectable indicates that the lesion has distinct margins and appears to be completely removed on visual inspection after endoscopic resection, histology confirms the complete removal of the lesion, and there is no dysplasia in the mucosa adjacent to the lesion.95
Management of Polypoid Dysplasia

Attempts have been made to distinguish IBD-related polypoid dysplasia (Figure 6, A and B) from sporadic adenoma based on clinical, pathologic, and molecular features. However, from a management standpoint, this distinction may not be of significance, because polypoid dysplasia that is amenable to endoscopic resection is completely removed endoscopically regardless of the nature of the polyp. Confirmation of negative polypectomy margins and an absence of dysplasia in the adjacent flat mucosa are critical. Subsequent surveillance intervals may vary depending on the polyp size, appearance, and degree of fragmentation on retrieval. Colectomy is not indicated for such lesions.

Most of the data regarding natural history of polypoid dysplasia have been generated from UC patients. Comparable studies on CD are scarce, because surveillance colonoscopy is limited to patients with colonic involvement. Quinn et al evaluated outcomes of polypoid (adenoma-like) dysplasia in the colon in 50 patients with CD. The authors showed that polypectomy and continued surveillance may be a safe option regardless of the site of the dysplasia (within or outside the field of previous or concurrent colitis), similarly to UC.

Management of Nonpolypoid Dysplasia

Traditionally, colectomy has been performed for invisible high-grade dysplasia in flat mucosa (Figure 6, C) because of high risk of synchronous colorectal carcinoma and progressive disease. The management for invisible LGD, which may resemble colonic tubular adenoma (Figure 6, D), or LGD with unusual morphology such as hypermucinous, traditional serrated adenoma-like, and eosinophilic LGD with few goblet cells (Figure 7, A through C) has been a matter of debate. A meta-analysis study reported that 22% of invisible LGD harbored synchronous colorectal carcinoma on immediate colectomy. However, emerging evidence suggests that, using more advanced technology such as chromoendoscopy or high-definition white-light colonoscopy, about 90% of dysplasia in IBD is indeed visible. Therefore, the 2015 SCENIC consensus recommends that patients with endoscopically invisible dysplasia—biopsies with unexpected dysplasia that was not visible on endoscopy—that is confirmed by a GI pathologist should be referred to an endoscopist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy. If the dysplasia becomes visible on repeat higher-resolution endoscopy, and is deemed amenable to endoscopic resection, complete endoscopic resection followed by surveillance may be offered (see below). If the dysplasia remains invisible despite use of the newer technique by IBD experts, the decision to undergo colectomy versus continued surveillance in these patients should be individualized.

For nonpolypoid dysplasia that is visible and endoscopically resectable, complete endoscopic resection and surveillance colonoscopy is recommended by the 2015 SCENIC consensus. However, this recommendation is conditional with a lesser degree of agreement among the panelists, because the possibility that nonpolypoid dysplasia may carry a higher risk of colorectal cancer than polypoid dysplasia is acknowledged. Other recent guidelines have suggested colectomy for such lesions given the difficulty in achieving complete endoscopic resection.

Natural History of LGD and IND

There are conflicting study results regarding the risk of neoplastic progression of LGD, and little is known about its natural history. In a recent prospective study of LGD in UC, 42 patients with LGD were followed with intensive surveillance. Eight patients (19%) progressed to higher-grade lesion, whereas 27 (64%) regressed and 7 (17%) had persistent LGD during 4-year follow-up. This study also showed that patients with 3 or more LGD at a single colonoscopy were at increased risk for progression.
A few recent outcome studies addressed the natural history of IND. The authors reported a progression to a higher-grade lesion in 15% (13 of 84) and 25% (18 of 71) during the mean follow-up of 28 and 99 months, respectively, supporting that IND is a biomarker for neoplastic progression, thus warranting close follow-up in a subset of patients.46,108,109

**Unconventional Precursor Lesions**

Although uncommon, serrated lesions resembling conventional hyperplastic polyp or sessile serrated polyp may be detected in IBD patients (Figure 7, D). Serrated lesions may be associated with neoplastic progression in IBD; some have been reported to be associated with invasive adenocarcinoma.110 However, data are limited and further investigation is needed for characterization.95,110–112 Patients with sessile serrated polyp–like lesions in the diseased colon should have repeat colonoscopy in 1 year following complete removal of the lesion (W. E. Jackson et al, unpublished data, 2015). In addition, villous hypermucinous mucosa harboring K-RAS mutation and very well-differentiated adenocarcinoma with low-grade dysplastic precursor lesions have been described in IBD.113,114 Thus, this type of epithelial change poses great diagnostic challenges to practicing pathologists. In such cases, consultation from GI pathologists with extensive experience may be helpful.

**Pathologic Characteristics of IBD-Associated Colorectal Adenocarcinoma**

Pathologic differences of adenocarcinomas arising in association with IBD compared with sporadic colorectal adenocarcinoma (CAC) have been reported. Synchronous carcinomas are common (20%–27%) in IBD-associated carcinoma.115–119 There are conflicting reports as to whether the IBD-associated CACs are evenly distributed or less frequent in the right colon.115,119,120 Microscopically, mucinous and signet-ring cell carcinomas are overrepresented in IBD.119,121,122 Also, IBD-associated carcinomas may show features of microsatellite instability–high tumors, such as Crohnlike lymphoid reaction, lack of tumor necrosis, and heterogeneity in histology; however, this resemblance is independent of microsatellite instability status.119 A subset of IBD-associated CACs is very well differentiated with bland cytology and inconspicuous desmoplasia, without obvious high-grade dysplastic precursors.114,120 The incidence of low-stage CAC (stage I–II) in IBD patients appears to be on the rise, possibly because of increased surveillance.120
POUCHITIS

Restorative proctocolectomy with ileal reservoir formation is the procedure of choice for UC and familial adenomatous polyposis. Pouchitis is an idiopathic inflammatory condition of the pouch, and is the most common pouch complication in UC, but is rare in familial adenomatous polyposis. The cumulative incidence of pouchitis in UC is reported to be up to 50%. Chronic antibiotics-refractory pouchitis is one of the causes of pouch failure.

Variable histologic features were postulated to predict development of pouchitis, such as backwash ileitis, pancolitis, duodenitis, and appendiceal inflammation and ulcer, with conflicting results.

The Pouchitis Disease Activity Index score and St. Mark’s Hospital criteria are available for the diagnosis of pouchitis, and the latter is being used in the United Kingdom. However, there are no standardized or widely used criteria in clinical practice in the United States. Rather, the diagnosis of pouchitis is rendered by a combination of clinical presentation, nutritional status, involvement of small bowel and upper GI tract, endoscopic findings, and pathology.

Histologic findings aid in the differential diagnosis of pouchitis, prepuce ileitis, cuffitis, CD, dysplasia, and cancer. Endoscopic biopsies usually consist of samples from the prepuce ileum, pouch mucosa, and anal canal (rectal) cuff, which are most often submitted separately. Documenting the degree of mucosal inflammation, PGM, presence of granuloma, and viral inclusions and the presence of dysplasia or neoplasia is informative. Of note, finding of granuloma, PGM, or fistula in pouch biopsy does not necessarily equate with CD.

IBD IN PSC

Inflammatory bowel disease in PSC patients appears to represent a distinct subgroup with clinicopathologic characteristics that are different from those of IBD without PSC. Inflammatory bowel disease associated with PSC confers a significantly higher risk for colorectal cancer, requiring surveillance colonoscopy at diagnosis.

Prevalence and Phenotype

The prevalence of IBD in PSC is as high as 60% to 80% in Western countries, of which 80% of cases are UC, 10% are CD, and the remainder are IC. On the other hand, 2% to 7.5% of IBD patients develop PSC. The association between PSC and IBD appears to be less strong in Eastern countries, with reported prevalence of IBD in 20% to 32% of PSC patients.

According to the population-based cohort study of 579 PSC patients performed in the Netherlands, 207 of 287 PSC-UC patients (83%) had pancolitis (E3), whereas 32
(13%) had left-sided colitis (E2), and 9 (4%) had proctitis (E1). Among 78 PSC-CD patients, 53 (72%) had colitis (L2), whereas 17 (23%) had ileocolonic (L3) and only 4 (5%) had ileal CD (L1). This study validates previous reports that IBD in association with PSC tends to present with extensive colon involvement, representing a distinct phenotype.133–137

**Clinicopathologic Characteristics**

Several studies reported clinicopathologic differences of PSC-IBD compared with IBD without PSC, including a higher frequency of rectal sparing, backwash ileitis, and heavier inflammation in the right colon, albeit milder degree of overall activity.133,137–139 In the report of Sano et al,138 11 (55%) of 20 PSC-IBD patients showed right-sided colitis on colonoscopy, and 13 (87%) of 15 showed right-side–predominant inflammation on histologic examination. On the other hand, some authors reported tendency for pancolitis in PSC-UC, and no statistically significant difference in the frequency of rectal sparing and backwash ileitis, using stricter histologic definitions.134 In keeping with recent findings,134 one population-based cohort study reported that backwash ileitis and rectal sparing were rare in PSC-UC.132

These discrepancies may be due to study population, geographical location, disease presentation, and definition of pancolitis, backwash ileitis, and rectal sparing. For example, colitis preceding PSC showed a higher frequency of pancolitis whereas IBD following PSC showed a predilection for right-sided colitis.139 Clinically, findings of endoscopic relative or absolute rectal sparing and predominance of inflammation in the right colon in patients with multifocal biliary stenosis on magnetic resonance cholangiopancreatography may be supportive of PSC diagnosis, negating the need for invasive procedure such as endoscopic retrograde cholangiopancreatography.130

**Cancer Risk and Surveillance**

Patients with PSC-IBD have a 4- to 10-fold increased risk for CAC compared with patients with UC without PSC.142,143 The risk of developing CAC is 3 times higher than that of patients with UC.144 Family history of IBD is less frequent among IBD patients in Asia than in the West.144–147 In PSC-IBD patients, CAC is diagnosed at younger age, is more common in the right colon, and tends to be of advanced stage at detection.140–142 Liver transplantation does not appear to reduce either CAC risk or disease activity in this population.137,143 Therefore, IBD patients with concurrent PSC are subject to immediate annual surveillance colonoscopy and biopsy of the entire colon.144,142

**IBD in Asia**

The incidence and prevalence of IBD in Asia have risen in the last 3 to 4 decades, though they are still lower in Asia than in the West.144 Inflammatory bowel disease is also common in Asian immigrants living in Western countries, indicative of the role of environmental factors.145–147 Ulcerative colitis is more common than CD in Asia; however, the rise of incidence is more rapid for CD than for UC.144 Family history of IBD is less frequent among IBD patients in Asia. The median age of onset is similar to that in the West; however, unlike the well-established bimodal age of onset in the West, the second peak is either indistinct or smaller at a younger age.144–147

**UC in Asia**

The incidence of UC in Asian regions is estimated to be 0.4 to 2.1 per 100 000 population (North America and North Europe: 6–20.3 per 100 000 population), and the prevalence rate is 6 to 30 per 100 000 population (North America and North Europe: 21.4 to 243 per 100 000 population).146

Ulcerative colitis in Asia appears to show overall equal gender distribution. The prevalence of extraintestinal manifestations is lower compared with that in the West.144–146 Most hospital-based cohort studies reported comparable proportions of each phenotype (E1 30%–60%, E2 16%–40%, E3 18%–35%) compared with the West.144,146,148,149 The disease course appears to be milder, resulting in less surgery.144–146 Colorectal cancer risk has not been well established, probably because of relatively short follow-up. Nevertheless, the cumulative risk of colorectal carcinoma in Asian UC patients appears comparable with that of the West.144,145

**CD in Asia**

The incidence of CD in the Asia-Pacific region is about 1.37 per 100 000.150 The major difference is a male predilection in Asia compared with the Western population, in which studies show equal gender distribution or a slight female predominance.144,145,147 The prevalence of extraintestinal manifestations is lower compared with that in the Western population.144,147 As in the West, smoking is positively associated with CD in Asia. Smoking may be a predictor of surgery and hospitalization outcomes, and cessation of smoking reduces disease progression.145,146

Published studies report a variable predominance of phenotype in CD; nonetheless, the ileocolonic (L3) phenotype appears to be the most common in Asia.145,147 Noncomplicated behavior (B1; nonstricturing, nonpenetrating) is the most frequent, comprising 40% to 69% of CD, followed by B2 (structuring; 20%–28%), and B3 (penetrating; 10%–31%).144 A small number of studies reported a higher frequency of perianal disease at diagnosis (33%–37%) compared with the West (11%–27%).151 The natural history appears to be similar to that in the West, with a comparable cumulative surgical resection rate.144,145

Pertinent and important differential diagnosis of CD in Asia includes ITB and Behcet disease. Both are prevalent in Asia and demonstrate overlapping clinical, radiologic, endoscopic, and histologic features with CD.147 Histologically, granulomas in ITB tend to be multiple, large, and confluent, often with caseous necrosis. In contrast, granulomas of CD are infrequent and small. Mucosal granulomas are common in both; however, submucosal granulomas are more common in ITB. Disproportionate submucosal inflammation and ulcers that are lined by epithelioid histiocytes are frequently observed in ITB.152 In addition, an endoscopic scoring system to distinguish ITB and CD has been developed. In this study, anorectal lesions, longitudinal ulcers, aphthous ulcers, and a cobblestone appearance were significantly more common in CD, whereas involvement of fewer than 4 segments, a patulous ileocecal valve, transverse ulcers, and scars or pseudopolyps were common in ITB.153 Recent studies incorporated the findings of computed tomography enterography such as intestinal fistulas, target signs, comb signs—a prominence of vasa recta in the mesentery—and lymph node enhancement, and showed an improved diagnostic accuracy.154

Behcet disease is an idiopathic systemic vasculitis. Intestinal involvement is reported in 3% to 60% of Behcet disease, of
which ileocecal involvement is the most common. Intestinal Behçet disease may be complicated by perforation, fistula, and stricture resembling CD. Lüé et al. and Li et al. evaluated endoscopic features to distinguish intestinal Behçet disease versus CD. Round ulcers in a focal distribution, large ulcers, the absence of aphthous ulcer, and cobblestone appearance were features in favor of Behçet disease, whereas CD tended to show irregular/geographic or longitudinal ulcers in segmental or diffuse distribution as well as pseudopolyps. In a study of 50 patients with intestinal Behçet disease, 9 cases had endoscopically evident ileal ulcers and 32 cases showed histologic ileal abnormalities, which included chronic ileitis (10), active ileitis (1), eosinophilic ileitis (1), amebiasis (2), nonspecific ileitis (12), and villous blunting (1). Vasculitis was detected in only 5 ileal mucosal biopsies (10%) in patients with Behçet disease. Clinical and endoscopic correlation is essential to distinguish CD from Behçet disease.

**SUMMARY**

Pathologic evaluation plays an essential role in the diagnosis and management of patients with IBD, and histologic findings should be interpreted in the clinical context. Knowledge of the clinical and surgical aspects of IBD, recognition of the main differential diagnoses and variant forms, and communication with clinicians are indispensable for optimal patient care. Understanding the clinical characteristics of IBD in Asia will not only help patient care but also foster the sharing of knowledge between the IBD communities of the West and the East.

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