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Histopathology of Pouch and Para-Pouch Inflammatory and Neoplastic Disorders

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BACKGROUND: Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is used to treat patients with ulcerative colitis or familial adenomatous polyposis who need colectomy. While this procedure substantially improves patient's quality of life and reduces cancer risk, it is associated with a variety of sequelae, including surgical complications, inflammatory disorders, and neoplasia. Pouchitis, cuffitis, and Crohn's disease of the pouch are the most common inflammatory disorders of the pouch and para-pouch.

OBJECTIVE: This study aimed to elaborate on the histopathology of common inflammatory and neoplastic disorders of the pouch and para-pouch.

DATA SOURCES: A Medline search for English language studies published between 1981 and 2021 using the PubMed search engine. The terms "ileal pouch-anal anastomosis," "pouchitis," "pouchitis activity score," "secondary pouchitis," "Crohn's disease of the pouch," "Crohn's-like conditions of the pouch," "pre-pouch ileitis," "cuffitis," "pouch adenocarcinoma," and "pouch neoplasia" were used.

STUDY SELECTION: The published human studies that reported histopathology of common inflammatory and neoplastic disorders of the ileal pouch were selected and reviewed.

CONCLUSIONS: Histologic examination plays an essential role in confirming inflammation in pouchitis, identifying etiology and clues for secondary pouchitis, and diagnosing neoplasia. A standardized, simple, and reproducible histologic grading system for pouchitis is needed. Pouch and para-pouch glandular dysplasia diagnosis is challenging and should always be reviewed by at least one gastrointestinal pathologist.

KEY WORDS: Adenocarcinoma; Crohn's disease of the pouch; Cuffitis; Dysplasia; Familial adenomatous polyposis; Ileal pouch-anal anastomosis; Pouchitis, Prepouch ileitis; Squamous intraepithelial lesion; Ulcerative colitis.

Restorative proctocolectomy with IPAA is an option for patients with ulcerative colitis (UC) or familial adenomatous polyposis (FAP) who need colectomy.[1] While this procedure substantially improves patient's quality of life in 95% of patients,[2] it is associated with a variety of sequelae.[1] Although clinical presentation, endoscopy, and imaging studies can detect many surgery-related structural and functional abnormalities following IPAA, histologic analysis of biopsy and/or resection specimens is critical to diagnosing inflammatory and neoplastic diseases of the pouch and para-pouch.[1] The term para-pouch refers to the structures outside the pouch body and includes the prepouch ileum, rectal cuff, anal canal/anal transitional zone (ATZ), and perianal area.

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Normal or Baseline Histology of Neoterminal Ileum and Ileal Pouch

The mucosa in the prepouch ileum may undergo colonic metaplasia (ie, villous blunting with or without inflammation, an adaptive change; Fig. 1A).[3] Similar mucosal changes including villous atrophy, an increase in the number of goblet cells, and diffuse lymphoplasmacytic infiltrate in the lamina propria and *muscularis mucosae* can be seen in the ileal pouch (Fig. 1B).[4] These changes are of no clinical significance in asymptomatic patients. Other adaptive changes include intraepithelial lymphocytosis[5] and mild-to-moderate tissue eosinophilia.[6]

Pouchitis

Pouchitis consists of a disease spectrum of various etiologies. It is defined as an inflammation of the ileal pouch. In UC patients undergoing IPAA, a cumulative prevalence is up to 50%. Pouchitis is diagnosed based on a combination of clinical symptomatology, endoscopic findings, and histology.[7] Although not clinically validated, the pouchitis disease activity index (PDAI)[8] and pouchitis activity score[9] have been developed for research purpose. The histology score of PDAI includes acute inflammatory components only (neutrophil infiltrate [none = 0, mild = 1, moderate and crypt abscess = 2, severe and crypt abscess = 3] and mean ulceration per low power field [none = 0, <25% area = 1, 25%–50% of area = 2, and >50% of area = 3], with a maximal score of 6). Association between symptoms, endoscopy, and histology scores in pouchitis using the PDAI is poor.[7,10] In the pouchitis activity score, both acute and chronic inflammatory components are separately scored.[9]

Several classifications of pouchitis have been proposed and used.[1] Commonly, pouchitis is classified as acute or chronic, or idiopathic or secondary. Histology plays an essential role in identifying underlying etiologies for secondary pouchitis, which may need specific treatment. Biopsies should be taken from the prepouch ileum, pouch, and rectal cuff/ATZ during pouchoscopy and submitted in separate containers. The distribution of abnormalities is important for further classification of pouch and para-pouch inflammatory disorders and glandular neoplasia (Table 1). Hematoxylin and eosin-stained sections should be evaluated systematically (Table 2).[11] In pathology practice, the following information (chronic [mononuclear] inflammation, active [neutrophilic] inflammation, cryptitis/crypt abscess, erosion/ulceration, the presence or absence of pyloric gland metaplasia [PGM], the presence or absence of granuloma, and the presence or absence of dysplasia) should be reported for pouch and para-pouch biopsies. However, given that pouchitis is a clinicopathologic diagnosis, rendering a diagnosis of pouchitis by the pathologist based on histologic inflammation alone without clinical and endoscopic information should be avoided.

Primary/Idiopathic Pouchitis

Primary or idiopathic pouchitis is considered when no identifiable etiologies exist. It mainly results from dysbiosis of pouch microbiota. Based on the response to antibiotic therapy, idiopathic pouchitis can be further subclassified into antibiotic responsive, antibiotic dependent, or antibiotic refractory. The main purpose of histologic evaluation in idiopathic pouchitis is to document the presence and degree of acute and chronic inflammation and neutrophil-induced epithelial injuries such as erosion and ulceration, cryptitis, and crypt abscesses (Fig. 2).

Secondary Pouchitis

Secondary pouchitis refers to pouchitis with identifiable etiologies. Histologic evaluation is helpful to identify or provide clues to such etiologies.

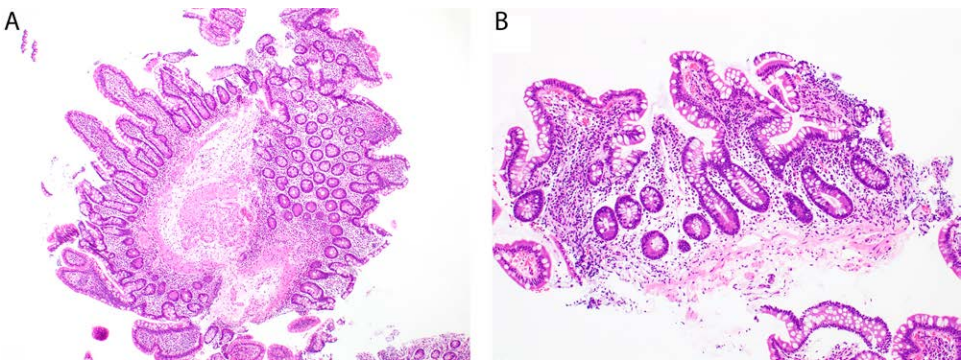

FIGURE 1. Colonic metaplasia of endoscopically normal neoterminal ileum and ileal pouch in asymptomatic patients. A, The biopsy from the neoterminal ileum shows features of colonic metaplasia such as focal villous blunting, slight crypt hyperplasia, and mild lymphoplasmacytic inflammation (H&E stain, 40×). B, The biopsy from the ileal pouch shows mild villous atrophy with an increased number of goblet cells and patchy lymphoplasmacytic infiltrate in the lamina propria, features of colonic metaplasia (H&E stain, 100×). H&E = hematoxylin and eosin.

TABLE 1. Distribution of disease in pouch and para-pouch inflammatory disorders and glandular neoplasia

Entity	*Prepouch ileum*	*Pouch*	*Rectal cuff/ATZ*
Isolated prepouch ileitis	Involved	Not involved	Not involved
Pouchitis	Variably involved	Involved	Variably involved
Cuffitis	Not involved	Not or minimally involved	Involved
CD of the pouch	Variably involved	Variably involved	Variably involved
Glandular neoplasia	Only rarely occurs	Only rarely occurs	More common

ATZ = anal transitional zone; CD = Crohn's disease.

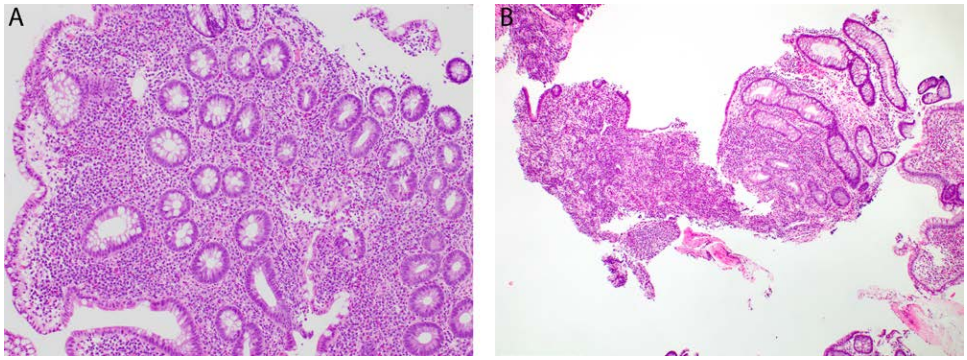

FIGURE 2. Histology of pouchitis. A, Biopsy from the pouch body shows neutrophilic (acute) and chronic inflammation and cryptitis (H&E stain, 100×). B, Biopsy from the pouch body, showing neutrophilic and chronic inflammation, erosion, and ulceration. In addition, there is a variable degree of villous blunting, mild crypt architectural distortion, and pyloric gland metaplasia (H&E stain, 40×). H&E = hematoxylin and eosin.

Ischemic Pouchitis

Ischemic pouchitis is characterized endoscopically by an asymmetric and sharply demarcated inflammation.[12] Histologically, ischemic pouchitis is characterized by the presence of hematoidin in the biopsy with this pigment seen in 80% of cases.[12] Neither PGM nor granuloma is a feature of ischemic pouchitis.

Infectious Pouchitis

Clostridium difficile pouchitis

The ileal pouch may be susceptible to *Clostridium difficile* infection due to colonic metaplasia. It has a spectrum of disease processes from asymptomatic colonization, symptomatic pouchitis, to fulminant disease.[13] Common symptoms are diarrhea, urgency, abdominal pain, and pelvic discomfort. Constitutional symptoms, features of systemic inflammatory response syndrome, frank sepsis, and shock may be present in severe or fulminant cases. Currently, the diagnosis of *C. difficile* pouchitis is made by enzyme-linked immunosorbent assay for toxin A and B and/or the polymerase chain reaction assay for *C. difficile* toxins using fecal material or pouch aspirate in the right clinical and endoscopic contexts.[13] Pseudomembranes are only identified in a minority of cases. Acute inflammation and colonic metaplasia can be seen in *C. difficile* pouchitis but are nonspecific.[14] However, histologic confirmation of acute inflammation in a symptomatic patient with a positive polymerase chain reaction result for *C. difficile* provides a line of evidence for *C. difficile* pouchitis rather than colonization.

Cytomegalovirus-associated pouchitis

Cytomegalovirus (CMV) infection of the pouch is rare.[15] Risk factors for CMV pouchitis include female gender, use of immunosuppressants, and liver transplantation. Presenting symptoms are diarrhea, abdominal pain, and fever. Endoscopically, inflammation is seen in all cases. Histologically, the biopsy shows intense inflammatory infiltration, and the presence of CMV-infected cells confirms the diagnosis. CMV-infected cells are usually endothelial cells, stromal cells, or uncommonly epithelial cells. These CMV-infected cells are large and contain basophilic chromatin with a clear halo underneath the nuclear membrane, rendering an "owl's eye" appearance. Eosinophilic inclusions are often seen in the cytoplasm. When in doubt, immunohistochemistry for CMV antigen might be helpful (Fig. 3).

Fungal infections

Histoplasma capsulatum infection has been reported in refractory Crohn's disease (CD) of the pouch on antitumor necrosis factor therapy.[16] The pouchoscopy revealed large and confluent ulcers extending from the ATZ to the pouch body and the biopsy showed patchy chronic active inflammation with numerous noncaseating epithelioid granulomas. Gomori methenamine silver stain revealed rare 2- to 5-μm intracellular yeasts, consistent with *Histoplasma capsulatum*.[16]

TABLE 2. Features to be evaluated in biopsies from the pouch and para-pouch and their definition

Features	*Definition*	*Clinical significance or associated disease*
Architectural distortion	Villous atrophy, crypt shortening, and branching	Mild to moderate: normal-appearing pouch Severe: pouchitis or CD of the pouch; prepouch ileitis; others
Chronic inflammation	Lymphoplasmacytic inflammation in the lamina propria	Mild to moderate: normal-appearing pouch Severe: pouchitis or CD of the pouch; prepouch ileitis
Acute inflammation	Extravascular neutrophil	Pouchitis
Cryptitis	Neutrophilic infiltrate in the crypt epithelium	Pouchitis
Crypt abscess	Clusters of neutrophils in the crypt lumen	Pouchitis
Crypt apoptosis	Individual crypt epithelial cell death	Autoimmune-mediated pouchitis, medications (NSAIDs), and cytomegaloviral pouchitis
Erosion	Surface epithelial injury with subsequent detachment from the basement membrane, usually accompanied by neutrophilic inflammation and/or fibrin	Pouchitis (acute, chronic, and acute on chronic) of variable etiologies
Ulceration	Inflammation with neovascularization (granulation tissue)	Pouchitis (acute, chronic, and acute on chronic) of variable etiologies
Exudate	Mixed inflammation with necrotic tissue or debris	Pouchitis (acute, chronic, and acute on chronic) of variable etiologies
Hematoidin	Extracellular golden-yellow crystalloid pigments and nonstainable on Prussian blue stain	Ischemic pouchitis
Hemosiderin	Granular and brown pigments, and stains blue on Prussian blue stain	Ischemic pouchitis; old hemorrhage
Thrombus	Fibrin in vascular spaces	Radiation-induced pouchitis or cuffitis, and ischemic pouchitis
Lamina propria fibrosis	Increased deposition of collagen in the lamina propria	Radiation-induced pouchitis or cuffitis; prolapse; CD of the pouch, chronic ischemia; and biopsy near anastomotic site
Ectatic capillaries	Dilated, irregularly shaped capillaries transversing the muscularis mucosae or in the lamina propria	Radiation-induced pouchitis or cuffitis
Pyloric gland metaplasia	Mucus gland(s) in the small intestinal or colonic mucosa resembling gastric pyloric glands or duodenal Brunner glands	CD of the pouch; chronic antibiotic-refractory pouchitis; severe pouchitis comparable with CD of the pouch; and prior injury
Noncrypt rupture-associated granuloma	Clusters of histiocytes not associated with damaged crypt	CD and infectious etiology
Viral inclusions	Smudging nuclei with or without enlarged cell size	Cytomegaloviral pouchitis
Fungal organisms	Fungal element in the tissue (intracellular)	Fungal pouchitis
Dysplasia	Neoplastic changes or clonal expansion of epithelium confined within the basement membrane	Glandular origin: precursor lesion of pouch adenocarcinoma Squamous intraepithelial lesion: precursor lesion of squamous cell carcinoma
Other features	Intraepithelial lymphocytosis (≥20 IELs/100 enterocytes) Eosinophilic infiltrate in the lamina propria	A subclinical response to an altered bacterial microenvironment in most cases

CD = Crohn's disease; IEL = intraepithelial lymphocytes; NSAIDs = nonsteroidal anti-inflammatory drugs.

Pouchitis Due to Multiple Infectious Agents

A case of synchronous CMV and *C. difficile* infection of the pouch has been reported.[17]

Autoimmune-Associated Pouchitis

A subset of patients with chronic antibiotic-refractory pouchitis have the following clinical features suggestive of autoimmunity: pouchitis only responding to corticosteroids, immunomodulators, or biologics; positive autoantibodies; and concurrent autoimmune disorders.[11] This form of pouchitis is classified as autoimmune-associated pouchitis. Histologically, it is characterized by the presence of deep crypt apoptosis in a background of chronic active inflammation (94%), villous blunting and crypt distortion (88%), ulceration (70%), and PGM (47%). An apoptotic score of 6 or greater per 10 high-power fields has a specificity of 98.6% and a positive predictive value of 90.9% in making a diagnosis of autoimmune-associated pouchitis.[11]

Other Pouchitis or Disorder

Diversion pouchitis

A diverting ileostomy may be performed in patients with IPAA with pouchitis refractory to medical treatment and/or in those with failure to thrive, which can lead to diversion pouchitis.[1]

Radiation pouchitis

Radiation-induced pouchitis was reported in 1 male patient who received pelvic radiation for prostatic

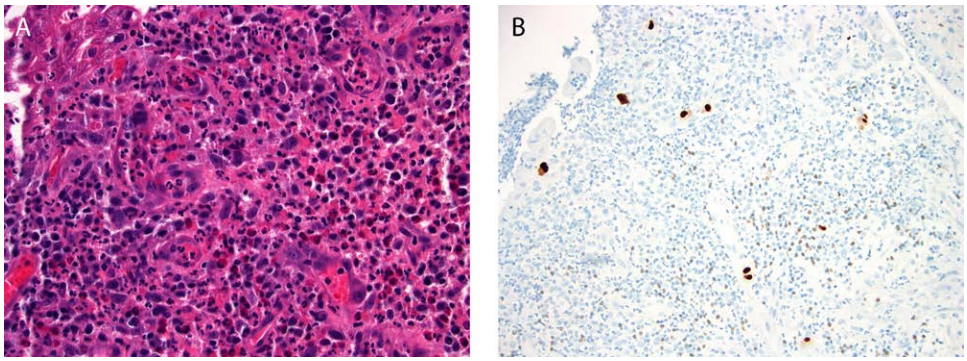

FIGURE 3. A case of cytomegalovirus-associated pouchitis. The biopsy shows chronic active inflammation with ulceration. A, A few enlarged endothelial cells are noted (H&E stain, 400×). B, Immunostain for cytomegaloviral antigen confirms the presence of infected cells with nuclear immunoreactivity (cytomegalovirus immunostain, 200×). H&E = hematoxylin and eosin.

cancer.[18] Histologically, the biopsy showed chronic active inflammation with erosion and, characteristically, ectatic vessels. In addition, there was thickening of the vascular wall, focal perivascular hyalinization, lamina propria scarring, and focal fibrin thrombus.[18] External beam radiation therapy used to treat patients with cervical cancer or anal squamous-cell carcinoma (SCC) may lead to pouch dysfunction.[19]

Pouch prolapse

Pouch mucosal prolapse can occur after IPAA and cause obstruction and dyschezia. Pouchoscopy reveals redundant mucosa. Histologically, the prolapsed mucosa shows fibromuscular proliferation, congestion, erosion, villous blunting, and reactive loss of mucin.[20]

Crohn's Disease of the Pouch

CD of the pouch and Crohn's-like conditions of the pouch have been used interchangeably.[1] CD of the pouch has an estimated incidence of 10% to 20% in UC and indeterminate colitis following IPAA.[21] It remains debatable whether CD of the pouch is a part of the IBD spectrum or a phenotype distinct from classic CD and classic UC. Diagnosis of CD of the pouch is based on a combination of clinical, imaging, endoscopic, and histologic findings after excluding surgical complications. There are 2 scenarios where this diagnosis is made: recurrence of disease in the pouch in patients with preoperative diagnosis of CD (Fig. 4) or with preoperative inadvertent diagnosis of UC, which turned out to be CD on histopathological assessment of colectomy (true CD of the pouch) and development of de novo disease in the pouch in UC patients after colectomy (Crohn's-like disease of the pouch) (Fig. 5).[1] These 2 conditions have different disease courses and prognoses.

Features suggestive of CD of the pouch include noncaseating, noncrypt-rupture-associated granulomas in biopsies of prepouch ileum, pouch body, rectal cuff, or other segments of GI tract; segmental or skip lesions (such as longitudinal ulcers) or strictures in the pouch or small bowel away from the anastomosis; and fistulas or abscess developed after 6 to 12 months of stoma closure and prepouch ileitis.[1] All specimens from the pouch and para-pouch should be carefully evaluated, and the presence or absence of granuloma should be clearly stated in the pathology report. A lack of granuloma does not exclude CD of the pouch as only 10% to 20% of the cases have granuloma. PGM is a common feature in CD of the pouch; however, it can also occur in pouchitis of comparable severity.[21] Likewise, the presence of transmural inflammation in excised pouch specimens is insufficient for diagnosing CD of the pouch because of low sensitivity (about 20%) and low specificity.[22] The combination of chronic mucosal injury and transmural lymphoid aggregates was seen in only 20% of surgically resected pouches with presumed CD of the pouch.[23]

Prepouch Ileitis

Prepouch ileitis can occur concomitantly with pouchitis[24–26] or alone by itself.[26] It is rare with an incidence of 2.6%. Endoscopically, prepouch ileitis shows visible inflammation such as friability, erosion, or ulcers involving the distal 10 cm of the afferent limb.[24] Its diagnosis requires histologic confirmation of acute inflammation.[24] Some authors consider prepouch ileitis a feature of CD.[24]

Isolated prepouch ileitis is characterized by diffuse inflammation extending proximally from the neoterminal ileum-pouch junction; it may be associated with nonsteroidal anti-inflammatory drug use or idiopathic.[26] Endoscopically or macroscopically, it demonstrates focal thickening and mucosal ulceration, with or without stricture. Microscopically, it shows villous atrophy, mucosal chronic inflammation, neutrophil-mediated epithelial injury, and variable degrees of ulceration with or without submucosal fibrosis.[26] Crypt rupture-associated granuloma, stricture, and fistula are uncommon, and transmural inflammation is absent.[26]

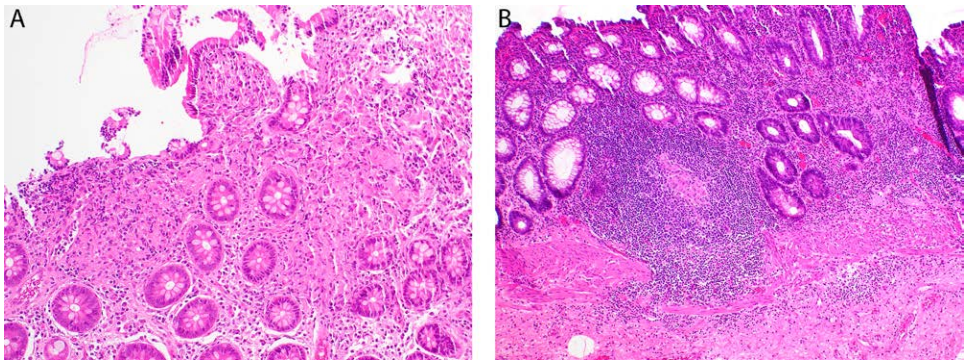

FIGURE 4. A case of Crohn's disease of the pouch in a patient with colonic Crohn's disease. A, Exuberant noncaseating granulomatous inflammation and chronic active inflammation in the pouch biopsy (H&E, 100×). B, Exuberant noncaseating granulomatous inflammation in the preceding colectomy specimen (H&E stain, 40×). Of note, these granulomas are not associated with crypt rupture. Special stains (acid-fast bacilli and Gomori methenamine silver) are negative for mycobacteria and fungal organisms on both specimens (images not shown). H&E = hematoxylin and eosin.

Cuffitis

Cuffitis is defined as inflammation of the rectal cuff with or without minimal pouchitis.[27] The IPAA procedure using a stapled technique leaves a 1.5- to 2.0-cm "cuff" of diseased rectal mucosa proximal to ATZ wherein cuffitis can develop. Cuffitis is one of the common complications of IPAA with an incidence rate of 12.9%.[27] Although most cases likely represent UC, some cases may be due to CD involving the cuff or due to ischemia.[27] Clinically, the patients present with bleeding, urgency, perianal pain, and diarrhea. Endoscopically, the cuff appears to be erythematous, friable, and nodular, or it has shallow or deep ulcers.[27] Histologically, most cases show chronic active colitis with or without ulceration. One case of de novo collagenous cuffitis has been reported. Biopsy from the cuff in this case showed focal fibroplasia in the lamina propria, attenuated crypts, soughing of surface epithelia, and thickened subepithelial collagen table with entrapped capillaries.[28]

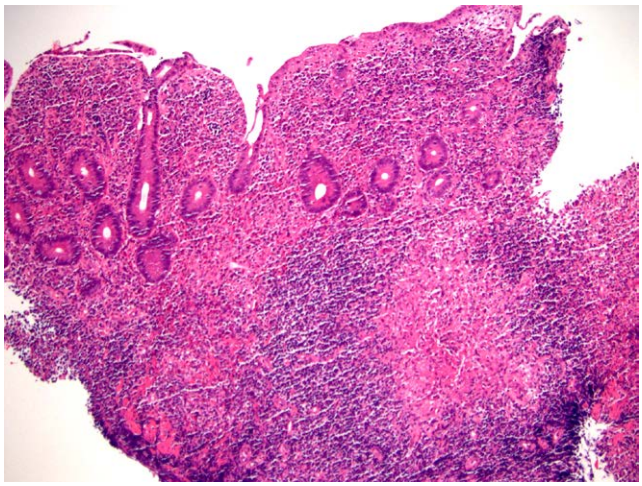

FIGURE 5. A case of de novo Crohn's disease of the pouch. Noncaseating granuloma in the lamina propria of the ileal pouch (H&E stain, 100×). Of note, these granulomas are not associated with crypt rupture. Special stains (acid-fast bacilli and Gomori methenamine silver) are negative for mycobacteria and fungal organisms (images not shown). H&E = hematoxylin and eosin.

Neoplasia in Patients With IPAA

Glandular Neoplasia in Patients with IPAA for UC

IPAA significantly reduces but does not completely eliminate cancer risk in patients with UC. The occurrence of adenocarcinoma following IPAA for UC is an infrequent but potentially lethal complication.[29] The incidence of pouch/para-pouch cancer is 0.2% to 1.2%.[30,31] Pouch and para-pouch adenocarcinomas in patients with IPAA for UC predominantly originate at the cuff or ATZ, and rarely in the pouch body or afferent limb.[30,32,33]

Pouchoscopic surveillance with biopsy is recommended for patients at risk, which include patients with a precolectomy diagnosis of colorectal neoplasia,[31] primary sclerosing cholangitis, chronic inflammatory disorders of the pouch, and family history of colorectal cancer in first-degree relatives.[1] The adjusted hazard ratios for pouch neoplasia in UC patients are 3.6 (95% confidence interval, 1.6–8.2) for preoperative dysplasia and 13.4 (95% confidence interval, 4.0–45.5) for preoperative cancer.[31] Biopsy from the afferent limb, pouch body, and rectal cuff/ATZ should be carefully evaluated for dysplasia, and the results should be clearly stated in the pathology report. A schema including negative for dysplasia, indefinite for dysplasia (IND), and positive for dysplasia can be used.[34] For cases that are positive for dysplasia, dysplasia should be further graded as low-grade dysplasia (LGD) or high-grade dysplasia (HGD).[34] Grading dysplasia should be based on the worst area, either cytologically or architecturally. IND or positive for dysplasia should be confirmed by at least 1 gastrointestinal pathologist.[1] Treatment of pouch and para-pouch dysplasias in patients with IPAA for UC is changing since the gradual adoption of the **S**urveillance for **C**olorectal **E**ndoscopic **N**eoplasia Detection and Management in Inflammatory Bowel Disease Patients: **I**nternational **C**onsensus (SCENIC) recommendations, which considers the endoscopic appearance (visible [polypoid, sessile/slightly raised, and depressed] vs invisible [flat]), endoscopic resectability (resectable vs unresectable), and histology of dysplasia (LGD vs HGD).[35]

Negative for Dysplasia

The category of negative for dysplasia in the afferent limb and pouch means several conditions: normal small bowel mucosa (Fig. 6A), small-bowel mucosa with colonic metaplasia, chronic active enteritis with reactive changes (Fig. 6B), chronic inactive enteritis with regenerative changes (Fig. 6C), and quiescent enteritis without evidence of dysplasia (Fig. 6D). Normal small-bowel mucosa has slender villi lined by absorptive epithelium interspersed with goblet cells. The crypts consist of Paneth cells in the bottom, goblet cells, and neuroendocrine cells. The cells on the surface contain smaller nuclei and more abundant cytoplasm when compared with the crypt cells, a phenomenon termed "surface maturation." The lamina propria has a few mononuclear inflammatory cells but is not expanded by them. Neutrophils are absent outside the capillaries. Afferent limb and pouch biopsy usually shows a variable degree of colonic metaplasia, but surface maturation should be present. When there is ileitis/pouchitis, the epithelium may lose mucin, and the nucleus becomes slightly hyperchromatic and enlarged. However, the degree of epithelial change is proportional to the inflammation. In chronic inactive enteritis, regenerative changes may mimic dysplasia, but a clinical history of recently treated ileitis/pouchitis flare supports a diagnosis of negative for dysplasia. In quiescent enteritis, there is architectural distortion, but surface maturation should be apparent for the interpretation of negative for dysplasia.

In rectal cuff/ATZ, the category of negative for dysplasia includes 3 scenarios: quiescent colitis without evidence of dysplasia, chronic active colitis with reactive changes, or chronic inactive colitis with regenerative changes.

Low-Grade Dysplasia

LGD means clonal expansion of glandular epithelium with mildly enlarged and hyperchromatic nuclei involving the crypts and surface epithelium in the absence of active inflammation.[34] In LGD, nuclei often maintain their polarity; that is, the long axis of the nucleus is perpendicular to the basement membrane of the crypts/surface epithelium. Significant cytological and architectural abnormalities (ie, marked pleomorphism, loss of nuclear polarity, cribriform glands, or exuberant papillation) should be absent. In many cases, the dysplastic lesion resembles intestinal "adenoma." However, in other cases, the lesion may not resemble intestinal "adenoma" (Fig. 7). Recent work on IBD-associated dysplasia recognized several nonconventional dysplasia such as hypermucinous, goblet cell deficient, terminal epithelial differentiation (crypt cell dysplasia), dysplasia with increased Paneth cell differentiation, and serrated dysplasia.[36,37] Whether this classification is applicable to the pouch/para-pouch glandular dysplasia remains unknown. Pathologists' awareness of these variants of dysplasia in IBD is important as these variants may occur in IPAA for UC.

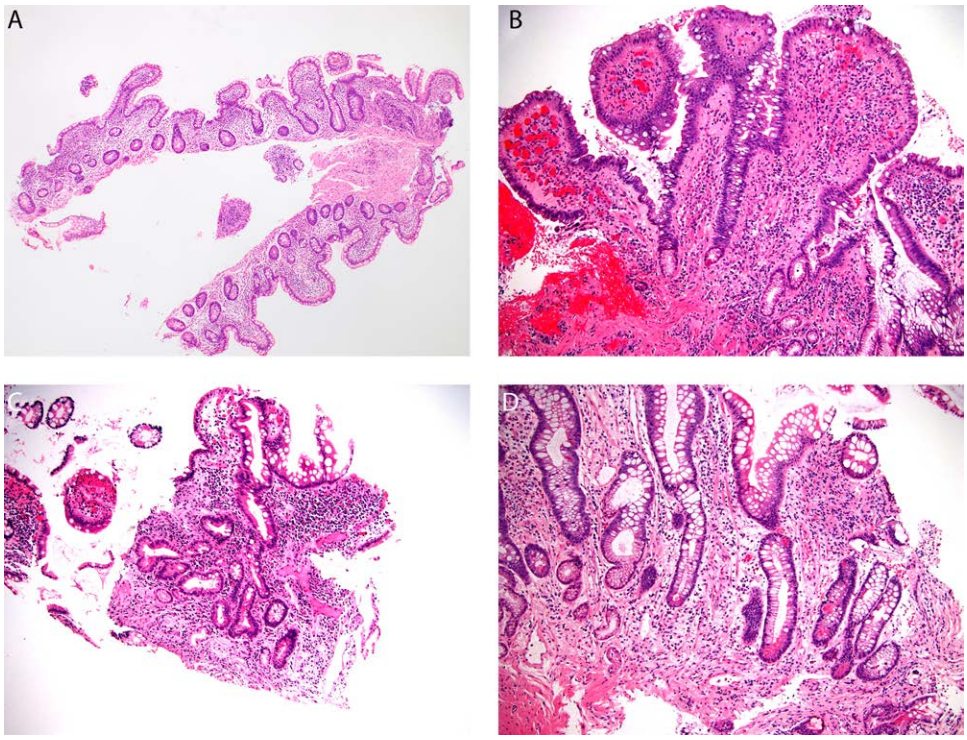

FIGURE 6. The category of negative for dysplasia in the pouch biopsy indicates several conditions: normal small bowel mucosa (A, H&E stain, 40×), chronic active enteritis with reactive changes and pyloric gland metaplasia (B, H&E stain, 100×), chronic inactive enteritis with regenerative changes (C, H&E stain, 100×), and chronic quiescent enteritis with pyloric gland metaplasia but without evidence of dysplasia (D, H&E stain, 100×). H&E = hematoxylin and eosin.

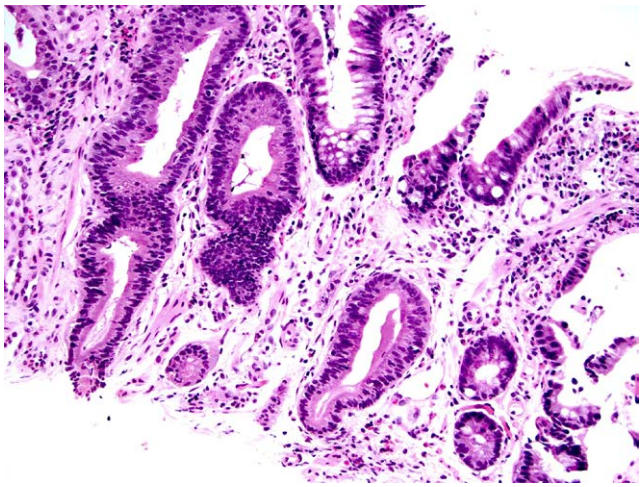

FIGURE 7. Biopsy from this ileal pouch shows atypical glands with slightly enlarged and hyperchromatic nuclei (H&E stain, 200×). The nuclear changes extend to the surface. No obvious architectural complexity, nuclear pleomorphism, or loss of nuclear polarity is noted. The overall features are diagnostic of low-grade dysplasia. H&E = hematoxylin and eosin.

High-Grade Dysplasia

HGD indicates the presence of greater degrees of cytologic and/or architectural abnormalities than those seen in LGD. Again, there should be no surface maturation in the area of dysplasia. In HGD, the enlarged and hyperchromatic nuclei usually show a greater degree of cytologic abnormalities such as loss of polarity and/or marked pleomorphism with irregular nuclear membrane (Fig. 8A). A higher degree of architectural complexity means cribriform (gland-in-gland) configuration (Fig. 8B) and/or exuberant papillation of the surface epithelium.

Indefinite for Dysplasia

IND is a legitimate but uncommon diagnostic category in pouch/para-pouch biopsy. It conveys a genuine concern for dysplasia; it is used when the interpretation is compromised due to the presence of concomitant acute inflammation, tangential section, ulceration, or suboptimal staining. IND was rendered in 2.3% of biopsies obtained during surveillance or diagnostic pouchoscopies.[38] In a few selected IND cases with features highly concerning for dysplasia, immunohistochemistry for p53 might be helpful. Aberrant expression of p53 (diffuse and strong nuclear immunoreactivity or a total lack of immunoreactivity) in the atypical cells supports a diagnosis of dysplasia.

Pouch and Para-Pouch Adenocarcinoma

Pouch and para-pouch adenocarcinomas have histomorphology similar to colitis-associated adenocarcinoma.[29] They tend to show tumor-infiltrating lymphocytes and mucin differentiation but lack dirty necrosis. In 1 case series, all pouch and para-pouch adenocarcinomas showed CK20 expression, 72.8% of cases had CDX2 expression, and 54.5% had CK7 expression. About 10% cases are mismatch repair-deficient.[29] Although a diagnosis of adenocarcinoma of the pouch and para-pouch regions can be made on biopsy, well-differentiated adenocarcinoma may develop in long-standing fistulas or present as a fistula that may be difficult to sample. Therefore, making such a diagnosis on endoscopically obtained biopsy can be extremely challenging. In such cases, generous and deep tissue sampling by colorectal surgeon may be required.[1] Most pouch and para-pouch adenocarcinoma diagnoses are made after examining the excised pouch specimen in patients with or without pouch dysplasia before surgery.[29] An approach for intestinal adenocarcinoma may be used to guide macroscopic and histologic examinations and synoptic reporting of carcinoma of the rectal cuff/ATZ, pouch, or prepouch ileum (Table 3).[39] For carcinoma in the anal canal below the dentate line, using the anal cancer protocol may be more appropriate.

Glandular Neoplasia in Patients With IPAA for FAP

Although IPAA significantly reduces cancer risk in patients with FAP, the incidence of adenoma is high following IPAA.[33] Most adenoma occurs at rectal cuff and ATZ after stapled IPAA (Fig. 9A). Endoscopic surveillance with polypectomy is the main treatment modality for ileal

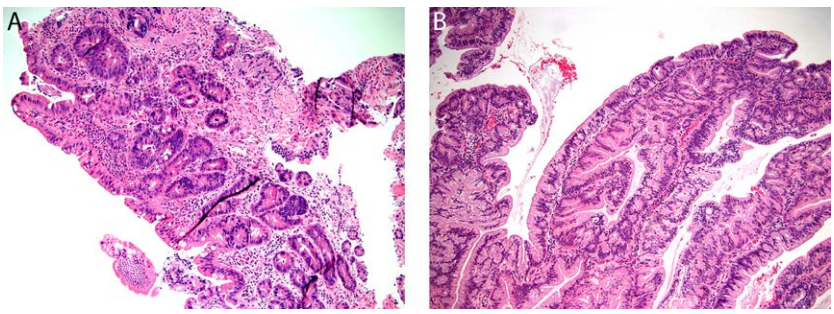

FIGURE 8. HGD can be diagnosed by the presence of either significant cytological abnormalities or architectural complexity in the area without surface maturation. A, This ileal pouch biopsy shows pleomorphic nuclei with loss of polarity, consistent with HGD (H&E stain, 100×). B, Another example of HGD represented by architectural complexity (cribriform glands and papillation) despite the nuclear change alone fall short of HGD (H&E stain, 100×). H&E = hematoxylin and eosin; HGD = high-grade dysplasia.

TABLE 3. Elements to be examined and reported in pouch and para-pouch cancer

Item	*Categories*
Procedure	Pouch excision and endoscopic en bloc resection of pouch/para-pouch lesion
Tumor site	Afferent limb
	Pouch body
	Anal transitional zone or rectal cuff
	Other (specify)
Histologic type	Adenocarcinoma and not otherwise specified
	Mucinous carcinoma
	Signet ring cell carcinoma
	Small-cell neuroendocrine carcinoma
	Large-cell neuroendocrine carcinoma
	Squamous cell carcinoma
	Other histological type (specify)
Histologic grade	Well-differentiated (G1)
	Moderately differentiated (G2)
	Poorly differentiated (G3)
	Undifferentiated (G4)[a]
	Cannot be assessed (Gx)
Tumor size	Greatest dimension in centimeters (cm)
	Cannot be determined (explain)
Tumor extent[b,c]	Invades lamina propria
	Invades submucosa
	Invades muscularis propria
	Invades through muscularis propria into subserosa or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration
	Invades visceral peritoneum
	Directly invades other organ(s) or structure(s) (specify)
Macroscopic tumor perforation	Absent
	Present
	Cannot be determined (explain)
Lymphovascular invasion	Absent
	Present
	Cannot be determined (explain)
Tumor budding[d]	Low (0–4)
	Intermediate (5–9)
	High (10 or more)
Margin status	Pouch excision
	Proximal margin, distal margin, radial margin,[e] and other margin(s) (specify)
	Endoscopic en bloc resection of pouch/para-pouch lesion
	Mucosal margin and deep margin[e]
Regional lymph nodes	Number of lymph nodes with tumor
	Number of lymph nodes examined
Distant metastasis	Not applicable
	Nonregional lymph node
	Liver
	Other (specify)
Pathologic stage classification	
TNM descriptors	m (multiple primary tumor)
	r (recurrent)
	y (posttreatment)
Pathologic tumor (pT) category[b]	pT1a: Tumor invades the lamina propria
	pT1b: Tumor invades the submucosa
	pT2: Tumor invades the muscularis propria
	pT3: Tumor invades through the muscularis propria into the subserosa or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration
	pT4: Tumor perforates the visceral peritoneum or directly invades other organs or structures (eg, other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa)

(Continued)

TABLE 3. *Continued*

Item	*Categories*
Pathologic nodal (pN) category	pNx: pN not assigned (no nodes submitted or found or cannot be determined based on available pathological information)
	pN0: No regional lymph node metastasis
	pN1: Metastasis in 1 or 2 regional lymph nodes
	pN2: Metastasis in 3 or more regional lymph nodes
Pathologic metastasis (pM) category	Not applicable: pM cannot be determined from the submitted specimen(s)
	pM1: Distant metastasis
Additional findings	None identified
	Afferent limb (ileitis, adenoma, and dysplasia)
	Pouch (pouchitis, adenoma, and dysplasia)
	Rectal cuff (cuffitis, adenoma, and dysplasia)
	Other polyp(s) (specify)
	Other (specify)
Special studies	Microsatellite status
	Mismatch repair protein immunohistochemistry result
Comments	Specify

[a]G4 refers to small cell neuroendocrine carcinoma or undifferentiated carcinoma.
[b]pT category is applicable to carcinoma arising from the rectal cuff, pouch, and prepouch ileum.
[c]Invasion level is determined based on gross and microscopic examination.
[d]Tumor buds are determined by the number in 1 "hotspot" field (in an area of 0.785 mm^2).
[e]If the carcinoma is at the inked radial/deep margin, it is a positive margin; if the carcinoma is within 1 mm from the inked radial/deep margin, it is designated as a positive margin with a measurement (in μm) of distance between the inked margin and carcinoma.

pouch adenoma in FAP patients. Histologically, most polyps are tubular adenoma (Fig. 9B).

Anal Squamous Intraepithelial Lesion and Invasive SCC

Anal squamous intraepithelial lesion and invasive SCC can occur in UC patients, including those who had IPAA.[19] Low-grade squamous intraepithelial lesion includes condyloma acuminatum and mild squamous dysplasia. Condyloma acuminatum is a papillomatous proliferation of epithelia with koilocytosis with hyperchromatic raisinoid nuclei and perinuclear halos. Mild squamous dysplasia shows cytologic atypia in the lower third of the epithelia only. High-grade squamous intraepithelial lesion (HSIL) includes squamous epithelium with moderate dysplasia, severe dysplasia, or SCC in situ. In HSIL, hyperchromatic cells with a high N:C ratio involve greater than one-third of the squamous epithelium thickness. Diagnosis of low-grade squamous intraepithelial lesion and HSIL is usually straightforward on hematoxylin and eosin–stained sections. In difficult cases, immunohistochemistry for p16 helps differentiate HSIL from its mimics (Fig. 10).

In invasive SCC, the tumor cells breach through the basement membrane into the lamina propria or beyond and often are composed of large eosinophilic cells with keratinization. When the tumor is poorly differentiated, immunohistochemistry with a panel of antibodies may be needed to confirm the squamous nature of the carcinoma. Immunostain for p16 should be performed in anal SCC as p16 immunoreactivity indicates a human papillomavirus-associated cancer, which may have better prognosis. Of note, well-differentiated SCC may develop in long-standing fistulas; diagnosing such cases can be extremely challenging and may need generous and deep-tissue sampling by the colorectal surgeon.[1]

Lymphoproliferative Disorder

Case reports of non-Hodgkin's lymphoma involving the pouch, sometimes in association with Epstein-Barr virus

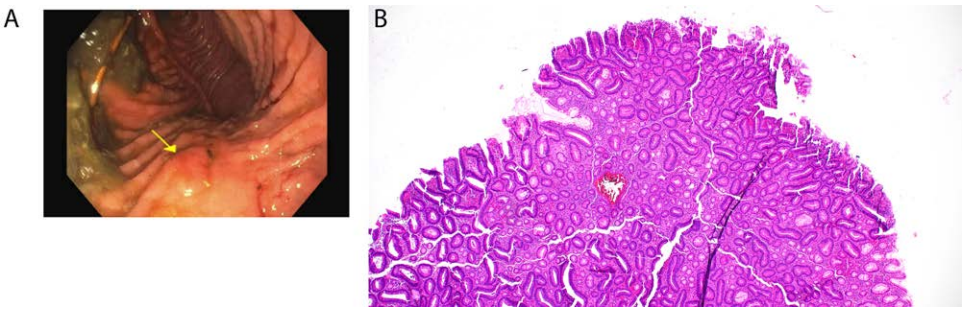

FIGURE 9. Adenoma at the anal transitional zone. A, Endoscopically, this lesion presents as a polyp (arrow). B, Histologically, this lesion is composed of proliferating glands lined by pencil-shaped and pseudostratified nuclei (H&E stain, 40×). H&E = hematoxylin and eosin.

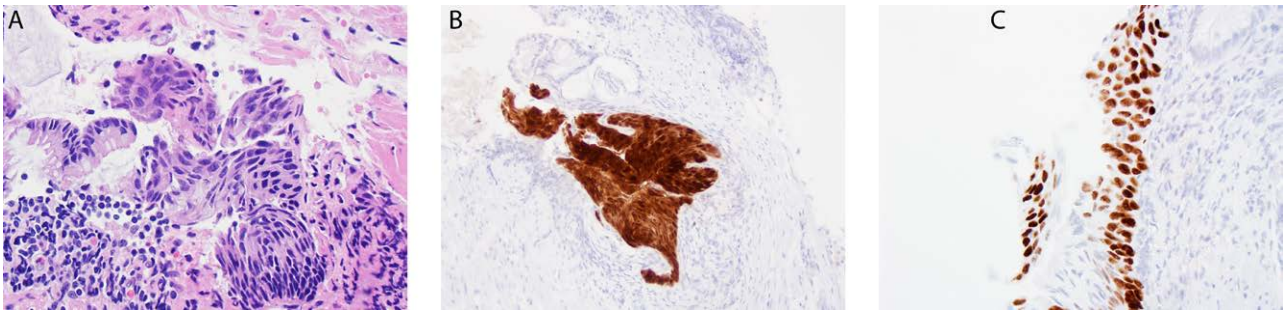

FIGURE 10. High-grade squamous intraepithelial lesion (HSIL) in anal transitional zone biopsy from a patient with IPAA. A, A small focus of squamous epithelia with enlarged and hyperchromatic nuclei is noted (H&E stain, 400×). The basement membrane is intact. B, Immunostain for p16 shows a block staining pattern in the lesion (p16 immunostain, 400×). C, Immunostain for p63 is strongly positive in the lesional tissue, confirming squamous origin of this lesion (p63 immunostain, 400×). H&E = hematoxylin and eosin; HSIL = high-grade squamous intraepithelial lesion.

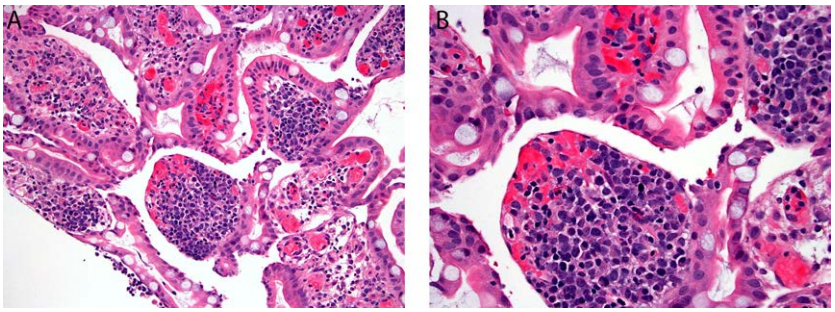

FIGURE 11. Biopsy from ileal pouch shows foci of dense and atypical mononuclear cell infiltrates (A, H&E stain, 100×; B, H&E stain, 200×). These atypical cells are CD20 positive by immunohistochemistry and Epstein-Barr virus positive by in situ hybridization (images not shown). H&E = hematoxylin and eosin.

infection, have been reported in patients with IBD.[40] Symptoms include diarrhea, urgency, and weight loss, and pouchoscopy reveals mass lesion. Biopsy from the lesion shows a proliferation of atypical mononuclear cells (Fig. 11). These cells are CD20-positive by immunochemistry and Epstein-Barr virus–positive by in situ hybridization. Attention to atypia of the mononuclear infiltrates and performing confirmatory ancillary tests are crucial in arriving at the correct diagnosis.

CONCLUSION

Pouchoscopy with biopsy is used to examine IPAA in patients for diagnosis of pouch diseases and surveillance of neoplasia. Histologic examination is important to document pouchitis and to identify etiologies for secondary pouchitis. All pouch, afferent limb, and rectal cuff/ATZ biopsies should also be evaluated for the presence or absence of dysplasia. A standardized, simple, and reproducible histologic grading system for pouchitis is needed as the patient population with IPAA has been steadily increasing worldwide. Pouch and para-pouch glandular dysplasia diagnoses are challenging and should always be reviewed by at least 1 GI pathologist. Overall, our knowledge on histopathology of pouch and para-pouch disorders remains limited to either case series or case reports.

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