Inflammatory Bowel Disease

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Frequently Asked Questions

1. What are the characteristic pathologic features of chronic ulcerative colitis in resection specimens?

Ulcerative colitis (UC) is characterized macroscopically by diffuse, continuous, mucosal-based inflammation that involves the rectum, either alone or in continuity with a variable length of the colon in a retrograde fashion. Patients are classified accordingly as having ulcerative proctitis, proctosigmoiditis, left-sided colitis, extensive colitis (i.e., beyond the splenic flexure), or pancolitis. The transition between the diseased distal mucosa and the proximal normal mucosa may appear gradual or abrupt; however, in some cases, a normal-appearing proximal colon belies the presence of more extensive microscopic involvement (Fig. 6.1).

The pathologic manifestations of UC vary depending on the state of disease activity and the cumulative sequella of prior inflammation. Macroscopically, they include petechia, hyperemia, or ulcerations superimposed on structural mucosal changes such atrophy, granularity, nodularity, or inflammatory polyps (Fig. 6.2). Microscopically, the mucosa is characteristically expanded and the lamina propria is densely infiltrated by plasma cells, lymphocytes, and eosinophils. The infiltrates extend from the surface to the basal lamina propria, separating the crypts from one another and often from the muscularis muco-

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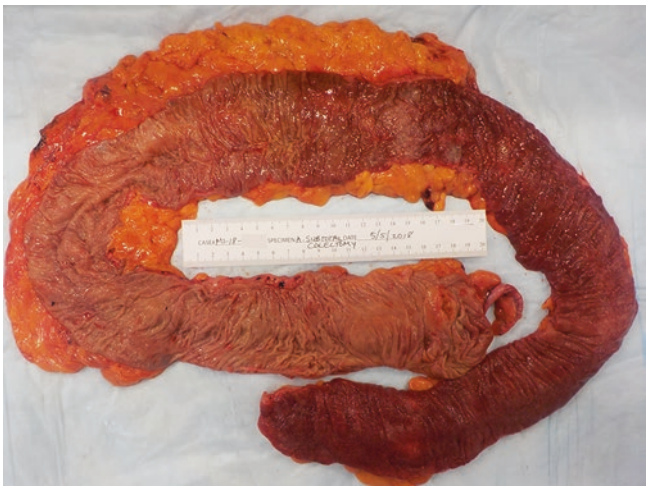

Fig. 6.1 Colectomy specimen showing active ulcerative colitis extending retrograde to the mid-transverse colon. Note the gradual macroscopic transition from the involved to the uninvolved colon

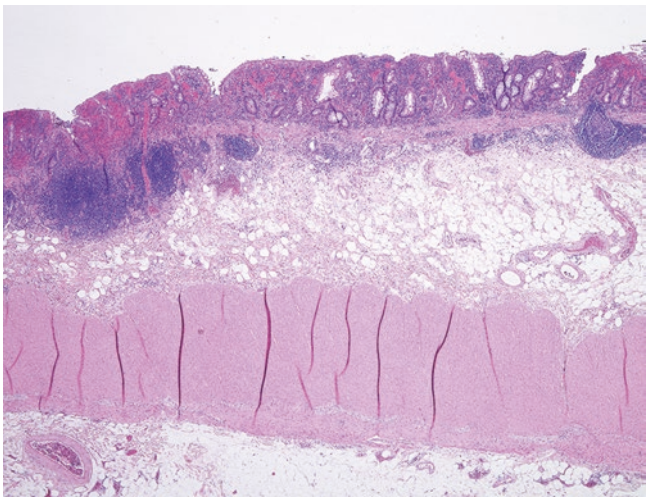

Fig. 6.3 Ulcerative colitis showing diffuse inflammation involving the mucosa and superficial submucosa

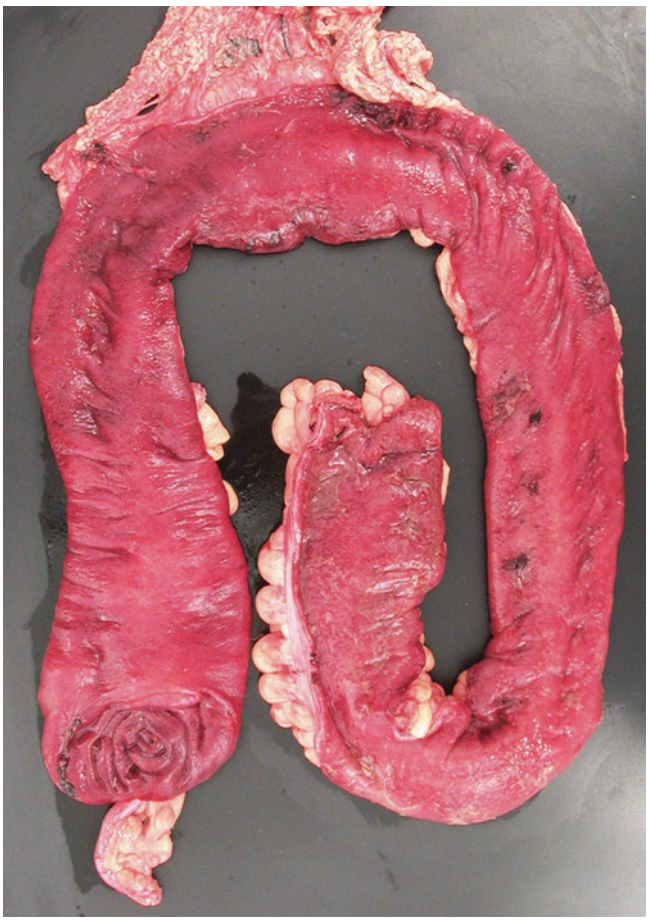

Fig. 6.2 Colectomy specimen showing ulcerative pancolitis featuring diffuse atrophy punctulated by scattered ulcers and inflammatory polyps

Fig. 6.4 Colectomy specimen showing fulminant ulcerative colitis characterized by extensive ulceration and toxic dilatation of the proximal transverse colon

sae. The mucosal architecture is variably altered, presenting skewed, distorted, and bifurcated crypts (Fig. 6.3). Active disease is characterized by erosions, broad-based ulcers, superficial fissures, cryptitis, neutrophilic crypt abscesses, and damaged crypts. The inflammatory infiltrates are generally limited to the mucosa and superficial submucosa; however, chronic ulcers may be accompanied by underlying regions of intramural and subserosal inflammatory infiltrates. Quiescent colitis is characterized by resolution of the neutrophilic inflammatory infiltrates and diminished lymphoplasmacytosis, but crypt architectural abnormalities resolve slowly if at all.

In fulminant UC, the mucosa is intensely hyperemic and extensively ulcerated or sloughed (Fig. 6.4). It may progress to generalized or segmental dilation culminating in toxic megacolon with thinning of the wall and potential perforation. The transverse colon is affected initially because its superior location in the supine patient permits gas and fluid to accumulate when peristalsis is diminished and its intraperitoneal location permits free expansion. Microscopically, fulminant colitis is characterized by

extensively denuded mucosa, penetration of ulcers into the muscularis propria, fissuring ulcers, vascular congestion, and phlegmonous neutrophilic infiltration.

Residual or partially sloughed mucosa and granulation tissue present as inflammatory polyps. They may be widely dispersed or clustered in individual colonic segments and assume diverse shapes, including filiform excrescences, broad-based mounds, or ragged, leaf-like tags.

The colonic wall in UC generally remains thin and pliant even in long-standing disease; however, some patients develop a foreshortened colon with a slightly, but uniformly, thickened wall. Stricturing due to severe localized inflammation is uncommon in UC and should raise concern for an unrecognized tumor or for Crohn disease (CD). References: [1, 2]

2. What are the characteristic pathologic features of Crohn colitis in resection specimens?

The majority of patients with CD have some degree of large intestinal involvement, including isolated colonic involvement in 20–30% and combined ileocolitis in 25–40%. Of these patients, 25–30% have pancolitis and the remainder have segmental disease, usually of the rectum or ileocecal region. Additionally, roughly 1/3 of patients with CD have perianal fistulas, fissures, or abscesses.

The macroscopic hallmarks of Crohn colitis are manifestations of transmural, segmental chronic inflammation (Fig. 6.5). Single or multiple diseased segments occur in any location and are sharply demarcated from adjacent normal segments. In nascent disease, the mucosa features pinpoint aphthous ulcers in a background of normal, edematous, or erythematous mucosa and the wall may show varying degrees of edema. With advancing disease, the ulcers coalesce into larger geographic or longitudinally oriented ulcers, the wall grows increasingly thickened and rigid, and the serosa becomes opacified or encased in creeping fat.

Deep fissuring ulcers, fibrous adhesions, creeping mesenteric fat, fistula tracts, and strictures are all distinctive features of CD (Fig. 6.6). Fusiform strictures occur anywhere, although most frequently in the ileocecal and anorectal regions, and they vary greatly in length. On sectioning the colonic wall, cicatrization obscures or obliterates the mural landmarks and extends into the pericolic fat (Fig. 6.7). As in UC, fulminant Crohn colitis may result in toxic megacolon.

Distinctive patterns of mucosal inflammation in CD include single or multiple parallel longitudinal ulcers with narrow bases ("bear claw" or "garden rake" ulcers) and a cobblestone pattern produced by intersecting longitudinal and transverse ulcers (Fig. 6.8). By contrast, some cases of Crohn colitis resemble UC macroscopically, featuring diffuse inflammation, atrophy, or inflammatory polyposis. Attention to localized thickening or stenosis may suggest the correct diagnosis, but in a subset of cases the distinction from UC depends entirely on histological recognition of Crohn-like characteristics.

Microscopically, colonic segments involved by Crohn colitis are characterized by transmural lymphoid aggregates, chronic inflammatory infiltrates, expansion and

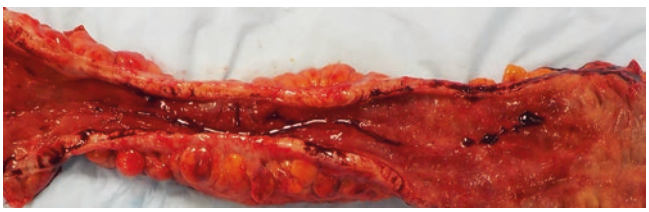

Fig. 6.6 Colonic Crohn disease with stricture resulting from contracture of the colonic wall. Note the corresponding segmental wrapping of mesenteric fat

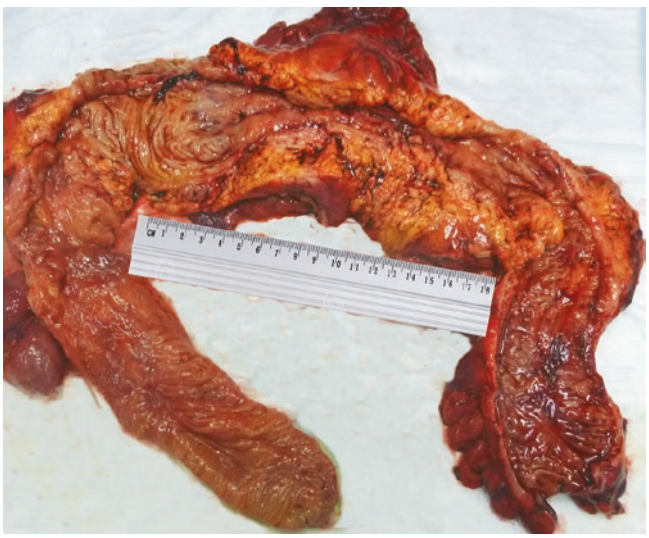

Fig. 6.5 Colonic Crohn disease with massive inflammatory thickening and stricture of the transverse colon

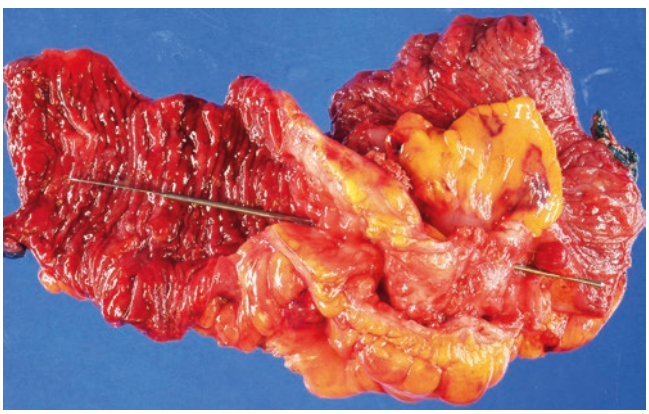

Fig. 6.7 Stricturing Crohn ileocolitis associated with mural thickening, fibrous serosal adhesions, gross deformity, and ileocolic fistula

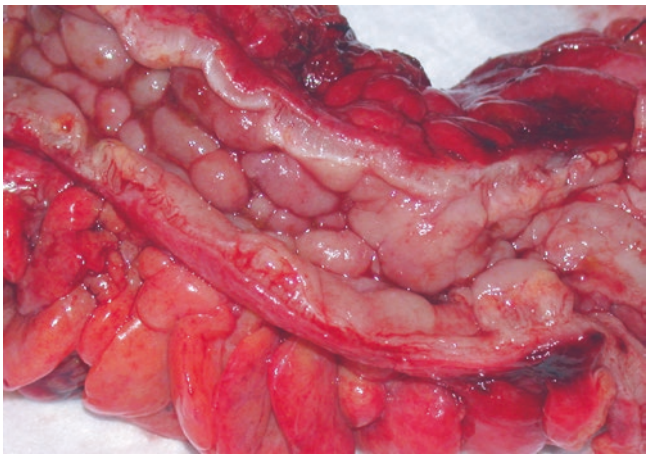

Fig. 6.8 Colonic Crohn disease showing mucosal cobblestoning corresponding to mounds of edematous mucosa surrounded by longitudinally and transversely oriented fissuring ulcers

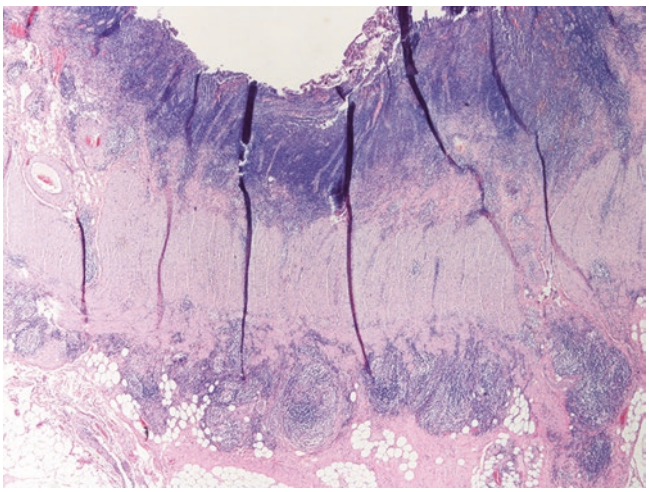

Fig. 6.9 Crohn disease with transmural lymphoid aggregates

splaying of the muscularis mucosae, fibrosis and fatty replacement of the submucosa, neural hypertrophy, deep fissuring ulcers, and fistula tracts (Fig. 6.9). The pericolic fat is fibrotic and chronically inflamed. Nonnecrotizing granulomas occur in approximately 50% of resection specimens and present in all layers of the colonic wall and in the pericolic lymph nodes.

References: [1, 2]

3. What are common pitfalls in the differential diagnosis between ulcerative and Crohn colitis in resection specimens?

Rectal Sparing in UC

Rectal involvement is a consistent feature of UC; however, macroscopic inspection may give a false impression of rectal sparing resulting from spontaneous or therapy-induced healing. Rectal sparing does occur, however, in patients with concomitant primary sclerosing cholangitis (PSC), in whom the colitis often is predominantly right sided and diminishes distally. Rectal sparing or patchy inflammation also occurs frequently in pediatric patients with UC.

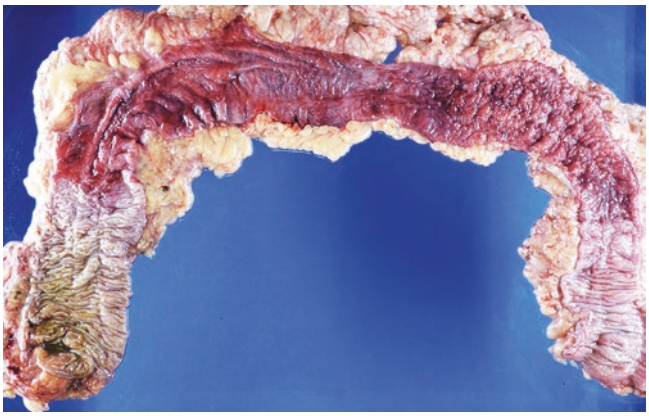

Fig. 6.10 Active ulcerative colitis showing gross sparing of the ascending and distal sigmoid colon. Microscopically, the sigmoid colon was chronically inflamed but the ascending colon was normal. The extent and distribution of inflammatory bowel disease are determined based on the combination of gross and microscopic findings since discrepancies are not uncommon

Discontinuous Inflammation in UC

Cognizance of exceptions to the typical continuous pattern of inflammation in UC is important to avoid an incorrect diagnosis of CD (Fig. 6.10).

Discontinuous involvement of the cecum, referred to as an isolated cecal patch, occurs in approximately 10% of patients with left-sided or distal UC. The histological characteristics and severity of the cecal inflammation generally mirror those in the remainder of the involved colon.

Ulcerative appendicitis affects 48–85% of nonobliterated appendices in resections from patients with UC, its prevalence being independent of the proximal extent of colitis. Although the appendix appears unremarkable macroscopically, it presents a microscopic mucosal-based inflammation that closely resembles the rest of the colon but remains limited to the mucosa even in severe UC. Unlike Crohn appendicitis, there is no mural expansion, transmural lymphoid aggregates, or granulomas. Endoscopically, the base of the appendicitis in UC often features a tell-tale ring of erythema, which helps distinguish it from CD.

Although patchy microscopic mucosal inflammation is a hallmark of CD, it also occurs at the transition zone between inflamed distal and normal proximal mucosa in UC.

Fulminant Colitis

Severe disease flares in patients with distal UC may result in patches of active inflammation in the previously uninvolved colon, which mimic features of CD

Fig. 6.11 Ulcerative colitis showing discontinuous fulminant colitis. The patient experienced a severe flare, which progressed to fulminant colitis requiring a colectomy. There are multiple foci of discontinuous inflammation in the previously uninvolved proximal colon (arrows)

and the severity of which mirrors that of the distal colon (Fig. 6.11). Active UC may also result in superficial fissuring ulcers, which may become deep in fulminant colitis. Their distinction from fissuring ulcers of CD depends on the absence of a granulation tissue lining, recognition of the context of fulminant colitis, and the absence of other classical Crohn features such as granulomas and transmural lymphoid aggregates.

Transmural Inflammation in UC

In UC, the colonic wall directly underlying foci of chronic ulceration may feature deep or even transmural chronic inflammation which is absent beneath the adjoining intact mucosa. Importantly, classical Crohn-like features such as lymphoid aggregates, neural hypertrophy, and lymphatic dilatation are either absent or inconspicuous.

Backwash Ileitis in UC

Backwash ileitis refers to inflammation of a short segment of the distal-most terminal ileum. It affects approximately 10% of resections with pancolitis, mirroring the degree of colonic inflammation in the proximal colon. Unlike Crohn ileitis, it does not result in the thickening of the ileal wall or linear ulceration and does not extend more than a few centimeters proximal to the ileocecal valve.

Granulomas in UC and CD

Although nonnecrotizing granulomas are a hallmark of CD, foreign body granulomas may be elicited by sutures, intraperitoneal contaminants, medications, or parasitic ova. Granulomas may also be associated with lytic crypt abscesses in UC, CD, and other colitides. CD-associated granulomas may contain conchoidal bodies, which are spherical aggregates of basophilic calcium phosphate and refractile crystals of calcium oxalate and are identical to the Schaumann bodies that occur in other systemic granulomatous disorders. They may be mistaken for ova or parasites. Conchoidal bodies are an isolated feature in less than 5% of CD resections but rarely can be numerous.

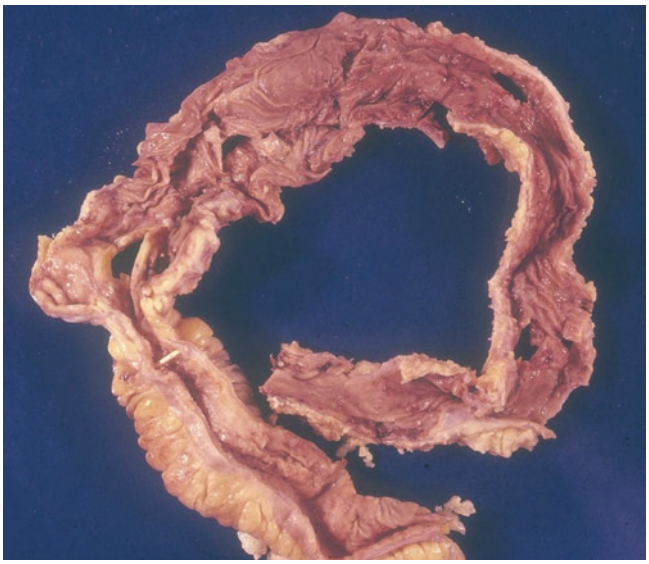

Fig. 6.12 Ileocolic resection with superficial Crohn colitis. The ileal segment exhibits typical features of Crohn ileitis, including fat wrapping and segmental thickening. The colon, in contrast, is thin walled, and the mucosa shows diffuse atrophy

Superficial Crohn Colitis

Rare patients with CD present with colitis that is diffuse and mucosal based rather than transmural, referred to as superficial or "UC-like" CD (Fig. 6.12). The distinction from UC depends either on the detection of granulomas in sections of the intestinal wall or lymph nodes, which may require numerous histological sections, or on the presence of concomitant Crohn ileitis.

Giant Inflammatory Polyposis

Rarely, segmental agglomerations of inflammatory polyps and entrapped feces in patients with IBD, most frequently UC, may form a tumor-like mass that elicits clinical and radiological signs of stenosis and suspicion of CD or malignancy. Histologically, the underlying colonic wall may contain deep fissures and transmural lymphoid aggregates, reinforcing the impression of CD; however, these are absent in the remainder of the colon. One study of 12 resected cases reported that ten patients were ultimately diagnosed as having UC despite that seven of the ten colectomies had classical Crohn-like transmural inflammation limited to the polyposis segment.

References: [3, 4]

4. When should one render a diagnosis of indeterminate colitis and what are the clinical implications?

Indeterminate colitis is diagnosed in up to 15% of colectomy specimens that are pathologically compatible

with IBD but resist clear subclassification as UC or CD due to overlapping or ambiguous features. Although the prototype of indeterminate colitis originally referred to fulminant colitis, the term is now applied in a variety of other circumstances where the pattern of inflammation deviates from the classical rules, whether spontaneously or as a result of therapy. For example, the colon may contain foci of transmural chronic inflammation beneath intact mucosa, but the absence of other classical features of CD, such as follicular lymphoid inflammation, neural hypertrophy, or granulomas, might be attributable to incomplete healing of severe UC. Long-standing refractory UC may present submucosal lymphoid aggregates, mild neural proliferation, pericolic fibrosis, or relative sparing of the rectum. Segmental interposition of grossly normal mucosa between segments with otherwise classical features of UC (excluding the isolated cecal patch or appendiceal inflammation) could warrant a diagnosis of indeterminate colitis unless subtle evidence of healed UC is found microscopically.

The term indeterminate colitis is applied to resection specimens only. The term "unclassified colitis," in contrast, is applied to biopsies from patients with clinical, endoscopic, and histological evidence of IBD that lack specific features to permit confident subclassification as UC or CD.

The distinction between UC and CD plays a pivotal role in determining whether or not patients will undergo restorative proctocolectomy with construction of a continent ileal pouch since CD carries substantially higher rates of complications and pouch failure. Follow-up studies of patients diagnosed with indeterminate colitis who elected to have pouch surgery report indices of long-term pouch function and quality of life, which are more similar to their counterparts with UC than CD; however, 6–14% experience serious Crohn-like complications such as fistulas or afferent limb strictures, which may require pouch revision or excision. As a result, many surgeons will be reluctant to perform pouch surgery in the setting of indeterminate colitis.
References: [5–9]

5. What are the characteristic histological features of chronic IBD in biopsies?

Endoscopic and pathologic assessments of the colorectal mucosa are essential components of the workup and management of patients with IBD. Adequate endoscopic sampling of the colon and rectum is required to avoid potential errors due to sampling variations. For the initial evaluation of patients with IBD, it is suggested that at least two biopsies be taken from the terminal ileum and at least four from the colon and rectum, including both grossly inflamed and normal-appearing mucosae.

The classical histological features of chronic IBD in biopsies include neutrophil infiltration of the crypt and surface epithelium and associated reactive epithelial changes combined with evidence of chronic mucosal damage such as architectural disarray, basal lymphoplasmacytosis, crypt shortfall, and metaplastic Paneth cells or pyloric glands (Fig. 6.13a–c). Assessment of the distribution of microscopic findings within biopsies (focal, segmental, and continuous) and between sites may provide additional information that would help classify chronic IBD.

The passage of time and therapy may result in alterations in histological features and patterns in follow-up biopsies. In histological remission, neutrophils are absent, goblet cell mucin is restored, and lymphoplasmacytic infiltration may be reduced, but abnormal mucosal architecture and metaplastic changes usually persist (Fig. 6.14a). It should be noted that no single histological feature is diagnostic of chronic IBD; rather, a combina-

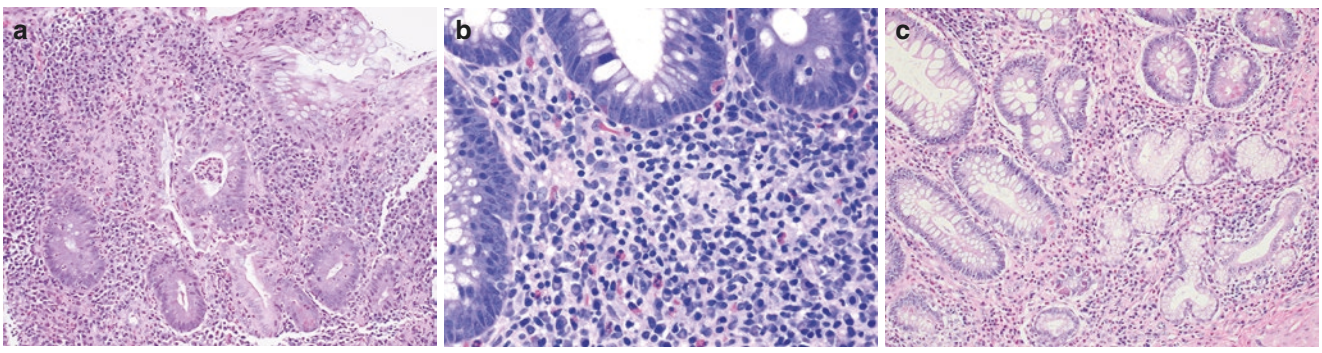

Fig. 6.13 (**a**) The mucosa in inflammatory bowel disease is expanded by a dense lamina propria infiltrate of mononuclear inflammatory cells. The crypts are reduced in number and distributed haphazardly. The crypt epithelium is infiltrated by neutrophils, and goblet cell mucin is markedly reduced. A crypt abscess is seen in the center. Neutrophils in the lamina propria are located mostly in blood vessels. (**b**) Basal lamina propria infiltration by lymphocytes, plasma cells, and eosinophils in a case of Crohn disease. Neutrophils are sparse. A few histiocytes are present in the center, suggestive of a microgranuloma. (**c**) Mildly active Crohn colitis featuring pyloric gland metaplasia

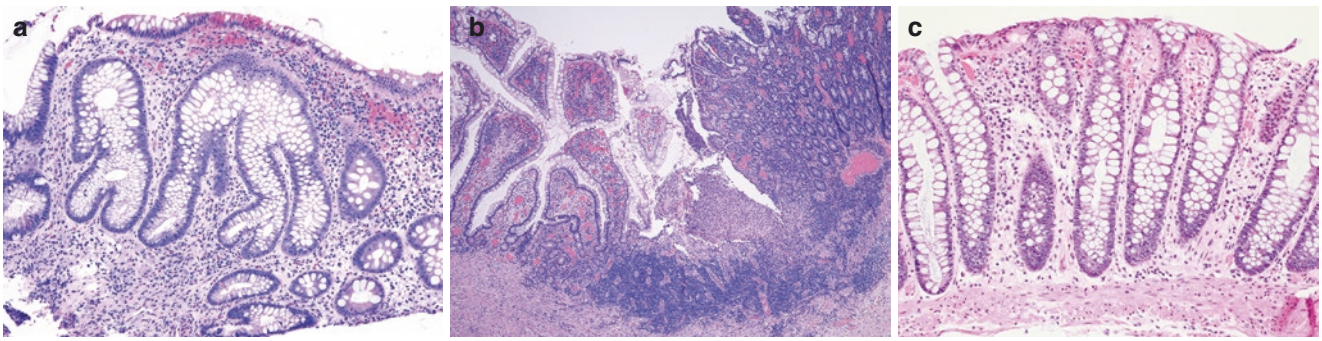

Fig. 6.14 (**a**) Inflammatory bowel disease in remission exhibiting marked crypt architectural distortion. (**b**) Aphthous ulcer in Crohn ileitis characterized by an abrupt mucosal breach filled with acute inflammatory exudate and with underlying lymphoid aggregates. (**c**) Normal colonic mucosa contains parallel crypts of uniform diameter that extend from the surface to the muscularis mucosae and are lined mostly by enterocytes and goblet cells with small basal nuclei. The lamina propria features a top-down gradient of mononuclear inflammatory cells

tion of histological features in conjunction with supportive clinical and endoscopic data is required to reach a definitive diagnosis.

Crypt and Surface Inflammation Active colitis or enterocolitis characterized by cryptitis, crypt abscesses, surface erosions, fissures, or ulcers is commonplace in UC and CD but by no means specific. A more specific feature of IBD is selective neutrophil infiltration of the crypt and surface epithelium combined with relative sparsity of neutrophils within the lamina propria, except areas adjacent to erosions and lysed crypt abscesses (Fig. 6.14b).

Architectural Disarray Normal colorectal crypts are parallel, evenly spaced, uniform in size, and extend from the surface to the muscularis mucosae (Fig. 6.14c). The crypt architecture near the anorectal junction may be irregular. Bifurcated crypts are uncommon except during expansion of the colonic surface area, i.e., in the pediatric age range. Disarray of the crypt architecture occurs in IBD as a result of severe or repeated bouts of inflammatory mucosal injury, producing skewed crypts, branching, budding, and other deviations in shape and size; surface irregularities; and crypt "shortfall," i.e., interposition of fibrous or chronic inflammatory tissue between the crypt bases and the muscularis mucosae. In severe cases, the mucosa becomes dramatically transformed, assuming either a haphazard or villiform appearance on one extreme or an atrophic, pauci-cryptal appearance on the other.

Basal Lymphoplasmacytosis Normal colorectal mucosa includes sparse mononuclear inflammatory cells, most of which are located in the upper third of mucosa, resulting in a top-down inflammatory cell gradient. In chronic inflammatory states, including IBD, the inflammatory cell population becomes dense and expands into the basal region of the lamina propria. Of note, mild basal lymphoplasmacytosis in cecal biopsies is normal.

Mucin Depletion Reduction in the mucin content of goblet cells is a reactive change that is proportionate to the severity of acute inflammation and is therefore a common but nonspecific feature of IBD. Near absence of mucin is characteristic of mucosa during recovery from ulceration. Uniformly reduced surface mucin may also occur in response to bowel preparation.

Granulomas Granulomas in CD range from inconspicuous clusters of a few epithelioid histiocytes, so-called microgranulomas, to compact collections of five or more epithelioid histiocytes, Langhans cells, and intermingled lymphocytes. They occur in 5–20% of biopsies from adult patients and more frequently in children. The differential diagnosis includes granulomatous infections such as lymphogranuloma venereum, tuberculous and nontuberculous mycobacterial colitis, syphilis and parasitoses, and a variety of other systemic granulomatous diseases. The granulomas of CD lack central necrosis or suppurative inflammation, are rarely larger than 0.4 mm, and are usually isolated and discrete rather than confluent. Foreign body granulomas resulting from ruptured crypts (cryptolytic granulomas) can pose a diagnostic pitfall since they occur in UC and other colitides (see question 6). Isolated multinucleated giant cells in the mucosa have no diagnostic significance.

Paneth Cell Metaplasia Paneth cells are a normal constituent of the basal crypts of the small intestinal and proximal colonic mucosa. Paneth cells that occur in mucosa originating beyond the distal transverse colon are considered to be a metaplastic adaptation to chronic mucosal injury and are commonplace in IBD, albeit not specific. The presence of metaplastic Paneth cells in otherwise normal mucosal biopsies is diagnostically useful, providing tell-tale evidence of healed colitis despite histological normalization. The metaplastic cells are usually grouped in their normal basal positions and are not iden-

tifiable without knowledge of the biopsy site; however, metaplasia can be recognized even in biopsies from the proximal colon when the Paneth cells are more numerous than usual, are noncontiguous, or proliferate beyond the crypt base.

Pyloric Gland Metaplasia Also referred to as pseudopyloric metaplasia, mucinous gland metaplasia, ulcer-associated cell lineage, and spasmolytic polypeptide-expressing metaplasia, this type of metaplasia is considered to be a ubiquitous response to long-standing chronic mucosal injury in the gastrointestinal tract. Although commonplace in IBD, especially in Crohn enteritis and colitis and in chronic pouchitis, it can occur in UC, in nonsteroidal anti-inflammatory drug (NSAID)-associated colitis, and in other chronic inflammatory disorders.

References: [10–13]

Table 6.1 Characteristic histological features of UC and CD in biopsies

Histological feature	UC	CD
Crypt architectural distortion	Variable	
Basal plasmacytosis	Present	
Distribution of inflammation	Diffuse	Diffuse or patchy
Location of inflammation	Mucosa ± superficial submucosa	Mucosa and deeper layers
Mucin depletion	Proportionate to active inflammation	
Cryptitis, crypt abscess	Variable	
Lamina propria neutrophils	Rare except in blood vessels and adjacent to erosions, ruptured crypts	
Epithelioid granulomas	Absent (except adjacent to damaged crypts)	5–20%
Paneth cell metaplasia	Common	Less common than UC
Pyloric gland metaplasia	Uncommon	Common

6. What histological features are most useful in discriminating between ulcerative and Crohn colitis in biopsies and what potential pitfalls should be avoided?

Biopsies are most helpful in the subclassification of IBD when they yield features that are specific for CD. The two most diagnostically significant features are nonnecrotizing epithelioid granulomas and focal inflammation (Table 6.1).

Granulomas should be distinguished from perivascular mesenchymal cells, nerves, smooth muscle bundles and tangential sections of crypts. Most such ambiguities can be resolved by comparing serial histological sections to obtain different views of the lesion. Cryptolytic granulomas elicited by ruptured crypt abscesses are nonspecific but can closely mimic the specific granulomas of CD (Fig. 6.15a). Most occur at the bases of crypts, but the location alone is nondiagnostic. The "missing crypt" sign corresponds to a granuloma that has replaced a lytic crypt abscess that became resorbed (Fig. 6.15b). Other clues that favor cryptolytic over Crohn granulomas include superposition on a partially lytic crypt abscess, the presence of intermingled or clustered neutrophils or eosinophils, a loose rather than compact appearance, pale or foamy histiocytic cytoplasm, and the presence of Touton giant cells (Table 6.2). It is helpful when crypt abscesses and recognizable cryptolytic granulomas are present in the neighboring mucosa. Granulomas that are composed of compact histiocytes with eosinophilic cytoplasm or are located within a lymphoid aggregate are likely related to CD (Fig. 6.15c).

Focal inflammation, i.e., discrete areas of inflammation abutting on otherwise normal mucosa, is suggestive of CD but should be interpreted cautiously (Fig. 6.16a). For example, focal inflammation in UC occurs during the course of healing, during inflammatory flares in patients with previously well-healed colitis, and in the transition zone between involved and uninvolved colonic segments. Crypt inflammation that is limited to only a few crypts, referred to as "focal active colitis," is predictive of CD in

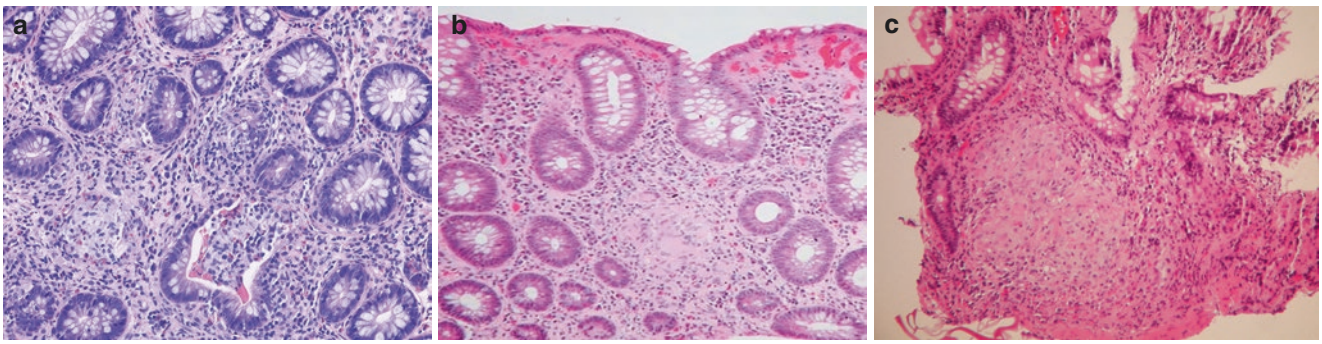

Fig. 6.15 (**a**) Cryptolytic granulomas in inflammatory bowel disease are associated with damaged crypts and are not diagnostic of Crohn disease. In addition to histiocytes and lymphocytes, they often contain neutrophils or eosinophils that originated in ruptured crypt abscesses. (**b**) A cryptolytic granuloma replaces a resorbed crypt abscess. (**c**) A nonnecrotizing granuloma in Crohn disease

children but is seen in adults in the setting of NSAID use, infections, and other conditions.

The presence of chronic submucosal inflammation in biopsies of IBD is not specific for CD since inflammation of the upper region of the submucosa occurs in UC as well (Fig. 6.16b). By the same token, submucosal involvement is not always present in CD. Although a biopsy series that suggests a continuous active colitis without submucosal involvement is more likely to indicate UC than CD, our policy is to avoid subclassification of IBD based on biopsies alone unless they reveal diagnostic features of CD. References: [14, 15]

Table 6.2 Distinguishing features between Crohn-associated and cryptolytic granulomas

	Crohn-associated	Cryptolytic
Location	Anywhere in mucosa	Usually basal mucosa
Boundaries	Well defined	Well or poorly defined
Intragranuloma neutrophils	None	Common, ± microabscesses
Intragranuloma eosinophils	Few	Common, ± microabscesses
Intragranuloma crypt epithelial cells	No	Common
Histiocytes	Lightly to moderately eosinophilic	Pale
Giant cells	Occasional, Langhans type	Occasional, Touton type
Nearby crypt abscesses	Variable	Present
Lymphoid aggregates	Common within lymphoid aggregates	Rare within lymphoid aggregates

7. How is infectious colitis distinguished from IBD in mucosal biopsies?

Acute infectious colitis is caused by various foodborne agents, other contaminated environmental sources, and person-to-person or zoonotic transmission. Most cases resolve within 2–4 weeks from the onset of symptoms, but some infections may linger for a month or longer. The pathogens implicated most frequently in immunocompetent patients in the US are *Clostridium difficile*, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, and *Escherichia coli* O157:H7, as well as Norwalk virus, enterovirus, rotavirus, adenovirus, and Coxsackie virus. Conventional laboratory testing fails to identify a specific agent in most cases but is being increasingly supplemented by highly sensitive polymerase chain reaction (PCR)-based stool tests.

Patients with acute colitis symptoms generally do not undergo endoscopic examination unless their presentation is atypical, they have specific risk factors, or they have already failed antibiotic therapy. The endoscopic changes include patchy or diffuse erythema, obscured vasculature, granularity, petechia, erosions, or, in certain cases, pseudomembranes. Certain pathogens, particularly *Yersinia*, *E. coli*, *Campylobacter*, *Salmonella*, and tuberculosis, tend to involve the right colon preferentially.

Biopsies performed during the initial week of symptoms feature edema and neutrophils in the lamina propria, neutrophil infiltration of the surface and crypt epithelium, and preservation of the parallel crypt architecture (Fig. 6.17a). At this stage, the normal top-down mucosal gradient of lymphocytes and plasma cells is maintained. Crypt abscesses are often dilated and lined by low cuboidal or flat epithelium. Ruptured crypts may elicit

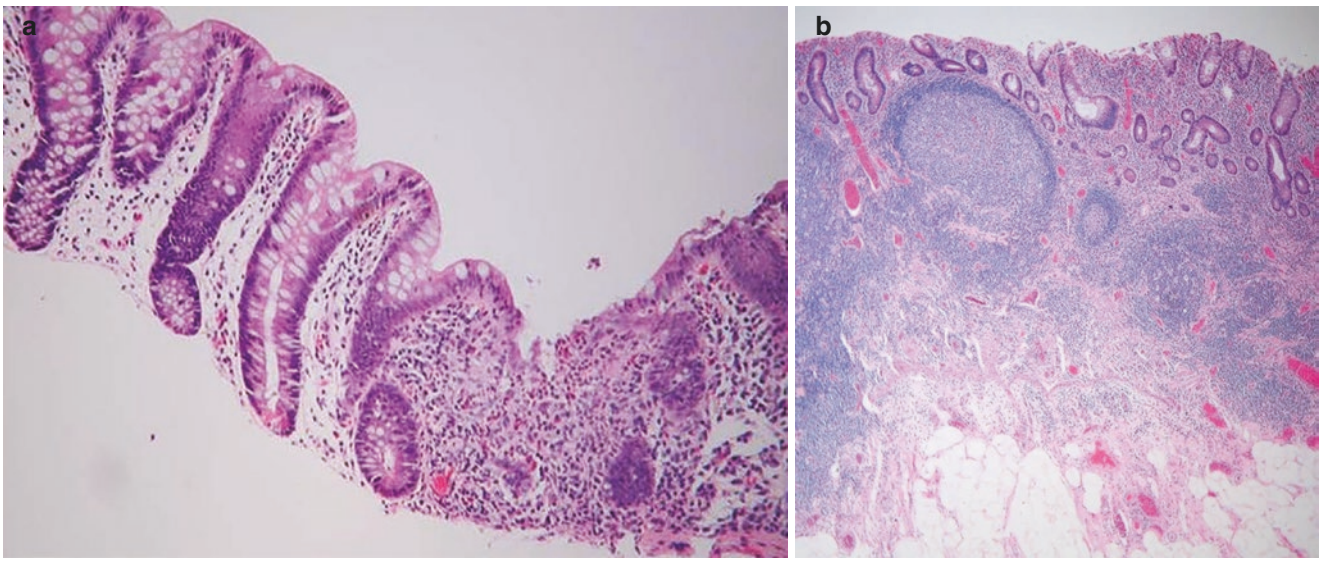

Fig. 6.16 (**a**) Focal colitis is a common feature of biopsies in Crohn disease but can occur in other settings such as reactivation of quiescent ulcerative colitis or in the transition zone of ulcerative colitis. (**b**) Ulcerative colitis with inflammation involving the mucosa and superficial submucosa. Submucosal inflammation in standard-sized biopsies should not be used as a criterion to favor Crohn disease over ulcerative colitis

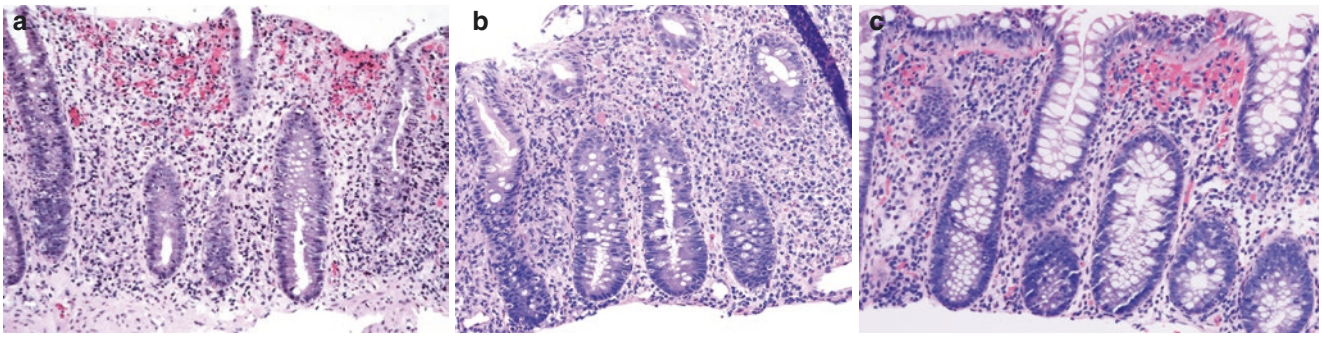

Fig. 6.17 (**a**) Biopsy of a patient with acute infectious colitis featuring preserved crypt architecture, lamina propria edema, and neutrophilic infiltrates involving the lamina propria and the crypt epithelium. (**b** and **c**) Beyond the first week from symptom onset, biopsies of patients with acute infectious colitis feature gradual increases in mononuclear cells and progressive involvement of the basal lamina propria

Table 6.3 Features distinguishing between IBD and acute and chronic infectious colitis

	IBD	Acute infectious colitis	Chronic infectious colitis
Architecture			
Irregular/villiform surface	Common, UC > CD	Uncommon	Uncommon
Crypt architectural distortion	Present	Absent	Mild
Crypt atrophy	Common	Uncommon	Uncommon
Edema	Uncommon	Common, especially in early stage	Variable
Inflammation			
Basal lymphoplasmacytosis, crypt shortfall	Common	Absent	Variable
Top-down mononuclear cell gradient	Absent	Present	Variable
Lamina propria neutrophils	Relative paucity	Present	Present
Cryptitis	Present	Present	Present
Crypt abscesses	Columnar lining epithelium	Cuboidal to flat lining epithelium	Variable
Granulomas	Nonnecrotizing (CD)	Rare, ill-defined (e.g., *Salmonella*)	Necrotizing (TB, fungi), nonnecrotizing (LGV, syphilis)
Epithelium			
Mucin depletion	Common	Common	Common
Paneth cell metaplasia	Common	Absent	Rare
Pyloric gland metaplasia	Present, CD>UC	Absent	Rare

a granulomatous reaction. Infections with *C. difficile*, *Shigella*, enterohemorrhagic strains of Escherichia coli and Klebsiella oxytoca may feature pseudomembranous exudates, lamina propria hemorrhage, or frank ischemic features such as microcystic or withered crypts.

Histologically, IBD contrasts starkly with acute infectious colitis even when biopsied at its inception (Table 6.3). The presence of full-thickness lymphoplasmacytosis, mucosal expansion, crypt disarray, shortfall, columnar-lined crypt abscesses, and relative paucity of neutrophils in the lamina propria are readily identified as features of IBD. Nonetheless, patients suspected of having acute infectious colitis are unlikely to undergo endoscopic biopsies until several weeks after the onset of symptoms, the exclusion of incipient IBD being one of the main indications. At this subacute stage, edema has subsided and mononuclear inflammation becomes dense and gradually occupies the basal lamina propria (Fig. 6.17b and c). Despite the resulting overlap with IBD, subacute infections can be recognized by noting the absence of crypt disarray or shortfall and by the presence of neutrophils in the lamina propria.

Chronic infectious colitis is relatively uncommon in Western countries, and its distinction from IBD can be challenging. The most common agents in immunocompetent patients are sexually transmitted diseases such as syphilis and lymphogranuloma venereum (LGV), *C. difficile*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*, *Mycobacterium tuberculosis* (Fig. 6.18), and *Entamoeba histolytica* (Fig. 6.19a and b). In some geographic locales, IBD may be mimicked by endemic strains of *Salmonella*, *Shigella*, and other enteropathogens as well as by schistosomiasis, but these are infrequently encountered in the US.

Syphilis (Fig. 6.20 and b) and LGV (Fig. 6.21) both involve the anus and rectum and are endoscopic mimics

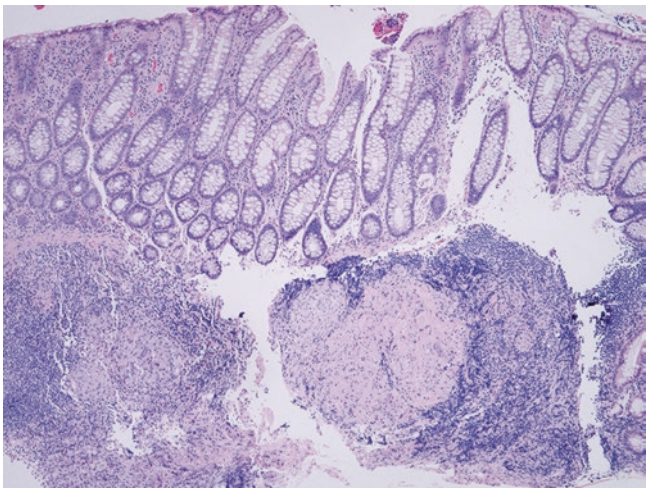

Fig. 6.18 Tuberculous colitis featuring large submucosal granulomas beneath intact mucosa. Early necrosis is seen in the granuloma on the left

of IBD. Histologically, they are characterized by mucosal expansion associated with dense plasmacytosis but only mild crypt architectural distortion. Other features that might suggest the diagnosis include band-like submucosal lymphoplasmahistiocytic infiltration, nonnecrotizing granulomas, and perivascular lymphoplasmacytic cuffing in the submucosa. Immunostaining for *Treponema pallidum* (*T. pallidum*) is diagnostic, but the organisms may be faintly stained and difficult to recognize.

Gastroenteric infections are both risk factors and potential triggers for the development of IBD, often within the first year after the infectious episode. The agents most commonly identified are *Campylobacter*, *Salmonella*, and *Shigella*, but *C. difficile* and *Aeromonas* have also been implicated. Histologically, serial biopsies over the span of a few months may show progression from an acute or subacute infectious pattern to classical IBD.

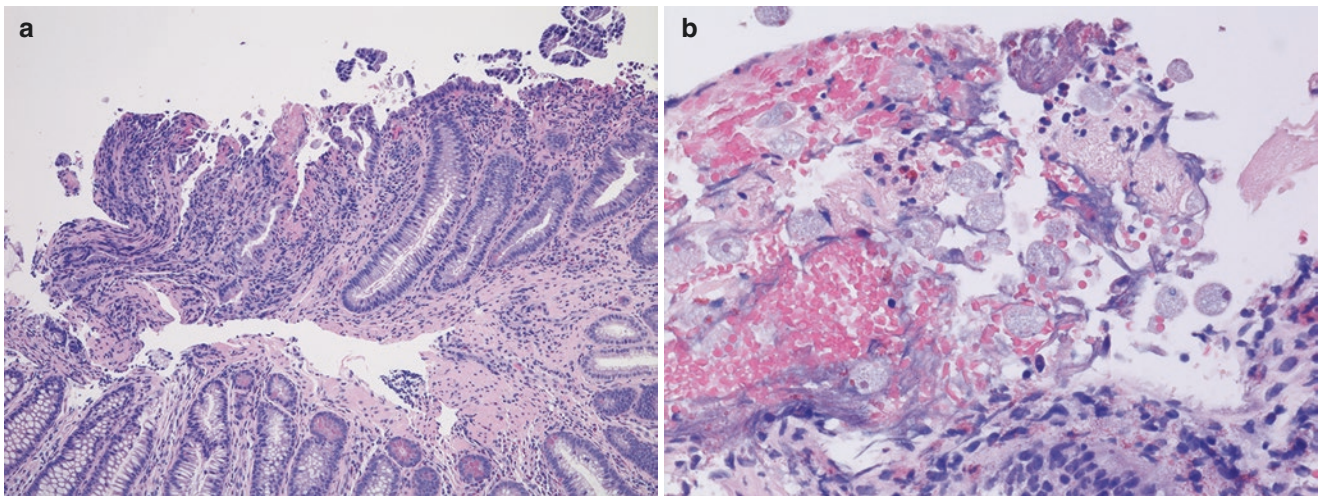

Fig. 6.19 Amebic colitis. (**a**) The mucosa features very mild chronic inflammation and an erosion surrounded by mucin-depleted epithelium. (**b**) Ameba histolytica trophozoites

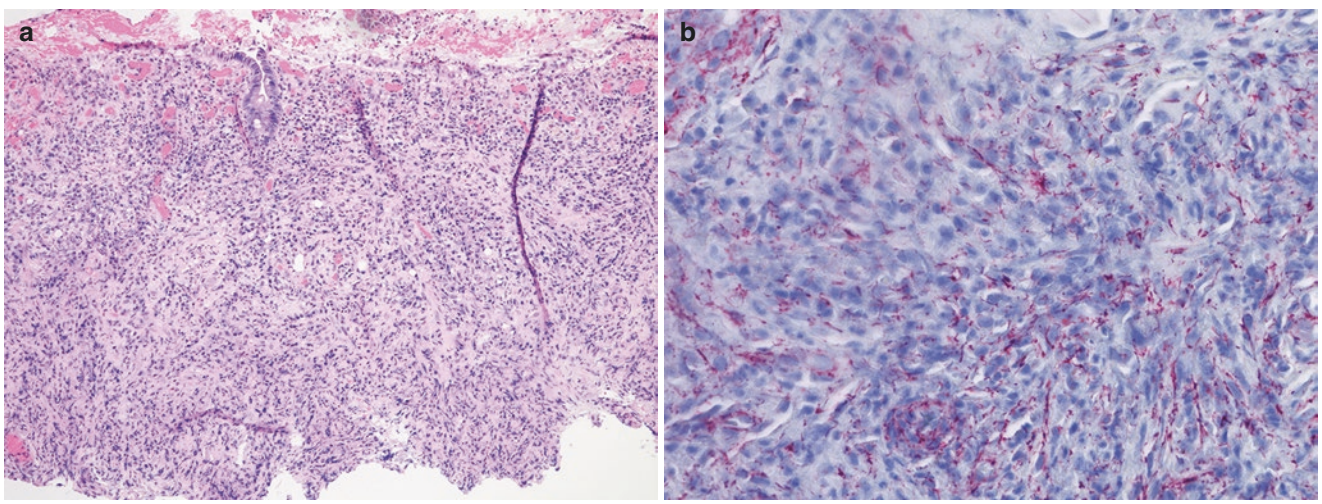

Fig. 6.20 Syphilitic proctitis. (**a**) Dense chronic inflammation in a rectal biopsy. (**b**) A clinical history relating prior anal condylomas elicited immunostaining for spirochetes

References: [13, 16–19]

8. What drugs and other toxic agents might mimic IBD in colorectal biopsies?

Drug-related colitis should always be considered in the differential diagnosis of IBD. The following commonly used drugs are particularly prone to mimic IBD in biopsies.

NSAIDs are cyclooxygenase (COX) inhibitors that are widely administered for a variety of complaints. They cause acute upper and lower gastrointestinal (GI) inflammation, the results of direct topical toxicity and local depletion of prostaglandins, and they elicit diverse histological effects, including reactive epithelial changes, ischemic-type injury, acute inflammation and ulceration, postinflammatory crypt architectural disarray, and pyloric gland metaplasia (Fig. 6.22a). Rarely, long-term NSAID use results in so-called diaphragm disease characterized by concentric protrusions of mucosa and submucosa, which can mimic stricturing CD.

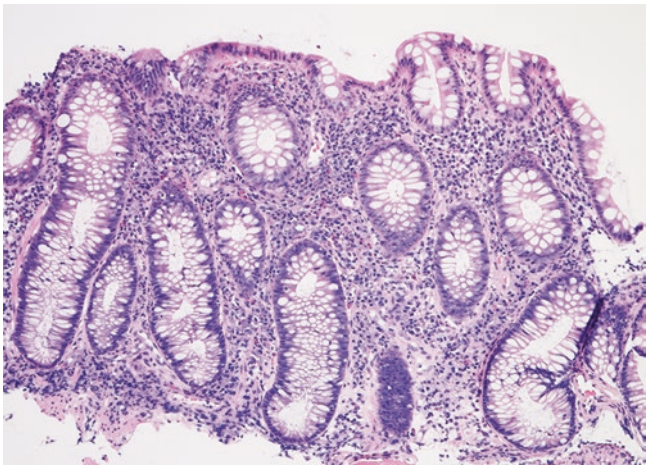

Fig. 6.21 Chlamydia proctitis. The histological features closely resemble those of inflammatory bowel disease, including full-thickness lymphoplasmacytosis and mildly distorted crypt architecture. Clinical data suggesting sexually transmitted disease are essential to the diagnosis

Mycophenolate mofetil (MMF) is an immune suppressant that is commonly used for prophylaxis of organ rejection in renal, cardiac, liver, and stem cell transplantation and for the treatment of autoimmune diseases such as autoimmune hepatitis, lupus nephritis, and autoimmune blistering diseases. GI side effects occur in 30–64% of patients, most commonly during the first 6 months of treatment. The histological effects have been grouped into four patterns: acute infectious-like (16%), ischemia-like (3%), graft-versus-host disease (GVHD)-like (19%), and IBD-like (28%). The latter group is characterized by crypt architectural distortion, acute and chronic inflammation, and dilated crypts with eosinophils and neutrophils (Fig. 6.22b).

Antitumor necrosis factor (TNF) agents include etanercept, a TNF- α inhibitor, and two anti-TNF-α antibodies, infliximab and adalimumab. In addition to the treatment of IBD, TNF-α inhibitors are used in the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and juvenile idiopathic arthritis. They have been reported to elicit paradoxical adverse effects, including new-onset IBD or flares of colitis in patients with IBD, the onset of which may occur days to years after the introduction of therapy.

Rituximab is a chimeric monoclonal antibody against CD20, a surface protein on most B lymphocytes. Initially approved for the treatment of non-Hodgkin B-cell lymphoma and later for rheumatoid arthritis, it is also used for other autoimmune disorders that involve B-cell activation, such as lupus, Wegener granulomatosis, dermatomyositis, and steroid refractory UC. New onset and exacerbation of UC-like colitis after rituximab salvage therapy have been reported. GI symptoms occur weeks to months after rituximab exposure. Biopsies mainly show UC-like features, including mixed inflammatory cell infiltrates, ulceration, and cryptitis.

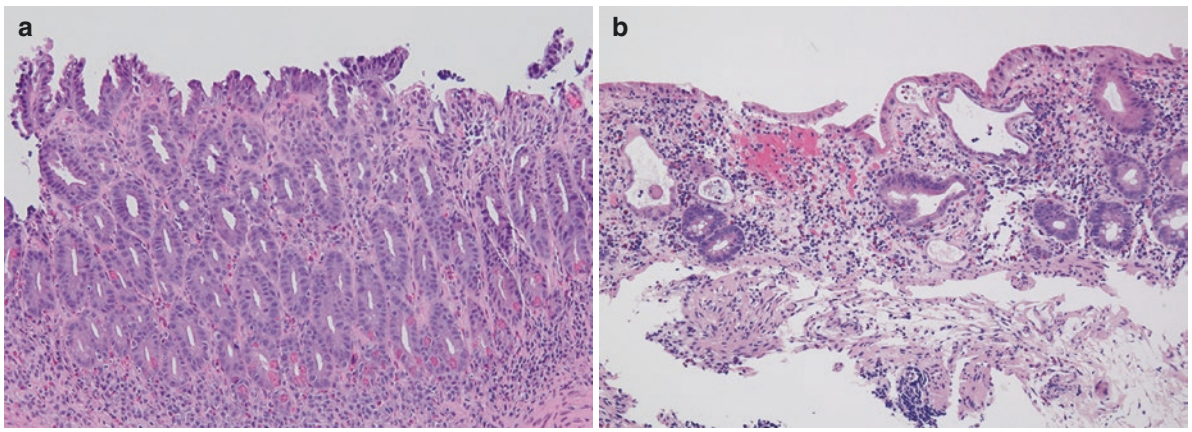

Fig. 6.22 (**a**) Chronic NSAID-associated enteropathy. The villi of the small bowel are blunted/atrophic. The crypt cells contain reactive nuclei, are devoid of goblet cells, and are reduced in size toward the surface, features that are reminiscent of ischemic change. (**b**) Mycophenolate-mofetil-associated colitis featuring damaged crypts lined by attenuated eosinophilic cytoplasm, some containing necrotic debris

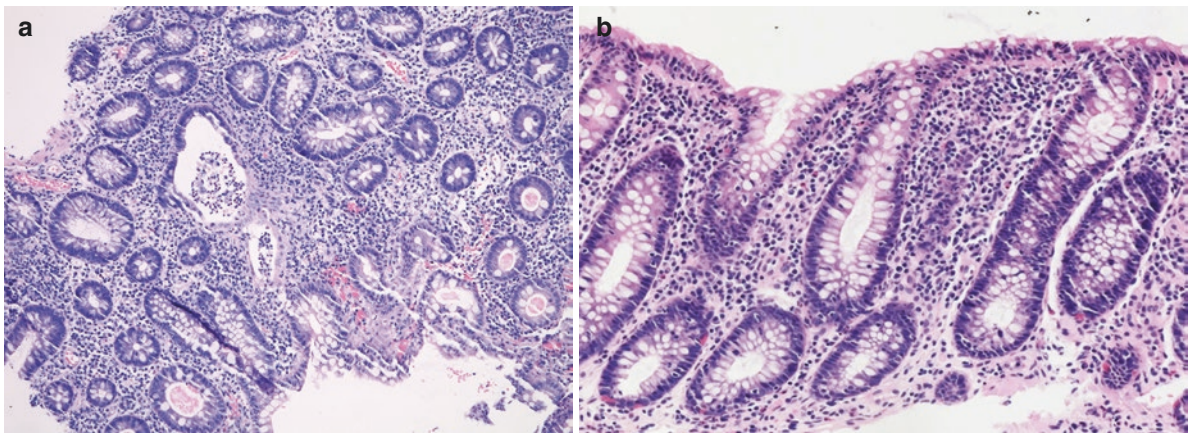

Fig. 6.23 Ipilimumab-associated colitis. (**a**) The dense lymphoplasmacytosis and crypt distortion in this case closely mimic inflammatory bowel disease. (**b**) Another case of ipilimumab-associated colitis in which the histology mimics lymphocytic colitis

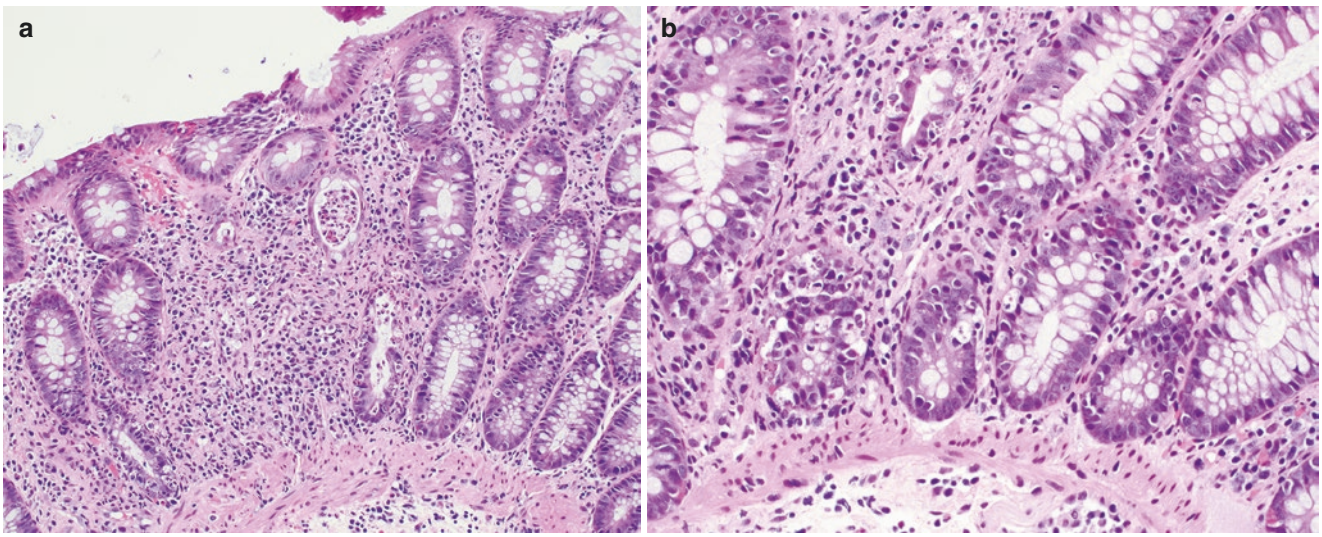

Fig. 6.24 (**a**) PD-1-associated colitis. Full-thickness lymphoplasmacytosis indicates chronicity, but the features in this case are otherwise nonspecific and the diagnosis requires knowledge of the drug history. (**b**) Another case of PD-1 colitis. The numerous crypt apoptotic bodies are consistent with immunotherapy-related drug toxicity

Ipilimumab is an immune checkpoint inhibitor that consists of a monoclonal antibody that targets CTLA-4, a protein receptor that competes with CD28 to bind B7, thereby downregulating T-cell activation. The drug is approved for the treatment of late-stage melanoma and is undergoing trials for the treatment of various other cancers. Treatment is associated with diarrhea in 21–35% of patients. Biopsies reveal marked lamina propria mixed inflammatory cell infiltrates composed of neutrophils, lymphocytes, plasma cells and eosinophils, cryptitis and crypt abscesses, and rarely granulomas (Fig. 6.23a). Intraepithelial lymphocytosis mimicking lymphocytic colitis may be seen (Fig. 6.23b). Life-threatening colitis with perforation has been reported.

Other immune checkpoint inhibitors include the anti-PD-1 agents pembrolizumab and nivolumab and anti-PD-L1 agents such as atezolizumab, which are approved for the treatment of a growing list of malignancies. The drugs act by limiting the effector function of activated T cells; however, disruption of the immune balance results in distinctive toxicity profiles, among them colitis and endocrine dysfunction. Eleven to 20% of patients develop GI symptoms such as diarrhea, abdominal pain, discomfort, and cramping, beginning from weeks to months after treatment onset, and 0.3–2.3% experience morbidity from colitis, including fatalities. Two histological patterns of colitis have been described. One is GVHD-like featuring varying degrees of apoptosis, cryptitis, crypt abscesses, crypt atrophy, and dropout (Fig. 6.24a and b). The other resembles lymphocytic colitis with surface epithelial damage, intraepithelial lymphocytosis, and occasionally apoptosis. Recurrent active anti-PD-1 colitis may result in crypt architectural distortion, basal lympho-

plasmacytosis, and Paneth cell metaplasia, closely mimicking IBD.
References: [20–26]

9. How does the pathology of pediatric IBD patients differ from that in adults?

Twenty to 25% of patients with IBD are diagnosed before the age of 20, most during adolescence; 18% before age 10; and 4% before age 5. In contrast with adult UC patients, most of whom present with distal or left-sided disease, up to 90% of pediatric UC patients either present from the outset with pancolitis or have aggressive disease that progresses to pancolitis in a short time. The incidence of pediatric CD is higher than that of UC and is reportedly increasing in Western countries. Children with CD are most likely to present with isolated colitis or ileocolitis, whereas isolated terminal ileitis is increasingly common in adolescents and adults. Up to 15% have proximal small intestinal disease, at least 40% have histological manifestations of CD in the upper gastrointestinal tract, and 15–20% develop perianal disease.

The histological diagnosis of IBD in pediatric patients may be challenging, thereby contributing to the relatively high proportion of pediatric patients, 30% in some studies, who are diagnosed with indeterminate colitis. Rectal sparing and patchiness are more prevalent in pediatric than in adult UC patients, with approximately 30% (range: 21–68%) of new onset pediatric patients having either complete or more frequently relative sparing of the rectosigmoid colon. In patients under 10, initial colonic biopsies reveal less crypt architectural distortion

Table 6.4 IBD differential diagnosis—helpful clinical and pathologic features

Entity	Predisposing conditions	Clinical features	Distinguishing pathologic features
Acute self-limited colitis	Travel, community, or institutional outbreaks; sexual transmission; antibiotic use	Acute onset, diarrhea, fever, dysentery, bleeding per rectum	Neutrophilic infiltration of mucosa, lamina propria edema (first 4–5 days), preserved crypt architecture, necklace-like crypt abscesses with flat epithelium, surface neutrophils with epithelial tufting, lack of basal lymphoplasmacytosis until 2–3 weeks; certain infections feature pseudomembranes and/or right-sided colonic predominance
Ischemic colitis	Elderly, comorbidities, cardiovascular disease, hypovolemic shock, drugs (vasopressors, oral contraceptives), heavy exercise, sickle cell disease	Abdominal pain, bloody diarrhea	Microcystic crypts with surface tapering and few or absent goblet cells, eosinophilic lamina propria, surface necrosis (Fig. 6.25)
Diverticular-disease-associated colitis	Elderly, diverticulosis	Pain, bleeding per rectum	Chronic colitis limited to diverticular colon, rectal sparing, IBD-like histology
Diversion colitis	Colon bypass surgery	Mucous discharge, bleeding	Lymphoid hyperplasia, mild crypt architectural distortion
Drug-associated colitis	Drug use (mycophenolate, immune checkpoint inhibitors, antihypertensives, chemotherapeutic, colchicine, many others)	Variable, diarrhea	Variable depending on drug
GVHD	History of bone marrow or solid organ transplantation	Diarrhea, skin rash, elevated liver enzymes	Glandular apoptotic bodies, crypt dropout (Fig. 6.26)
Lymphocytic colitis and collagenous colitis	Elderly, female (collagenous), celiac disease, and other autoimmune diseases	Insidious or abrupt onset, nonbloody watery diarrhea, fecal incontinence	Preserved crypt architecture, increased lamina propria mononuclear cells ± top-down gradient, increased intraepithelial lymphocytes (variable in collagenous colitis), subepithelial collagen band (collagenous colitis) (Fig. 6.27)
Autoimmune enteropathy	Children, less commonly adults, genetic predisposition (IPEX syndrome, APECED syndrome), posttherapy for hematological malignancies	Intractable diarrhea	Surface and crypt epithelial apoptotic bodies, reduced or absent goblet cells and/or Paneth cells, mononuclear cell infiltration of lamina propria; sometimes little or no histological changes (Fig. 6.28)
CVID	Adults	Variable, recurrent sinonasal respiratory and other infections	Paucity of plasma cells in lamina propria (70%), intraepithelial lymphocytes, follicular lymphoid hyperplasia, apoptotic bodies (Fig. 6.29)
Chronic granulomatous disease	Children, X-linked inheritance	Recurrent bacterial and fungal infections, diarrhea	Pigment-laden macrophages, eosinophilic cryptitis, paucity of neutrophils

GVHD graft-versus-host disease, *IPEX* immune dysregulation, polyendocrinopathy, enteropathy, X-linked, *APECED* autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, *CVID* common variable immunodeficiency

and other evidence of chronicity than in adolescents and adults. Atypical features of UC such as backwash ileitis, periappendiceal inflammation, and isolated cecal patch are as common in children as in adults.

Mucosal lesions of CD in children can be subtle and lacking in features of chronicity. Early histological manifestations include aphthous lesions; focal active colitis, i.e., localized neutrophilic and lymphoplasmacytic infiltrates in an otherwise normal background; and increased lamina propria eosinophils. Epithelioid granulomas are more common in children with CD than in adults. Their presence has been linked to more extensive disease and perianal complications. Upper GI inflammation occurs in most children with CD, even in the absence of symptoms and of radiological or endoscopic manifestations, and granulomas are detected in up to 40%. Focally enhanced gastritis featuring a localized mixed neutrophilic and mononuclear inflammatory infiltrate occurs in approximately half of children with CD. This and other patterns of upper GI inflammation also occur in UC, albeit less frequently.

References: [15, 27–31]

10. What is the differential diagnosis of IBD in biopsies?

The major differential diagnoses of IBD in biopsies are listed in Table 6.4, along with associated characteristic clinical and histological features.

References: [16, 32–34]

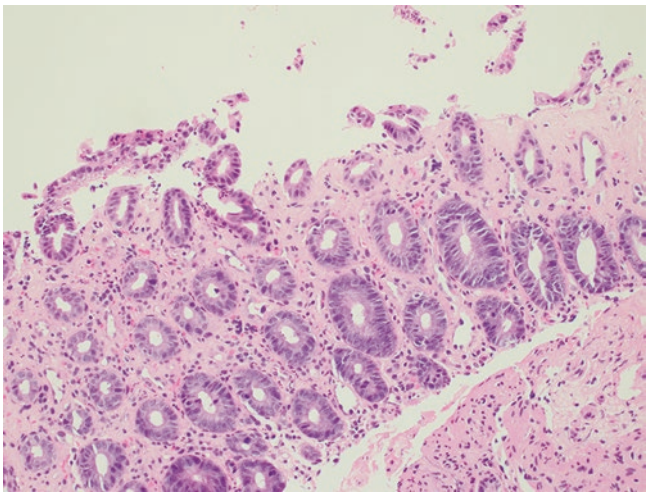

Fig. 6.25 Ischemic colitis characterized by densely eosinophilic hyalinized lamina propria and withering, goblet-cell-depleted crypts near the luminal surface

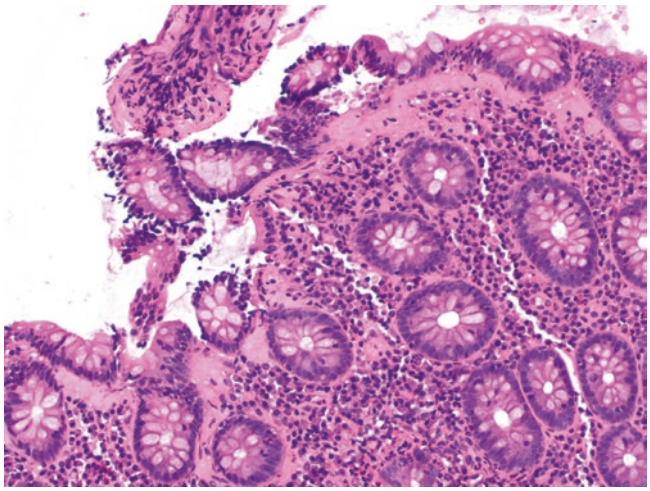

Fig. 6.27 Collagenous colitis featuring preserved crypt architecture, lamina propria expansion due to lymphoplasmacytosis, and a thickened subepithelial collagen band

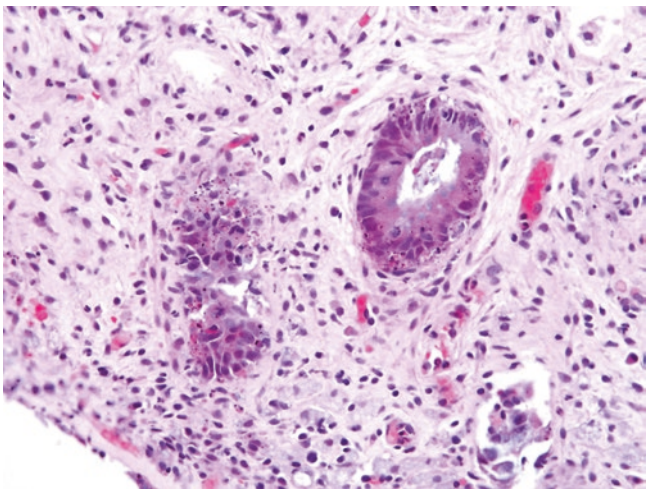

Fig. 6.26 Graft-versus-host-disease characterized by numerous crypt apoptotic bodies, damaged crypts, and crypt dropout

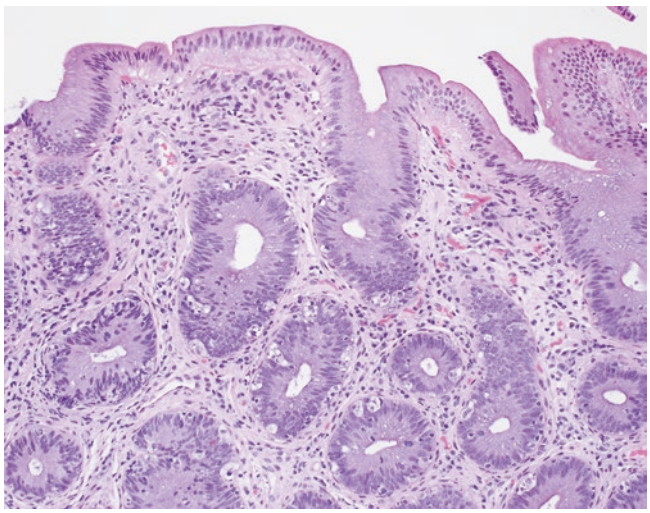

Fig. 6.28 Autoimmune enteropathy featuring complete loss of goblet cells and numerous crypt apoptotic bodies. Paneth cells are absent in many cases

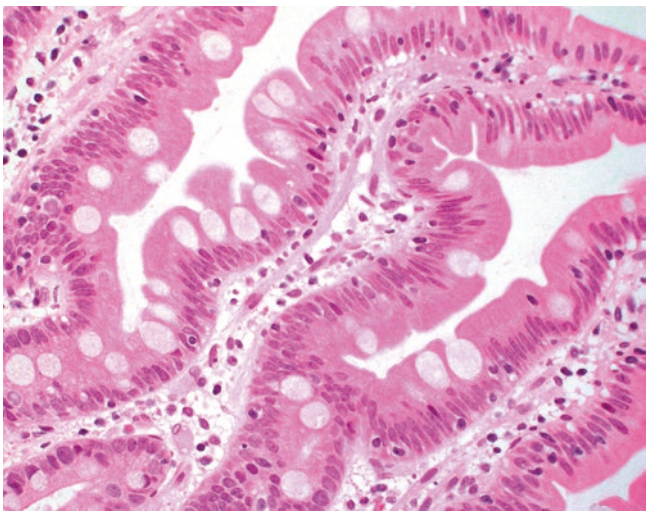

Fig. 6.29 Common variable immunodeficiency usually features a paucicellular lamina propria due to reduced density or absence of plasma cells, as well as surface intraepithelial lymphocytosis and lymphoid hyperplasia

11. What are the upper GI manifestations of ulcerative colitis and Crohn disease?

Severe gastroduodenal involvement occurs in approximately 5% of patients with CD; however, routine diagnostic endoscopy identifies macroscopic inflammation in 30–64% and histological inflammation in up to 80% of CD patients when endoscopically visible lesions are targeted. Children with UC are reported to have IBD-like inflammation in the upper GI tract with nearly the same frequency as those with CD.

The prevalence of granulomas in CD is highest in children, approximately 30%, and decreases with age to approximately 15% (Fig. 6.30a). The differential diagnosis includes cryptolytic granulomas, infections, sarcoidosis, chronic granulomatous disease, and malignancy.

Other upper GI manifestations of CD include focally enhanced gastritis (Fig. 6.30b), characterized by focal perifoveolar or periglandular mononuclear or neutrophilic infiltrates, active chronic gastritis that closely

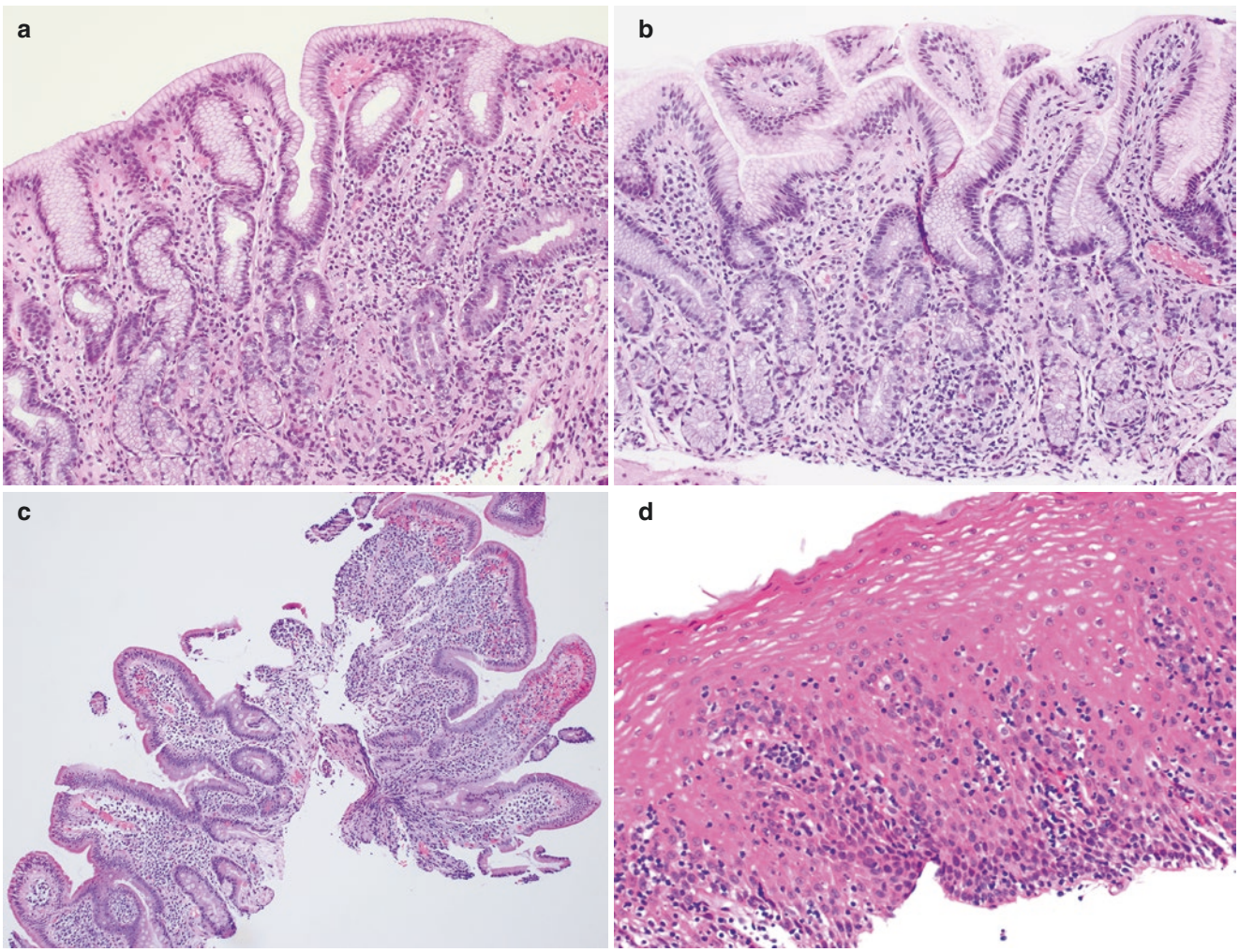

Fig. 6.30 (**a**) Crohn gastritis with an epithelioid granuloma. (**b**) Focally enhanced gastritis in Crohn disease characterized by periglandular neutrophilic and lymphohistiocytic infiltrates. (**c**) Chronic duodenitis in a patient with ulcerative colitis. (**d**) Lymphocytic esophagitis featuring peripapillary lymphocytosis, which can be seen in patients with Crohn disease

mimics *Helicobacter pylori* infection, and intraepithelial lymphocytosis of the small intestine, which may be evident before the diagnosis of IBD has been made. Duodenal ulceration and villous atrophy are reported in UC as well as CD but need to be distinguished from other common etiologies such as peptic duodenitis and NSAID-associated inflammation. IBD-like diffuse chronic duodenitis (Fig. 6.30c) with lamina propria lymphoplasmacytosis has been described as a unique upper GI manifestation of UC that may predict adverse outcomes, including colectomy and pouchitis.

Esophageal inflammation, including "lymphocytic esophagitis" manifested by peripapillary lymphocytosis (Fig. 6.30d), can be attributed to known CD if accompanied by granulomas; however, it does not otherwise discriminate between gastroesophageal reflux disease and other etiologies.

References: [35–39]

12. What are the main complications of ileoanal pouch surgery for IBD?

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for medically refractory UC or colitis-associated dysplasia. Although Crohn colitis is considered to be a relative contraindication for IPAA due to the risk of pouch failure and its potentially serious complications, many centers perform the procedure selectively in patients with isolated colitis and no evidence of fistulizing disease. As a result, pouch retention rates exceeding 85% have been reported. The postoperative complications of IPAA include septic complications such as leaks, fistulas, and abscesses; nonseptic complications such as stenosis, pouchitis, and cuffitis; mechanical complications such as prolapse; and the long-term development of dysplasia or cancer.

Pouchitis Pouchitis is the most common complication, affecting nearly half of patients. The risk factors for developing pouchitis include extensive UC, backwash ileitis, risk polymorphisms of NOD2/CARD15, PSC, and use of biologics or NSAIDs. Pouchitis encompasses a spectrum that ranges from acute antibiotic-responsive to antibiotic-dependent to chronic antibiotic refractory disease. Specific causative factors include infections with cytomegalovirus, *Clostridium difficile*, or *Candida*; treatment-associated factors such as radiation and chemotherapy; ischemia; PSC; IgG4-associated disease; and autoimmune pouchopathy.

Histological evaluation has limited value in grading pouchitis compared with endoscopic scoring. Villous blunting, crypt hyperplasia, and mildly increased mononuclear cells in the lamina propria are frequently observed in biopsies from asymptomatic patients and are thought to be adaptive. However, potentially informative findings should be sought, including viral inclusions (CMV), granulomas (infections, drugs, or CD), prominent apoptotic bodies (autoimmune enteritis), IgG4-positive plasma cells, pyloric gland metaplasia (chronic mucosal injury), and dysplasia.

Cuffitis Inflammation of the rectal cuff that interposes between the anastomosis and dentate line is one of the more common complications of IPAA. Patients with symptomatic cuffitis may present with increased frequency, urgency, abdominal or pelvic pain, or rectal bleeding. Cuffitis is generally isolated and attributable to a flare of UC, which can be managed with topical treatments. However, it can present atypically in conjunction with pouchitis, accompanied by stricture or fistula formation, or as de novo CD, all of which are more difficult to manage. The respective origins of pouch and rectal biopsies may be very difficult to distinguish histologically due to inflammatory and adaptive changes, and even the clinician may not be certain as to the location of the anastomosis. The histological features of cuffitis span the gamut of changes of IBD.

CD of the Pouch Secondary CD after IPAA for UC or indeterminate colitis may develop weeks to years after surgery. The reported incidence ranges from 2.7% to 13% but is more typically in the 5–10% range. By analogy with conventional CD, it is classified into inflammatory, fibrostenotic, and penetrating types with their respective histological manifestations. Differentiating CD of the pouch from other inflammatory conditions such as fecal stasis, ischemia, anastomosis-related changes, and NSAID-induced injury can be challenging. The diagnosis is suspected or favored when there is Crohn-like inflammation of the neoterminal ileum, when nonforeign body granulomas are identified in biopsies, and when CD is diagnosed on review of prior resection specimens (Fig. 6.31a–c).

References: [40–46]

13. What are the defining histological characteristics of dysplasia in IBD?

Dysplasia in IBD is defined as unequivocal intraepithelial neoplasia of the intestinal epithelium, i.e., neoplasia that is confined to the basement membrane in which it originated. To qualify, the histological abnormalities should not be attributable to reactive or regenerative epithelial changes caused by inflammation.

In most cases, dysplasia in IBD resembles that of conventional adenomatous polyps. The nuclei are characterized by hyperchromatic staining, high nuclear-to-cytoplasmic ratios, crowding, overlapping, and

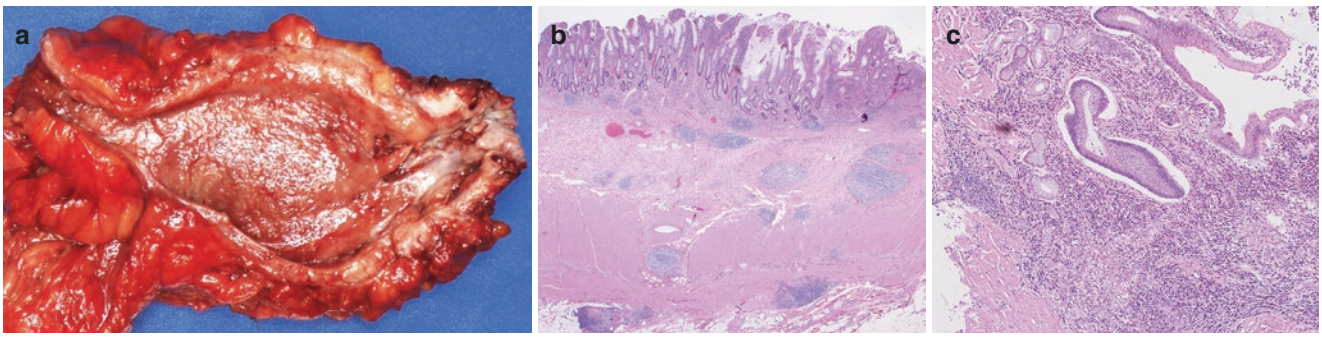

Fig. 6.31 Ileoanal pouch with Crohn disease. (**a**) Resected pouch showing perianal disease, mural thickening, and loss of compliance. (**b**) Histologic sections of the failed pouch show marked mural thickening, transmural lymphoid aggregates, and architectural distortion of the mucosa. (**c**) The mucosa is chronically inflamed, featuring lymphoplasmacytosis, crypt distortion, pyloric metaplasia, and an epithelioid granuloma (bottom center)

anisocytosis. The cytoplasm is characterized by aberrant differentiation (Fig. 6.32a). The differentiation between goblet cells and enterocytes is indistinct, and there may be excessive columnar mucinous cells, goblet cells, dystrophic (upside down) goblet cells, or Paneth cells (Fig. 6.32b). The architectural growth pattern is analogous to that of conventional tubular, villous, or mixed sporadic adenomas, although the microscopic patterns tend to be less uniform. Less frequently, dysplasia assumes serrated or flat growth pattern, as discussed in the next section (question 14).

Dysplasia is graded according to the nomenclature and criteria of the IBD Morphology Study Group. An alternative but mostly analogous Vienna nomenclature is used in some European practices. Grading is based on a three-tier scale comprising low-grade dysplasia (LGD), high-grade dysplasia (HGD), and invasive adenocarcinoma. An additional "indefinite for dysplasia (IND)" category provides a means of classifying mucosa that eludes definitive distinction between reactive and dysplastic or that is uninterpretable for technical reasons. Examples may include cases showing concerning cytological and/or architectural changes in the basal crypts but with surface maturation, worrisome features in the presence of active inflammation or ulceration, tangential sectioning of the specimen with the mucosal surface not well represented, and severe cautery, crushing, or other processing artifact that makes histological assessment difficult.

The distinction between LGD and HGD depends mainly on the degree to which the polarity of the dysplastic epithelium is retained or lost. The nuclei in LGD maintain a parallel orientation and are confined to the basal halves of the epithelial cells. Cytologically, they are typically crowded, ovoid, or penicillate and variably hyperchromatic. Their nuclear membranes are thin, nucleoli are inconspicuous, and mitotic figures are morphologically typical (Fig. 6.32a and b). HGD is characterized by loss of nuclear polarity, which is manifested by skewed or markedly stratified nuclei or by cribriform glandular architecture (Fig. 6.33a and b). The nuclei show high nuclear-to-cytoplasmic ratios, marked anisocytosis, thick or irregular nuclear membranes, prominent nucleoli, or atypical mitotic figures. Since the individual abnormalities in dysplasia lie on a continuum, interobserver variation is unavoidable in some cases.

Dysplasia usually involves the entire length of the crypt with little or no epithelial "maturation" toward the epithelial surface. However, maturation may occur in dysplasia with a villous growth pattern, the atypia of the basal crypt epithelium diminishing or even normalizing within the villous tips. In such lesions, grading is assigned according to the features of the basal epithelium. Surface maturation is less commonly encountered in nonvillous dysplasia and should be interpreted cautiously since it is one of the histological hallmarks of reactive mucosa.
References: [47–49]

14. What is the spectrum of nonadenomatous dysplasia in IBD?

Most cases of dysplasia in IBD are histologically similar to conventional tubular, villous, or mixed colorectal adenomas; however, other types of dysplasia are recognized based on their distinctive combinations of growth pattern and cellular characteristics. Endoscopically, dysplastic foci may be visible or invisible and can be polypoid or flat.

Sessile Serrated Lesion-Like These lesions are typically elevated (polypoid) and are characterized histologically by a serrated, architecturally irregular growth pattern reminiscent of sporadic sessile serrated lesions; however, they also feature atypical nuclear cytology. The epithelium combines goblet cells and columnar cells with microvesicular cytoplasm (Fig. 6.34a). Analogous lesions without significant nuclear atypia, the so-called serrated epithelial change (also known as

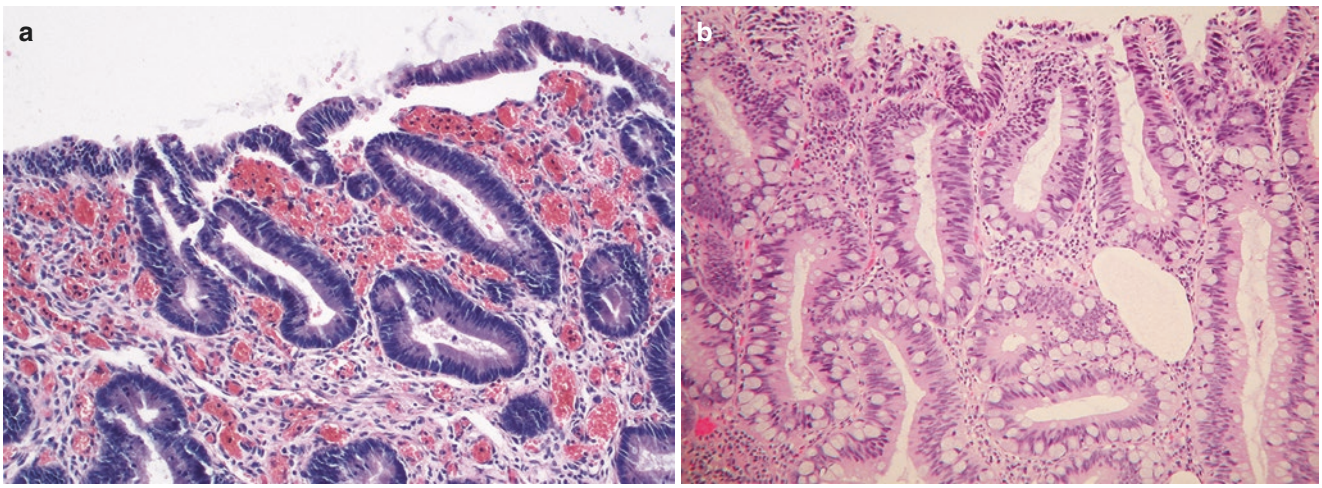

Fig. 6.32 (**a**) Low-grade dysplasia characterized by crypt and surface epithelium with hyperchromatic, enlarged, elliptical nuclei that retain parallel orientation and basal polarity. The cytoplasm is undifferentiated. This type of dysplasia resembles conventional colorectal adenomatous epithelium cytologically but lacks the typical crowded tubular or villous architecture. (**b**) Low-grade dysplasia featuring mildly hyperchromatic, crowded nuclei, and numerous dystrophic goblet cells

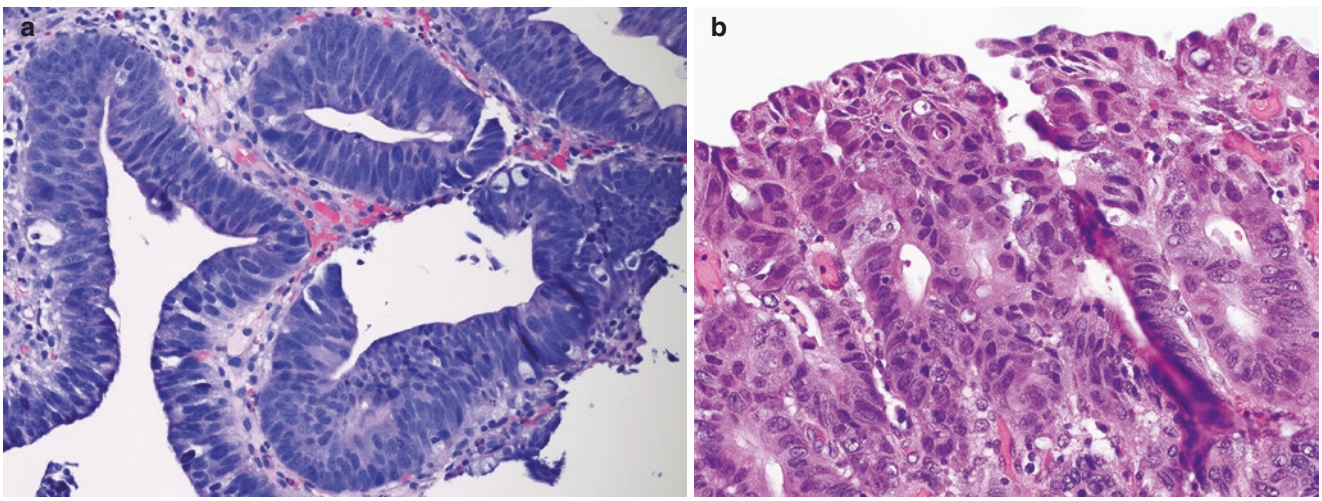

Fig. 6.33 (**a**) High-grade dysplasia characterized by nuclear hyperchromasia, enlargement, and stratification. (**b**) High-grade dysplasia featuring nuclear pleomorphism and disarray, high nuclear-to-cytoplasmic ratios, and partial loss of nuclear polarity

"flat serrated change" or "hyperplastic-like mucosal change") found in random biopsies of flat mucosa from IBD patients, do not seem to pose high risks for the development of cancer.

Traditional Serrated Adenoma-Like These polypoid lesions are characterized by tubulovillous architecture with ectopic crypts and consist of columnar cells with eosinophilic cytoplasm and variable goblet cells. The nuclei are elongated and hyperchromatic and may contain small nucleoli (Fig. 6.34b). Most lesions occur in the left colon and harbor *KRAS* mutations. Clinical follow-up of IBD patients after endoscopic resection of these polyps reportedly has a similar rate of progression to HGD or carcinoma as conventional LGD.

Goblet-Cell-Deficient Dysplasia This type of dysplasia consists of noncrowded tubular crypts lined by nongoblet columnar cells. The crypts are typically similar in height to those in the surrounding mucosa (flat lesion), but elevated lesions and direct progression to carcinoma may occur (Fig. 6.34c). One follow-up study of IBD patients reported a similar rate of progression to HGD and cancer as in those with conventional LGD.

Crypt Cell Dysplasia This uncommon type of dysplasia presents as noncrowded, nonelevated crypts (flat lesion) lined by cytologically atypical but differentiated columnar cells, i.e., goblet cells, enterocytes, basal Paneth cells, and endocrine cells. The nuclei are ovoid, vesicular, or hyperchromatic and extend to the luminal

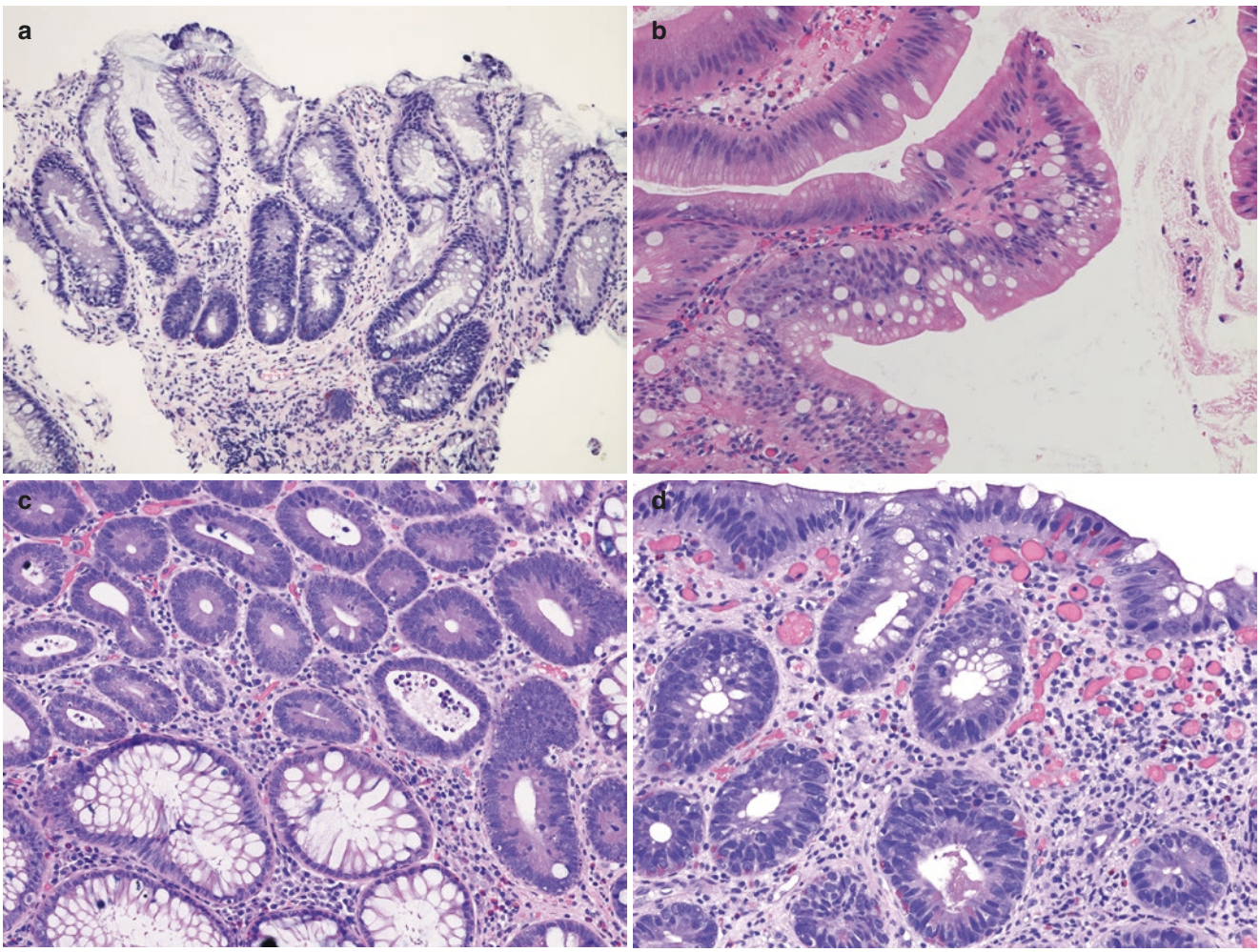

Fig. 6.34 (**a**) Dysplasia reminiscent of a sessile serrated lesion characterized by disorganized serrated growth pattern and mixed goblet and microvesicular columnar cells with atypical nuclei. Surface maturation is present, especially on the left side. (**b**) Dysplasia with traditional serrated adenoma features, such as eosinophilic cytoplasm and pencillate nuclei. (**c**) Goblet-cell-deficient dysplasia featuring noncrowded crypts of normal height lined by uniformly basophilic columnar cells. (**d**) Crypt cell dysplasia characterized by noncrowded crypts of normal height lined by differentiated goblet cells, enterocytes, Paneth cells, and Kulchitsky cells, most of which contain relatively large, vesicular to hyperchromatic nuclei with minimal surface maturation

surface without significant maturation (Fig. 6.34d). In view of its architectural similarity to the surrounding mucosa, it is not surprising that this type of dysplasia accounts for a disproportionate share of dysplasia encountered in nontargeted endoscopic biopsies (flat dysplasia). The distinction from reactive mucosa can be challenging in the setting of active inflammation.

Hypermucinous Dysplasia This is another uncommon type of polypoid dysplasia, which consists of columnar epithelium with a villous, tubulovillous, or serrated growth pattern; gastric-type foveolar-like apical mucin globules; and variable numbers of interspersed goblet cells. Importantly, the nuclear size and degree of atypia decrease toward the luminal surface, and superficial biopsies may belie the presence of deep dysplasia. This type of dysplasia has been variably termed "mucinous dysplasia" or "villous dysplasia" (Fig. 6.35a and b). The biological behavior of this type of dysplasia is currently unknown.

References: [50, 51]

15. How is dysplasia distinguished from reactive epithelial changes in IBD?

The distinction between dysplastic and reactive epithelium in IBD is a common and impactful challenge, especially in the setting of active or resolving colitis, but truly problematic cases are the exception rather than the rule (Table 6.5). A hallmark of reactive crypts is the base-to-surface "maturation gradient," which describes the gradual transition from phenotypically undifferentiated, mitotically active basal colonocytes with relatively

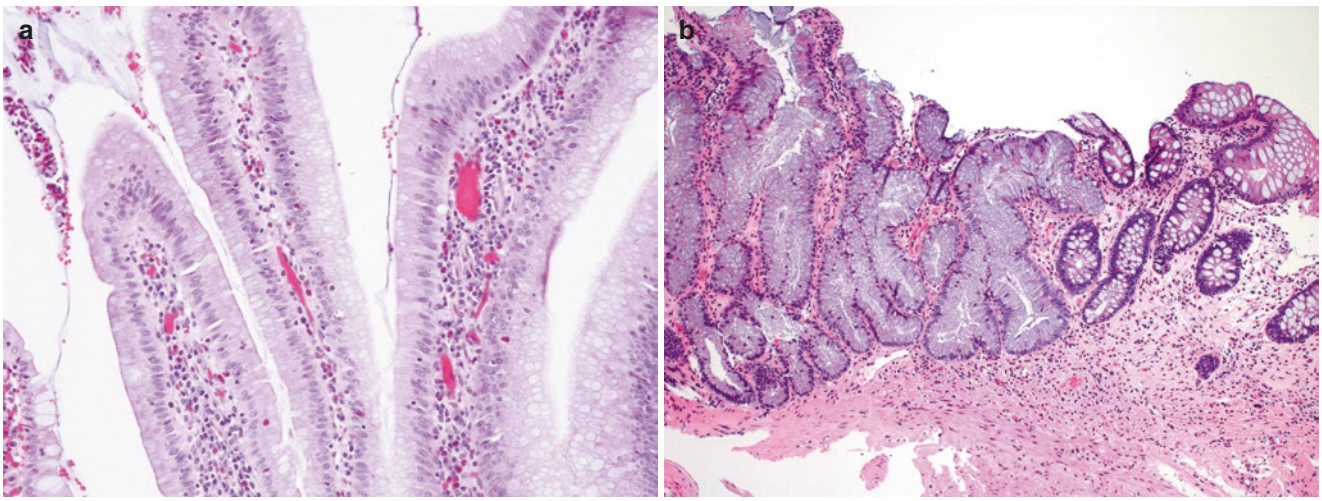

Fig. 6.35 Hypermucinous (villous) dysplasia showing a villous architecture with mixed gastric foveolar and goblet cell features (**a**). The lesion is sharply demarcated from adjacent nondysplastic colonic mucosa in this example (**b**)

Table 6.5 Distinguishing features between reactive and dysplastic epithelium in IBD

Histological feature	Nondysplastic	Dysplastic
Differentiation toward mature epithelium	Yes	None or minimal except certain types, such as villous dysplasia
Sensitivity to inflammatory milieu	Highly sensitive	Relatively insensitive
Transitions between phenotypes	Gradual	Abrupt
Persistence after resolution of active inflammation	Variable	Always

high nuclear-to-cytoplasmic ratios to differentiated surface enterocyte and goblet cell epithelium with small, normochromatic nuclei. In severe inflammation and early regeneration, expansion of the reactive basal epithelium along the crypt axis may resemble dysplasia by displacing the maturation gradient toward the surface (Fig. 6.36a). Nondysplastic epithelium is more responsive than dysplasia to local variations in inflammatory activity. Thus, atypia associated with intense inflamma tion merges gradually with mature colonocytes in adjoining less inflamed mucosa (Fig. 6.36b and c).

In contrast, dysplastic epithelium extends uniformly from the base to the surface with little or no surface maturation (Fig. 6.36d), and its interface with adjacent nondysplastic epithelium is more abrupt. Notable exceptions to this rule are villous and serrated dysplasias in which the surface epithelium is relatively bland and is potentially underdiagnosed if the crypt bases are not sampled. Other features that favor dysplasia are diffuse nuclear hyperchromasia, uniformly prominent or enlarged nucleoli, atypical mitotic figures, loss of nuclear polarity, and dirty intraluminal necrosis. Whenever possible, biopsies should be interpreted in conjunction with clinical history and, in problematic cases, should be reviewed by pathologists with experience in IBD.
References: [48, 52, 53]

16. What is the value of adjunctive markers in distinguishing dysplasia from reactive epithelial changes in IBD?

Immunohistochemical stains may play an adjunctive diagnostic role but do not replace histology as the gold standard. The best studied immunostains involve the aberrant expression of proteins implicated in colorectal carcinogenesis. Alterations of *TP53* are frequent and relatively early events in the inflammation-dysplasia-cancer sequence. Whereas normal synthesis and degradation of wild-type TP53 maintain low homeostatic levels of the nuclear protein, many mutations interfere with degradation and result in nuclear overexpression. Mutations can occur prior to emergence of the histological features of dysplasia, albeit infrequently (<5%), but their prevalence increases progressively in LGD, HGD, and adenocarcinoma. The most widely used reagent is the clone DO-7 antibody. A wild-type expression pattern seen in normal and reactive epithelia presents weak (1+) or occasionally moderate (2+) but heterogenous staining and is typically limited to the lower half of the crypts (Fig. 6.37a and b). Mutant TP53 overexpression presents a pattern of homogeneous strong (2–3+) nuclear expression which spans the entire crypt axis (Fig. 6.38a and b). Alternatively, certain "null" mutations can cause complete absence of TP53 expression. Both overexpression and silencing of TP53 expression are supportive of dysplasia in equivocal cases where the morphology is strongly suggestive but are not diagnostic in themselves.

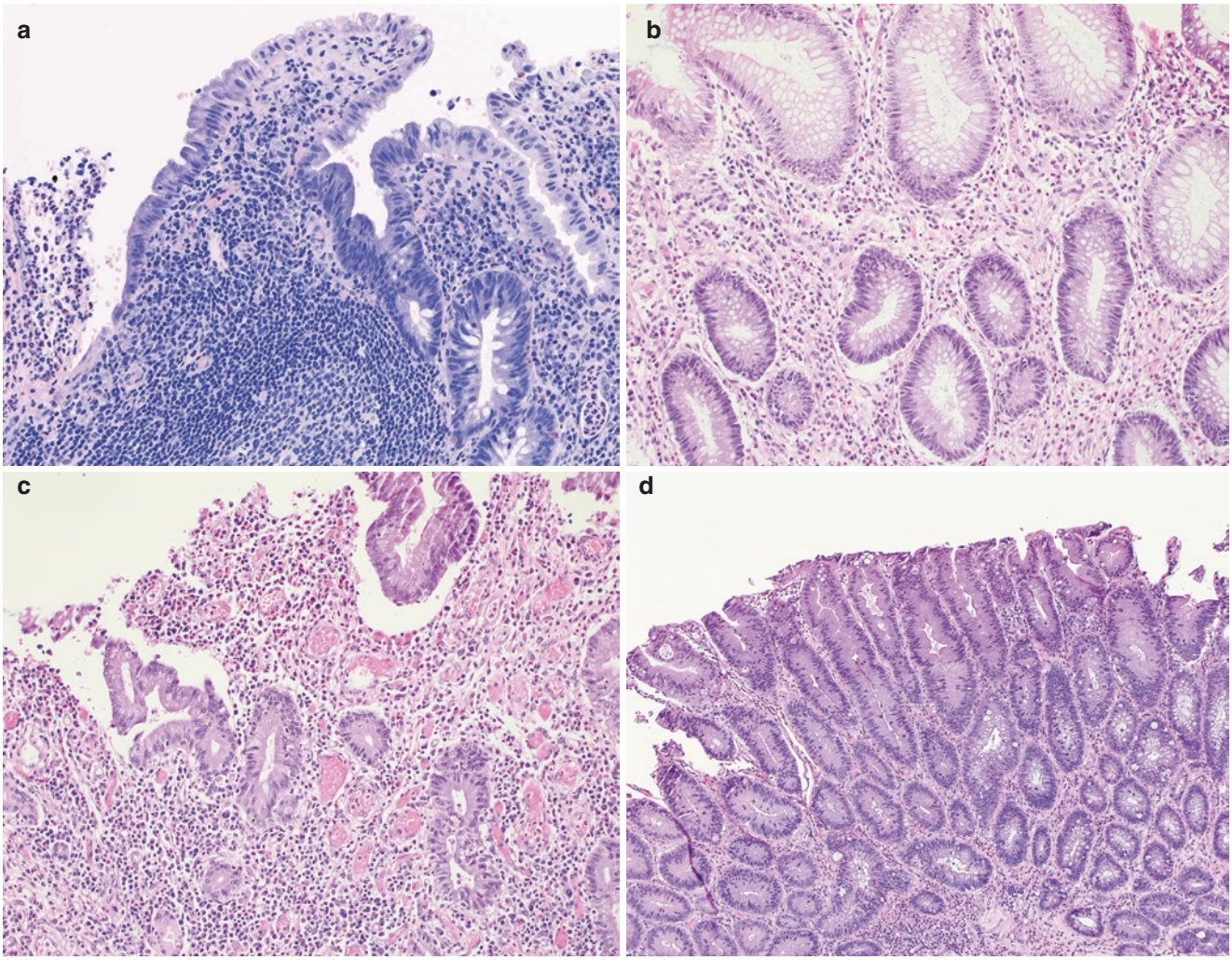

Fig. 6.36 (**a**) Regenerative epithelium in the setting of active inflammation and erosion. The epithelium of the central crypt and the surface near the erosion (left) consist of undifferentiated columnar cells with hyperchromatic nuclei, but they mature gradually in the less inflamed mucosa into differentiated cells with small bland nuclei (right). (**b**) Reactive mucosa in the setting of inactive IBD. Mild basal nuclear atypia gives way gradually to more mature epithelium in the upper crypts. (**c**) Reactive epithelium in the setting of active inflammation is characterized by normochromatic nuclei and relatively low nuclear-cytoplasmic ratios. If dysplasia is suspected, it is reasonable to recommend endoscopic reexamination after anti-inflammatory therapy. (**d**) Despite the presence of some active inflammation, low-grade dysplasia is easily diagnosed based on the crypt crowding and uniform epithelial atypia. The presence of slight surface maturation is commonplace in dysplasia

Cytoplasmic alpha-methylacyl-CoA racemase (AMACR) overexpression has been reported in IBD-related neoplasia. Low-level expression of AMACR in inflamed and normal mucosa limits its diagnostic value, but coexpression with TP53 has a confirmatory role, reportedly occurring in 76% of neoplastic biopsies, 30% of biopsies with indefinite dysplasia, and only 0.6% of nonneoplastic biopsies.

Cytoplasmic expression of CK7 occurs in 61% of dysplastic tissues and less frequently in inflamed mucosa. In one study, combined immunostaining for CK7 and TP53 afforded 95% sensitivity and 82% specificity for dysplasia using carefully adjusted threshold values.

It should be mentioned that using TP53 immunostain to help diagnose dysplasia in IBD is not universally endorsed because regenerating crypts may also potentially show strong TP53 expression. AMACR and CK7 do not appear to be reliable markers for IBD dysplasia and are thus not currently used in practices: [47, 54–57]

17. How are sporadic adenomas distinguished from IBD-associated dysplasia?

Sporadic colorectal adenomas, which are dysplastic by definition, can occur incidentally in patients with IBD, particularly those in the age range where adenomas are prevalent. Experience has shown that the occurrence of adenomas in patients with IBD does not have a significant impact on the risk of developing cancer and that adenomas may be managed by simple polypectomy in the same manner as in non-IBD patients.

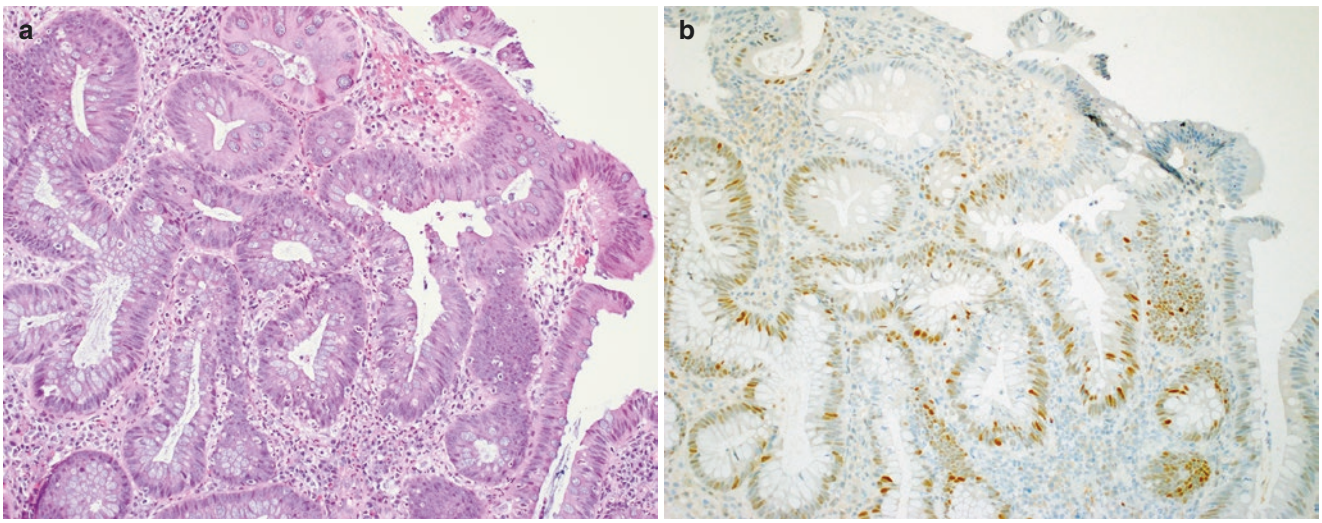

Fig. 6.37 (**a**) A case of active colitis with crypts and surface epithelium on the right showing mildly crowded, hyperchromatic nuclei, which may be interpreted as "indefinite for dysplasia." (**b**) Immunostain reveals a wild-type expression pattern of TP53 expression consisting of heterogenous, mostly 1+ staining limited to the crypts

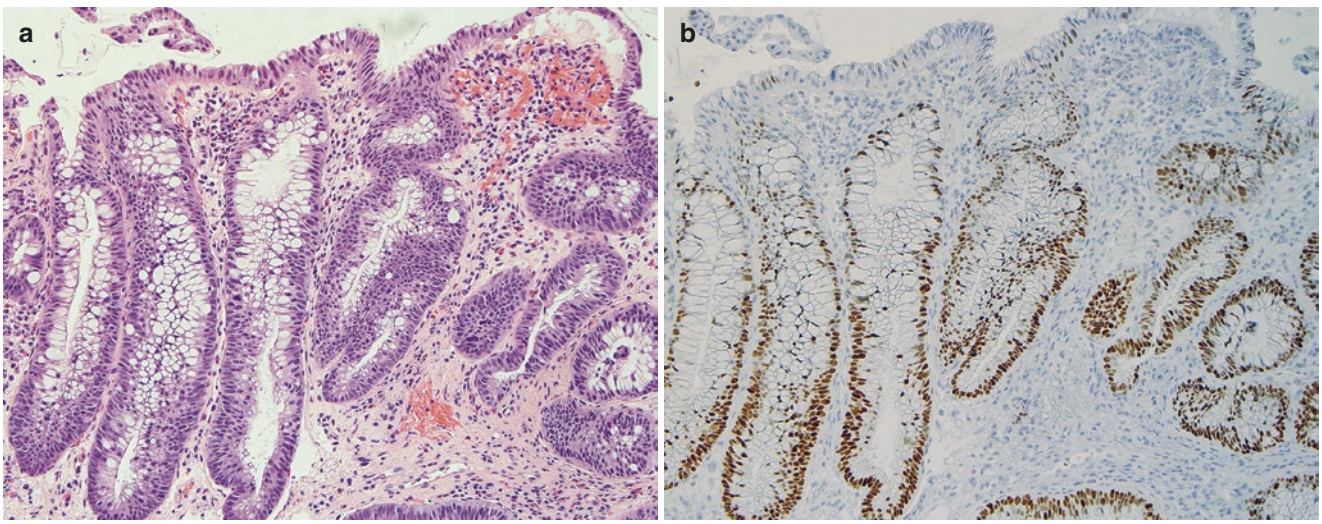

Fig. 6.38 A case of low-grade dysplasia (**a**) showing homogeneous 3+ expression of TP53 in dysplastic crypts (**b**)

Histological criteria, such as sharp circumscription from the surrounding mucosa or a top-down rather than a bottom-up pattern of dysplasia, may support a diagnosis of adenoma, but none have been proven to be definitive.

An adenoma can be diagnosed when the surrounding mucosa is both endoscopically and histologically normal, as in the right side of the colon of patients with left-sided UC. Likewise, pedunculated dysplastic polyps comprising a discrete dysplastic head and nondysplastic pedicle are considered to be sporadic even if the surrounding mucosa is involved by colitis. Studies have shown that patients with IBD who have sessile dysplastic polyps that appear adenoma-like, i.e., endoscopically discrete, dome shaped, and symmetrical, can be managed by simple polypectomy even when they occur in the background of colitis and even if they contain HGD.

Nonetheless, in recent years the pathological distinction between sporadic adenoma and IBD-associated polypoid dysplasia has been rendered largely moot by the use of advanced endoscopic methods for local resection. Following endoscopic resection, biopsy sampling of the immediate adjacent mucosa is advisable and at least one reexamination should be carried out within a few months.

References: [48, 49, 52, 58]

18. How is a diagnosis of dysplasia integrated into the clinical management of patients with IBD?

Patients with IBD are predisposed to the development of colorectal cancer. The magnitude of risk is simi-

lar for patients with UC and CD of similar duration and disease extent, with standardized incidence ratios of approximately 2–2.5. The peak age of cancer victims is 45–55 years, and nearly 1/3 are under age 40. Patients at the highest risk are those who have concurrent PSC, anatomically extensive disease, long disease duration, persistent disease activity, IBD onset at a young age, and a family history of early colorectal cancer.

Endoscopic examination to detect dysplasia, the earliest recognizable cancer precursor and best predictor of neoplastic progression, plays a key role in prevention by providing a window of opportunity for therapeutic intervention before cancer develops. The standards of care recommended by professional gastroenterology organizations include a screening examination after 8–10 years of disease, or immediately upon a diagnosis of PSC, followed by periodic surveillance examinations entailing careful inspection and biopsy sampling throughout the large intestine. Biopsies are both random and targeted to any suspicious lesions. Because dysplasia in IBD can be flat and indistinct or may be obscured by surrounding inflammatory changes such as inflammatory polyps or strictures, surveillance examinations are best performed with high-resolution optics or with dye spray techniques (chromoendoscopy).

The natural history and management of patients with IBD-associated dysplasia depend on its endoscopic characteristics. A recent international consensus statement (SCENIC: Surveillance for Colorectal Endoscopic Neoplasia Detection and Management of Inflammatory Bowel Disease) has classified dysplastic lesions in IBD as either visible or invisible. Visible dysplasia is subclassified as either polypoid or nonpolypoid and is modified to describe any ulceration and whether the borders are distinct or indistinct. This terminology replaces older terms such adenoma-like polyps and DALM (dysplasia-associated lesion or mass), which are no longer recommended.

Following a biopsy diagnosis of LGD, the cumulative 5-year probability of developing HGD or cancer ranges from 23 to 54%, but the risk can be reduced substantially if the dysplastic lesion can be identified visually and resected. Thus, once polypoid LGD has been resected, the cumulative risk of long-term progression to carcinoma is less than 3% both in UC and CD. Biopsies taken adjacent to the resection site can be used to confirm that complete endoscopic resection has been achieved.

"Invisible" dysplasia refers to randomly detected, i.e., nontargeted lesions, including those that are truly invisible and those that are camouflaged by background inflammatory changes. As expected, visible dysplasia accounts for the great majority of dysplastic biopsies, especially when chromoendoscopy is used. Nevertheless, random biopsies have not been abandoned by most practitioners; in fact, their yields are comparable to those of targeted biopsies in patients diagnosed previously with dysplasia. When invisible dysplasia is encountered under standard white light examination, the patient should be referred for examination by chromoendoscopy or with high-definition optics.

Carcinoma and unresectable dysplasia are indications for colectomy regardless of their endoscopic features. Surgery is also considered when dysplasia is invisible or multifocal, especially if it is high grade, and for patients with inflammatory changes that might limit the effectiveness of endoscopic examination, such as inflammatory polyposis or stenosis. Patients with indefinite dysplasia or with dysplasia that has been removed endoscopically should have close endoscopic follow-up at short intervals.

It is recommended that biopsy diagnoses involving potential dysplasia be confirmed by at least one other pathologist with experience in GI pathology whenever they are likely to impact management decisions.
References: [58, 59]

19. Are there distinctive pathological features of colorectal carcinoma in IBD?

The mean age of patients with IBD who develop colorectal cancer is 10–15 years younger than their sporadic counterparts. Cancers arise in regions of the colon that are chronically inflamed. In UC, most cancers occur in the left side, particularly the rectosigmoid colon, whereas in CD they are more evenly distributed between the left and right sides. Approximately 10% of cancers in IBD are multiple, especially in younger patients.

In resected specimens, cancers in IBD patients present as exophytic or ulcerated masses, plaques, or strictures which often mimic inflammatory lesions (Fig. 6.39a–d). Some deceptively flat, inconspicuous tumors are more easily detected by palpation in the unfixed state than by visual inspection. Compared with sporadic cancers, they are poorly delimited, irregularly shaped, and asymmetrical. Classical round, ulcerated lesions with heaped-up edges and smooth borders are rare in IBD and are likely to be coincidental sporadic cancers.

Most colorectal cancers in IBD have conventional morphology; however, at least 15% are mucinous, compared with ~10% in the general population, and up to 7% comprise signet ring cells, compared with ~1% in the general population. Approximately 10% have extremely well-differentiated, low-grade tubuloglandular features, which are rarely encountered outside the IBD setting (Fig. 6.39e). They consist of individual round or elliptical glands with relatively mild cytological atypia that elicit little or no desmoplastic reaction. Other rare subtypes such as goblet cell, adenosquamous, clear cell, and hepatoid carcinomas have been reported.

Long-standing chronic fistulizing perianal disease in CD predisposes to both adenocarcinoma and squamous cell carcinoma, which can arise within fistula tracts, making them notoriously difficult to diagnose, or near

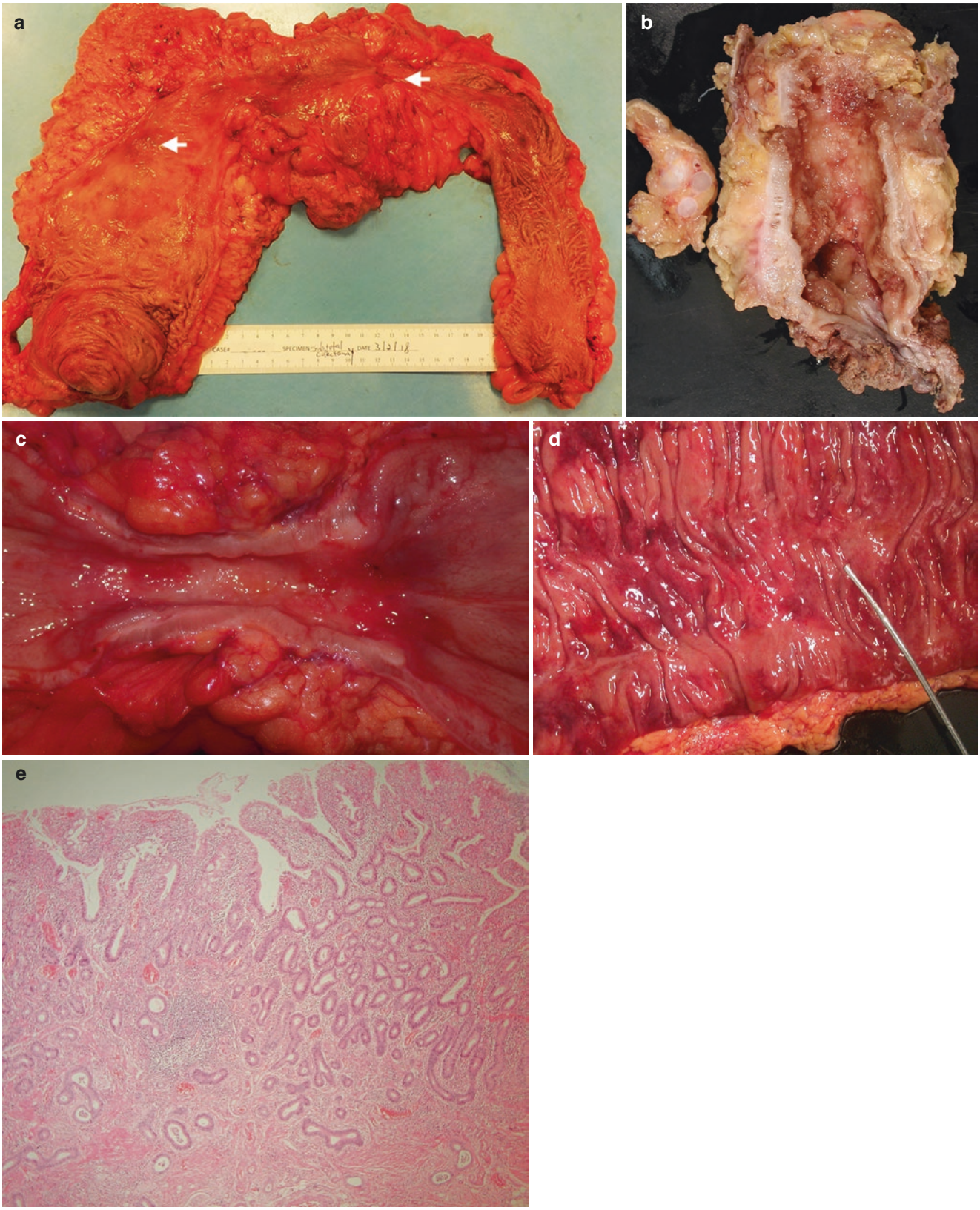

Fig. 6.39 (**a**) Ulcerative colitis with two ulcerated cancers (arrows). Note the absence of distinct borders. (**b**) Proctectomy specimen and lymph nodes showing advanced mucinous adenocarcinoma in the setting of ulcerative colitis. (**c**) Stricturing carcinoma of the transverse colon in a patient with Crohn disease. Microscopic examination revealed signet ring adenocarcinoma. (**d**) Diminutive cancer with ill-defined borders (probe) in a patient with ulcerative colitis. (**e**) Low-grade tubuloglandular adenocarcinoma arising from mucosa with low-grade dysplasia. The infiltrative glands have round profiles and open lumens, and they elicit little or no desmoplastic stromal reaction

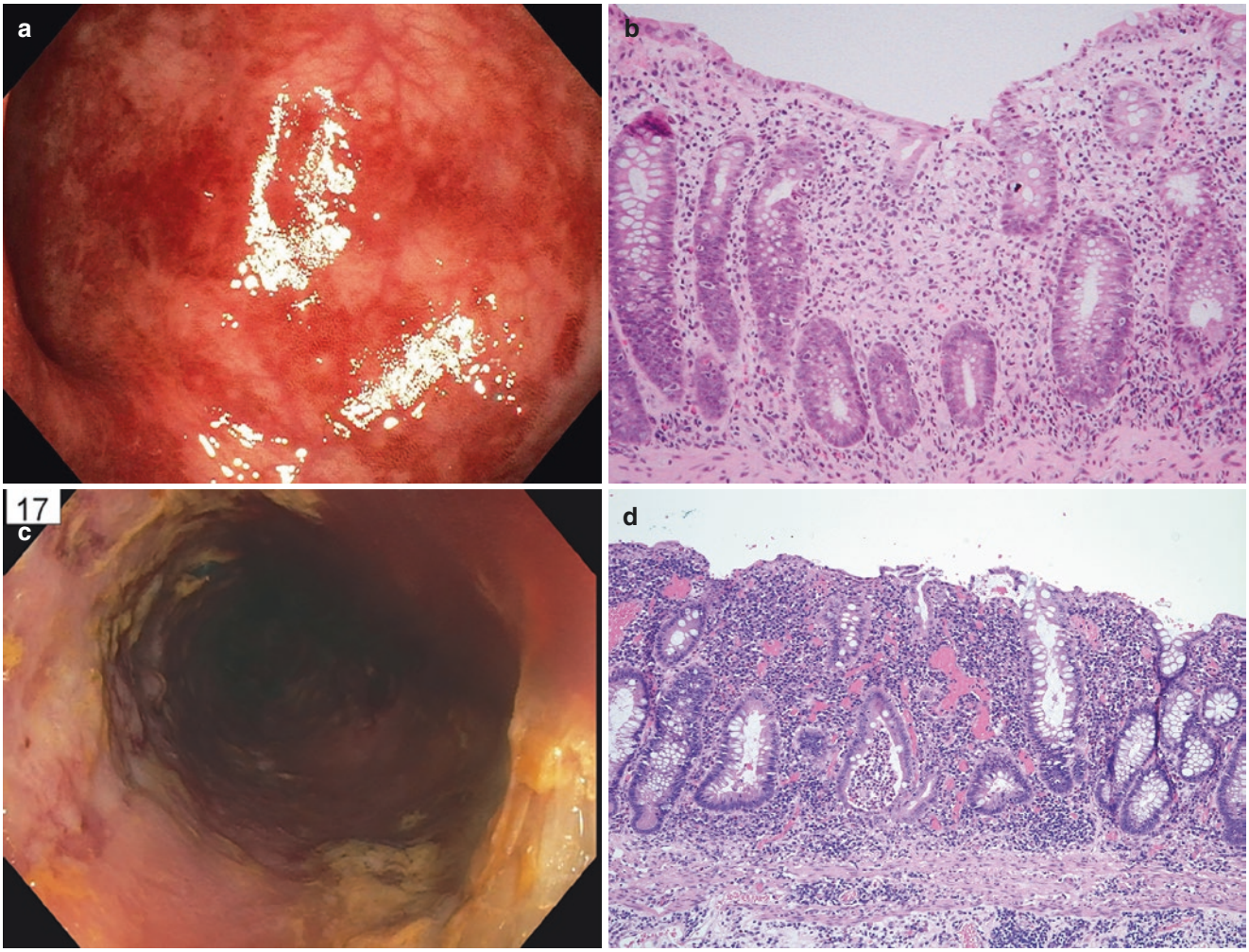

Fig. 6.40 (Case 1). (**a**) Endoscopically, the patient's colonic mucosa at the time of her initial presentation was characterized by slight surface granularity, patchy erythema, and partially obscured vascular pattern. (**b**) Microscopic appearance of acute infectious colitis. The crypts retained their normal caliber and parallel orientation. The lamina propria was edematous and infiltrated by neutrophils, and the crypts exhibited neutrophilic cryptitis and crypt abscesses. Note the incipient basal lymphoplasmacytosis, which typically appears during the second week after symptom onset. (**c**) Four months later, the colon was characterized endoscopically by nodularity, ulcers, and completely obscured vascular pattern, which are typical features of idiopathic chronic inflammatory bowel disease. (**d**) Microscopic features of chronic inflammatory bowel disease include dense, full-thickness infiltration of the lamina propria by mononuclear inflammatory cells; irregularly shaped crypts that fall short of the muscularis mucosae; and neutrophilic cryptitis and crypt abscesses with relatively few neutrophils in the lamina propria

fistula openings in the anal canal, rectum, or perianal skin. Crohn ileitis is associated with a roughly 60-fold risk of ileal adenocarcinoma. The diagnosis is often delayed because obstructive symptoms are so commonplace in CD. The macroscopic presentation may closely mimic that of benign strictures; as a result, the diagnosis may not be recognized by the pathologist until histological sections are examined.

The stage distribution of cancers in patients with IBD is similar to that of their sporadic counterparts. Cancers detected in the course of routine endoscopic surveillance examinations have lower stages than those presenting symptomatically. Published survival data for cancers complicating IBD are too scanty to permit clinical comparisons to patients in the general population.

References: [60–65]

Case Presentation

Case 1

Case History

A 37-year-old woman was admitted to the emergency department with an 8-day history of progressively worsening diarrhea, nausea, abdominal bloating, chills, and light-headedness. She denied recent travel or antibiotic use and had no

significant medical conditions, HIV risk factors, or family history of IBD. Flexible sigmoidoscopy revealed mild mucosal erythema and granularity (Fig. 6.40a). A biopsy was performed. A PCR-based stool pathogen test was positive for *Shigella* and enteroinvasive *E. coli*, and she was discharged on azithromycin. A stool culture was positive for *Shigella* and negative for *E. coli* 0157:H7. Telephone follow-up 3 days later disclosed a marked improvement in her symptoms.

Histology

The first biopsy features preserved crypt architecture, neutrophil infiltration of the lamina propria and surface and crypt epithelium, reduced goblet cell mucin, and minimal basal lymphoplasmacytosis (Fig. 6.40b).

Differential Diagnosis

- Subacute infectious colitis
- Incipient inflammatory bowel disease
- Irritable bowel syndrome

The histological features are typical of infectious colitis. The finding of minimal basal lymphoplasmacytosis suggests a duration of infection for at least 1–2 weeks. Features of chronicity would be prominent even in incipient IBD. Irritable bowel syndrome presents little or no histological changes.

Four months later, the woman returned to the emergency department with complaints of bloody diarrhea and abdominal cramps but no nausea or fever. Flexible sigmoidoscopy revealed ulcerations and loss of the colonic folds and vascular markings (Fig. 6.40c). Stool tests were negative for pathogens and *C. difficile* toxins. The second biopsy features full-thickness lymphoplasmacytosis, crypt architectural distortion, crypt shortfall, and crypt abscesses (Fig. 6.40d).

Differential Diagnosis

- Recurrent infectious colitis
- Chronic infectious colitis
- New onset of inflammatory bowel disease

Ancillary Studies

None.

Final Diagnosis

Progression of infectious colitis to inflammatory bowel disease.

Follow-Up

A colonoscopy revealed normal mucosa beyond the splenic flexure, and additional workup disclosed no involvement of the small intestine or other evidence of CD. The patient was diagnosed with left-sided UC, possibly triggered by her earlier infection, and was managed with mesalamine.

Take-Home Messages

- Acute infectious colitis can be diagnosed in biopsies in the setting of supportive clinical data and absence of other causes of colitis (drugs, radiation, etc.).
- Basal lymphoplasmacytosis begins to appear during the second week from onset. Infections that persist beyond 2–3 weeks can gradually evolve histological features of chronicity, resulting in diagnostic ambiguity just when persistent symptoms begin to elicit clinical concerns for IBD.
- IBD presents characteristic histological features, including full-thickness lymphoplasmacytosis, crypt distortion and shortfall, and selective neutrophil infiltration of the crypt epithelium. The combination of these features is histologically quite specific.
- Acute infections are a recognized risk factor for the development of IBD, with hazard ratios of approximately 4.1 during the first year. The most common pathogens are *Salmonella* and *Campylobacter*, but no etiological link has been established with any specific pathogens or commensal organisms. Potential factors include shifts in the host microbiome, stimulation of acute inflammation, and incapacitation of host protective mechanisms.

References: [19, 66, 67]

Case 2

Case History

A 41-year-old woman with long-standing well-controlled UC had been undergoing annual colonoscopic surveillance examinations for the past 10 years with no dysplasia detected.

Endoscopy showed an elevated, broad-based lesion with a villiform surface in the proximal sigmoid colon (Fig. 6.41a). Despite having indistinct boundaries, the lesion was estimated to be 5–6 cm in size. The remainder of the colonic mucosa was flat and atrophic appearing.

Histology

A superficial biopsy of the sigmoid lesion showed villiform mucosa (Fig. 6.41b). The nuclei in some of the villi were enlarged, hyperchromatic, and crowded (Fig. 6.41c), while the nuclei in other areas were small and normochromatic (Fig. 6.41d).

Differential Diagnosis

- Indefinite for dysplasia
- Low-grade dysplasia
- High-grade dysplasia

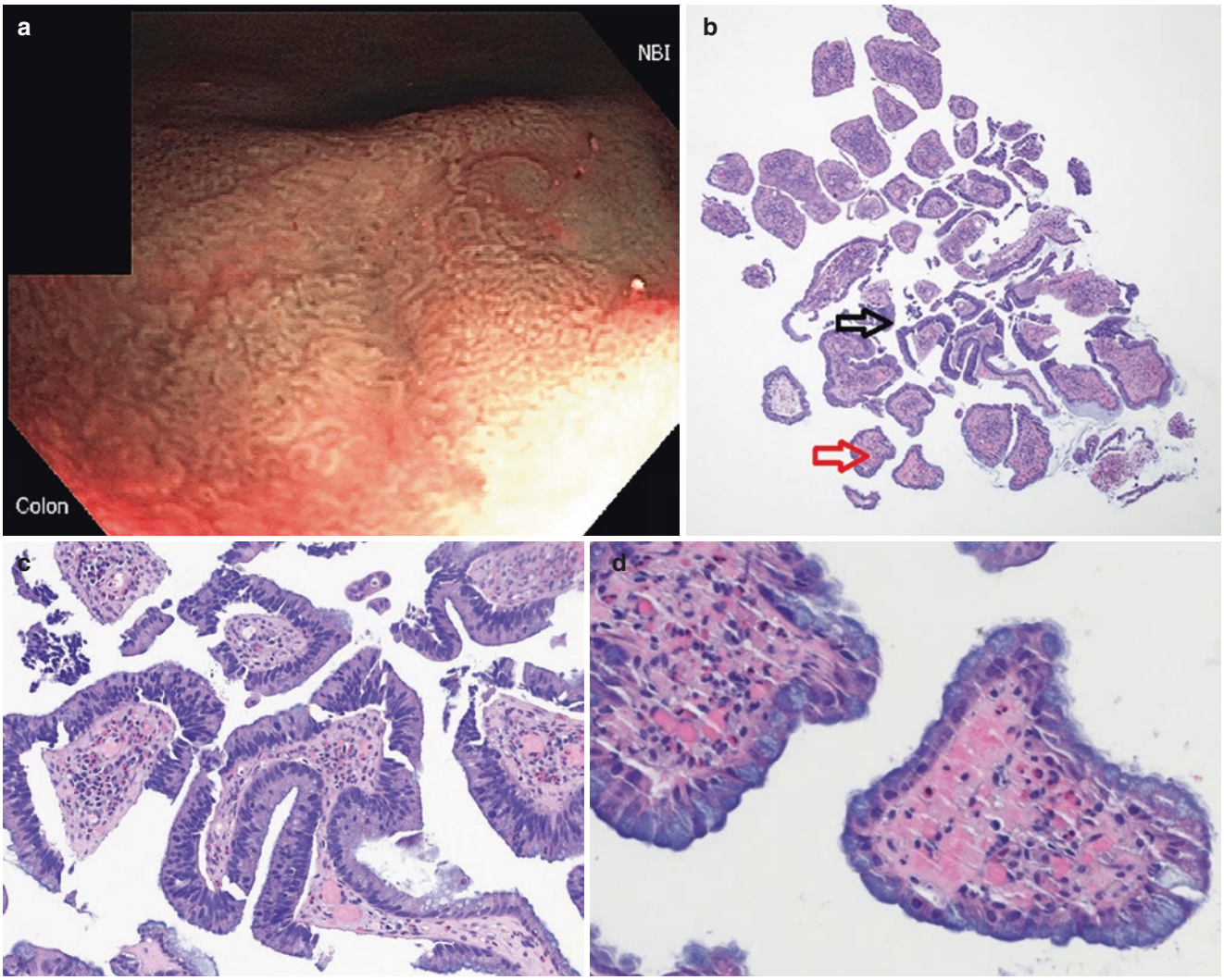

Fig. 6.41 (Case 2). (**a**) Endoscopic appearance of broad-based, slightly elevated lesion with villiform surface. (**b**) Villiform tissue sampled from the surface of the lesion. (**c**) Higher magnification revealed that some of the villi (indicated by a black arrow in **b**) were lined by low-grade dysplastic columnar epithelium characterized by uniformly enlarged, elliptical, hyperchromatic nuclei. (**d**) Other villi (indicated by a red arrow in **b**) were lined by nondysplastic cuboidal epithelium containing small, normochromatic nuclei

Management Options

- Repeat the examination with chromoendoscopy.
- Repeat the examination and biopsies in 3 months.
- Advise the patient to undergo colectomy.

Ancillary Studies

None.

Final Diagnosis and Management

Tentatively LGD based on the most severe changes; however, histological evaluation of the entire lesion is required since it might contain invasive cancer or HGD. The clinical impression was that the size and location of the lesion precluded an endoscopic resection. The patient was therefore advised to undergo a colectomy.

Follow-Up

The patient underwent colectomy (Fig. 6.42a). Complete histological evaluation of the lesion showed areas of LGD and negative for dysplasia in the villi (Fig. 6.42b and c) but revealed HGD at the crypt bases (Fig. 6.42d). No cancer was found.

Take-Home Messages

- Villous dysplasia may exhibit surface maturation that is discordant with findings in the deep crypts.
- Biopsies that contain nondysplastic villous structures should be followed up as potentially significant.
- Colectomy is the standard of care for endoscopically visible, nonresectable dysplasia.

References: [47, 53, 58]

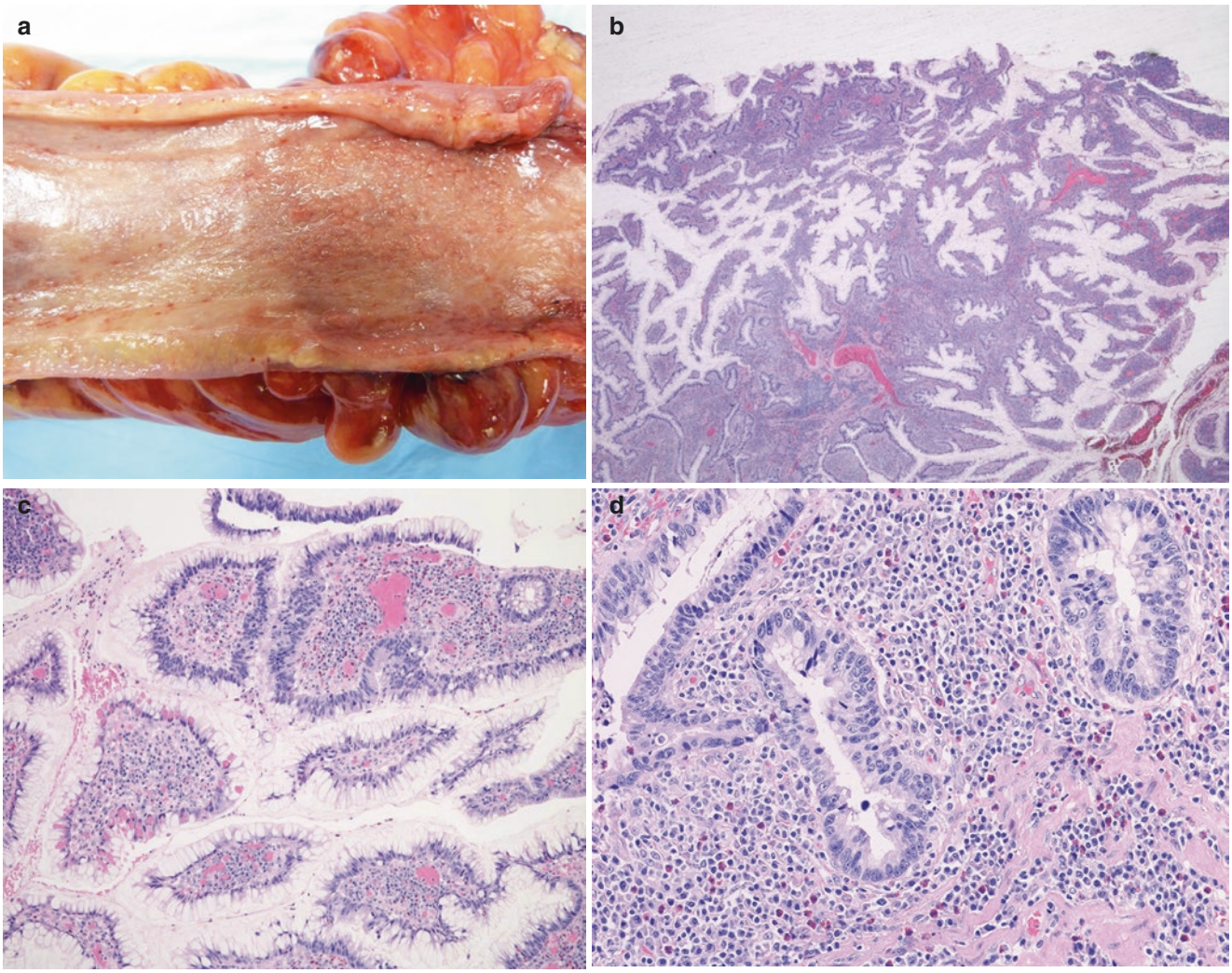

Fig. 6.42 (Case 2). (**a**) Villiform dysplasia in the colectomy specimen. Surgical management was elected over attempted endoscopic mucosal resection due to the large size of the lesion and its lack of well-defined margins. (**b**) Villous dysplasia at low magnification. (**c**) Higher magnification revealed hypermucinous epithelium with low-grade dysplasia involving some of the villi. (**d**) High-grade dysplasia seen in the deep crypts characterized by large, vesicular, variably stratified nuclei

Case 3

Case History

A 48-year-old man with a 15-year history of well-controlled Crohn colitis had undergone annual colonoscopic surveillance examinations with biopsies, by his private gastroenterologist, for the past 7 years. A recent examination disclosed LGD in a single random biopsy of the sigmoid colon, which surprised the gastroenterologist since he had not noted any suspicious findings during the examination and saw none on reviewing his endoscopic photographs. The slides were reviewed by a second pathologist, who confirmed the diagnosis. The patient was referred to a gastroenterologist specializing in IBD, who reexamined the colon with chromoendoscopy under high-definition optics but saw nothing suspicious. Specifically, white-light image of the sigmoid colon mucosa showed slightly obscured mucosal vasculature, a characteristic of quiescent colitis. There was focal black pigmentation from a prior India ink tattoo (Fig. 6.43a). Chromoendoscopy of the sigmoid colon revealed a normal pattern of mucosal pits (Fig. 6.43b).

Histology

A nontargeted biopsy of the sigmoid colon was performed (Fig. 6.43c).

Differential Diagnosis

- Negative for dysplasia
- Indefinite for dysplasia
- Low-grade dysplasia
- High-grade dysplasia

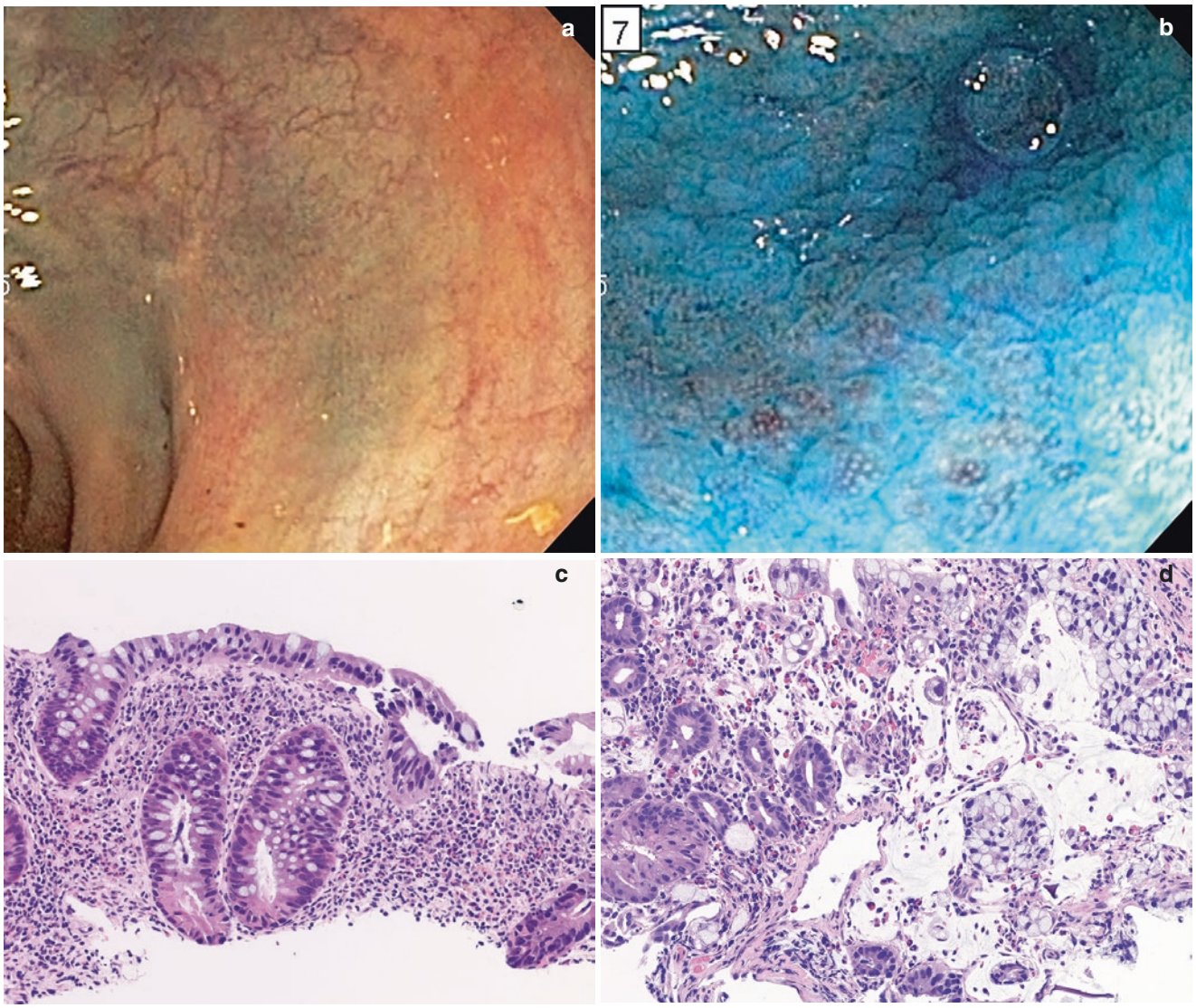

Fig. 6.43 (Case 3). (**a**) Endoscopic appearance of inactive chronic colitis under white-light illumination characterized by slightly obscured mucosal vasculature. An India ink tattoo had been previously administered to mark the location. (**b**) Appearance of the mucosa after spraying with methylene blue revealed a normal mucosal pit pattern. (**c**) Low-grade dysplasia, crypt cell type. The dysplastic epithelial cells had differentiated into enterocytes, goblet cells, and Paneth cells, the latter occupying the crypt bases, mimicking normal colonic mucosa. However, the nuclei are abnormally enlarged and hyperchromatic along the entire crypt axis. (**d**) Poorly differentiated adenocarcinoma identified in the same location as prior biopsies that had featured low-grade crypt cell dysplasia

Ancillary Studies

None.

Final Diagnosis

Low-grade dysplasia (crypt cell type).

The mucosa is flat and chronically inflamed, and the crypts assume an uncrowded tubular growth pattern. The lining epithelium replicates normal crypt epithelium with respect to differentiation into enterocytes, goblet cells, and basal Paneth cells but contains enlarged, hyperchromatic, and moderately pleomorphic nuclei along the length of the crypts and extending to the surface. The dysplasia is classified as low-grade on the basis of its retained cellular polarity and highly differentiated cell phenotypes.

This case exemplifies a distinctive type of dysplasia referred to as crypt cell type. Its flat, uncrowded growth pattern accounts for the lack of a visible lesion at endoscopy under optimal conditions of high-definition optics and chromoendoscopy.

There are few studies in the literature addressing this type of dysplasia. One study published in abstract form reported that crypt cell dysplasia accounted for 48% of 52 nontargeted dysplasia biopsies from 30 patients who underwent surveillance during a period of 44 months.

Follow-Up

Despite being advised to undergo colectomy, the patient elected to continue surveillance on an accelerated schedule and continued to have repeated biopsies showing LGD in the sigmoid colon. On the sixth examination, a small elevation was seen in the sigmoid colon and a biopsy was positive for poorly differentiated adenocarcinoma with signet ring cells (Fig. 6.43d). The colectomy specimen contained a stage III adenocarcinoma.

Take-Home Messages

- Dysplasia in IBD can be endoscopically occult even with optimal endoscopic techniques and is likely to be missed if biopsies are targeted to visible lesions only.
- The natural history and biological characteristics of crypt cell dysplasia warrant further study.
- Nevertheless, any unresectable LGD should be considered a relative indication for colectomy, especially if it is detected repeatedly and the diagnosis is confirmed by a second pathologist.

References: [51, 68]

Case 4

Case History

A 44-year-old male with a 12-year history of UC had been on anti-inflammatory therapy with mesalamine until recently when he began to experience progressive constipation and bloating. Colonoscopic examination revealed active inflammation and multiple mucosal polyps in the sigmoid colon, quiescent colitis with scattered polyps in the descending and transverse colon, and luminal occlusion of the proximal transverse colon, preventing completion of the examination. A subsequent barium study revealed multiple filling defects in the ascending and transverse colon, deep mural fissures, and evidence of pericolic inflammation. The patient underwent an abdominal colectomy.

Gross

Subtotal colectomy specimen showed segmental erythema and mass-like agglomerations of polyps in the ascending, transverse, and sigmoid colon. The polyps had filiform and leaf-like configurations and a soft consistency (Fig. 6.44a).

Histology

The colon was ulcerated and covered by a canopy of congested mucosa with irregular, partially dilated crypt architecture. The wall was punctuated by deep fissuring ulcers surrounded by chronic inflammation. The subserosa showed lymphoid aggregates (Fig. 6.44b), transmural chronic inflammation, and fibrosis (Fig. 6.44c). The remainder of the colon showed diffuse chronic inflammation, which was limited to the mucosa (not shown). No granulomas were identified in any of the colonic sections or pericolic lymph nodes.

Differential Diagnosis

- Crohn colitis
- Indeterminate colitis
- Ulcerative colitis with massive inflammatory polyposis

Ancillary Studies

None.

Final Diagnosis

Ulcerative colitis with massive inflammatory polyposis.

Follow-Up

Six months later, the patient underwent a completion proctectomy and ileoanal pouch anastomosis. Two years later, he was doing well with good pouch function and no manifestations of IBD.

Take-Home Messages

- Inflammatory polyps are commonplace in chronic IBD and rarely cause symptoms other than being a potential source of bleeding.
- Rarely, segmental mass-like agglomerations of inflammatory polyps form in IBD, both UC and CD. This condition, referred to as massive, giant, or filiform inflammatory polyposis, may cause luminal obstruction and elicit clinical suspicion of CD-associated stricture or carcinoma.
- The segments involved by polyposis may exhibit Crohn-like features, including chronic fissuring ulcers and transmural chronic inflammation, which are likely caused by fecal entrapment and stasis.
- The distinction between UC and CD should be based on the pathology of the rest of the colon in conjunction with preoperative clinical data.
- A pathological diagnosis of indeterminate colitis is recommended when the polyposis is extensive or if insufficient supportive clinical data are available.

Reference: [3]

Case 5

Case History

A 40-year-old woman with ulcerative pancolitis since age 13 underwent an endoscopic surveillance examination in which a 2-cm nodule was found in the proximal sigmoid colon. She was offered a choice of continued surveillance or colectomy and opted for the latter.

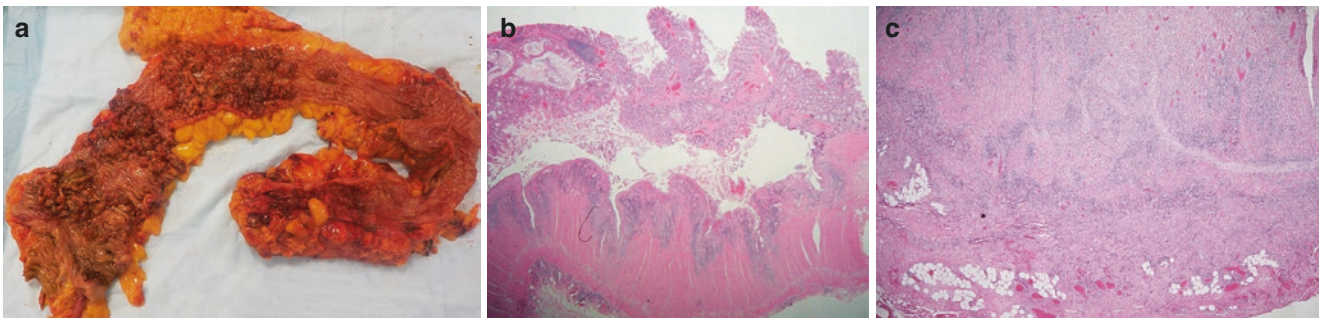

Fig. 6.44 (Case 4). (**a**) Subtotal colectomy specimen showing massive segmental inflammatory polyposis. (**b**) Ulcerated colonic mucosa covered by a canopy of partially detached mucosa. Note the fissuring ulcers and transmural chronic inflammation. (**c**) Ulcerative colitis with Crohn-like transmural chronic inflammation and subserosal fibrosis limited to the segment with massive inflammatory polyposis

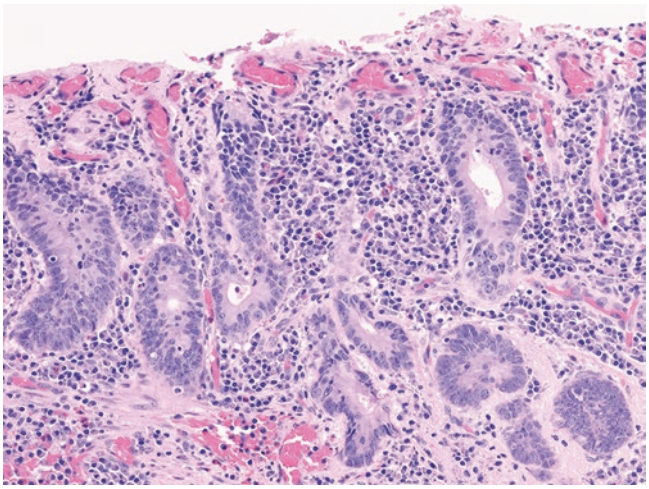

Fig. 6.45 (Case 5). Colonic mucosa comprising crypts lined by goblet-cell-deficient epithelium featuring slightly atypical nuclei with nucleoli and no surface maturation. Despite surface congestion and stripped surface epithelium, there was little or no active inflammation to account for the epithelial changes. (Note the irregularly shaped crypt bases which corresponded, in retrospect, to incipient adenocarcinoma)

Histology

A section from the nodular area revealed chronic inflammation with surface congestion and stripped surface epithelium but little or no active inflammation. The crypts were lined by columnar cells with basally polarized, mildly hyperchromatic, and pleomorphic nuclei and slightly eosinophilic cytoplasm. Goblet cells were absent. There was no evidence of maturation toward the surface. Several of the basal glands had irregular contours (Fig. 6.45).

Differential Diagnosis

- Indefinite for dysplasia
- Low-grade dysplasia
- High-grade dysplasia

The changes were interpreted as LGD, goblet-cell-deficient type, based on the lack of active inflammation, the extent and uniformity of the nuclear atypia, and the lack of surface maturation.

Follow-Up

A total colectomy was performed.

Histology

Lower magnification of the nodular area in the sigmoid colon revealed deep mural invasion by small glands with open lumens and irregular to elliptical profiles (Fig. 6.46a). The nuclei were relatively bland, and there was no surrounding desmoplasia (Fig. 6.46b); however, deeper regions of the tumor contained clusters of poorly differentiated glands with desmoplastic stroma (Fig. 6.46c and d).

Differential Diagnosis

- Superficial misplaced dysplastic glands with transition to poorly differentiated adenocarcinoma
- Conventional moderately to poorly differentiated adenocarcinoma
- Low-grade tubuloglandular adenocarcinoma with progression to poorly differentiated adenocarcinoma

Ancillary Studies

None.

Final Diagnosis

Low-grade tubuloglandular adenocarcinoma with progression to poorly differentiated adenocarcinoma.

Take-Home Messages

- Although inflammation can result in reactive epithelial changes that mimic dysplasia, the distinction can often be made based on the presence or absence of maturation.
- A diagnosis of LGD should lead to serious consideration of colectomy, especially when associated with a visible mass.
- LGD can progress directly to adenocarcinoma without an obligatory stage of HGD.

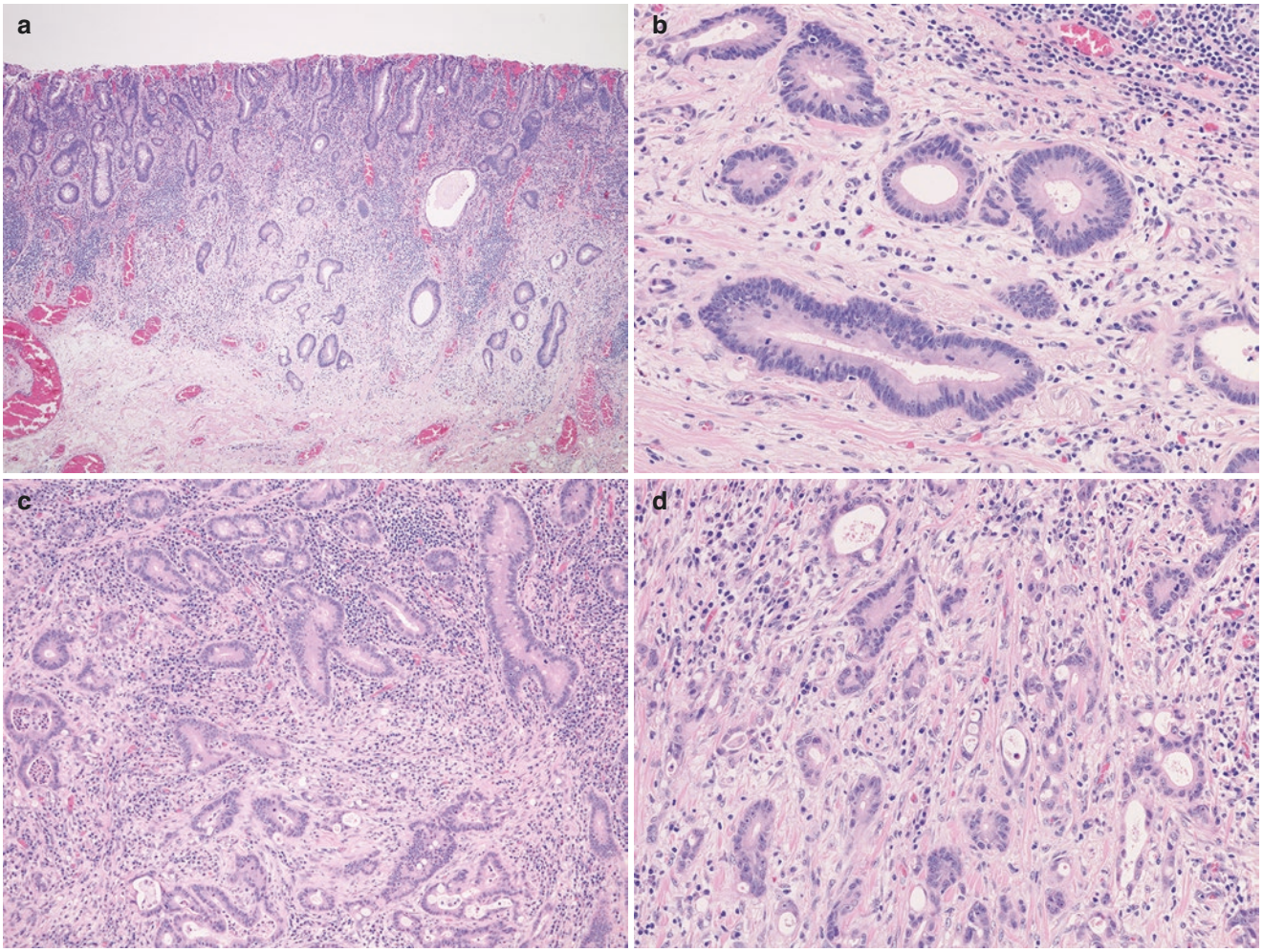

Fig. 6.46 (Case 5). (**a**) Low-grade tubuloglandular adenocarcinoma at low magnification consisted of deeply invasive elliptical glands with open lumens and little or no desmoplastic stromal reaction. (**b**) The invasive glands at higher magnification were round to elliptical. Cytologically, they closely resembled the overlying dysplastic mucosal crypts. (**c**) The deepest regions of the tumor consisted of conventional poorly differentiated adenocarcinoma. (**d**) Poorly differentiated adenocarcinoma with desmoplastic reaction

- Low-grade tubuloglandular adenocarcinoma is a distinctive cancer subtype that accounts for approximately 10% of IBD-related intestinal cancers.
- It usually originates from LGD or even indefinite dysplasia.
- It carries an excellent prognosis on its own but can progress to more aggressive histological subtypes.

Reference: [69]

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