The histopathological approach to inflammatory bowel disease: a practice guide

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Abstract Inflammatory bowel diseases (IBDs) are lifelong disorders predominantly present in developed countries. In their pathogenesis, an interaction between genetic and environmental factors is involved. This practice guide, prepared on behalf of the European Society of Pathology and the European Crohn's and Colitis Organisation, intends to provide a thorough basis for the histological evaluation of resection specimens and biopsy samples from patients with ulcerative colitis or Crohn's disease. Histopathologically, these diseases are characterised by the extent and the distribution of mucosal architectural abnormality, the cellularity of the lamina propria and the cell types present, but these features frequently overlap. If a definitive diagnosis is not possible, the term indeterminate colitis is used for resection specimens and the term inflammatory bowel disease unclassified for biopsies. Activity of disease is reflected by neutrophil granulocyte infiltration

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and epithelial damage. The evolution of the histological features that are useful for diagnosis is time- and disease-activity dependent: early disease and long-standing disease show different microscopic aspects. Likewise, the histopathology of childhood-onset IBD is distinctly different from adult-onset IBD. In the differential diagnosis of severe colitis refractory to immunosuppressive therapy, reactivation of latent cytomegalovirus (CMV) infection should be considered and CMV should be tested for in all patients. Finally, patients with longstanding IBD have an increased risk for the development of adenocarcinoma. Dysplasia is the universally used marker of an increased cancer risk, but inter-observer agreement is poor for the categories low-grade dysplasia and indefinite for dysplasia. A diagnosis of dysplasia should not be made by a single pathologist but needs to be confirmed by a pathologist with expertise in gastrointestinal pathology.

Keywords Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Consensus · Practice guidelines

Introduction

Inflammatory bowel diseases (IBDs) are lifelong disorders that are predominantly observed in developed countries. In their pathogenesis, an interaction between genetic and environmental factors is involved. The term IBD was initially coined to cover two specific diseases: ulcerative colitis (UC) and Crohn's disease (CD). In a broader sense, it is nowadays also in use for other forms of chronic colitis, such as microscopic colitis (including lymphocytic and collagenous colitis), but these are not discussed in this review.

The intention of the Consensus, which was supported by the European Society of Pathology (ESP) and the European Crohn's and Colitis Organisation (ECCO) was to address different aspects of histological diagnosis in IBD: (1) procedures required for a proper diagnosis, (2) features that can be used for making a diagnosis on endoscopic biopsies, (3) features that can be used for making a diagnosis on surgical specimens, (4) criteria that establish a diagnosis or a differential diagnosis (how many features should be present for a firm diagnosis), (5) impact of therapy on IBD histopathology, (6) criteria to diagnose and grade dysplasia and (7) features defining disease activity.

The Consensus paper, which is based on previous evidence-based ECCO Consensus publications [1, 2], was recently published in the *Journal of Crohn's and Colitis* [3]. The paper summarises the Consensus statements, followed by comments on evidence and opinion with specific emphasis on the clinicopathological interface, e.g. technical procedures necessary for accurate diagnosis of IBD on endoscopic biopsies (number and handling of biopsies, etc.). It also provides detailed information regarding the strategy and the methods used for the development of the evidence-based guidelines.

The aim of this paper is to provide a solid basis for the histopathological diagnosis of UC and CD on both resection specimens and biopsy samples: It focusses on the histological criteria for diagnosis and differential diagnosis and contains illustrative images. The content of the present and the previous [3] publication was approved by all participants in the consensus meetings.

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Procedures for the diagnosis of IBD

The histological examination of endoscopic biopsies or resection specimens is a crucial element in the diagnostic work-up of a patient with suspected IBD and assists in making a final diagnosis, particularly in differentiating between UC and CD and other forms of colitis. However, IBD is a clinical diagnosis and, as such, is based upon clinical information, endoscopic findings and morphological features observed in biopsies, as well as data from laboratory and imaging procedures. Thus, for a correct interpretation of biopsy specimens from patients with suspected IBD, detailed clinical information is essential.

In patients with suspected IBD, histological examination should be performed before initiation of treatment because drug treatment can induce changes in morphology. Since lesions may be focal, multiple sections from each tissue sample should be examined. In order to detect mild or focal lesions and to increase diagnostic accuracy, serial sectioning of biopsy specimens is superior to step sectioning, and the diagnostic yield increases with the number of sections examined [4–6].

However, the optimal number of sections to be examined in daily practice has not been established, the numbers varying between two and six in different studies [6, 7]. For daily practice, we recommend step-sections with two or three tissue levels, each consisting of five or more sections [8]. Staining with haematoxylin and eosin (H&E) suffices for a diagnosis, and special stains, including immunohistochemistry, are not needed.

The pathology report in all cases of chronic colitis should give an indication of disease activity, as reflected in the extent of neutrophil granulocyte infiltration and epithelial damage. In cases of UC, a distinction should be made between quiescent disease, inactive disease and active disease, and the latter should be graded. This has led to the introduction of scoring systems for the assessment of disease activity in UC, and these are used in clinical drug trials [9]. In CD, there is less evidence supporting the validity of histological grading of disease activity, but data from recent drug trials indicate that patients showing mucosal healing have a better outcome [10, 11]. In CD, inactivity in a biopsy may not reflect inactivity of IBD because of the discontinuous and transmural character of the disease, which induces sampling error, and also because as a rule biopsy samples of the ileum are limited, whereas the ileum may be the only bowel segment involved.

A surgical specimen requires systematic protocolled gross examination, with photographic documentation prior to fixation, as soon as the specimen is removed. Specimens should be opened longitudinally along the antimesenteric or antimesocolic side, except when a carcinoma is suspected, in which case it is advisable to leave a small segment unopened during fixation. Macroscopic aspects that constitute potential diagnostic features [13, 14], including transmural extension and fistulas, should be recorded. Special attention should be paid to lesions suspicious for neoplasia. Tissue samples for microscopy should include lymph nodes, terminal ileum and appendix. An optimal number of samples has not been established, but multiple samples, both from affected mucosa and macroscopically normal mucosa, improves the diagnostic yield. Burroughs and Williams [12] recommended that one section should be taken per 10 cm of resected bowel, in addition to sampling of any lesion. The site of a tissue sample should be recorded, e.g. by stating its distance to a specified resection margin.

Ulcerative colitis

Macroscopy

Gross examination of a resection specimen in UC classically shows diffuse and continuous chronic inflammation without skip lesions, which involves the rectum and spreads proximally with gradually decreasing severity of inflammation (Table 1). The transition between the involved and the normal mucosa is sharp (Fig. 1a). The mucosa has a friable granular appearance and shows superficial ulcers (Fig. 1b). In severe disease, these ulcers may undermine the adjacent mucosa, finally resulting in denudation of the mucosal surface or deep penetration through the muscularis mucosae [15, 16]. Extensive ulceration with sparing of remaining mucosal islands may give rise to inflammatory polyps, which are common in the sigmoid and descending colon but rare in the rectum (Fig. 1c). In fulminant colitis, the macroscopic appearance of the mucosa is not sufficiently distinct to differentiate UC from CD [17, 18] and serositis may be observed [19].

Table 1 Macroscopic features for the diagnosis of inflammatory bowel disease

	Ulcerative colitis	Crohn's disease
Localisation GI tract	Especially colon	Whole GI tract
Ileum	Not except in backwash ileitis	Often involved
Colon	Left>right	Right>left
Rectum	Commonly involved	Typically spared
Distribution GI tract	Diffuse (continuous)	Segmental (discontinuous)
Ulcers	Superficial ulcers	Aphthous ulcers, confluent deep linear ulcers
Inflammatory polyps	Common	Uncommon
Skip-lesions	Absent	Present
Cobblestone pattern	Absent	Present
Deep fissures	Absent except in fulminant colitis	Present
Fistulae	Absent except in fulminant colitis	Present
Mucosal atrophy	Marked	Minimal
Thickness of the wall	Normal	Increased
Fat wrapping	Absent	Present
Strictures	Uncommon	Present

Fig. 1 Gross examination of a resection specimen in ulcerative colitis classically shows diffuse and continuous chronic inflammation, with a sharp transition between the involved and the normal mucosa (**a**). The mucosa has a friable granular appearance and shows superficial ulcers (**b**). Extensive ulceration with sparing of remaining mucosal islands gives rise to inflammatory polyps (**c**). Long standing disease with atrophic mucosa lacking mucosal haustration and adenocarcinoma (*arrows*) within a stricture (**d**)
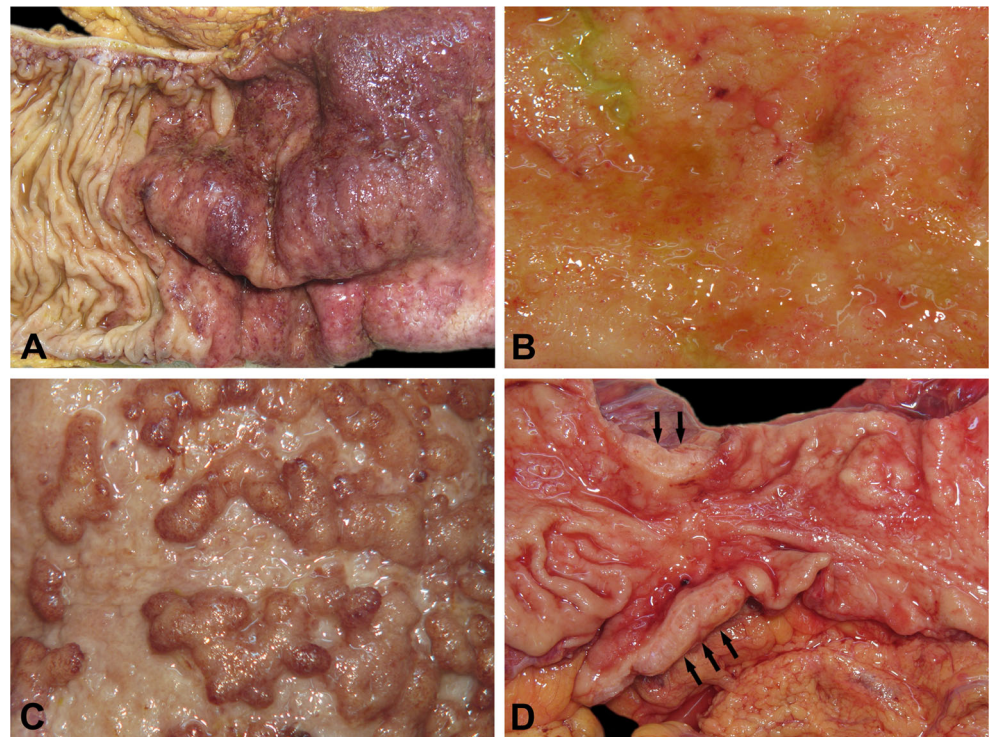
Awareness of unusual macroscopic distribution patterns, such as rectal sparing, caecal patch and backwash ileitis is important to avoid diagnostic errors. The rectum may be spared in untreated children (30 %), adults with fulminant colitis (13 %) or patients receiving topical and/or systemic treatment (44 %) [18, 20–23]. Another therapy-related finding is patchiness, i.e. discontinuous rather than continuous inflammation [20, 23]. When left-sided colitis is associated with inflammation surrounding the appendiceal orifice, this is called 'caecal patch'. Such discontinuous periappendiceal inflammation has been diagnosed in up to 75 % of patients with distal disease [24–26]. Backwash ileitis occurs in approximately 20 % of patients with pancolitis. It has rarely been described as primary ileal inflammation in patients with subtotal or left-sided colitis only [27]. This finding, however, needs further validation, particularly as it is difficult to

Table 2 Microscopic features used for the diagnosis of inflammatory bowel disease

	Ulcerative colitis	Crohn's disease
Crypt architectural irregularity	Diffuse (continuous)	Focal (discontinuous)
Chronic inflammation	Diffuse (continuous)	Focal (discontinuous)
	Decrease proximally	Variable
Patchiness	Uncommon	Common
Localisation of inflammation	Transmucosal Sometimes in submucosa	Transmural
Serositis	Absent except in fulminant colitis	Present
Lymphoid aggregates	Frequent in mucosa, submucosa	Common, transmural
Granulomas	Absent, except with ruptured crypts	Common
Acute inflammation	Diffuse (continuous)	Focal (discontinuous)
Crypt epithelial polymorphs	Diffuse (continuous)	Focal (discontinuous)
Crypt abscesses	Common	Uncommon
Mucin depletion	Present, pronounced	Uncommon, mild
Neuronal hyperplasia	Rare	Common
Muscular hypertrophy	Absent	Present
Paneth cell metaplasia	Present	Uncommon
Pyloric gland metaplasia	Rare	Present

distinguish from Crohn's terminal ileitis [28, 29]. In longstanding UC, tissue repair is associated with fibrosis, which, in contrast to CD, is commonly restricted to mucosa or submucosa. This fibrosis rarely causes benign strictures (3.2–11.2 %), which have to be differentiated from tumour-related stenoses (Fig. 1d) [30]. In the quiescent phase of the disease, mucosal haustration disappears, resulting in an atrophic smooth mucosa.

Histology

The histological diagnosis of UC is based upon four main categories of features: mucosal architecture, lamina propria cellularity, neutrophil granulocyte infiltration, and epithelial abnormality (Table 2). Awareness of the normal range of appearances of colorectal mucosa is necessary for optimal interpretation of biopsy specimens [31].

The assessment of abnormal lamina propria cellularity in UC refers to increased and/or altered distribution of cell types normally present in the colorectal mucosa. Apart from areas of frank ulceration, the inflammatory infiltrate in untreated disease is limited to the mucosa, diffuse or continuous without any variations in intensity or skip lesions, and its severity increases characteristically towards the rectum [32, 33]. A homogeneous increase in cellularity occurs throughout the lamina propria, for which the term transmucosal is used, and this can be best appreciated in the lower third, which has the lowest cell density in normal mucosa (Fig. 2a, b) [31].

Plasma cells are predominantly observed between the base of the crypts and the muscularis mucosae (basal plasmacytosis) (Fig. 2c). This feature is helpful in differentiating between a first attack of UC (63 %) and infectious colitis (6 %), but not CD (62 %) [8, 34]. Neutrophils, which reflect disease activity, are present in the lamina propria and/or

Fig. 2 Diffuse (continuous) inflammation with basal plasmacytosis, yet only mild crypt atrophy (shortening or 'gland lift-off') in early stage ulcerative colitis (**a**, original magnification, ×100), compared to marked crypt architectural distortion with crypt branching in longstanding disease (**b**, original magnification, ×75). Plasma cells are predominantly observed between the base of the crypts and the muscularis mucosae ('basal plasmacytosis') (**c**, original magnification, ×400). Disease activity is indicated by cryptitis and crypt abscess formation, which may lead to crypt destruction with a granulomatous reaction ('cryptolytic granuloma'), which should not be mistaken as diagnostic feature of Crohn's disease (**d**, original magnification, ×250). Patchiness of inflammation in longstanding disease (**e**, original magnification, ×150). Marked crypt architectural distortion and hypocellular stroma in quiescent disease (**f**, original magnification, ×150)
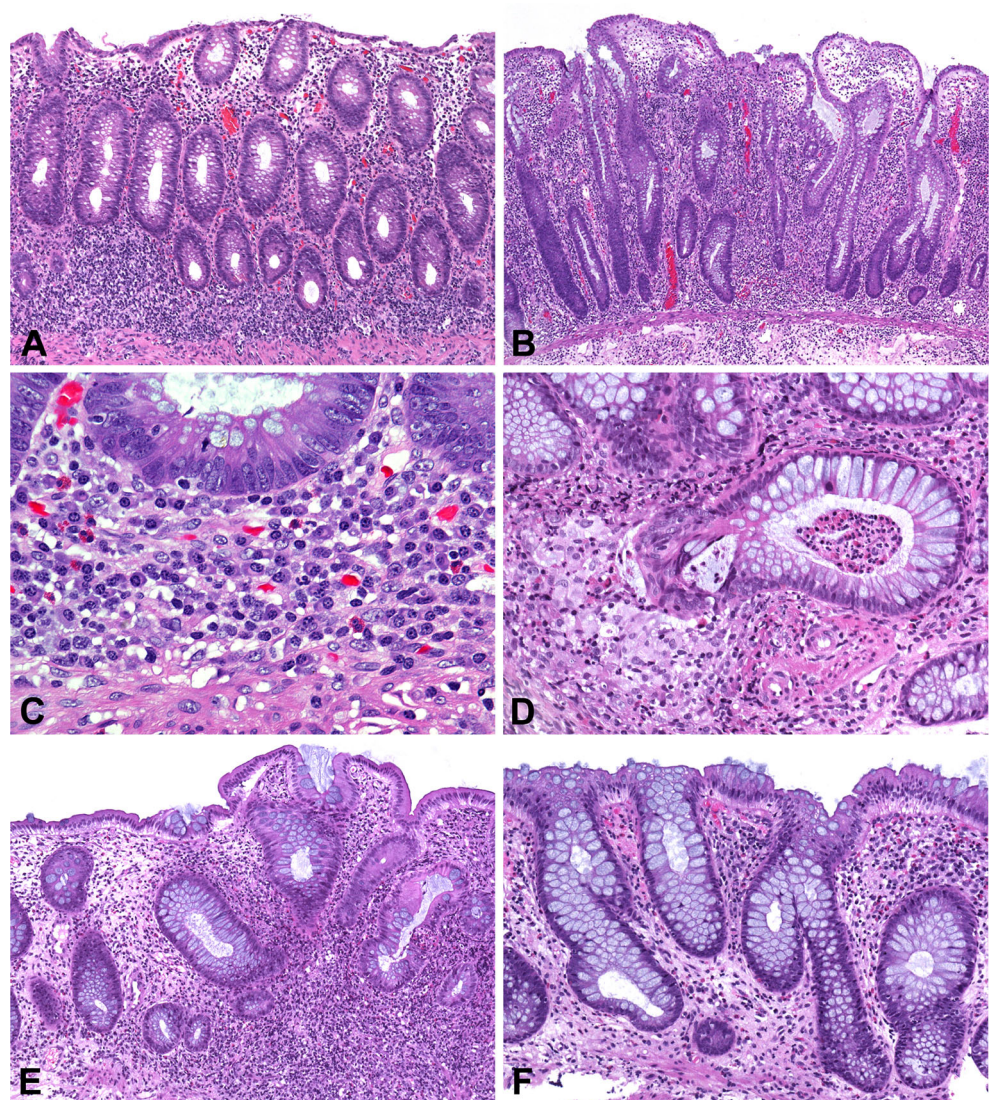
invade the surface or crypt epithelium, resulting in cryptitis (presence of neutrophils within crypt epithelium) or crypt abscesses (presence of neutrophils within crypt lumina). Crypt abscesses are more common in UC (41 %) than in CD (19 %) [31]. The number of eosinophils is variable. Granulomas are not observed, except for those in response to foreign bodies or to mucin from ruptured crypts (cryptolytic granulomas) (Fig. 2d) [35].

Alterations in mucosal architecture due to chronic inflammation are reflected in crypt architectural abnormalities (distortion, branching and atrophy), decreased crypt density (separation of adjacent crypts by lamina propria equivalent to or greater than one crypt diameter) and changes of surface topography (surface irregularity) [31]. Normal crypts are straight, parallel and extend from immediately above the muscularis mucosae to the surface.

Crypt distortion implies crypts that are no longer parallel, vary in diameter and/or are dilated (Fig. 2b). Crypt branching represents regeneration through fission: branching of more than 10 % of crypts or presence of more than two branched crypts in a well-oriented biopsy specimen with at least 2 mm of muscularis mucosase is abnormal [7, 31]. Crypt atrophy is defined as shortened crypts, accompanied by an increased layer of lamina propria stroma between the crypt basis and the muscularis mucosae [31]. In UC, distorted crypt architecture with crypt branching and atrophy is present in 57–100 % of cases, and irregular villiform architecture in 17–30 % of cases, more frequently than in CD (27–71 % and 12 %, respectively) [8, 31, 34, 36].

Epithelial abnormalities include surface epithelial damage, mucin depletion, and metaplastic changes [28]. Surface epithelial damage, such as flattening, focal cell loss, erosions, and ulcers reflect the activity of disease. Mucin depletion, defined as reduction in the number of goblet cells and/or reduced quantity of intracellular mucin, is a weak diagnostic feature in UC as it also occurs in other reactive processes, such as infectious colitis and CD [4, 34, 37]. Paneth cell metaplasia (in the left colon), inflammatory polyps, hypertrophy of the muscularis mucosae, and the much less frequently observed submucosal fibrosis are additional features of chronicity [38].

In *early stage disease*, the diagnosis of UC can be challenging. Preserved crypt architecture and absence of a transmucosal inflammatory infiltrate do not rule out early stage UC, in which case the distinction from infectious colitis (acute self-limiting colitis) is a major concern [39]. Its histological features are not diagnostic, and up to 30 % of patients with this pattern will eventually progress towards IBD [40]. Focal or diffuse basal plasmacytosis is the earliest diagnostic feature with the highest predictive value for diagnosis and can be identified in 38 % of patients within 2 weeks after presentation [41].

In *longstanding disease*, there is widespread architectural crypt distortion and increased cellularity of the lamina propria.

In this situation, confusing features occur such as patches of normal mucosa, discontinuous inflammation and rectal sparing. This needs to be kept in mind to avoid misdiagnosis, such as changing a diagnosis of UC into CD. With time, (under treatment), the extent of involvement of the colon tends to decrease, ultimately resulting in complete restoration of the rectal mucosa in 34–44 % of patients. In parallel, the distribution pattern may change from diffuse (continuous) to patchy (discontinuous) (Fig. 2e) [20, 32, 42], with or without treatment [43]. This type of histological evolution may result in diagnostic dilemmas, in particular when clinical information is not available [44]. As discontinuity and patchiness are both features characteristic for CD, the accuracy of the initial diagnosis of UC may erroneously be questioned, particularly in the absence of information on treatment.

In (clinically) *quiescent disease*, the mucosa may still show features, which reflect sustained damage, such as architectural abnormalities and reduced crypt density [45]. During regeneration, the mucin content of goblet cells is restored [46]. The inflammatory infiltrate is of variable density, and as a result, the lamina propria may either appear hyper- or hypocellular (Fig. 2f). Neutrophils are not observed in quiescent disease, but the number of eosinophils does not change [47]. Ultimately, basal plasmacytosis decreases resulting in normal cellularity of the lamina propria. Histological findings predictive of ensuing clinical relapse in patients with quiescent disease are persistence of basal plasmacytosis, mildly active disease or a high number of eosinophils [41, 48, 49].

Pouchitis

Proctocolectomy with ileal pouch anal anastomosis (IPAA) is the procedure of choice for most patients with UC requiring colectomy. 'Pouchitis' refers to active inflammation of IPAA mucosa and is considered as a primary 'non-specific, idiopathic inflammation of the neorectal ileal mucosa' [50, 51].

Three to 20 % of patients develop persistent or recurrent episodes of pouchitis, which, based upon the duration of symptoms, may be acute (<4 weeks) or chronic (>4 weeks). While in patients with acute pouchitis antibiotic therapy is usually effective, approximately 10–15 % of these patients develop chronic pouchitis, refractory to this treatment (chronic refractory pouchitis) [52]. Some patients may develop CD-like complications including perianal fistulas and inflammation, stenoses or fistulas in the pre-pouch ileum and/or the pouch. The diagnosis of pouchitis is based on a combination of clinical symptoms, endoscopic and histological findings. Histological changes may be patchy and more prominent in the lower and posterior regions of the pouch. Consequently, multiple biopsies from these sites are essential for the diagnosis [53].
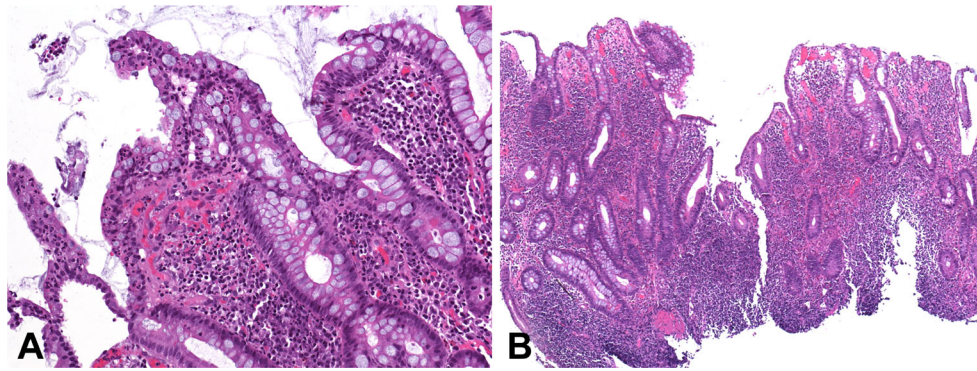
Fig. 3 Pouchitis with patchy infiltration of the lamina propria and the surface epithelium by neutrophils causing aphthous erosion (**a**, original magnification, ×150). In refractory disease, severe inflammation with increased lamina propria cellularity, presence of neutrophils within lamina propria and epithelium, Crohn's-like fissures and mucosal architectural distortion may be observed together with crypt hyperplasia and villous atrophy (colonic metaplasia) (**b**, original magnification, ×75)

Chronic inflammatory changes, present in up to 87 % of biopsies from 'healthy' pouches, consist of architectural distortion, villous atrophy, crypt hyperplasia and infiltration of the lamina propria by mononuclear cells, eosinophils and histiocytes. Neutrophils are rarely present. Villous atrophy and crypt hyperplasia are considered adaptive changes ('colonic' metaplasia). Mild ischaemic changes occasionally occur, while some patients develop features of mucosal prolapse, most often in the anterior wall. In pouchitis, patchy intraepithelial neutrophil infiltrates become more numerous and cryptitis ensues, with crypt abscesses and ulcerations (Fig. 3a). As colonic metaplasia occurs more frequently in cases with pouchitis, it may be a reparative rather than an adaptive response [54].

The histology of chronic refractory pouchitis is mostly identical to that of 'usual' pouchitis. In this situation, other possible causes such as infections [particularly cytomegalovirus (CMV)] should be considered. The development of CD-like complications in chronic pouchitis may cast doubt on the initial diagnosis. Biopsy specimens usually show features of severe inflammation with neutrophils within the lamina propria and invading the epithelium, resulting in erosions, ulcerations and mucosal architectural distortion (Fig. 3b). Histology of pouches excised for these complications may show deep submucosal lymphoid aggregates and granulation tissue-lined fistulous tracts. Similar changes, and even granulomas, have been observed in blind ending rectal stumps left in situ after total colectomy for UC [55]. The occurrence of CD-like complications and the presence of deeply situated lymphoid aggregates do not refute a diagnosis of UC. CD should only be diagnosed after IPAA surgery when re-examination of the original proctocolectomy specimen shows typical features of CD [56]. Pyloric gland metaplasia is associated with chronic mucosal damage and can be encountered not only in UC but also due to trauma, prolapse, non-steroidal anti-inflammatory drug-induced injury and CD [57].

Crohn's disease

Macroscopy

CD can affect any part of the gastrointestinal tract, but it occurs most commonly in the terminal ileum, often in association with the right colon (Table 1). Isolated large bowel involvement occurs in approximately 20 % of cases, preferentially in the right colon. Warren [58] distinguished three basic patterns of large bowel involvement: CD limited to the rectum, stenosing large bowel CD and diffuse Crohn's colitis typically with reduced involvement of the rectum. Approximately 75 % of patients with large bowel CD at some point during the course of the disease develop perianal manifestations, including skin tags, deep ulcers, fissures, fistulae, abscesses, blind sinus tracts and strictures [58].

Characteristically, macroscopic examination of a resection specimen with CD shows a discontinuous pattern of inflammation. Diseased segments are frequently separated by areas of uninvolved, i.e. normal, bowel (skip lesions) (Fig. 4a) and transition from involved to uninvolved areas is usually abrupt. The serosal surface of an involved bowel segment is often hyperaemic and may be covered with inflammatory exudate, but in longstanding cases, serosal adhesions occur. Mainly in small bowel CD, but less frequently also in large bowel CD adipose tissue expands towards the antimesenteric surface, which is called 'fat wrapping'. Fat wrapping is a valuable diagnostic criterium for the diagnosis of CD [59], and it also occurs in segmental colitis associated with diverticulosis, along with other Crohn's colitis-like changes (such as fissuring ulcers, granulomas and transmural lymphoid aggregates) [60, 61].

The earliest grossly visible mucosal lesions are small aphthous ulcers that typically develop over lymphoid follicles along the mesenteric margin of the bowel wall [62] and are bordered by quite normal mucosa (Fig. 4b). As aphthous

Fig. 4 Gross examination of a resection specimen in Crohn's disease classically shows a discontinuous pattern of inflammation (skip lesions). Mainly in the small bowel, adipose tissue expanding towards the antimesenteric surface may be observed ('fat wrapping', *arrow*) (**a**). The earliest grossly visible mucosal lesions are small aphthous ulcers that typically develop over lymphoid follicles (**b**). As the aphthous ulcers enlarge, they coalesce to large deep serpiginous or linear ulcers with overhanging oedematous mucosal edges (**c**). At sites of transmural inflammation with fibrosis and fibromuscular proliferation the bowel wall may become thickened and strictures may develop; prominent fat wrapping is seen as secondary finding (*arrows*) (**d**)
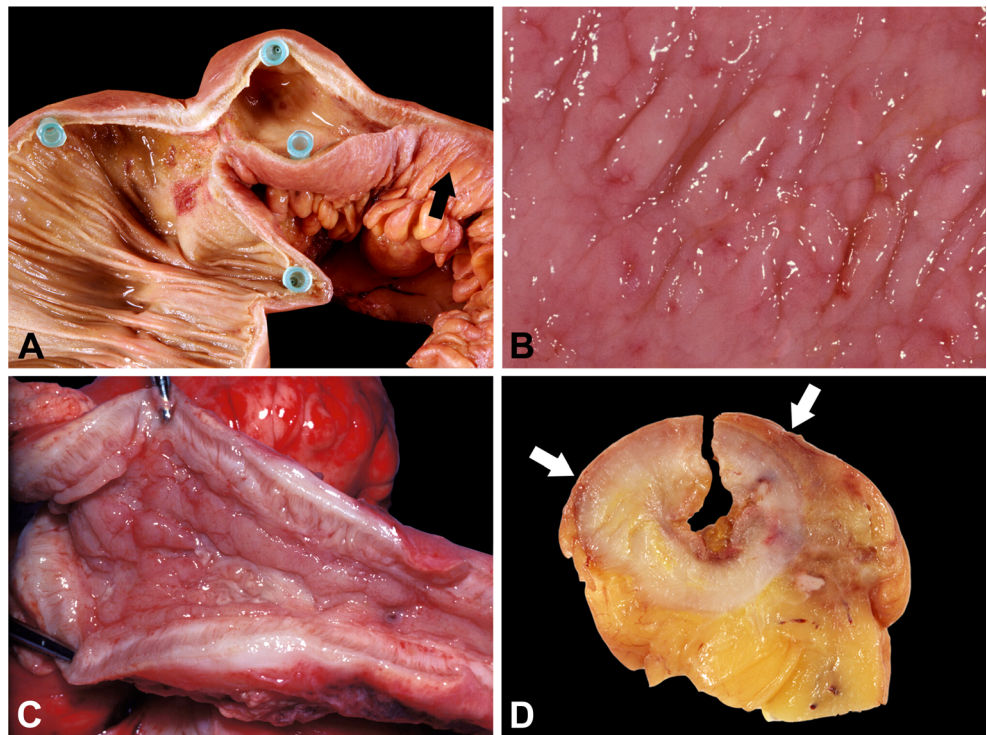
ulcers coalesce, they form large deep serpiginous or linear ulcers with overhanging oedematous mucosal edges (Fig. 4c). Islands of oedematous, non-ulcerated mucosa, separated by deep discrete ulcers, give rise to the classic cobblestone appearance. As in UC, inflammatory polyps occur. Healed ulcers leave depressed scars.

Fistulae are a common finding in small bowel CD. Although relatively rare, they occur also in CD in the colon, mainly in patients with ileocolitis. Free perforation, however, is exceptional. At sites of transmural inflammation with fibrosis and fibromuscular proliferation, the bowel wall becomes thickened and increasingly rigid (Fig. 4d). Strictures ensue, more often in the small than in the large intestine.

Histology

A variety of microscopic features support the diagnosis of CD (Table 2). Focal (discontinuous) chronic inflammation, focal crypt architectural distortion and granulomas not related to crypt injury are the features with highest diagnostic value. These, as well as an irregular villous architecture, are features in favour of a diagnosis of CD in endoscopic ileal biopsy samples. When the ileitis is in continuity with proximal colitis, the features should be used with caution, because they occur also in backwash ileitis in UC.

Focal (discontinuous) chronic inflammation implies increased cellularity of the lamina propria (with lymphocytes and plasma cells), of variable density throughout the biopsy specimen and not confined to the superficial mucosa. One or more circumscript foci with increased mononuclear cell density with or without infiltration of neutrophils will be found, against a background of normal mucosa or mucosal samples with variable intensity of inflammation. Normal lymphoid aggregates are not considered as focal inflammation. Assessment of differences in cellularity between multiple biopsy specimens is more reproducible than differences within a single biopsy specimen. In a biopsy, the inflammation may extend into the submucosa. As in UC, the presence of neutrophils in the lamina propria or in the epithelium, including cryptitis and crypt abscesses, indicates active disease and signifies epithelial damage (Fig. 5a, b).

An epithelioid cell granuloma is a discrete collection of at least five epithelioid cells (activated histiocytes with homogeneous slightly eosinophilic cytoplasm), with or without multinucleated giant cells [31]. In CD, granulomas are often poorly delimited. Multinucleated giant cells may be absent and necrosis is unusual. Only granulomas not related to crypt injury should be regarded as a feature in support of CD (Fig. 5c) [35]. Notably, non-caseating granulomas, small collections of epithelioid histiocytes with giant cells or isolated giant cells, occur also in infectious colitis (acute self-limiting colitis), parasitic infections and intestinal tuberculosis and should not be regarded as evidence in favour of CD.

As in UC, the chronic inflammatory process induces alterations in mucosal architecture. These are generally less prominent than in UC and focal or discontinuous. Pyloric gland metaplasia is related to mucosal ulceration and repair [63] and

Fig. 5 Focal (discontinuous) mucosal inflammation in Crohn's colitis (**a**, original magnification, ×150) with fissuring ulceration (**b**, original magnification, ×100) and vaguely defined epithelioid cell granuloma not related to crypt injury (**c**, original magnification,×400). Pyloric gland metaplasia in chronic ileitis (**d**, original magnification, ×150). Involvement of the upper gastrointestinal tract in Crohn's disease with focally enhanced gastritis (**e**, *arrows*, original magnification,×100) and duodenitis (**f**, original magnification, ×100)
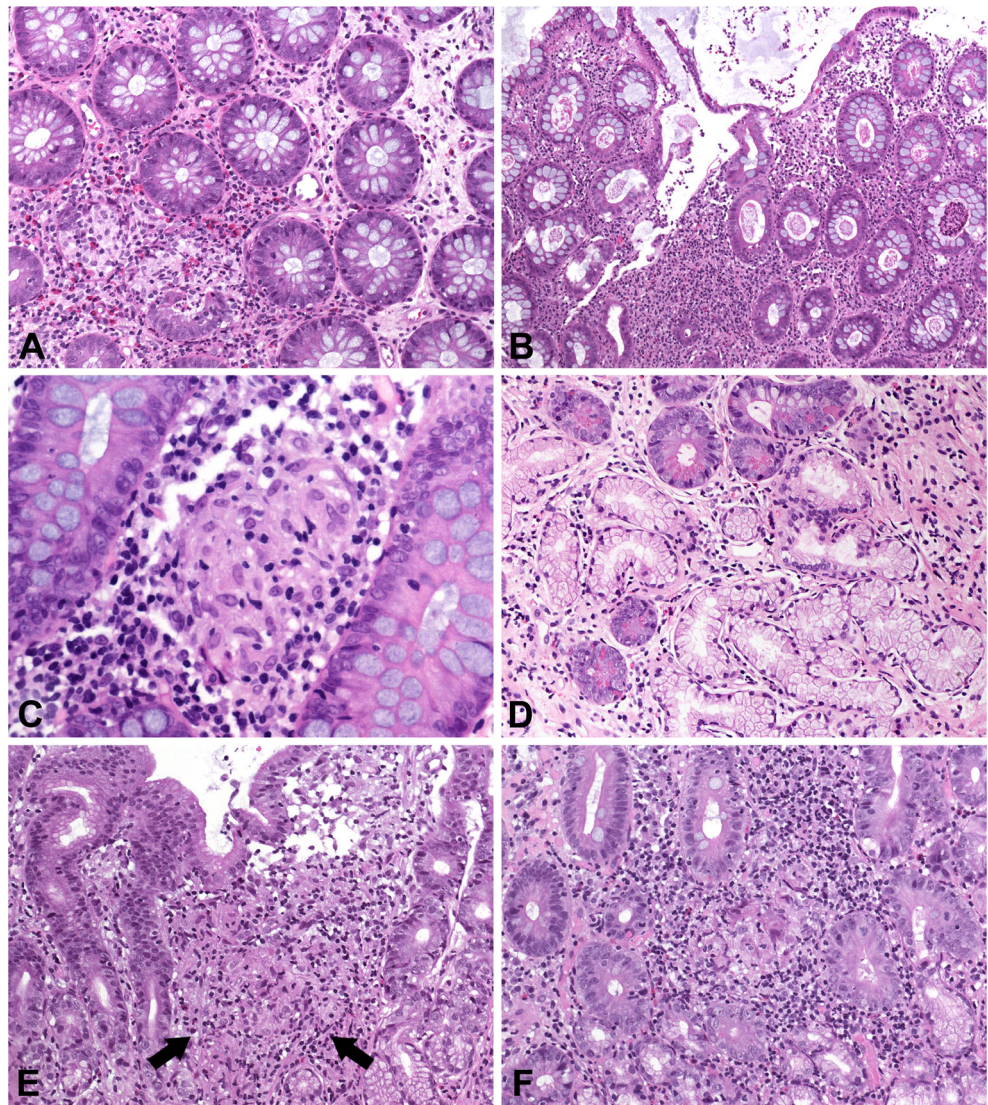
is observed in 2–27 % of ileal biopsies from patients with CD but very common in ileal resection specimens (Fig. 5d). It has been rarely described in resection specimens with backwash ileitis in UC, only in combination with active ileal inflammation and/or ulceration [27] but not in ileal biopsies from patients with UC [28, 29, 64].

Transmural lymphoid aggregates (identifiable only in resection specimens and usually not in ulcerated areas) and granulomas are features supporting a diagnosis of CD. In a study on colectomy specimens from cases with fulminant colitis, granulomas and lymphoid aggregates proved to be the two most specific predictors of a final diagnosis of CD [18].

When only a single feature is present, this is not regarded as sufficient for a reliable diagnosis of CD. Most expert clinicians and pathologists agree that the presence of granulomas and at least one other feature establishes a diagnosis of CD [65]. The second feature can be either inflammation or, more

specifically, architectural abnormalities. While focal architectural abnormalities favour CD, a pseudovillous appearance of the colorectal mucosal surface is more consistent with a diagnosis of UC. The presence of granulomas is not a prerequisite for a diagnosis of CD. Granulomas are more often observed in children and adolescents than in adults. Additional useful features are focal chronic inflammation without crypt atrophy, focal cryptitis (although with poor reproducibility [66–68]), aphthous ulcers, disproportionate submucosal inflammation, neural hypertrophy (nerve fibre hyperplasia [13, 69]), increased number of intraepithelial lymphocytes [68] and in the colon proximal location of ulceration and architectural distortion. When multiple biopsies are available, ileal involvement, colonic inflammation with a decreasing proximal to distal gradient, as well as the absence of features highly suggestive or diagnostic for UC, such as diffuse inflammation, crypt irregularity and reduced crypt density, also support a diagnosis of CD. Particularly in children and adolescents,

biopsies from the upper gastrointestinal tract can provide additional diagnostic clues.

Indeterminate and unclassified colitis

In approximately 5 % of IBD cases, a definite diagnosis of UC or CD cannot be established, most often due to either insufficient clinical, radiologic, endoscopic or pathological data, or overlapping features of both disorders [70]. Labels such as 'indeterminate colitis', 'inflammatory bowel disease unclassified (IBDU)', 'chronic inflammatory bowel disease unclassified' and 'chronic idiopathic inflammatory bowel disease not otherwise specified' are in use for such cases.

The term 'indeterminate colitis' (IC) was first introduced in 1970 by Kent et al. [71] in a study on colectomy specimens of patients with IBD with overlapping features of UC and CD. It is probably the most commonly used terminology, but a universally accepted definition for this label has not been established. The introduction of endoscopy with endoscopic biopsy changed clinical management and the pathologist's perception. Subsequently, the term IC was increasingly used also for patients presenting with clinical features of chronic IBD, with inflammation restricted to the colon and no small bowel involvement, when endoscopy was non-conclusive and diagnostic features for either CD or UC were absent on biopsies while infectious colitis and other causes of colitis had been excluded.

As a consequence, IC signifies diagnostic uncertainty as to whether a patient has UC or CD and a diagnosis of IC on endoscopic biopsies is not based upon specific histological features [68, 72]. To solve the problem of the ambiguous significance of the term IC, the working party of the 2005 Montreal World Congress of Gastroenterology and the pathology task force of the International Organization for Inflammatory Bowel disease attempted to clarify a definition [73, 74]. The ESP/ECCO working group for the European Consensus in pathological findings in IBD equally favours an agreement on terminology, in order to allow comparison between different studies.

The term IC should be restricted to cases in which comprehensive histological examination of (a) surgical specimen(s) is possible. The term IC should be avoided on endoscopic (preoperative) biopsies, on which the term IBDU is preferred when a patient with chronic colitis clearly has IBD based upon the clinical history, but macroscopy and/or endoscopic biopsies show no definitive features of either UC or CD. The arguments underpinning this proposal are as follows:

1. As originally proposed, the term IC was originally proposed for colectomy specimens.
2. Some diagnostic microscopic features cannot be assessed on endoscopic biopsy samples.

3. There are no generally accepted positive histological features for a diagnosis of IC on endoscopic samples.
4. Post-operative examination of resection specimens in such cases usually provides definitive evidence of UC or CD [75, 76].

Both IC and IBDU are 'temporary diagnoses'. Diagnostic uncertainty occurs more often in children. However, a histological pattern of non-diffuse acute and chronic inflammation with architectural changes confined to the colon, not allowing a final diagnosis, can also be observed in adults as part of the natural history of UC or secondary to treatment [20, 32]. Epidemiological studies have shown that most cases with uncertain diagnosis behave like UC [72].

Children and adolescents

IBD is an important cause of gastrointestinal pathology in children and adolescents. About 10–15 % of patients are diagnosed before the age of 18 years [77]. Paediatric-onset IBD is distinctly different from adult-onset IBD, which may hamper a diagnosis with as a result delayed or inadequate therapy. The gold standard for diagnosing paediatric IBD remains endoscopic evaluation of the upper and lower gastrointestinal tract, with mucosal biopsies for histopathological confirmation [78–80].

Children with untreated UC commonly present with subtotal or extensive colitis, but with less severe inflammation, less epithelial injury and less architectural abnormalities than UC in adults [21, 22, 77, 80–82]. Backwash ileitis occurs with similar frequency [83], but children more often present with unusual histologic inflammation patterns, such as patchiness (21%) and (relative) rectal sparing (30%) [21, 22, 84]. As children approach adulthood, the degree of inflammation and architectural distortion approaches that found in adults. However, in rectal biopsies, a similar degree of inflammation is seen regardless of age group [81, 82].

At onset, CD in children is associated with more colitis and less ileitis [85]. When the disease is severe, all biopsies obtained during a single colonoscopy tend to show chronic inflammation (with or without neutrophils), including in the rectal mucosa, which introduces difficulties in differentiating between CD and UC. In such a case, the presence of areas with inflammation alternating with areas with much less (or without) inflammation each of the multiple colonic biopsies should be noted, since focal distribution of inflammation is highly suggestive of CD. The frequency of granulomas is higher in children than in adults [86, 87].

In addition, in paediatric patients with CD upper gastrointestinal involvement is more frequent than in adults [88]. In paediatric patients, focal inflammation may be found in the oesophagus, the stomach, and the duodenum (Fig. 5e, f) [89].

However, focal inflammation of the upper gastrointestinal tract does not exclusively occur in CD, as focally enhanced gastritis is observed in children with UC [90]. In particular, although *Helicobacter pylori*-negative focally enhanced gastritis is more common in children with CD (43–76 %), the lesion is also seen in UC (8–21 %) [91–95]. Granulomas are only found in CD [96]. Finally, according to recent literature data, children with focally enhanced gastritis are about 15 times more likely to have IBD, particularly CD, than non-IBD controls, proving this type of gastritis to be a valuable finding in cases of indefinite diagnosis [95].

Interaction between infection and inflammatory bowel disease

The interaction between infection and IBD is complex: Infections have been associated with the onset of IBD, but they might also trigger flare-ups of the disease or a relapse of symptoms and thus complicate the clinical picture [97]. Moreover, infectious forms of colitis, e.g. tuberculosis, have to be considered in the differential diagnosis, particularly in developing countries.

Testing for reactivation of latent CMV infection should be performed in all patients with severe colitis refractory to immunosuppressive therapy [98, 99]. In addition, testing should be performed on biopsies with prominent granulation tissue associated with large ulcers [98, 100]. In UC, the risk of CMV reactivation is significantly higher than in CD (10–56.7 % vs. 0–29.6 %) [101]. The risk depends also on the type of immunosuppressive drugs used and is higher in steroid-refractory than in steroid-responsive patients (25–30 % vs. 0–9.5 %) [99, 101].

Although inclusion bodies indicative of a CMV infection can be detected in H&E-stained slides, immunohistochemistry or molecular techniques are more sensitive and have a high diagnostic accuracy (Fig. 6a, b) [101]. On H&E-stained slides, CMV typically presents as large (cytomegalic) cells of (mainly) mesenchymal origin, e.g. endothelial cells and fibroblasts in granulation tissue. These are typically two- to fourfold larger than normal, with large amphophilic intranuclear inclusions, surrounded by a clear halo, and smaller cytoplasmic inclusions. However, some infected cells are morphologically less characteristic and the morphology of ganglion cells and necrotic or apoptotic cells may resemble CMV inclusions. Due to sampling error, however, false-negative biopsies are common and in studies the sensitivity of detection ranges from 10 to 87 % [101]. Immunohistochemistry, using monoclonal antibodies directed against CMV immediate early antigen, increases the diagnostic yield in comparison with H&E staining [98, 102] and its sensitivity approximates 93 % [103]. Semiquantitative immunohistochemistry, reporting the number of infected cells and/or the number of CMV-positive biopsy fragments, may have a predictive value [100, 104, 105]. The qualitative polymerase chain reaction (PCR) can also be used on biopsy tissue to detect viral DNA, although the significance of a positive result in the absence of histological features of infection remains unclear. Quantitative real-time PCR may be more accurate in differentiating between infection and disease, but a universally accepted cut-off value has not been defined [106].

Histology does not allow reliable detection of bacterial superinfection of the small or large intestine. This holds true especially for *Clostridium difficile* infection, as the histologically characteristic pseudomembranous colitis is usually not

Fig. 6 Cytomegalovirus detection in inflammatory bowel disease: comparison of H&E (**a**, original magnification, ×200) and immunohistochemistry (IHC) (**b**, original magnification, ×200) in serial sections, unequivocally positive cells detected by H&E are *circled*. These cells are also seen in IHC. In addition, several other infected cells are visible by IHC only (*arrows*)
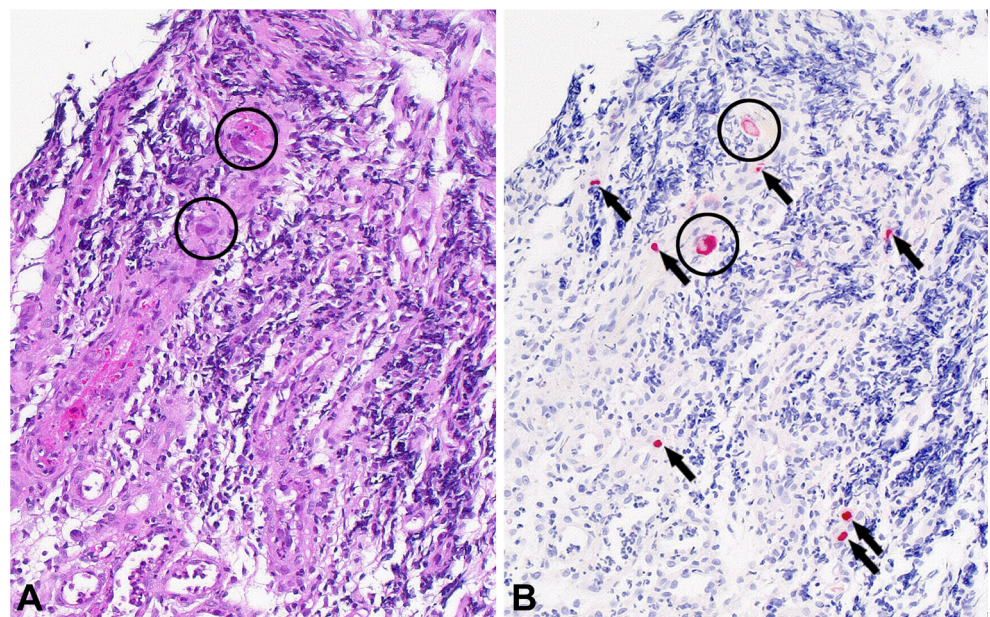
Fig. 7 Flat dysplasia in ulcerative colitis with marked nuclear hyperchromasia and pleomorphism (**a**, original magnification, ×100). The lesion is positive for p53 upon immunohistochemistry (**b**, original magnification, ×100). Raised or elevated dysplastic non adenoma-like (colitis-associated) lesion with irregular neoplastic glands (varying configuration, size and diameter) and varying amounts of stroma (**c**, original magnification, ×75). Note dysplastic goblet cells (**d**, original magnification, ×150)
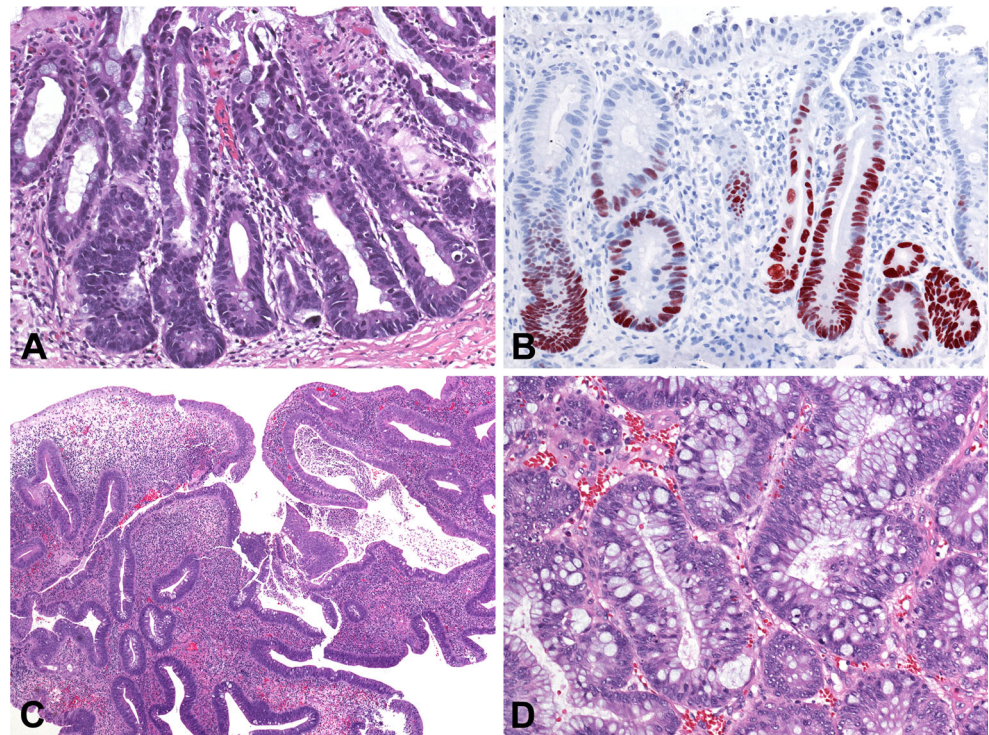
present in IBD patients treated with immunosuppressive agents [107–109].

Dysplasia and cancer

Patients with IBD carry an increased risk of colorectal cancer [110–113]. The most important risk factors are young age at onset, long disease duration and extensive large bowel involvement, indicating a cumulative effect of intestinal inflammation (dysplasia–carcinoma sequence). Additional risk factors include primary sclerosing cholangitis, severe inflammation, polypoid mucosal lesions and a family history of colorectal cancer [113–116].

Although the increased risk is well established for patients with UC, the less abundant data available for CD indicates similar risk, given a similar duration and extent of disease [116–119]. In addition, in CD an increased risk of small bowel adenocarcinoma exists, most commonly in the distal jejunum and ileum [120–123].

Dysplasia is the best and most reliable marker of increased risk of malignancy in patients with IBD [111, 125]. It is defined as 'histologically unequivocal neoplastic epithelium without evidence of tissue invasion' [124]. For diagnostic purposes, the dysplasia concept comprises of four distinct categories: negative for dysplasia (regenerating epithelium), indefinite for dysplasia ('questionable' dysplasia) and positive for low- or high-grade dysplasia [126]. Inter-observer agreement is poor for low-grade dysplasia and indefinite for

Table 3 Microscopic and clinical features used for the differential diagnosis of neoplastic lesions in inflammatory bowel disease

	Colitis-associated dysplasia	Adenoma-like lesion (sporadic adenoma)
Age	<50 years	>60 years
Extent of disease	Usually total	Usually subtotal
Activity of disease	Usually active	Usually inactive
Disease duration	Long (>10 years)	Short (<10 years)
Associated flat dysplasia	Common (no sharp delineation)	Absent (sharp delineation)
Histology of lesion	Irregular neoplastic glands (varying configuration, size and diameter) with varying amounts of stroma	Regular neoplastic glands (similar configuration, size and diameter) with low amounts of stroma
Increased (mononuclear) lamina propria inflammation	Usually present	Usually absent
Mixture of benign/dysplastic crypts at surface	Usually present	Usually absent

dysplasia [127–130]. Confirmation of dysplasia by a pathologist with expertise in gastrointestinal pathology has been recommended by the ECCO/ESP Consensus panel (based upon similar recommendations for Barrett's oesophagus) [3,131].

Dysplasia related to IBD develops only in areas with chronic inflammation in any part of the colorectum and is often multifocal [111, 125]. Microscopic features used for diagnosis are analogous to those characterising neoplasia, in general, including both architectural and cytological abnormalities [126].

There are two distinct macroscopic patterns of dysplastic lesions in patients with IBD: flat and elevated. According to the American Gastroenterological Association technical review on the diagnosis and management of colorectal neoplasia in IBD [113], the term flat dysplasia refers to lesions that are endoscopically undetectable, whereas elevated dysplasia refers to endoscopically detectable lesions. It should be noted, however, that the term 'flat dysplasia' has also been used to describe endoscopically detectable, but only slightly raised lesions (Fig. 7a, b). Hence, flat dysplasia is generally detected in random biopsies from endoscopically unremarkable mucosa. It carries a high risk for cancer: in cases in which flat high-grade dysplasia had been diagnosed, a synchronous adenocarcinoma was found in 42–67 % of cases [113, 132].

Elevated or raised dysplastic lesions are a heterogeneous group including adenoma- and non-adenoma-like lesions (Fig. 7c, d) [133, 134]. Non-adenoma-like lesions can appear as large velvety patches, irregular plaques, irregular bumps and nodules, wart-like lesions, large sessile polypoid lesions with a broad base or even as localised strictures [133, 135]. Adenoma-like lesions are usually well circumscribed and small, sometimes sessile similar to some sporadic adenomas unrelated to UC. Several clinical and microscopic features help to differentiate colitis-associated dysplasia from adenoma-like lesions (Table 3) [70, 133, 136, 137]. The distinction is important as the clinical management differs significantly, ranging from local therapy (polypectomy) to proctocolectomy. According to a recent large retrospective analysis of patients undergoing proctocolectomy for dysplasia, patients with high-grade dysplasia had cancer in 29 %, compared to 3 % for patients with low-grade dysplasia. In addition, patients with elevated non-adenoma-like dysplasia had cancer in 25 %, compared to 8 % for patients with flat dysplasia. Hence, the cancer risk of patients with a diagnosis of high-grade dysplasia or elevated non-adenoma-like dysplasia is substantial, and the threshold for surgery should be low given the high likelihood of finding cancer in the corresponding resection specimen [3, 138, 139].

Recent studies have focussed on ancillary methods to improve inter-observer variability in detecting dysplasia. The *p53* tumour suppressor gene is a key factor in the initial steps of IBD-associated carcinogenesis [140]. p53 protein is overexpressed in 33–67 % of patients with dysplasia and in 83–95 % of patients with IBD-associated carcinomas [141, 142]. However, occasional p53 protein expression in regenerating non-dysplastic epithelium limits the diagnostic value of this marker.

Conflict of interest The authors declare no conflict of interest.

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