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Histopathology of Crohn's disease and ulcerative colitis

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SUMMARY BOX

Goal

To review the important histologic features required for the diagnosis, assessment of disease activity and early detection of malignancy. The variability of features with time and treatment and difficult differential diagnostic problems will be discussed.

Key points

1 Histopathology can help to solve many diagnostic problems, especially when multiple biopsies of the colon and ileum are available

2 Exacerbations and remissions are reflected by mucosal inflammation and activity of variable intensity, including healing

3 Multiple biopsies are also indicated for the early detection of pre-cancerous lesions and cancer in ulcerative colitis and Crohn's disease

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases of unknown cause. Clinically, both conditions usually begin gradually, but they can start abruptly and sometimes even present as fulminant disease. The clinical course is characterized by exacerbations and spontaneous or drug-induced remissions. UC primarily affects the mucosa of the large bowel, while CD is a transmural disease that can affect the whole gastrointestinal tract. The various clinical patterns are reflected in the microscopic features observed in biopsies obtained from surgical specimens or during endoscopy. Endoscopic mucosal biopsies will not show all the characteristic features of CD. Review of biopsies, in combination with clinical, laboratory, radiographic and endoscopic observations, is used for the diagnosis of UC and CD and the differentiation from other conditions. Such differentiation is important because a precise diagnosis is essential for appropriate treatment.**1-3** A correct diagnosis is possible in the large majority of patients; still, in some patients with acute onset or fulminant disease, a precise diagnosis may be difficult to reach, resulting in a temporary diagnosis of indeterminate colitis (IC). Biopsies also allow assessment of disease activity and identification of pre-cancerous lesions and cancer. In clinical practice, often only rectal biopsies are obtained for diagnosis. However, in contrast with UC, the rectum is not always involved in CD and lesions in CD frequently occur in a background of normal mucosa. Therefore it is more appropriate to take multiple endoscopic biopsies in different segments of the colon (and ileum) during the initial work-up of a patient presenting with inflammatory diarrhea or during follow-up and screening for cancer. Multiple biopsies permit an in-depth analysis of the distribution of inflammation and are essential for the recognition of dysplasia. It also increases diagnostic accuracy by 5–41%. Carcinoma can occur during the course of the disease as a late complication.

THE NORMAL INTESTINE

The gastrointestinal (GI) tract is a hollow tube consisting of three layers: mucosa, submucosa, muscularis propria and loose areolar tissue covered by mesothelium where the tract borders on the body cavity (serosa). In the colon, the surface of the mucosa is flat and its architecture is characteristic with crypts as straight tubes, in parallel alignment. The crypt base rests upon a layer of smooth muscle cells, the muscularis mucosae, which separates the mucosa from the submucosal connective tissue. The distance between the crypts and the internal diameter of the crypts is constant. The crypt architecture is maintained throughout the colon, except in the presence of lymphoid collections, in zones of transition to small intestinal mucosa (ileocecal valve) or to squamous epithelium (the anorectum) and in normally occurring grooves in the surface. In the small intestine, the surface is irregular due to the presence of finger-like villi of uniform size and shape. In the ileum, the villi are taller and the crypts less deep compared with the jejunum. Surface, villi and crypts are covered with a single-cell layer of columnar epithelium, separated from the connective tissue lamina propria by the basement membrane complex. The epithelial cells form a heterogeneous group with mature cells (absorptive enterocytes and goblet cells) lining the surface, villi and upper part of the crypts, immature crypt cells including stem cells in the base of the crypts and endocrine cells. Paneth cells are present in the base of the crypts in the small intestine and caecum. Epithelial cells have a barrier and secretory function and are involved in the immune response (secretion of SIgA). In the colon they do not constitutively express the major histocompatibility class II antigens (MHC). Epithelial cell turnover ranges between 2 and 8 days.[4–6]

The lamina propria extends from the subepithelial basement membrane complex to the muscularis mucosae. It is composed of extracellular matrix, fibroblasts and various types of leukocytes. The presence of leukocytes is necessary because the mucosa is continuously challenged by luminal antigens, which results in a 'controlled' or 'physiologic' inflammation. Lymphocytes are the largest subtype. According to the location, they are subdivided into intraepithelial lymphocytes (IEL), lamina propria lymphocytes (LPL) and lymphocytes organized in follicles in association with epithelial cells (lymphoepithelial complexes). The latter may extend across the muscularis mucosae (Fig. 18.1). They constitute the mucosa associated lymphoid tissue (MALT) where the immune response is induced. GALT (gut associated lymphoid tissue) is especially prominent in the appendix and terminal ileum where it forms the Peyer's patches along the anti-mesenteric border. Four compartments are distinguished in Peyer's patches: the follicle, dome,

follicle-associated epithelium and interfollicular regions. The specialized follicle-associated epithelium, overlying lymphoid aggregates is distinct from the surrounding villous epithelial surfaces. It characteristically has fewer goblet cells and contains membranous cells or M cells. The M cell is a specialized epithelial cell that transports luminal antigens, thus allowing access to immunocompetent cells. It plays a key role in mucosal-based immunity and antigen tolerance. IELs are present in-between the epithelial cells lining the surface. They are mainly CD8(+) T lymphocytes. LPLs are B cells (15–40%) and T cells (40–90%) and a limited number of natural killer cells. B cells are mainly present as plasma cells with a predominance of IgA over IgM and IgG containing cells. The majority of the T cells are CD4(+) cells (65%). A second important subtype of leukocytes in the lamina propria are the cells of the monocyte/macrophage lineage. In the colon they are diffusely present in the subepithelial part of the lamina propria. They are a heterogeneous group composed of cells having more phagocytic properties and cells equipped for antigen presentation. They appear often as foamy histiocytes.[7,8] Other myeloid cells that normally reside in the lamina propria are eosinophils and mast cells. Neutrophils should not be present. Fibroblasts are located randomly, distributed throughout the lamina propria and in the most superficial portion and the pericryptal fibroblast sheet, tightly apposed to the subepithelial basement membrane complex.[4,5]

An adequate immune response implies migration of immune cells, cell recognition and interaction of cells requiring adhesion and deadhesion. Proteins involved in leukocyte recruitment and migration belonging to the large family of 'adhesion molecules' are therefore variably expressed on endothelial cells and leukocytes. Molecules involved in cell interactions can also be identified. Examples of these are proteins such as CD40, CD40 ligand (CD40L), CD28 and CD80 and CD86. These molecules act as ligand-receptor pairs. They can be expressed on T cells (CD40L) and monocytes acting as antigen presenting cells (CD40) and by doing so, induce cell activation.[4,5]

In the submucosa, the ganglionated plexuses of Meissner and Henle of the ENS are found. Ganglia are composed of enteroglial cells and neurones. The muscularis propria is composed of two layers of smooth muscle separated by a thin layer of connective tissue in which the ganglionated myenteric plexus (Auerbach's) can be observed.

ULCERATIVE COLITIS

Gross features

UC starts from the rectum, spreads proximally and in continuity, involving a variable length of the colon. Pancolitis normally stops abruptly at the ileocecal valve, but in some cases a limited distal ileitis, called backwash ileitis, is observed.[9] These ileal lesions are in continuity with colonic lesions and characterized microscopically by diffuse inflammatory lesions with regular shortening of the villi. In patients with limited UC, the transition from diseased to normal mucosa is usually gradual and only occasionally abrupt. Atypical presentations can be observed. Some patients have left-sided involvement of the colon and cecal (cecal patch) or appendiceal involvement.[10] The affected sites are separated by normal mucosa. Diffuse duodenitis and extensive involvement of the upper small bowel can occur in severely ill UC patients.[11]

The gross appearance varies with the activity of the disease. Lesions are usually limited to the mucosa. Stenoses, fistulas and significant thickening of the wall are rare. In the acute form, the mucosal surface is wet and glaring from blood and mucus with numerous petechial hemorrhages. Ulcers of various sizes can appear. They may be small, rounded and superficial or more irregular and somewhat geographic in configuration. Fissuring ulcers are not seen, except in some cases of toxic megacolon. Ulcers can become more extensive and undermine the mucosa so that mucosal bridges with an underlying inflammatory infiltrate develop. Multiple confluent ulcerations provoke denudation of the mucosa. The serosal side may appear congested, often to a larger extent than the mucosal lesions.

Following healing of mucosal ulcers, elevated sessile reddish nodules – pseudopolyps – appear in an otherwise flat surface. They are typically small and multiple, but may have a filiform configuration (Fig. 18.2). There is some variability in the prevalence of the lesions depending upon the colonic segment involved. Pseudopolyps are common in the sigmoid and descending colon and rare in the rectum where mucosal friability predominates. In the more advanced stages, the entire bowel becomes fibrotic, narrowed and shortened. During remission, the mucosa may become normal again. Healing often occurs in an irregular way leading to a discontinuous, heterogeneous aspect of the mucosa, which can be confused with CD. Treatment may increase the heterogeneous nature of the lesions. **In children, lesions may initially be heterogeneous.** Topical treatment of the rectum can induce complete rectal healing. UC with rectal sparing, although rare, must therefore not be confused with CD.[12] In severe, active forms, the entire colon, or a segment, may become dilated (toxic megacolon). Inflammation may extend towards the submucosa. In such cases, the wall is thin and perforation can occur.

Microscopic features of ulcerative colitis

Diagnostic features

The microscopic pattern of UC is characterized by an inflammatory reaction with special distribution and structural abnormalities of the mucosa (Table 18.1). Inflammation is characterized by increased intensity of the lamina propria cellular infiltrate with alterations of the composition and changes in distribution. The normal lamina propria infiltrate is located in the upper part of the mucosa and this pattern persists in infectious colitis. In UC, the infiltrate is more extensive and extends diffusely towards the deeper part (transmucosal) (Fig. 18.3). Accumulation of plasma cells near the mucosal base, in-between the crypt base and the muscularis mucosae (basal plasmacytosis), is common. Focal or diffuse basal plasmacytosis (combined with crypt distortion) is

a strong predictor for the diagnosis of chronic idiopathic inflammatory bowel disease (IBD) and occurs in over 70% of the patients.[2]

The presence of neutrophils, indicating a change in the composition of the inflammatory infiltrate, is another important feature. When combined with unequivocal epithelial cell damage, it indicates disease activity.[13] This feature can be assessed with good reproducibility. Neutrophils within epithelial structures, such as the crypt wall (cryptitis), or the crypt lumen and wall (crypt abscesses) or in association with crypt damage (crypt destruction) are helpful for the diagnosis, but the predictive value of these features is limited. Cryptitis and crypt abscesses can indeed also be seen in infectious colitis, Crohn's colitis and diversion colitis. In UC however, they are generally more common, being present in 41% of the cases while in CD they are found in 19% of the cases.[2]

Eosinophils may be so numerous as to suggest eosinophilic colitis, particularly in chronic disease or when the disease is quiescent. This is partly explained by the reduction of other inflammatory cells, induced by medical treatment.

Structural changes include an irregular surface or a villiform surface and a disturbed crypt architecture. This can be assessed with good reproducibility. Overall, an irregular surface is present in approximately 60% of cases with UC.[14] Crypt alterations are more common and more widespread; they are observed in 57–100% of cases. Low power examination is important for the differential diagnosis with CD where similar **architectural** alterations are less common (27–71%) and less diffuse.[2] They can however, also be seen after surgery, in drug-induced lesions and in rare forms of chronic infectious colitis such as chronic *Shigella* dysentery. Crypt distortion includes shortened crypts that become widely separated from the underlying muscularis mucosae, crypt drop-out and especially prominent crypt budding (branching crypts, bifid crypts) (Fig. 18.4). Mucosal atrophy is a combination of crypt drop-out and shortening of crypts. These alterations can be evaluated on perpendicular sections (preferentially), but also on transverse or tangential sections. For the latter, one can rely on differences in intercryptal distance and variability of the internal crypt diameter (Fig. 18.5).[15]

Several other features may help to establish a diagnosis of UC or to evaluate the severity of the condition. These include mucosal ulcerations and erosions, mucin depletion, Paneth-cell metaplasia and diffuse thickening of the muscularis mucosae (Fig. 18.6). Erosions and widespread surface epithelial damage are more common in UC than in CD. Severe, almost total mucin depletion is another feature that distinguishes UC from CD, where preserved mucin secretion is more common. Paneth cells in crypts distal to the ascending colon suggest IBD, usually UC.

Granulomas are not present in UC but isolated giant cells or a histiocytic reaction around a ruptured crypt, mimicking granuloma formation, can occasionally be seen. 'Cryptolytic lesions' or pericryptal granulomas present a special diagnostic problem. According to several authors these granulomas are not reliable for a diagnosis of CD and occur in UC.[2, 16] Yet, in a series of 22 patients with suspected IBD, this lesion was present in colorectal biopsies in 14 cases. Ten patients were subsequently found to have CD.[17]

The diagnostic sensitivity and specificity of the above-mentioned features has been assessed mainly on rectal biopsies. UC is also characterized by a special distribution of inflammation and architectural distortion with increasing intensity from the proximal towards the distal colon. For proper assessment of this feature, examination of multiple biopsies obtained in different segments is needed.

Variation in time: evolution

The pattern of the various microscopic features varies in time and depends upon the severity of the disease. In the early, acute phase, crypts are often still regular in shape and size. The most characteristic feature is mucin depletion, associated with neutrophils infiltrating crypt and surface epithelium and inducing crypt abscesses and secondary crypt destruction. The cellular infiltrate in the lamina propria is homogeneously increased in intensity and mixed in composition. It may show a transmucosal distribution. Crypt architectural abnormalities appear only during the evolution of the disease. The natural history of crypt distortion has been examined in a study comparing the evolution of the histology in patients after first attacks of inflammatory bowel disease and infectious colitis. Biopsies were taken before any treatment was given (0–15 days), between 16–30 days, between 1–4 months and between 4–10 months. Crypt distortion started in the second period being present in almost 25% of the patients that eventually had IBD. In the period from 4–10 months, almost 75% of these showed crypt distortion.[1] Treatment may induce some reversibility.

Basal plasmacytosis also becomes more prominent in the course of the disease, mainly after two weeks of symptom duration. It is seen in 54% of biopsies obtained two weeks after the start of the symptoms and in more than 80% in samples obtained after 4 weeks. During the first attack of IBD, it is commonly the only finding. It can start as focal plasmacytosis. From 16 days onwards, focal plasmacytosis develops into diffuse plasmacytosis. This feature is usually also present in biopsies obtained during a flare-up **and may predict relapse**.[18] During the natural course, the cellular lamina propria infiltrate can remain homogeneously increased and mixed in composition with a predominance of lymphocytes and plasma cells. The distribution pattern may, however, become patchy.[19] These data show that it may be important to obtain further biopsies one month following the start of symptoms and treatment, if the diagnosis is not clear during the initial examination.

The inactive, quiescent phase of UC is characterized by the presence or persistence of more severe crypt architectural abnormalities, while mucin secretion returns to normal. The lamina propria infiltrate is mononuclear and may be moderately increased in intensity. In a more chronic phase, lymphoid aggregates and follicles, mainly situated in the deeper part of the mucosa, will develop or increase in number.

Disease activity

Histology as a tool for the measurement of disease activity of UC was introduced in the 1950s. The alterations in intensity and composition of the lamina propria infiltrate, which can be observed in

routinely processed sections stained with hematoxylin and eosin, allow a distinction between active, inactive and quiescent disease. Active disease is defined by the presence of neutrophils in association with epithelial cell damage.[13] Inactive chronic disease is defined as the presence of architectural changes and an increase of lamina propria mononuclear cells. Quiescent disease means the presence of structural changes without alterations in intensity and composition of the lamina propria infiltrate. Over the years, several microscopic scores for the assessment of disease activity in UC have been developed, generally for study purposes (Table 18.2).[20,21] The reproducibility of activity scores has not been studied extensively, but the limited data available show good agreement between different observers.[22] The microscopic pattern of activity generally correlates well with endoscopic features of severity, although in endoscopically inactive disease, microscopic features of activity may persist. The activity scores may be used to either document disease evolution, or to assess clinical efficacy in therapeutic trials. Histological assessment of disease activity could be important for the prediction of relapse. Clinical trials have indeed shown that persistent active inflammation **and basal plasmacytosis are** associated with an increased frequency of relapse (Fig. 18.7).[23]

In fulminant disease, mucosal inflammation may extend towards the submucosa and focally even towards the muscularis propria (proportionate inflammation). Transmural lymphoid hyperplasia is however highly unusual.

A significant association between disease activity and numbers of immunoglobulin-containing cells in the lamina propria has been demonstrated.[24] Upregulation of adhesion molecules and other markers is also related with disease activity. Several studies have shown increased or aberrant colonic epithelial cell expression of HLA-DR, MHC class II molecules and reduction or disappearance with different types of treatment. The expression of activation markers **or the presence of** immunoglobulin-containing cells are however not useful in routine practice.

Medical treatment

Topical and systemic medical treatments have a major impact upon histology in UC. Mucosal injury and neutrophils can diminish substantially within 4 weeks, or even disappear. Normalization with disappearance of architectural alterations of the crypts and surface together with reduction of the cellular lamina propria infiltrate takes more time, but can occur (Fig. 18.8).[25] In many cases, the inflammatory features become discontinuous and heterogeneous. This may make a differential diagnosis between UC and CD difficult. It is therefore important to know treatment and its effects upon histology when analysing a biopsy.[26]

Pouchitis

Treatment of ulcerative colitis with total colectomy and creation of a continent ileoanal anastomosis is not uncommonly accompanied by inflammation of the ileal pouch. Histologically there is normally slight mucosal inflammation, but occasionally crypt abscesses, ulceration and blunting of the villi are seen. Sequential biopsies of pouches suggest that villous atrophy and chronic inflammation of the small intestinal mucosa may be followed by colonic metaplasia, so that pouchitis ultimately represents a form of ulcerative colitis in metaplastic ileal mucosa. Granulomas and transmural inflammation, which are considered to be diagnostic for CD can be observed in pouchitis, following surgery for ulcerative colitis. Review of the original surgical specimen and of any other material available is essential before considering changing a diagnosis of ulcerative colitis into Crohn's disease.[27]

CROHN'S DISEASE

Gross features

CD can affect different segments of the GI tract. The appearances are similar at all levels. The terminal ileum and proximal colon are the most common sites, followed by the anorectum and colon. Perianal disease varies between 14–76%. Involvement of the upper gastrointestinal tract is uncommon. The length of the segments involved is variable and the lesions are separated by uninvolved 'skip areas'. Macroscopic lesions are apparent on the mucosal and serosal side of the bowel wall. In the Vienna classification proposed by an International Working Party for the World Congress of Gastroenterology in 1998, a distinction is made between inflammatory disease, stricturing disease – defined as constant luminal narrowing – and penetrating disease, defined by the occurrence of intra-abdominal or perianal fistulas, inflammatory masses and/or abscesses. Fistulas are commonly associated with strictures and therefore the clinical distinction is often limited to two types: the perforating type and non-perforating type with predominantly mucosal lesions. The mucosal appearance is usually heterogeneous. Lesions of different size are simultaneously present. The mucosa may appear normal or may show multiple small (1–2 mm in size) punctiform, rounded nodules or superficial erosions known as 'aphthoid lesions'. Over a period of time, the erosions become confluent and give rise to larger longitudinal ulcers, known as serpiginous ulcers.[28] The combination of longitudinal and transverse ulceration in an edematous mucosa induces a characteristic 'cobblestone' aspect. Ulcerations are more common on the mesenteric border of the small intestine. They can become deeply situated fissuring ulcers reaching the muscularis propria or pass through the muscularis and give rise to abcesses or fistulas between involved segments and adjacent organs or nearby uninvolved loops. Fistulas are defined as abnormal communications between the lumen of the gut and the mesentery and/or another hollow organ or the abdominal wall and skin. Histologically, they are composed of granulation tissue, surrounding a lumen, which is mostly filled up by nuclear debris and inflammatory cells, in particular neutrophils.[29] Granulomas are present in approximately 25% of the perianal fistulas or abscesses. Fistulas are often associated with strictures. Strictures are characterized by luminal narrowing and bowel wall thickening with or without prestenotic dilatation. In high-grade stenosis,

the luminal diameter is less than 0.5 cm. They are often associated with severe ulcerations with complete circumferential loss of the mucosa (Fig. 18.9). In rare cases, CD can present a macroscopic picture of the left colon with continuous involvement, reminiscent of UC, in association with ileal disease.[30]

Being a transmural disease, the bowel wall is thickened with involvement of the submucosa, the muscularis propria, the subserosa and mesenteric fat. The serosal surface reveals prominent distended blood vessels and may show fibrinous exudate with or without adhesions to adjacent loops. Mesenteric fat partially surrounds the intestine, extending from the mesenteric attachment anteriorly and posteriorly corresponding to the involved segment. This phenomenon, known as 'fat wrapping', is specific for CD. It is observed in 75% of the surgical specimens (Fig. 18.10). Fat wrapping is defined on a transverse section of the intestine and defined as being present when more than 50% of the intestinal circumference is affected. The corresponding mesentery is usually thickened and retracted. Fibrous strands are present in the mesenteric fat, irradiating from the intestine and surrounding thickened, hypertrophied fat lobules.[31] The mesenteric lymph nodes are commonly swollen, but the number and size of the swollen lymph nodes in CD is not different from that observed in UC.[32]

Inflammatory pseudopolyps of the colon and small intestine (in approximately 20% of the cases), identical to those described in UC can be observed in CD. These are usually tall mucosal outgrowths measuring a few millimeters in length, but giant forms have been described. Such giant forms are more common in CD than in UC. In extinguished cases, the characteristic lesions may no longer be present. The specimen shows merely neuromuscular and vascular lesions and a proper diagnosis may be difficult.

Microscopic features

Granuloma

Granulomas in histological sections are a key feature of CD.[33] It should however be remembered that granulomas can occur in other conditions, especially infectious diseases, such as tuberculosis and *Yersinia pseudotuberculosis* and occasionally in drug-induced colitis. A granuloma is defined as a collection of monocyte/macrophage cells and other inflammatory cells with or without giant cells (Fig. 18.11). The macrophages appear as large cells with abundant pale eosinophilic cytoplasm and large oval nucleus. They are arranged in clusters. Because of this epithelial cell-like morphology, they are called epithelioid cells. The cells can be closely packed together, and have a sarcoid-like aspect but a 'loose' expanded form of granuloma is more common in CD (Fig. 18. 12). Central necrosis and caseation are rare findings and should raise suspicion of tuberculosis. Giant cells may contain calcified conchoid bodies.[27,34] Associated inflammatory cells are lymphocytes, usually CD4+ T cells, showing expression of CD28, the ligand for the B7-related cell surface proteins CD80 (B7-1) and CD86 (B7-2).

The granuloma has to be distinguished from the microgranuloma, which is smaller and composed of histiocytes. They are smaller than the epithelioid cells in the genuine granuloma. The number of histiocytes in the microgranuloma is also smaller than in the granuloma (7–18 versus 25–90) while the number of lymphocytes is comparable (4–11 versus 2–15). Microgranulomas are usually situated in the upper part of the mucosa. The frequency in CD is not well established, but seems to vary between 12% and 24% of endoscopic biopsies obtained in patients with CD. The exact meaning of the microgranuloma is still unclear. They seem more common in inactive disease.[35] Granulomas must also be distinguished from granulomatous crypt abscesses, a crypt abscess with a giant cell and with or without an excess of histiocytes, and from cryptolytic granulomas. The latter are defined by the rupture of the epithelial lining and the presence of histiocytes with or without giant cells. While this lesion seems more common in CD it has also been reported in genuine UC.

Granulomas can be detected in otherwise healthy mucosa or in inflamed tissue. They develop in all layers of the intestines from the mucosa to the serosa but are most frequent in the submucosa. They are also common in draining lymph nodes being present in approximately 20–50% of the cases. Rarely does the granulomatous inflammation affect extraintestinal sites, such as the skin, liver, lungs, eyes and ovaries.

The frequency of finding granulomas in CD varies between 15% and 85%, but is rarely higher than 50–60%. The results depend highly on tissue sampling (number of biopsies, number of sections examined, endoscopic or surgical samples). For surgical samples the frequency varies between 15–82% and for endoscopic samples between 3–56%. The highest numbers are observed in children, both in surgical series (82%) and in endoscopic series. In pediatric CD, the incidence of granulomas is two-fold compared with adults but it is reduced after the second year of the disease and after the age of 16 years. The lowest number comes from a surgical series composed of older patients. In general, granulomas are more common in the distal colon and rectum. Granulomas are as common in CD of the upper gastrointestinal tract as in the ileum and colon. The frequency of detection for the stomach and duodenum varies between 3% and 58% and is higher when biopsy samples are taken in macroscopic lesions.

The number of examinations can influence the frequency of detection of granulomas. A granuloma was found in 23% and 47% respectively, of the patients in whom one (2.5 ± 1.4 biopsy samples) and four colonoscopies were performed (8.0 ± 1.8 samples). Increasing the number of biopsies increased the diagnostic yield. For 1–6 biopsy samples, the diagnostic frequency varies between 11–47%. Six biopsy samples seems an optimal number. When multiple serial sections are examined in the pathology laboratory the frequency of detection further increases with 50%.

While the diagnostic value of the granuloma in CD is generally accepted, its clinical and prognostic significance remain unclear. Several studies have examined the relation between the presence of granulomas and prognosis looking at the recurrence rate, either clinically or the risk of a new surgical intervention. The results are conflicting. In 8 of 14 studies the presence of

granulomas had no influence upon the outcome. In three series recurrence was diminished and in three other series recurrence rate was increased.[34]

Mucosal lesions

Early mucosal lesions

Various types of early microscopic lesions have been described in CD. They occur as focal lesions, in a background of normal mucosa in contrast with UC where diffuse epithelial necrosis is seen. Early lesions in CD include epithelial patchy necrosis, the aphthoid ulcer or mucosal microulcerations (loss of 1–6 cells). Other features include the occurrence of a naked surface of the dome area overlying a mucosal lymph follicle and loss of M cells. Ulcers at the base of crypts with neutrophils streaming into the bowel lumen, which leads in a later phase to mountain peak ulcers, villous abnormalities and damage of small capillaries (including capillary thrombi) with subsequent loss of surface epithelial cells (summit lesion) have been reported (Figs 18.13 and 18. 14).[35–39] In general, limited necrosis of surface epithelial cells is common while crypt epithelial cells are rarely involved (an exception is the ulcer at the crypt base). Overall, biopsies of early lesions do not yield essential diagnostic information. An exception to this may be the aphthoid ulcer. This ulcer has a predilection for the epithelium overlying the lymphoid follicles, although it can occur in other sites too. According to some studies, biopsies of aphthoid ulcers show more commonly the characteristic granulomas, which are diagnostic for CD.[34]

Diagnostic features

Although the degree of mimicry with UC can be high, the presence of aphthoid ulcers, fissure ulcers, transmural inflammation, fistulas, lymphangiectasia, fibrous stricturing and neural changes is predominantly a feature of CD. Six of these features proposed cannot, however, be reliably detected on endoscopic samples. A diagnosis of CD on endoscopic samples of the colon therefore relies heavily on the identification of the microscopic features of IBD. It has been suggested that the diagnosis of CD should be based upon the presence of an epithelioid granuloma with one other feature suggestive or diagnostic for IBD, or the presence of three other features in the absence of granulomas, provided that specific infection has been excluded.[40] The mucosal lesions of IBD consist of epithelial alterations and a cellular inflammatory response. The former include cytological and architectural changes, indicative of damage and repair. The cellular inflammatory response consists of changes in intensity of the infiltrate, alterations in composition and changes in the distribution pattern. These features have been examined in a number of studies of rectal and colorectal biopsies and surgical specimens. Only a limited number have acceptable sensitivity, specificity and predictive value and are sufficiently reproducible (Table 18.3). Features that favor CD are epithelioid granulomas, relatively unchanged crypts or segmental distribution of crypt atrophy and crypt distortion together with discontinuous focal or patchy inflammation and mucin preservation in the epithelium at an ulcer edge, and the presence of a mixture of normal samples (skip lesions) and inflamed samples in a set of biopsies obtained in the same area.[1,2,14,41–43] Focal inflammation is defined as a small collection of inflammatory cells in otherwise normal mucosa. It can present as a focal aggregation of neutrophil polymorphs in a pericryptal position, a lesion which is suggestive for CD but not pathognomonic. Patchy inflammation is diagnosed when the mucosal background shows inflammation of varying intensity. The diagnostic value of patchy inflammation is limited because a similar pattern can be seen in UC in long-standing disease or following treatment. Another reliable feature which helps to distinguish CD from UC in favor of CD is the presence of neuronal changes (Fig 18.15).[42] These are however only rarely observed in endoscopic biopsy samples because of the superficial nature of the latter. Most of the studies examining the features of IBD have been performed in adults. Separating CD and UC might be different in children and adolescents. Discontinuous inflammation and density of infiltration prevail in children while the diffuse type of infiltration is more common in CD in adults. However, granulomas are more common in children, being present in 26% of the biopsies and 42% of the patients.

Ileal biopsies have rarely been included in studies examining the microscopic features of CD. The presence of ileal lesions is however another key lesion, which allows to discriminate between UC and CD. Important diagnostic microscopic features of CD are architectural abnormalities of the villi (irregularity and blunting or broadening), preserved mucin secretion or increased mucin production (hypercrinia) by epithelial cells, mucoid or pseudopyloric metaplasia, active chronic inflammation and the presence of granulomas.[44] Pseudopyloric gland metaplasia is however a non-specific feature related with ulceration, healing and the ulcer associated cell lineage (Fig 18.16).[45]

Immunohistochemical analysis of mucosal biopsies reveals expression of various cytokines and other mediators, such as interleukin-10, interleukin-12, interleukin-15 and tumor necrosis factor alfa (TNFα). Some markers may be more specific for CD but increased expression indicates mainly ongoing immune response and has no diagnostic value at present.

The value of multiple, multi-step biopsies

The importance of stepwise biopsies for the diagnosis of either CD or UC has received little attention in the literature. Most studies have focused on single rectal biopsies. Discontinuous inflammation in stepwise biopsies does not distinguish CD from UC in adults. It can be found in approximately 30% of patients with long-standing UC but it discriminates in children and in patients with a short history of the disease. The presence of an inflammatory infiltration with decreasing intensity from caecum to rectum favors a diagnosis of CD.[12,46] In combination with ileal biopsies, multiple colonic biopsies are useful for the diagnosis.

Disease activity: effect of treatment

Microscopic assessment of disease activity in CD is difficult because of the segmental and transmural character of the disease. Yet, several scoring systems have been designed and even used in clinical trials. These scores are usually based on the microscopic analysis of multiple biopsies from different segments. The correlation between endoscopic findings, clinical indices of disease activity and microscopic scores is variable.[47] This reflects the fact that mucosal biopsies are not representative of the transmural inflammation and that clinical features are not always reliable indicators of disease activity at the tissue level. Mucosal biopsies however do reflect mucosal inflammation. Monotherapy with corticosteroids or 5-ASA has only a limited influence upon mucosal lesions in CD, although long-term combination treatment may induce normalization. Reduction of epithelioid granulomas with persistent chronic inflammation has been reported following long-term treatment with prednisolone, sulfasalazine and 6-mercaptopurine. In contrast, polymeric diet and immunomodulatory therapy with azathioprine and infliximab can profoundly influence the histologic lesions and induce healing.[48–50]

The submucosa, muscularis propria and serosa

Lesions of the enteric nervous system

Abnormalities of the enteric nervous system (ENS) are common in CD. The major structural abnormalities are irregular hypertrophy and hyperplasia of nerve fibres and alterations of neuronal cell bodies and enteric glial cells in ganglia of the submucosa and plexus myentericus. The abnormalities of the nerve fibres are most prominent in the submucosa, mainly in involved areas. They have been called 'neuromatous lesions'. Mucosal nerve fibre hypertrophy is only seen in areas overlying submucosal fibre hypertrophy and cannot reliably be assessed on routinely hematoxylin and eosin-stained slides. Nerve fibre hypertrophy is commonly associated with inflammation and granulomas in the plexus myentericus are not uncommon. A three-fold increase in the number of ganglion cells of the ileal myenteric plexus was recorded in a series of 24 cases with CD. All these features were shown to be highly suggestive for a diagnosis of CD with a significant difference between UC and CD and they can be detected with great reliability.[51]

Ultrastructural studies have shown that nerve fibres or axons appear as swollen, empty structures.[52] The specificity of this lesion for CD has however not been confirmed. A relative increase in myenteric neurones containing nitric oxide synthase (NOS), vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide (PACAP) and an abnormal pattern of VIP containing fibres have been recognized in CD.[53] Immunohistochemistry revealed also increased MHC class II (HLA-DR) membranous expression on enteric glial cells in macroscopically involved and uninvolved areas. The enhanced expression is positively correlated with the local intensity of the cellular inflammatory infiltrate. Induction of HLA-DP and DQ antigens on glial cells is restricted to areas of moderate and high inflammatory activity.[51]

Vascular lesions

Inflammatory cell infiltration of blood vessels and obliterative lesions have been observed with microscopy in surgical samples from patients with CD in a number of studies. The frequency varies between 3% and 85%. The frequency of vascular granulomatous inflammation varies between 3–100% of the cases examined (Fig. 18.17).[54] Granulomas are not only found in association with blood vessels. They may even be more common in lymphatic channels. While the nature and the exact frequency of granulomatous vasculitis in CD remain to be determined, its occurrence and diagnostic significance are unquestionable. Lymphangiectasia in the submucosa is another common finding in CD in addition to granulomatous vasculitis.[55]

Lymphoid hyperplasia

Lymphoid aggregates and nodules with or without germinal centres are common in the mucosa and even more numerous in the submucosa in CD. They occur also in the muscularis propria, in the vicinity of the myenteric plexus and in the subserosa. This transmural lymphoid hyperplasia is believed to be characteristic for CD and is not observed in UC or IC.[56]

Edema, fibrosis, fibromuscular obliterations, strictures

Widening of the submucosa by edema is common in CD and probably a sign of active disease. Strictures are a common complication of CD and an indication for surgery in approximately 50% of all CD patients. Histological studies of strictures show marked expansion of the muscularis mucosae by an irregular increase in the number of smooth muscle cells in this layer and the presence of large amounts of collagen, laminin and tenascin. Types V and III collagen can be abundantly present (Fig. 18.18). Mast cells can be numerous. In addition to the expansion of the muscularis mucosae *per se*, islands of smooth muscle cells and myofibroblasts are noted in disorganized fashion in the adjacent submucosa. Smooth muscle cell fibres may interconnect the muscularis mucosae and propria. The submucosa contains dense masses of large amounts of collagenous material and the luminal margin of the muscularis propria is disorganized with numerous collagenous septae invaginating its ragged edges and extending into the muscularis. In general the muscularis propria is also greatly increased in thickness, although it may be interrupted in certain areas.[57,58]

Upper gastrointestinal disease

Upper GI disease is present in approximately 8–40% of the cases. The variability is explained by the methods of examination such as symptomatology, endoscopy with biopsy or radiology, used to evaluate upper GI involvement. Of all the sites within the GI tract, which may be affected by CD, the esophagus has been suggested as the one least likely involved. Early changes include microscopic disease or aphthous ulcerations. The latter should not be confused with other conditions, such as herpetic esophagitis. Biopsies are the method of choice for the differential diagnosis and the finding of granulomas implies CD. More extensive disease includes ulceration and stricture formation. Fissuring ulceration or fistula formation is uncommon. Most cases of esophageal CD are associated with CD elsewhere in the gut, but there are a few reports of cases in which CD initially presented in the oesophagus.[59]

In the stomach, three major patterns may be distinguished. First, reactive gastritis or *Helicobacter pylori*-associated gastritis not related with CD, minor but characteristic lesions known as focally enhanced gastritis, and CD of the stomach with histological evidence of granulomatous infiltration.[3] Focally enhanced gastritis is characterized by a focal infiltration of CD3+ lymphocytes and CD68+ histiocytes with granulocytes. It was found in 48% of a series of 75 CD patients and in only 0.8% of the controls.[60] Granulomatous infiltration is observed in 2–10% of CD patients (Fig. 18.19). Besides typical granulomas, the gastric wall may also show transmural, often focal lymphoid infiltrates, lymphangiectasias, submucosal and subserosal fibrosis, fissures and ulceration. Generally, CD of the stomach is associated with disease in more typical sites. More than 80% of patients with gastric CD have duodenal bulb involvement. The finding of a granuloma in a gastric biopsy should not automatically be considered as CD. Granulomatous gastritis can have many other causes, as shown in a study of 71 patients in which CD was finally diagnosed in only 52%.[61]

Granulomatous appendicitis

Crohn's disease affecting the appendix is well documented and is present in up to 25% of cases. The disease is also reported as being isolated to the appendix. The histological features of CD in the appendix include thickening of the wall, transmural inflammation, patchy lymphoid aggregates throughout the wall, fissured ulceration and epithelioid granulomas. Isolated 'granulomatous' inflammation in the appendix is however not necessarily CD. It may be the result of a number of diverse and unrelated causes such as parasites, foreign body reaction and bacterial infections.

INDETERMINATE COLITIS

The term 'colitis indeterminate' was initially proposed for a small group of cases in which there was difficulty in distinguishing CD from UC (and even infectious diseases) in the excised specimen. The difficulty was due to the fact that features of both conditions were present in the same specimen. Most of the cases had fulminant disease and the classification was essentially temporary before a final diagnosis was established.[56] Later, 'indeterminate colitis' (IC) was applied as a temporary classification to cases where a definite diagnosis was not possible with endoscopic samples because of absence of diagnostic features discriminating between CD and UC. The diagnostic accuracy of a single rectal biopsy is estimated to be 37–77% for CD patients and 67–70% for UC patients. Multiple endoscopic biopsies of the colon can already solve many problems for CD. In difficult cases with pancolitis, the differential diagnosis can sometimes be solved by analysis of ileal biopsies or gastric biopsies. A special type of focal gastritis has been observed in CD. Indeterminate colitis is by definition a disease limited to the colon. The morphologic features of 'indeterminate colitis' diagnosed on endoscopic samples include lesions suggestive or diagnostic for IBD such as (minimal) architectural distortion, inflammatory features (usually transmucosal inflammation) which do not allow a firm distinction between UC and CD because of their patchy nature and absence of small bowel involvement. While only a minority of patients have a diagnosis of IC, it is important to realize that such a diagnosis has certain consequences. It means that the patient has IBD and that other conditions, especially infections, are less likely or indeed excluded. Relapse of symptoms due to complications, such as cytomegalovirus (CMV) infection is equally excluded (Fig. 18.20). A diagnosis of IC also means that the patient needs careful follow-up in order to reach a definite diagnosis.

DIFFERENTIAL DIAGNOSIS

Ulcerative colitis or Crohn's disease

Several studies have examined a large variety of mucosal biopsy criteria for the distinction between UC and CD and shown wide overlap.[2] The situation is different when surgical specimens are involved, because CD is characterized by transmural inflammation, whereas UC is a mucosal disease. In most studies examining endoscopic mucosal biopsies, the criteria, which discriminate between UC and CD, have a sensitivity and specificity exceeding only 75%. The histological diagnosis is largely based on the finding of granulomas in addition to the presence of criteria for the diagnosis of IBD, especially mucosal distortion. Segmental distribution of crypts or crypt atrophy, segmental distribution of mucin depletion, mucin preservation at the edge of an ulcer or in crypts with surrounding neutrophils, the occurrence of focal inflammation simultaneously with severe diffuse or patchy inflammation in a set of biopsies, have a significant discriminative value in favor of CD. Furthermore, in contrast to UC, typical CD shows a segmental or focal distribution of the disease in the bowel and focal or patchy inflammation within a biopsy specimen. These features can reliably be assessed with good agreement between observers. In contrast, Paneth-cell metaplasia has only limited discriminative value while cryptitis and crypt abscesses have no significant discriminative value (Table 18.4).

Infectious and drug-related colitis

A variety of infectious or drug-related colitides may clinically mimic CD or UC, especially those cases with abrupt clinical onset. Acute inflammatory diarrhea accompanied by fever and evidence in stool of an inflammatory process such as pus, mucus and blood, and dysentery, a more severe manifestation of inflammatory diarrhea with, in addition abdominal pain cramps and rectal tenesmus, is indeed often due to infectious agents. These can be divided into two subgroups – organisms that elicit an inflammatory process by penetrating the mucosa, and those that elaborate cytotoxins without invading the cells. Worldwide, invasive bacterial agents constitute the most important subgroup of etiologic agents. A precise diagnosis is essential for a proper treatment. Histology, in collaboration with other methods plays an important role in establishing a correct diagnosis.[41] The histology of infectious-type colitis is variable, due to the natural course of the disease and to differences in the virulence of the bacterial strain and the reaction of the host, but in general it shows a picture of active inflammation with normal mucosal architecture. A normal biopsy or mild edema can be seen when bacteria are non-invasive. Active inflammation may be mild or severe with extensive necrosis. In mild or moderate disease, neutrophils are found in the upper part of the lamina propria. Cryptitis, with neutrophils usually in the upper, more luminal part, superficial crypt abscesses and erosions are common. The lesions show a focal or patchy distribution. Neutrophils are more common in the early phase of the disease. Residual lesions appear later. An increase of plasma cells is observed 7–10 days after the initial onset of the disease. Increased numbers of IgA- and IgM-containing plasma cells are found in the mucosa in patients with *Campylobacter* colitis, in contrast with patients with active UC, who show increases of IgA and IgG. The crypts remain parallel, but they are often smaller at the upper part. The distinction between IBD and infective type colitis relies mainly on the absence of features (architectural and basal plasmacytosis) which direct towards a diagnosis of chronic idiopathic inflammatory bowel disease. In rare occasions, such as *Entamoeba histolytica* or CMV infection, the pathogen can be identified. CMV infection constitutes a special situation. It may be present in the early stage of the disease of UC but it can also be responsible for relapse of symptoms or cause pouchitis. Histology is the best method for identification of this infection. Relapse of symptoms can also be the result of infection with *Clostridium* difficile. The differential diagnosis of CD includes mainly bacterial diseases due to *Yersinia enterocolitica* and *Campylobacter jejuni*, which can both affect the ileum and proximal colon (Fig. 18.21). Special attention is required for tuberculosis and amoebiasis because of the indolent nature of these infections and the negative effect of a treatment with corticosteroids or immunosuppressants. Tuberculosis is commonly found in the terminal ileum and ileocecal region but, in contrast to CD, it is rare in the large intestine. Unlike the longitudinal serpiginous ulcers of CD, tuberculous ulcers tend to be circumferential or transverse. Examination of ileal or colonic biopsies can reveal specific features. Granulomas are usually multiple and large and can be confluent. Positive Ziehl staining suggests intestinal tuberculosis. Central necrosis of a lymph follicle is suggestive of *Yersinia infection*. *Salmonella*, *Shigella* and *Campylobacter* infections can mimic UC.

A medication history is indispensable in the investigation of patients with diarrhea. A variety of drugs given either topically or systematically can cause colitis, ileocolitis or proctitis. Some of these may mimic UC. Non-steroidal anti-inflammatory drug (NSAID)-induced lesions present a significant clinical problem. Usually the patients are elderly. NSAIDs can induce small bowel and colonic lesions. Colitis induced by NSAIDs can present as non-specific colitis, *de novo* colitis, reactivation of quiescent inflammatory bowel disease, allergic colitis (with eosinophils), constipation with perforation (stercoral ulcer), non-specific ulceration and fistulas related to diverticulosis. The microscopic distinction between active UC and drug-induced colitis is usually not so difficult because NSAID-induced lesions lack major inflammation although architectural alterations of the mucosa are common. The distinction with inactive UC is therefore more difficult (Fig. 18.22). In NSAID-induced pathology, apoptosis of epithelial cells may be common in the crypts (as in graft-versus-host disease).[62] Other drugs that can cause colitis or proctitis are penicillamine, gold salts, isotretinoin and methyldopa. Oral contraceptives and cocaine tend to mimic ischemic colitis.

Diverticular disease-associated colitis

A clinical syndrome of chronic colitis, localized to the sigmoid colon and occurring in association with diverticular disease, has been recognized repeatedly. Mucosal biopsies of this condition show features of IBD including a distorted crypt architecture and basal plasmacytosis. Colonic mucosa both proximal and distal is usually normal. The inflammatory features can mimic UC or CD. The relation of the inflammatory reaction with genuine IBD is unclear. Overall, it seems that diverticular disease-associated chronic colitis will precede the onset of conventional ulcerative proctitis and colitis or genuine CD in only a minority of cases.[63]

Diversion colitis

Diversion colitis is an inflammatory process that occurs in the bypassed colonic segment after surgical diversion of the fecal stream. In a defunctioned, previously normal rectum, mild inflammation is already apparent at 3 months. When continuity is restored, the changes disappear. Histologic abnormalities show a spectrum of changes ranging from mild colitis to those seen in severe active ulcerative colitis. Lesions include aphthous ulcers, crypt distortion, atrophy and abscesses, a villous colonic surface, mucin granulomas and a mixed inflammatory infiltrate with patchy lymphoid hyperplasia. The latter is a particular feature of this condition. All these findings may mimic IBD. When the original process leading to diversion of the fecal stream is not an inflammatory bowel disease the histological diagnosis of diversion colitis is easy. However, when there is underlying UC, the differential diagnosis is difficult. Features favoring diversion colitis are variation in severity of the lesions seen on multiple biopsies taken from one single area and the absence of morphologic changes in the proximal (not bypassed) segment.

It has been shown that the defunctioned rectum from patients suffering from unequivocal ulcerative colitis who have undergone proximal colonic resection may show transmural inflammation, fissures and epithelioid granulomas.[3] While these features would suggest a diagnosis of CD, the temptation to change the underlying diagnosis must be resisted, because the changes may represent further manifestations of diversion colitis. Only follow-up of the patient and the eventual appearance of lesions in the small intestine may force a change of diagnosis. In general, it seems that the condition worsens in UC, while diversion is favorable in CD.

Lymphoid hyperplasia

Lymphoid hyperplasia is observed in chronic ulcerative colitis *per se*, in a separate entity, described as lymphoid follicular proctitis and in diversion colitis.

Microscopic colitis: collagenous and lymphocytic colitis

Collagenous colitis is a disease of the large intestine, characterized by the presence of a thickened collagen layer underneath the intercryptal surface epithelium and, circumferentially, around the upper part of the crypts and by increased mucosal inflammation. For a proper diagnosis, it is necessary to obtain several (at least three) colonic biopsies, because the thickness of the subepithelial collagen table varies throughout the colon. To reduce false positivity a minimal value of 10 μ**m** has been proposed. Plasma cells and lymphocytes are increased in the lamina propria and eosinophils may be focally numerous. Neutrophils are occasionally seen and crypt abscesses are rare. Surface epithelial cells are flattened or cuboidal and sometimes desquamated and goblet cells are reduced in number and size. Yet overall, the colonic mucosa has a preserved or only minimally distorted crypt architecture. It should not be confused with rare forms of amyloid colitis, where the subepithelial thickening is due to deposition of amyloid (Fig. 18.23).

The microscopic picture of lymphocytic colitis is characterized by diffuse lesions with an increase of inflammatory cells in the epithelium and lamina propria. The infiltrate is mixed in composition with eosinophils, neutrophils (cryptitis and crypt abscesses), lymphocytes, plasma cells and mast cells. The number of intraepithelial lymphocytes is significantly increased (24.6 ± 3 for 100 epithelial cells; normal value 4.6 ± 1.5), whereas a non-significant increase of interepithelial lymphocytes is noted in UC and CD. Epithelial mucin depletion is common in lymphocytic colitis.

Microscopic colitis may be associated with primary ileal villous atrophy (PIVA), without alterations in the upper small intestine. Microscopic colitis is clinically and morphologically different from IBD. Yet, in some cases, collagenous or lymphocytic colitis can precede (or follow) genuine UC or CD.

Endometriosis

Ileal endometriosis may present with acute, chronic or recurrent distal small bowel obstruction, in the same way as Crohn's ileitis. The differential diagnosis with CD may be very difficult and is mostly not possible pre-operatively. Intestinal endometriosis may mimic CD, but can also be associated with CD. Endometriotic deposits in the bowel can induce microscopic mucosal lesions resembling inflammatory bowel disease.

Miscellaneous

Microscopic lesions similar to CD have been reported in ileal and colonic biopsies from patients with reactive arthritis and ankylosing spondylitis. Only a minority of these patients developed genuine CD. Less common diseases, such as the colitis of Behçet's disease and other vasculitides can mimic CD. Endoscopic biopsies are often inconclusive, except when small vessels are involved. In chronic granulomatous disease and Hermansky–Pudlak syndrome, a colitis complete with granulomas, which is indistinguishable from CD, can occur. The diagnostic feature is the presence of characteristic histiocytes in both mucosa and submucosa. Occasionally, malignancies may simulate CD on radiological examinations. The most common examples of these are in the colon: the poorly differentiated signet-ring cell carcinoma and metastases in the wall, and in the small intestine: a neuroendocrine cancer of the terminal ileum. Mucosal biopsies may show mild inflammatory features and architectural alterations. The finding of such features must be interpreted cautiously and, as always, histology has to be combined with the clinical history and other data in order to reach a definite diagnosis and to solve the differential diagnostic problem.

DYSPLASIA AND CANCER

Endoscopy with multiple biopsies is used for secondary prevention and in surveillance programmes for the early detection of colorectal cancer in patients with long-standing UC. This is based on the finding that precancerous lesions can be identified in biopsies. These lesions are called 'dysplasia'. **More recently, the term "intraepithelial neoplasia" has been proposed.** Dysplasia was defined by an international Inflammatory Bowel Disease–Dysplasia Morphology Study Group as 'unequivocal, non-invasive (confined within the basement membrane), neoplastic transformation of the epithelium excluding all reactive changes'.[64] This definition stresses the nature and origin of the lesion, but its identification relies upon the recognition of morphological features resulting from cytological and architectural changes in routinely processed and hematoxylin and eosin-stained sections. Accumulated experience from several prospective studies shows that 6–10 different biopsies from different sites might be sufficient to detect significant dysplasia. Generally, the histological features of dysplasia in IBD are comparable with those seen in colonic adenomas in non-colitic patients and include cytological criteria, such as variations in nuclear position, size and chromatin pattern combined with architectural distortion (Fig. 18.24). Although the morphological spectrum forms a continuum, dysplasia is divided into different categories according to the severity

of the alterations, because of different implications for patient management (Table 18.5). In the most commonly used classification, proposed by the International Study Group, two grades are distinguished. The category 'low-grade dysplasia' includes cases of mild and moderate dysplasia. The category 'high-grade dysplasia' includes some cases of moderate dysplasia (particularly those with prominent architectural alteration) and all cases of severe dysplasia and carcinoma *in situ*. The grade of dysplasia is always determined by the features of the most dysplastic portion. The distinction between high- and low-grade dysplasia is dependent primarily on the degree of cytologic alterations. This classification appears to be reproducible, although in general, it appears that interobserver agreement is better for high-grade dysplasia.

Surveillance studies have shown that a distinction has to be made between IBD-related dysplasia, especially the polypoid or raised type also known as dysplasia associated lesion or mass (DALM) and sporadic adenoma occurring in IBD. While the latter is unequivocally a neoplastic and hence a dysplastic lesion, its development is unrelated to the underlying IBD. Furthermore, recent evidence suggests that the molecular pathogenesis of IBD-associated dysplasia is different in terms of order and timing of genetic events. DALM in IBD should in fact be defined as a poorly circumscribed protruding lesion surrounded by dysplastic flat mucosa. It should also be distinguished from ALM (adenoma-like mass), when there is no surrounding dysplasia.[65] The differential diagnosis between polypoid IBD-associated dysplasia and inflammatory pseudopolyps or dysplasia in inflammatory pseudopolyps is another problem. Dysplasia in inflammatory polyps is rare. The major problem is that these polyps frequently contain areas of residual regeneration and it may be difficult to make a clear distinction between unequivocally neoplastic changes and regeneration. The differential diagnosis between reparative lesions and 'genuine' dysplasia in general may be difficult. Whereas high-grade dysplasia can usually reliably be distinguished, the distinction between repair and low-grade dysplasia may present a serious problem. Reparative cells of the surface may be distinguished from 'genuine' dysplastic cells because of their shape (cuboidal or low columnar versus crowded and high columnar) and because mucus secretion in dysplastic cells is often abnormal. In addition, the presence of inflammation orients also to reactive changes. Some of the more recently developed treatment modalities may indeed decrease the inflammatory reaction before completion of reparative phenomena. This discrepancy can result in follow-up biopsies showing little or no inflammatory activity and marked regeneration. The latter represents pseudodysplasia and should not be mistaken for dysplasia. Because of the diagnostic problems related to dysplasia other markers have been examined and tested to improve the reliability of the diagnosis. Changes in nuclear DNA content, reflecting gross chromosomal alterations can be identified with flow cytometry. Inactivation of tumour suppressor genes, such as p53 can be identified using immunohistochemistry for the demonstration of mutant p53 protein expression. Both the detection of aneuploidy and overexpression of p53 can be useful for a correct diagnosis (Fig. 18.25).

Colorectal cancer in UC is predominantly located in the sigmoid and rectum. The prognosis is similar to the one found in the general population. The tumour stage is essential for the prognosis.

Carcinoma is also a well-recognized complication of CD, where it can develop in the small intestine and in the colon in areas where there is or has been inflammatory disease. The carcinomas are often multiple. They are usually adenocarcinomas and are often associated with the presence of dysplasia in the colon and in the small intestine, suggesting that the development of malignancy in CD is similar to that of UC.[66] The histological features of dysplasia are identical to those seen in UC and the same classification can be used. Patients with CD may also be at an increased risk for the development of perianal squamous carcinoma and both UC and CD appear more than usually susceptible to malignant lymphoma.

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Fig. 18.1 Normal colon. Mucosal lymphoid follicle extending towards the submucosa. The germinal centre is stimulated (H&E × 25).

Fig. 18.2 Ulcerative colitis. Inflammatory pseudopolyps in ulcerative colitis are typically multiple. They can have a filiform configuration (H&E × 1).

Fig. 18.3 Ulcerative colitis. The microscopic diagnosis of ulcerative colitis is based upon widespread mucosal distortion (shortened and branching crypts) and transmucosal inflammation with basal plasmacytosis. Activity can be recognized by the presence of neutrophils infiltrating the wall of some crypts (H&E × 10).

Fig. 18.4 Ulcerative colitis. Distortion of the mucosal architecture can persist in quiescent ulcerative colitis. The crypts are widely separated from the underlying muscularis mucosae. Some of the crypts are branching. (H&E × 10).

Fig. 18.5 Ulcerative colitis. Transverse section of the mucosa showing bifid crypts characterized by the presence of double **lumina**. The diameter of the lumina and the intercryptal space are variable. (H&E × 25)

Fig. 18.6 Ulcerative colitis. Quiescent phase characterized by an abnormal architecture and diffuse thickening of the muscularis mucosae. (H&E × 10)

Fig. 18.7 Ulcerative colitis. Mucosal atrophy with loss of crypts. Neutrophils are still present in the lumen and wall of one of the crypts indicating persistent activity. (H&E × 10) (With permission from Geboes *et al. Gut* 2000; **47**: 404–409.)

Fig. 18.8 Ulcerative colitis. Mucosal biopsy obtained 6 weeks after the start of medical treatment with 5-ASA showing limited mucosal distortion and disappearance of activity. (H&E × 10)

Fig. 18.9 Crohn's disease. Small intestine: high-grade stenosis. The mucosa is ulcerated. Lymphoid hyperplasia is present in the deeper parts of the bowel wall. (H&E × 1)

Fig. 18.10 Crohn's disease. Small intestine: fat wrapping is a characteristic feature of Crohn's disease. It is characterized by the overgrowth of mesenteric fat.

Fig. 18.11 Crohn's disease. Rectal biopsy: a granuloma, so called because of the round appearance, is a collection of epithelioid cells with giant cells as in the picture or without. (H&E × 10)

Fig. 18.12 Crohn's disease. In Crohn's disease the granulomas have often a loose aspect as illustrated by this lesion laying close to a ganglion of the myenteric plexus. (H&E × 25)

Fig. 18.13 Crohn's disease. Aphthoid ulcer in the ileum: early mucosal ulcer, centrally located and appearing as a mountain top ulcer. (H&E × 4)

Fig. 18.14 Crohn's disease. Early mucosal lesions in CD can be associated with damage of small capillaries as illustrated here by the presence of a fibrin plug in the lumen of a small vessel (immunohistochemistry × 40).

Fig. 18.15 Crohn's disease. Crohn's disease is characterized by the presence of granulomas and by hyperplasia of the submucosal nerves, sometimes called 'neuromatous lesion'. (H&E × 10)

Fig. 18.16 Crohn's disease. Ileal biopsies can help to establish the diagnosis of Crohn's disease. The villi are irregular. Mucoid or pseudopyloric metaplasia indicates previous ulceration. (H&E × 10)

Fig. 18.17 Crohn's disease. Granulomatous vasculitis is another lesion, which is not uncommon in Crohn's disease. (H&E × 10)

Fig. 18.18 Crohn's disease. Small intestine. Fibrosis is a common complication of Crohn's disease. It is characterized by abnormal deposition of collagens, illustrated here by the presence of collagen V in the edges of a mucosal ulceration (immunohistochemistry × 10).

Fig. 18.19 Crohn's disease. Stomach. Gastric mucosal biopsy containing two characteristic granulomas. (H&E × 10)

Fig. 18.20 Ulcerative colitis. Relapse of disease symptoms in ulcerative colitis can be due to infection with cytomegalovirus. The virus can be recognized by typical nuclear inclusions. (H&E × 25)

Fig. 18.21 *Yersinia pseudotuberculosis* infection. Ileal biopsy showing a characteristic granuloma with central necrosis. The lesion must be differentiated from tuberculosis and Crohn's disease. (H&E × 10)

Fig. 18.22 Colitis caused by non-steroidal anti-inflammatory drugs. There is mucosal ulceration and distortion of the crypt architecture. The lesions are however discontinuous and inflammation is moderate. (H&E × 4)

Fig. 18.23 Amyloid colitis. Collagenous colitis, one of the subtypes of microscopic colitis is characterized by thickening of the subepithelial collagen table. The lesion can be mimicked in amyloid colitis as illustrated in this figure of a colonic biopsy stained with Congo red and showing the red color of the subepithelial amyloid band. (Congo red × 10)

Fig. 18.24 Ulcerative colitis. Low-grade dysplasia, on the right panel of the figure is characterized by the presence of tall columnar cells with increased staining of the cytoplasm and elongated nucleus. (H&E × 10)

Fig. 18.25 Ulcerative colitis. Dysplasia in ulcerative colitis. Positive nuclear staining for p53 is clearly present in some samples and absent in others (immunohistochemistry × 4).

Table 18.1 Microscopic features suggestive for a diagnosis of ulcerative colitis

Architecture
Severe crypt architectural distortion
Severe widespread decreased crypt density
Frankly villous surface
Inflammatory
Heavy diffuse transmucosal lamina propria cell increase
Diffuse basal plasmacytosis
Miscellaneous
Increased intensity of the alterations towards the distal colon
Severe mucin depletion
Paneth-cell metaplasia distal to the hepatic flexure

Table 18.2 Example of a scoring system for the assessment of severity in ulcerative colitis. Subgrades are defined for each grade. Examples are given for grade 0 and 1

Grade 0	*Structural (architectural change)*	
	Subgrades	0.0 No abnormality
		0.1 Mild abnormality
		0.2 Mild or moderate diffuse or multifocal abnormalities
		0.3 Severe diffuse or multifocal abnormalities
Grade 1	*Chronic inflammatory infiltrate*	
	Subgrades	1.0 No increase
		1.1 Mild but unequivocal increase
		1.2 Moderate increase
		1.3 Marked increase
Grade 2	*Lamina propria neutrophils and eosinophils*	
	2A Eosinophils	
	2B Neutrophils	
Grade 3	*Neutrophils in epithelium*	
Grade 4	*Crypt destruction*	
Grade 5	*Erosion or ulceration*	

Table 18.3 Microscopic features with sufficient reproducibility, discriminative and predictive value, useful for the differential diagnosis between normal and IBD, acute infectious colitis (AIC) and IBD and CD, and UC

Mucosal architecture
Mucosal surface, normal, irregular, villous
Crypt atrophy (shortened, widely spaced crypts)
Distorted, dilated, branching crypts
Inflammatory changes
Basal plasmacytosis, increase in cells in basal third of lamina propria
Increased lamina propria cellularity (round cells and neutrophils)
Basal lymphoid aggregates
Specific features
Epithelioid granuloma
Basal giant cells
Excess histiocytes in lamina propria
Features related with activity (separating IBD from normal)
Neutrophils in surface epithelium
Neutrophils in crypt epithelium
Ulceration

Table 18.4 Frequency of detection (%) of the reproducible features for different diagnoses

	Normal	Infective	IBD	UC	CD
Architecture					
Irregular surface	0–5	0–7	39	63	24
Branched crypts	0–5		75	63–83	39–67
Crypt shortening	0–5	0		29–78	12–37
Chronic inflammation					
Increased basal cellularity	0	0		63	62
Increased lamina propria cellularity	0–19	30	89–93	76–92	72–81
Granulomas	0	0–2	25–27	0–5	21–100
Discontinuous inflammation	7			10	26
Epithelial alterations					
Mucin depletion	17			35–69	5–57
Mucin preservation at ulcer edge				–	+++
Neuronal changes				2	75

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

Table 18.5 Biopsy classification of dysplasia **(intraepithelial neoplasia)** in inflammatory bowel disease

Negative
Indefinite
Positive
Low-grade dysplasia
High-grade dysplasia