Karel Geboes · Sonia Nemolato
Maria Leo · Gavino Faa *Editors*

Colitis

A Practical Approach to Colon Biopsy Interpretation

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Preface

Inflammatory bowel disease is a group of chronic inflammatory disorders primarily involving the digestive tract and particularly the colon. These diseases have been reported from all over the world. They affect children and adults. Inflammatory bowel diseases must be differentiated from other conditions such as infectious colitis and microscopic colitis because treatment is different. Histopathology plays a major role in the differential diagnostic process. Because of the widespread use of colonoscopy, the number of biopsies arriving in the laboratories of pathology is increasing. At present, the diagnosis of colitis is therefore a routine task of pathologists and a challenge.

This book aims to provide a methodological approach to the microscopic analysis of biopsies from the colon obtained for a possible diagnosis of colitis. The data presented are based on personal routine clinical practice and research, on teaching and training experience, and on a review of the literature. The book has been developed in a close collaboration between academic and nonacademic pathologists because this provides a realistic approach of the needs. In the first four chapters, it gives an update of the normal histology of the colonic mucosa, of the procedures needed for optimal biopsies, and of the basic lesions observed in colitis, illustrated by schematic drawings. The following chapters are dealing with the particular histology of the major types of colitis. Because of this, there may be some redundancy of information but we preferred not to eliminate this completely. The final chapter is devoted to scoring systems for disease activity in inflammatory bowel disease, an issue which may become a new challenge for pathologists for these conditions.

We are particularly grateful to Maria Leo for the artistic work in making the drawings and to Dr. Van Eyken for his help in providing microphotographs.

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Introduction

The first colon fiberscope prototypes were developed in 1963, but it was not until American Cystoscope Makers, Inc., entered the field in the late 1960s that clinical colonoscopy began to flourish. Endoscopy presented some advantages in the ability to see variations in the color of the mucosa, visual resolution of tiny lesions, and the means to obtain tissue diagnosis. In the early 1970s, various studies demonstrated the value of colonoscopy with biopsy for the differential diagnosis of inflammatory bowel diseases (IBD) [1, 2]. By the early 1980s, it became clear that the diagnosis and differential diagnosis of IBD, colitis in general, and diarrhea are indications for colonoscopy and biopsy as stated in guidelines of the American Society for Gastrointestinal Endoscopy. Over the years, the number of endoscopic biopsies of the colon coming to the pathology laboratory has therefore gradually increased, and today they present a daily challenge for pathologists.

Diarrhea (four or more bowel movements per day, liquid stools) lasting more than 4 weeks, abdominal pain, and constipation are common symptoms in adults. The prevalence is approximately 1–5 %, making it a major cause of disability [3]. A small number of patients (approximately 1 %) need specialized investigations or hospitalization [4].

The etiology is highly variable and includes, among others, infections, endocrine diseases, chronic inflammatory bowel disorders, food intolerance, and drugs. Patients with chronic diarrhea, with or without the passage of blood, are likely to be fully investigated. Several studies show that colonoscopy with biopsy is useful in the investigation of chronic diarrhea without blood loss, yielding a histological diagnosis in 22–31 % of patients who had a macroscopically normal colon at colonoscopy. One study evaluating more than 800 patients found that 122 (15 %) had abnormal histopathology. Of those with abnormal biopsies, 2 % would have been missed if only a flexible sigmoidoscopy had been performed. Colonoscopy is the method of choice in patients older than age 50 years [4–9]. Histological diagnoses include a variety of conditions such as spirochetosis, pseudomelanosis coli, and microscopic colitis. Various forms of colitis can thus be present in the absence of radiological and endoscopic lesions or features of colitis. Ileocolonoscopy with biopsy is certainly indicated in patients with chronic diarrhea with blood loss.

Because of the limitations of the patterns of tissue response to a varied range of insults, the precise histological diagnosis of colitis requires a good knowledge of the normal histology of the mucosa, of the different etiological possibilities, and of the microscopic features of different types of colitis [10–13]. The purpose of the present work is to review the normal histology of the colon mucosa, of the biopsy procedures which are needed, of the different elementary lesions which can help to reach a diagnosis for colitis and to discuss the most common types of colitis.

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Chapter 1
The Normal Biopsy: Mucosa and Submucosa

Peter Van Eyken, Daniela Fanni, Clara Gerosa, and Rossano Ambu

Abstract The digestive tract is a hollow tube consisting throughout of three coats or layers. The first layer, the mucosa, is made up of an epithelial lining which borders on the lumen of the bowel and rests upon a basement membrane, the lamina propria and the muscularis mucosae. The second coat is the submucosa. The muscularis propria, the third layer, 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. The subserosa is composed of loose areolar tissue covered by mesothelium where the tract borders on the body cavity (serosa). Endoscopic biopsies are limited to the mucosa and upper part of the submucosa. A good understanding of the normal histology of the mucosa and submucosa is essential for analysis of endoscopic biopsies of the colon.

Keywords Crypt • Mucosa • Architecture • Innominate groove • Intestinal epithelial cell • Goblet cell • Enteroendocrine cell • Paneth cell • Pigmented macrophage • Foamy macrophage • Muciphage • Neutrophil • Cytokine • Fibroblast • Collagen • Basement membrane • Lymphocyte • Lamina propria • Eosinophil • Mast cell • Interepithelial lymphocyte • Macrophage • Muscularis mucosae • Submucosa • Adhesion molecule • Integrin • Selectin

Please see Fig. 1.1 for the key to the illustrations.

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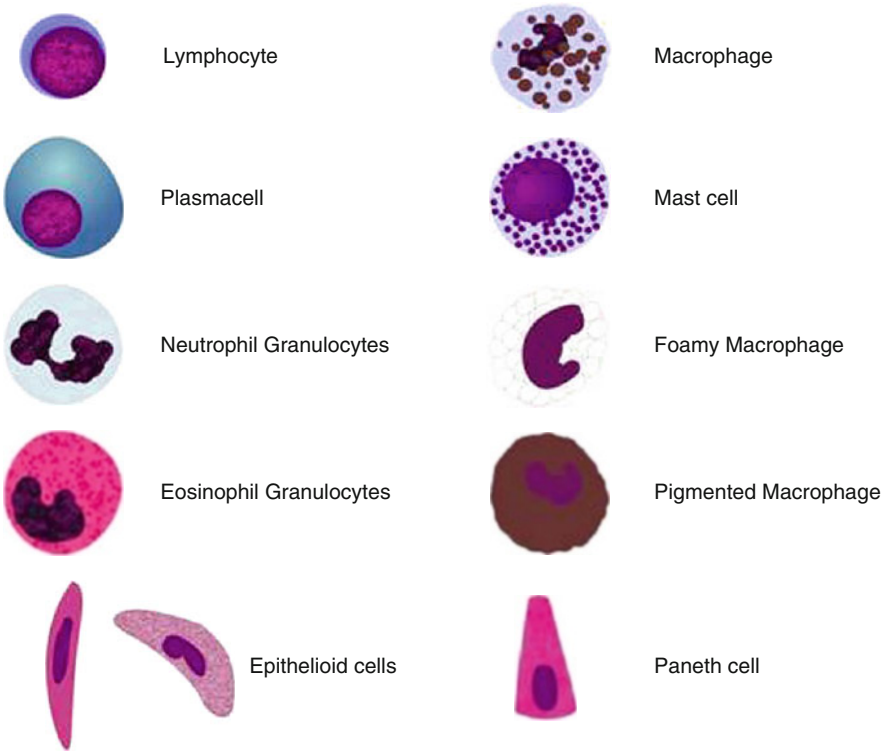

Fig. 1.1 Key to identification of cells in the illustrations

1.1 Normal Mucosal Architecture

The mucosa of the colon has a smooth surface and tubular crypts which open into the surface or into innominate grooves or lines. The latter are mucosal areas where several crypts open into one central crypt. They can be seen as delicate, inconstant spiculations on the colonic margin on barium enemas. The crypts are formed in early postnatal life and the number increases steadily by crypt fission, a process in which new crypts are formed by branching off from existing crypts to accommodate the growth of the organ into adulthood [1]. Crypt fission or branching is therefore not unusual in biopsies from children. The organization of the crypts is responsible for a characteristic normal pattern with roundish pits on the mucosal surface which can be observed during magnifying colonoscopy or confocal laser endomicroscopy (CLE) of the colon (Fig. 1.2). According to the "Kudo classification," the normal appearance is called "pit pattern I" [2]. CLE fluorescein sodium imaging of the normal colon shows a similar surface crypt architecture with ordered and regular crypt orifices covered by a homogeneous epithelial layer with visible "black-hole" goblet cells. Changes in the crypt architecture or pit pattern occur during

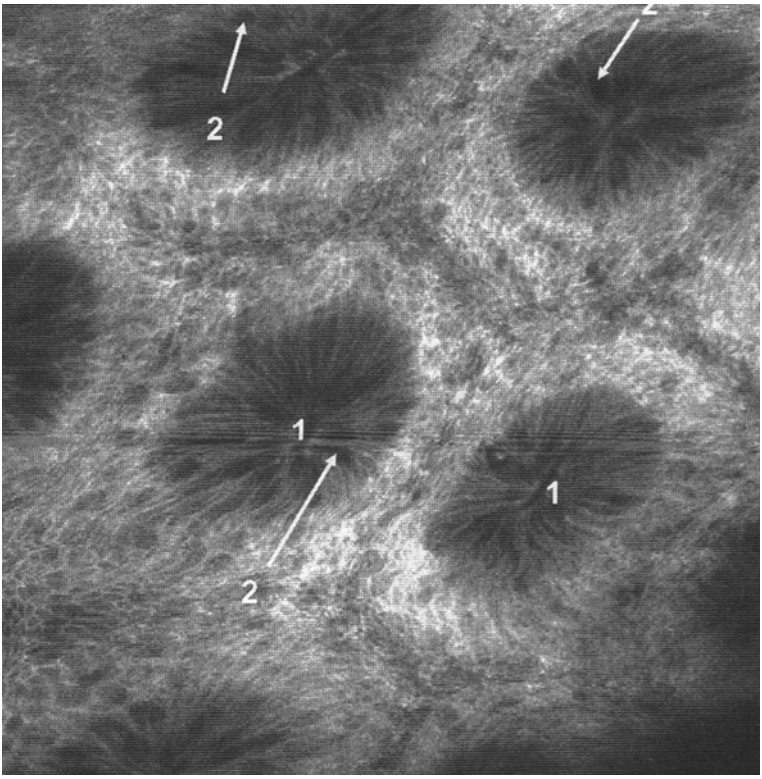

Fig. 1.2 Confocal laser endomicroscopy of the surface of the colon mucosa showing the regularly rounded pits (*1*) and goblet cells (*2*)

carcinogenesis but also as a result of chronic inflammation and can be identified with the advanced endoscopic techniques.

The normal surface and crypts are lined by a single layer of low columnar epithelial cells resting on a basement membrane composed of extracellular matrix components including laminins, collagens (predominantly collagen IV), proteoglycans, calcium-binding proteins such as fibulin, and various other structural or adhesive proteins. The membrane supports and separates the epithelium from the underlying connective tissue or lamina propria but also influences the behavior of epithelial cells by controlling their shape, gene expression, adhesion, migration, proliferation, and apoptosis. The normal membrane measures up to 3 μm or 4 μm [3]. This membrane is thickest in the rectum. The tubular glands or crypts are tightly packed. Variations in the number of glands per defined area are minimal. The diameter of the crypts and the distance between the crypts are fairly constant. The mean diameter varies between 45 and 105 μm. The inter-glandular distance varies from 4.5 to 36 μm [4]. The glands have a straight, test tube shape with minimal branching. They run a parallel course from the surface to the muscularis mucosae. The crypts are surrounded by a pericryptal fibroblast sheath composed of fibroblasts and myofibroblasts (Fig. 1.3).

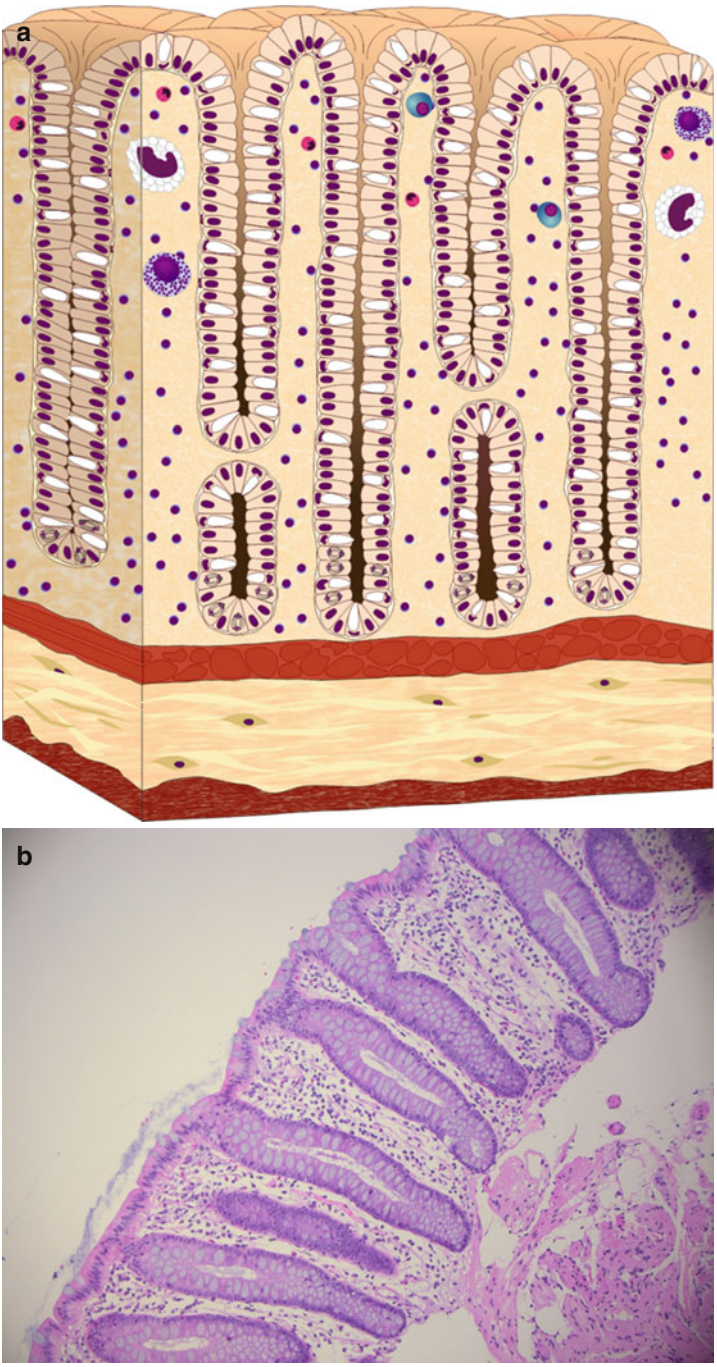

Fig. 1.3 The normal mucosa is composed of surface epithelial cells and tubular glands embedded in a loosely arranged stroma [(**a**) schematic view; (**b**) microscopy ×10] of perpendicular sections. (**c**) is a schematic view of a transverse section. (**d**) Higher magnification of microphotograph showing the cells in the lamina propria (×20)

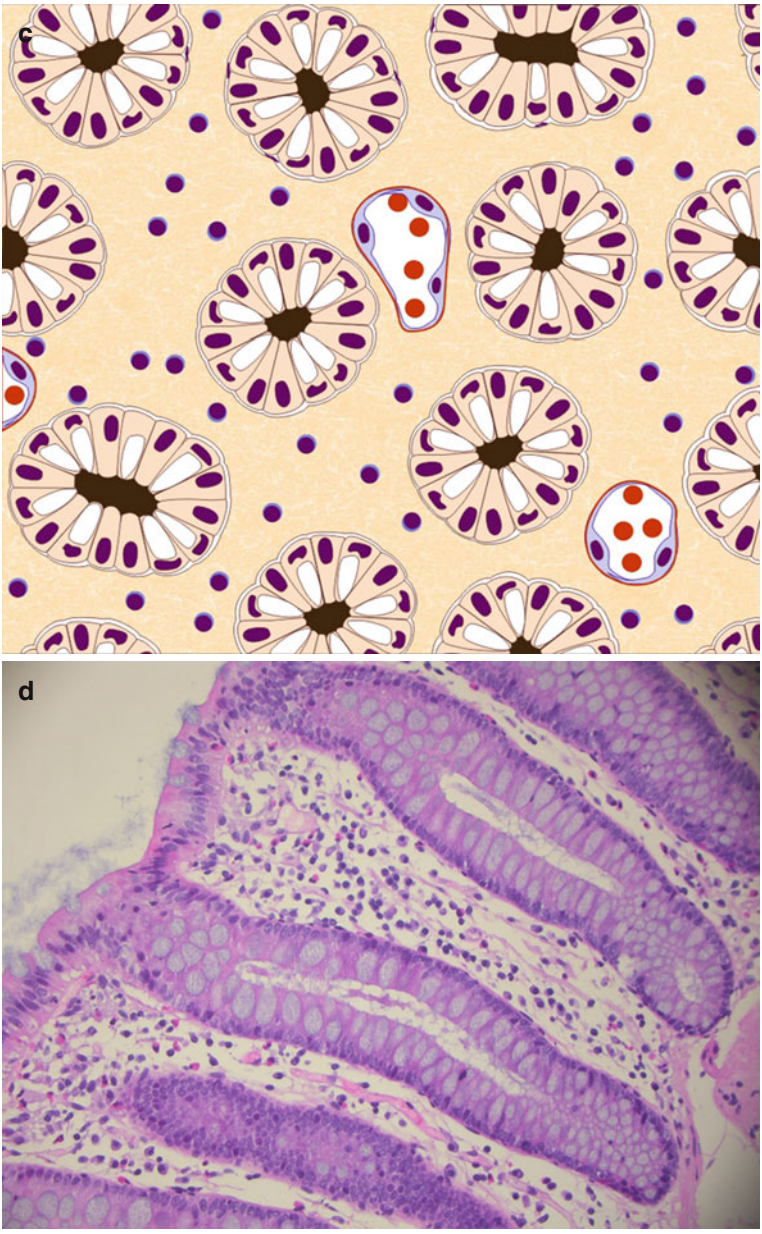

Fig. 1.3 (continued)

1.2 Normal Cell Types

The intestinal mucosa is continuously challenged by potentially injurious dietary and microbial luminal factors and acts as a barrier while it is also involved in secretion, terminal digestion, absorption, and transport of nutrients, water, and electrolytes.

1.2.1 Epithelial Cells

The intestinal epithelial cells form a heterogeneous group composed of surface-lining cells (absorptive cells and goblet cells), crypt cells, and specialized cells such as enteroendocrine cells. The absorptive cells contain no mucin. The cytoplasm is mildly eosinophilic and nuclei are located basally. They are involved in the formation of a mechanical barrier by the presence of tight junctions in which different proteins are incorporated. Epithelial cells are important for resorption and play a major role in secretion and humoral immunity (secretion of secretory immunoglobulin A = SIgA). Goblet cells contain an ovoid mucoid vacuole. Crypt cells are important for epithelial cell renewal [5]. The crypts contain endocrine cells, precursor cells, and occasional Paneth cells (in the right colon). The endocrine cells, usually situated at the base of the crypts, contain fine eosinophilic granules with secretory proteins. The nuclei are not basal but on the luminal side. Paneth cells are involved in the production of defensins and lysozyme (antimicrobial peptides) and constitute the niche for leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5) stem cells in intestinal crypts. In colon crypts, CD24+ (CD = cluster differentiation) cells residing between Lgr5 stem cells may represent the Paneth cell equivalent [6]. Human colonic crypts are lined by a clonal population derived from a multipotential stem cell. Undifferentiated cells at the base of the crypts are precursors of other epithelial cells [7]. These cells can migrate from the crypt base to the surface in 3–8 days, which allows for rapid repair.

Specialized surface epithelial cells such as the follicle-associated epithelial (FAE) cells and the M cells (M = microfold or membrane) covering the lymphoid follicles of Peyer's patches are well equipped for antigen handling. In the colon, they are found in association with mucosal lymphoid aggregates.

1.2.2 Lamina Propria Cells

The lamina propria cells include lymphocytes, cells of the monocyte/macrophage lineage, eosinophils, mast cells, connective tissue cells, vascular structures and nerve endings (in the small intestine), and smooth muscle cells in the muscularis mucosae.

In animals raised in germ-free environments, very few leukocytes are found in the lamina propria. The number increases rapidly following conventionalization forming the normal immune system in the digestive tract. These cells are usually situated in the upper part of the lamina propria. In the normal human rectal mucosa, the number of nuclei in the lamina propria for a well-defined area is fairly constant. Relative to the left colon and rectum, the right colon contains greater numbers of inflammatory cells in the lamina propria.

The lymphocytes are a heterogeneous and dynamic population. Functionally, they are grouped in an inductor (of which Peyer's patches and the well-organized

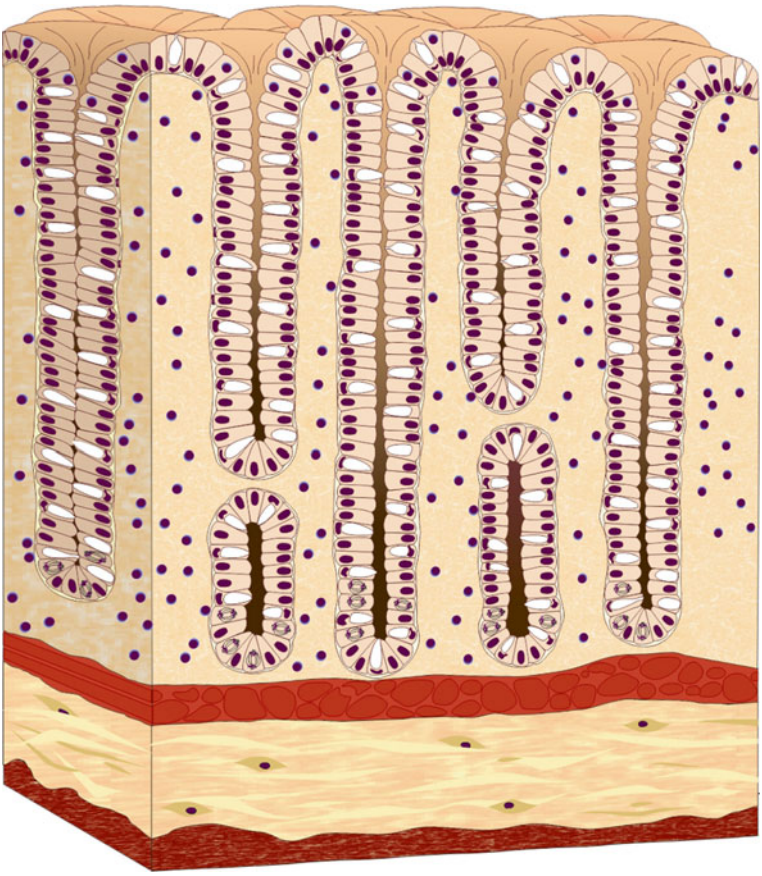

Fig. 1.4 Normal distribution of intraepithelial lymphocytes

mucosa-associated lymphoid tissue in general are the major examples) and an effector immune system. Architecturally, different compartments can be distinghuished: the inter- or intraepithelial lymphocytes (I.E.L.), the lamina propria lymphocytes (L.P.L.), and the lymphocytes organized in follicles in the mucosa in association with epithelial cells (lymphoepithelial or lymphoglandular complexes) or not. The interepithelial lymphocytes are mainly present in between the surface-lining cells (Fig. 1.4). The normal number in the colon is estimated at four to five per 100 surface epithelial cells. They tend to be more numerous on the right side as compared with the left side, and one should not count intraepithelial lymphocytes overlying a lymphoid aggregate (where they are normally present in large numbers). They are mainly T lymphocytes expressing the CD3/CD8 suppressor, cytotoxic phenotype (CD = cluster differentiation). The lamina propria lymphocytes are B (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 (7/2/2)

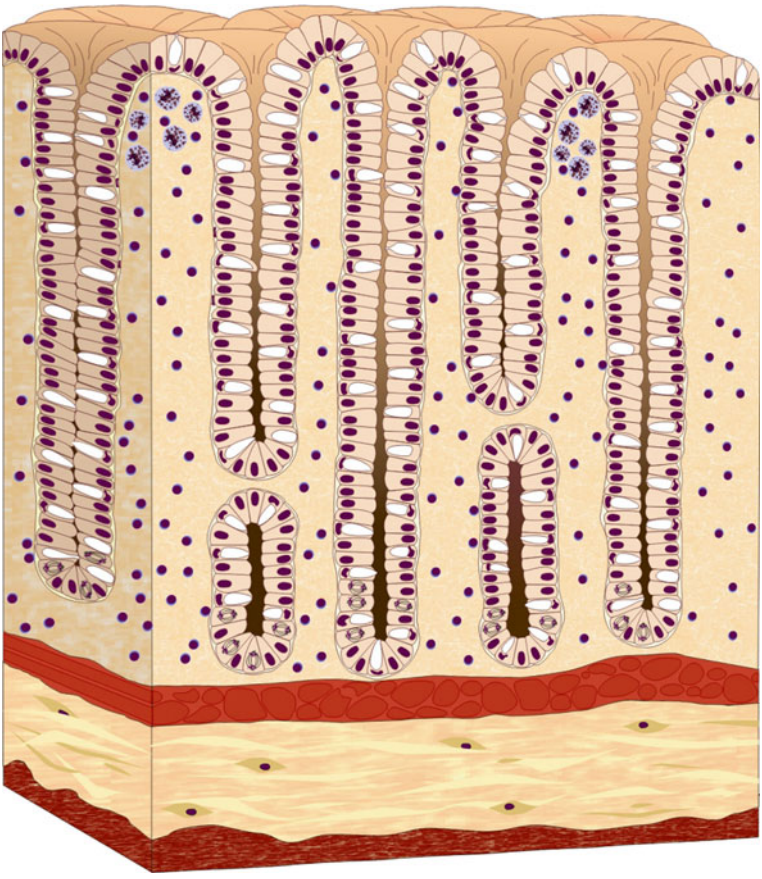

Fig. 1.5 Normal colon with superficial macrophages. Cells of the monocyte macrophage lineage are normally present in the upper part of the lamina propria

(Ig = immunoglobulin) in the rectum and 90 %/6 %/4 % in the large intestine. The majority of the T cells are CD4+ helper cells (65 %).

Cells of the monocyte–macrophage lineage are usually not conspicuous in normal mucosal samples of the colon (Fig. 1.5). As all other tissue macrophages, they are derived from bone marrow stem cells through a very complex cascade of differentiation events, which, among others, requires the presence of interleukin (IL)-1, IL-3, and IL-6. When present, they are normally found in the upper part of the lamina propria, underneath the superficial small blood vessels just below the subepithelial collagen layer. This localization allows them to participate in the regulation of inflammatory responses to bacteria and antigens breaching the epithelium. In addition, they protect the mucosa against pathogens and scavenge dead cells and debris. The cytoplasm of the macrophages commonly contains dense inclusions of varying sizes and shape. It is weakly PAS (periodic acid Schiff) positive [8]. In order to maintain mucosal homeostasis, resident intestinal macrophages are typically

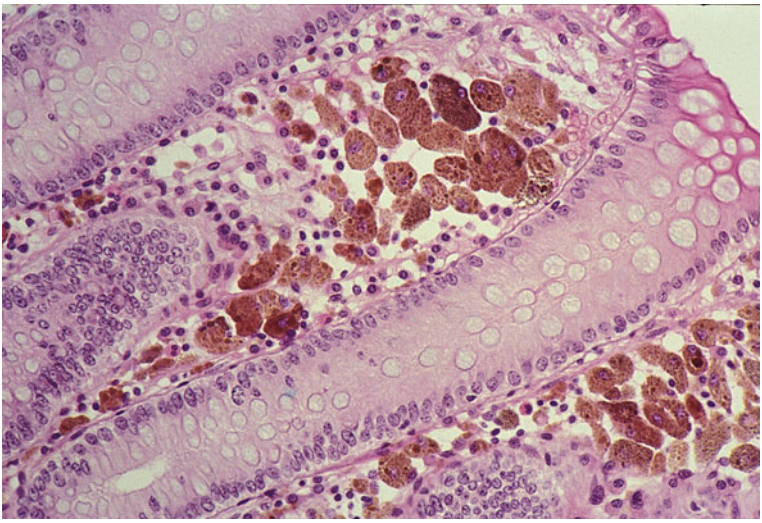

Fig. 1.6 Pigmented macrophages in the lamina propria are a hallmark of pseudomelanosis coli, usually due to laxative abuse (×20)

CD14 negative and thus regarded as anergic. They do not produce proinflammatory cytokines. However, in any case of intestinal infection or inflammation, blood CD14-positive monocytes are rapidly recruited, accumulate in the lamina propria, and actively fight against invading microorganisms by direct phagocytosis and degradation, as well as release of inflammatory mediators [9, 10]. Immune histochemical studies have shown that the macrophages or histiocytes in the lamina propria of the human intestine are a heterogeneous population. They express usually CD68/PG-M1. They can show a positive staining with antibodies directed against the S100 protein and they are frequently HLA-DR (HLA = human leukocyte antigen) positive. Some of the cells have a strong membrane adenosine triphosphatase activity but weak acid phosphatase, while others, especially in the colon, have a strong acid phosphatase activity [11]. In healthy mucosal conditions, the resident macrophages of the gut will continuously be replenished through the recruitment of new circulating monocytes [12]. They are quite easy to identify when exo- or endogenous material accumulates or when they become very numerous. Most lesions result from a proliferation of histiocytes with either engulfed infectious agents or cellular or extracellular debris. Their cytoplasm frequently shows dense inclusions of different size and shape. Based on these inclusions, intestinal macrophages can be categorized into two main groups, i.e., pigmented and nonpigmented macrophages. Pigmented lesions include melanosis or pseudomelanosis coli, atmospheric dust, barium deposits, and hemosiderosis (Fig. 1.6). Accumulation of nonpigmented (foamy) macrophages presents a differential diagnostic issue of muciphages, lysosomal storage diseases, and infections including Whipple's disease (extremely rare in the colon) and *Mycobacterium avium* complex infection (Fig. 1.7). Muciphages are mucin-rich phagocytes resulting from mucosal damage, mainly seen in the

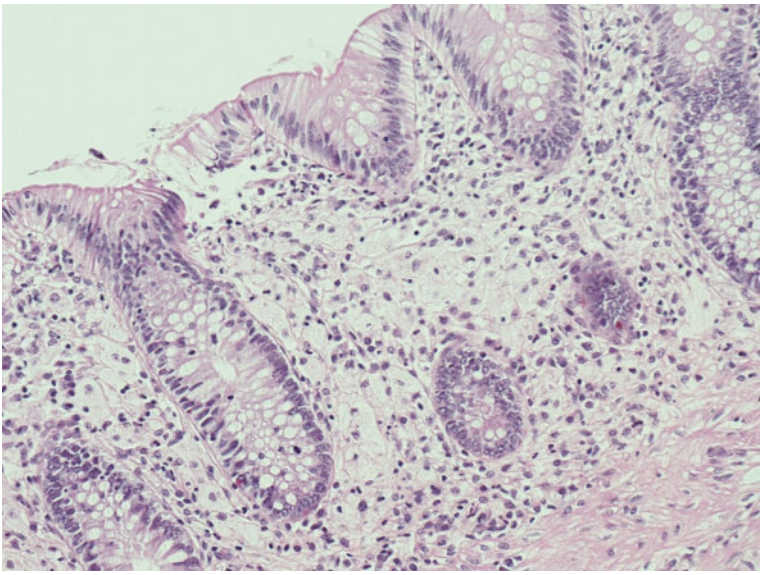

Fig. 1.7 Microphotograph showing the presence of numerous foamy macrophages, suggestive of lysosomal storage disorder. Oil red O stain on frozen sections confirmed the presence of lipid material (×10)

terminal phase of repair after previous injury and/or in situations of low-grade injury [13]. They may also be observed in the normal mucosa, particularly in the rectum (40–68 % of all rectal biopsies). The most common localization of these muciphages is the superficial lamina propria or the basal mucosa. Positive histochemical staining for PAS combined with diastase digestion is strongly suggestive, like expression of CD68 and lysozyme. The main type of mucinic acid is sialomucin. The nature of the cytoplasmic inclusions in foamy macrophages is highly variable. The deposits may be microorganisms, normal mucins or lipids, or abnormal glycoproteins or glycolipids. For this reason, different staining procedures (PAS, Oil Red O) are required, eventually associated with electron microscopy study or polymerase chain reaction (PCR) [12].

Eosinophils are normally present in the lamina propria of the colon (Fig. 1.8). They differentiate from hematopoietic progenitor cells into mature eosinophils in the bone marrow. Eosinophil migration from the bone marrow into the peripheral circulation is primarily regulated by IL-5. Circulating eosinophils interact with the endothelium in the gastrointestinal tract by a regulated process involving the coordinated interaction between adhesion molecules, chemokines, and their receptors. Eosinophils initially home to the gut in the prenatal period, independently of the bacterial flora. The mature eosinophils are terminally differentiated cells with limited survival in the tissue, in the absence of survival-promoting cytokines such as IL-5. In the gastrointestinal tract, they reside for at least 1 week. The number of eosinophils is usually low. For the colon, most authors propose a diagnostic threshold of 20 eosinophils per high-power field present as focal aggregates or more diffuse in the lamina propria and muscularis mucosae. However, normal values for tissue eosinophils in the colon vary widely. Location of the biopsy is an important variable. In

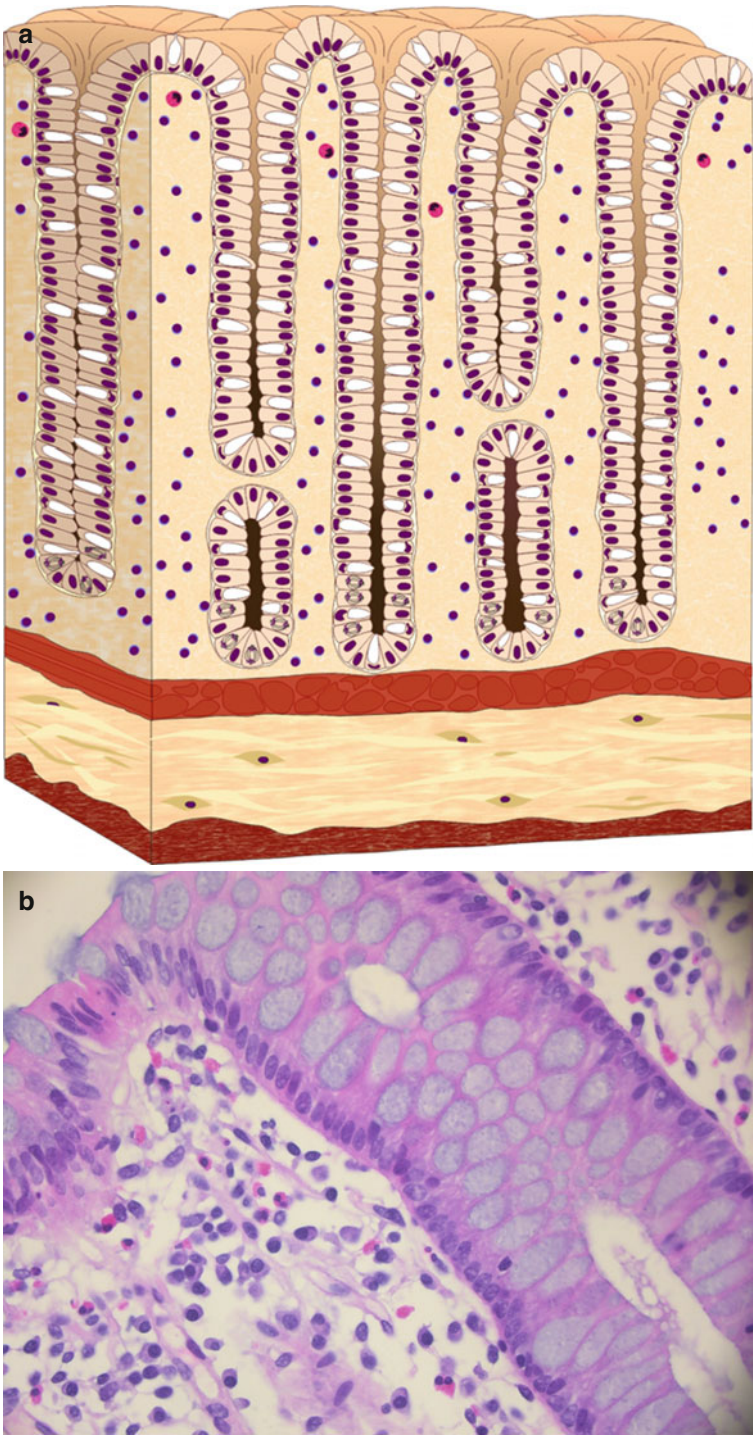

Fig. 1.8 Eosinophils are normally present in the mucosa of the colon in variable numbers as shown in the schematic presentation (**a**) and in the microphotograph (×40) (**b**)

humans, the appendix, cecum, and ascending colon contain the highest numbers. Lamina propria eosinophils are, on average, 3 times more numerous in the ascending compared with the descending colon. The normal value may range from <10 per high-power field in the rectum to >30 in the cecum. Geographical differences have also been observed with a 35-fold increase in samples from asymptomatic patients in New Orleans compared to Boston. Furthermore, mucosal eosinophils are slightly more numerous and may be in an intraepithelial position in samples obtained in April and May, corresponding to periods of high pollen counts. The distribution of the eosinophils is usually patchy. They are only rarely seen in an intraepithelial position, usually in crypts in the ascending colon. The function of eosinophils is not entirely known. They may play a role in organogenesis and tissue repair as well as a protective role, but through the release of substances such as major basic proteins (MBP-1 and MBP-2), eosinophilic cationic protein (ECP), and eosinophil peroxidase (EPO), they can have a toxic effect and a proinflammatory influence [14–16].

Mast cells develop from CD34-positive or c-kit-positive progenitor cells of the bone marrow. They contain abundant specific basophilic metachromatic granules in their cytoplasm. They constitute 2–5 % of mononuclear cells in the gastrointestinal lamina propria, with an average level of 13 cells per high-power microscopic field in the colon (Fig. 1.9) [17]. They are less numerous than eosinophils. They can be visualized with special stains such as toluidine blue or with immune histochemistry using antibodies directed against mast cell tryptase or c-kit (CD117). Increased, normal, or decreased numbers of mast cells have been noted in patients with inflammatory bowel disease, collagenous colitis, and gluten-sensitive enteropathy. Increases have also been linked to the irritable bowel syndrome and other forms of chronic diarrhea.

Neutrophils or neutrophilic granulocytes are normally not present outside the lumen of capillaries. More than three neutrophils in the lamina propria outside capillaries would be abnormal [18]. Neutrophils are also formed from stem cells in the bone marrow and normally reside in the bloodstream. They are one of the first cells to be recruited to a site of injury and are the hallmark of inflammation. They migrate through the endothelial lining and interstitial tissue following chemical signals such as interleukin-8 in a process called chemotaxis. Outside the blood vessels, they are short lived (1–2 days) although survival can be promoted by factors. Neutrophils express and release cytokines which can amplify the inflammatory reaction. They are capable of ingesting microorganisms or particles. Neutrophils are also capable of releasing various proteins (contained in three types of granules). These include a variety of enzymes such as metalloproteinases (gelatinase or MMP-9), myeloperoxidase, collagenase, and various others. By the release of these substances, neutrophils can induce breakdown of the fibrovascular stroma and induce damage. The presence of neutrophils in the mucosa of the colon is therefore considered as a sign of "disease activity."

Fibroblasts are distributed randomly throughout the lamina propria or in a sheath surrounding the crypts and tightly apposed to the subepithelial basement membrane. Fibroblasts are responsible for the synthesis of collagen, a major protein of the extracellular matrix. The normal intestinal wall contains type I (68 %), type III (20 %), type V (12 %), type IV, and type VII collagens. Type I, III, IV, and V collagens are present in the lamina propria. Type V collagen is also present in the

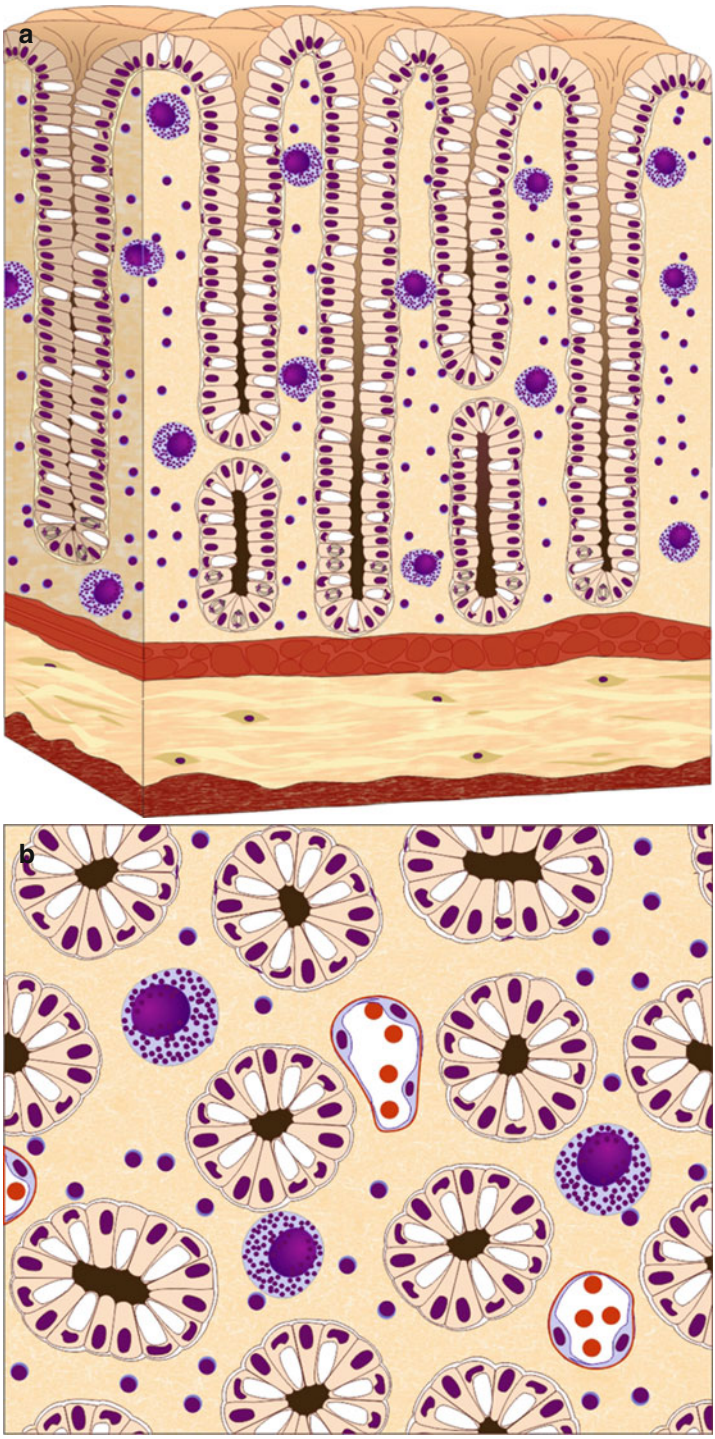

Fig. 1.9 Mast cells are normal components of the lamina propria cellular infiltrate in a perpendicular (**a**) and transverse section (**b**)

submucosa. Type VII collagen is confined to the basement membranes of intercryptal surface epithelium in a punctate manner [19].

Arteriolar branches from the submucosal plexus penetrate the muscularis mucosae and then break up in a leash of capillaries in the mucosa. The capillaries ascend along the glands and reach the surface of the mucosa where they form a honeycomb pattern around the openings of the glands, just beneath the surface epithelium. This pattern can be visualized with CLE imaging showing the hexagonal appearance with a regular-ordered network of capillaries demarcating the luminal crypt orifice [20]. With CLE fluorescein sodium 10 % imaging of the normal colon, the surface crypt architecture is classically represented by ordered and regular crypt orifices covered by a homogeneous epithelial layer with visible "black-hole" goblet cells within the subcellular matrix.

A lymphatic plexus is normally present immediately superficial to, within, and below the muscularis mucosae. Lymphatics may extend upward for a short distance but they are not seen above the level of the lowest one-sixth of the crypts [21]. In samples from patients with IBD, lymphatics can occur in the more superficial third of the lamina propria, probably as a result of lymphangiogenesis [22].

The muscularis mucosae, the layer which separates the mucosa from the submucosa, is fully developed between 17 and 20 weeks of gestation. This layer is composed of smooth muscle cells organized in a very thin layer of outer longitudinal and inner circular smooth muscle cells. These are plump, bipolar, spindle-shaped cells with a central nucleus. In the muscle coat, they are densely packed together, running roughly parallel to each other and separated from each other by spaces measuring only a few tens of nanometers and mainly occupied by collagen fibrils.

Perikarya of nerve cells, so-called ganglion cells can occasionally be found in the normal colonic mucosa. They can appear as single cells or in clusters and were found in up to 20 % of mucosal biopsies [23].

1.3 The Submucosa

In endoscopic biopsies, usually only a small part of the submucosa is present. It is a layer of dense or loosely arranged connective tissue that supports the mucosa and connects it with the underlying muscularis propria. Blood vessels and lymphatics are running through the submucosa. In its upper part, underneath the muscularis mucosae, the submucosal (Meissner) nerve plexus, which develops around 8–12 weeks, can be observed. The plexus is composed of small ganglia and nerve fibers. Lymphoid aggregates can occasionally be seen at the junction with the mucosa.

1.4 Variability of Microscopic Features

Histopathology represents a snapshot in time of a complex and dynamic biologic process that shows the normal variations and variations induced by the duration and activity of disease processes. The mucosa of the alimentary tract is indeed a

microworld composed of various cell types forming an organized and dynamic community which is well equipped for a variety of functions, but rapidly changing. Organized community means that the cell types can be described structurally in different compartments including the epithelial cells lining the surface and the crypts, and the lamina propria cells present in a stroma together with connective tissue cells, vascular structures, and smooth muscle cells in the muscularis mucosae. Dynamic community means that there is continuous cell renewal for most cell types including epithelial cells, lymphocytes, and monocytes. In the colon, epithelial cell turnover ranges between 2 and 8 days. Cell renewal is influenced by exogenous and endogenous factors. An adequate immune response implies migration of immune cells, cell recognition and interaction of cells requiring adhesion, and de-adhesion of cells. Proteins incorporated in the cell wall are important for these cellular interactions. These proteins have been called adhesion molecules. They can be classified into families including the "immunoglobulin superfamily" with members such as the major histocompatibility (MHC) class II antigens, CD4, CD8, ICAM (intercellular adhesion molecule), and VCAM (vascular cell adhesion molecule); "the integrins" such as LFA (lymphocyte function-associated antigen), involved in the interaction between lymphocytes and other cells; and "the selectins" such as ELAM (endothelial-leukocyte adhesion molecule), involved in neutrophil–endothelial adhesion [24, 25].

Because of the multitude of exogenous influences, the mucosa is well equipped for defense and many cells present in the intestinal mucosa play a role in this defense system and will adapt to a changing environment [6]. These changes can be observed during inflammation. The intensity and pattern of the changes depends however upon host and environment. The cellular inflammatory reaction, for instance, can show differences when samples from immune-competent and immune-depressed patients are concerned. The reaction will be different in transplant patients compared with immune-competent patients. Neutropenia, for instance, can occur during aplastic anemia or chemotherapy for malignant disease or in hematologic diseases. One complication of neutropenia that may occur is an acute necrotizing inflammation in the cecum and terminal ileum. This condition is known as "neutropenic colitis" (synonyms: necrotizing enteropathy, typhlitis, and the ileocecal syndrome). Several reports have identified various bacteriological agents as causative factor. Microscopic examination shows extensive mucosal and variable submucosal necrosis and paucity of a neutrophilic response because of the underlying disease [26].

In a similar way, a variety of anti-inflammatory drugs can influence the features of inflammation [27]. This is why it is important for the pathologist to have clinical information concerning treatment, immune status of the patient, and duration of the disease.

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Chapter 2
The Endoscopic Biopsy

Karel Geboes and Karen Deraedt

Abstract Pathology is one of the tools for reaching a diagnosis. Like all procedures in medicine, the analysis of biopsies has some limitations. The diagnostic yield can be increased by using good-quality samples, by optimizing the number of samples and sections, by optimal preparation of the samples, and by confronting the findings with appropriate clinical information. Numbers of samples needed depend on the indication for the endoscopic procedures. When reading a biopsy, analysis can be improved with a systematic approach. This implies a proper knowledge of the normal histology and of potential artifacts. The pathologists should take note of the origin, the number, and the size of the samples and subsequently evaluate the architecture and cytological aspects of the specimen. The analysis can be improved by using a checklist or pro forma report.

Keywords Endoscopic biopsy • Diagnostic yield • Sampling • Sampling error • Diagnostic accuracy • Orientation • Optimal number of biopsies • Detection of dysplasia • Number of biopsies • Origin of biopsies • Size of biopsies • Architecture • Sensitivity • Specificity • Spirochetosis • Artifact • Bowel preparation • Pseudolipomatosis • Barium

2.1 Biopsy Procedures

In routine clinical practice, endoscopic biopsies are obtained for diagnostic purposes and during a follow-up of the patient. Follow-up biopsies are used for confirmation of a diagnosis, for assessment of disease activity, and for cancer

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surveillance or identification of complications. Optimally, the pathologist should be aware of the precise goal of the biopsy.

The diagnostic yield of histopathology depends upon the experience of the pathologist and on the quality of the biopsy samples and is influenced by sampling errors. Diagnostic accuracy increases when biopsy samples are analyzed by expert pathologists and by training nonexpert general pathologists although the quality of the samples may be more important [1, 2]. The quality of the samples is influenced by a variety of elements such as the size and shape of the biopsy forceps, the nature and location of the disease, the experience of the endoscopist, and the number of samples. Samples are usually obtained with pinch biopsy forceps. Currently, a wide variety of single-use and reusable instruments are available. Disposable instruments may be superior probably because the forceps are sharper [3]. A distinction can be made between those with oval or elongated and those with round cups. Generally, the samples obtained with oval elongated cups are deeper and those with oval fenestrated cups are larger. A forceps with round cups may be more appropriate for children in order to avoid complications. The size of the biopsy forceps determines partly the size (surface and depth) of the samples. The small forceps has a width of 1.8 mm when opened. The average forceps has a 2.4–2.8 mm diameter and allows to obtain samples containing the muscularis mucosae (and upper submucosa) in 60 % of the cases. Therefore, endoscopic biopsies are not so appropriate for a diagnosis of vasculitis or amyloidosis, because non capillary blood vessels are mainly located in the submucosa. The larger Jumbo forceps has a 3.4 mm diameter. Samples obtained with this forceps are larger, but they usually contain not more submucosa and the risk of complications (perforation and bleeding) may be more important, whereas it is minimal with the smaller forceps (if the patient has normal coagulation). A forceps can have a central spike for improved anchorage, so that it stays in position in the mucosa, during the procedure. The spike can induce artifacts which should not be confused with erosions. Colitis can be a diffuse process, a more right-sided process, or a discontinuous disease. This is not only important for Crohn's disease but also for a diagnosis of collagenous or lymphocytic colitis. Thickening of the subepithelial collagen table in collagenous colitis is indeed not homogeneous. It is therefore important to have biopsies from the different areas of the colon (and ileum) because the location of lesions can help for the diagnosis. This implies that several biopsies are obtained, ideally from diseased and healthy areas (if present), and that the biopsy specimens from different segments are presented in different containers to the pathology lab. Random samples from the same area can be in a single container. The lesions which are biopsied may be important. Indeed, according to some studies, biopsies of aphthoid ulcers more commonly show granulomas, which are diagnostic for Crohn's disease. Sampling should include also normal mucosa because this may reveal also significant features [4]. The ECCO (European Crohn's and Colitis Organisation) recommendation published concerning sampling states that at the onset of the disease or during the first examination, "For a reliable diagnosis of inflammatory bowel disease (IBD), ileocolonoscopy rather than rectoscopy should be performed. A minimum of two biopsies from at least five sites along the colon, including the rectum, and the terminal ileum should be obtained. In patients with fulminant colitis, two samples from at least one site should be obtained [5]."

During follow-up of patients with colitis, a smaller number of biopsy samples may confirm the diagnosis and give information regarding disease activity. When the goal of the biopsy is confirmation of the diagnosis, it is appropriate to review the original set of biopsies. Furthermore, it is important to take into account the treatment given to the patient and the duration of the disease. In postsurgical follow-up of patients with Crohn's disease, biopsies of the neo-terminal ileum are indicated when disease recurrence is suspected. Where patients have undergone ileal pouch-anal anastomosis, biopsies of the afferent limb are useful when Crohn's disease is suspected. Multiple biopsies are indicated when the patient is investigated during screening for dysplasia (intraepithelial neoplasia). Crohn's disease and ulcerative colitis carry an increased cancer risk. A pathway of "colitis–dysplasia–cancer" has been identified and this allows surveillance of patients with an increased risk (long-standing disease, extensive colitis, ulcerative colitis with primary sclerosing cholangitis, persistent microscopic disease activity, family history, etc.). It has been estimated that 33–64 biopsies are required to detect dysplasia with 90 and 95 % probabilities, respectively. Yet, with 20–40 biopsies, less than 0.1 % of the colorectal mucosa is covered [6, 7]. Current practice guidelines recommend to take 4 biopsy specimens from every 10 cm (0.05 % of the entire area of the colon) of diseased bowel in addition to macroscopically atypical lesions [8]. However, the detection rate of IBD-related dysplasia can substantially be improved with targeted biopsies obtained with the newly developed endoscopic techniques such as magnifying colonoscopy, and this procedure should replace the random biopsy guidelines in the future because overall the diagnostic yield of random biopsies is poor [5]. Training of endoscopists is also an important issue. In the literature, there are guidelines for numbers and site of biopsies for the most common conditions. This is however not so for all diseases that can affect the colon. In general, when no guidelines are available, it seems appropriate to take biopsies from lesions but also from noninvolved areas and to submit these samples to the laboratory in separate containers with an indication of the site of origin.

All tissue samples should be fixed immediately by immersion in buffered formalin or an equivalent solution prior to transport to the laboratory of pathology. Orientation of the samples using filter paper (submucosal side down) before fixation may yield better results, because it allows perpendicular sections and thus a better assessment of architectural abnormalities. Without previous orientation, sections can be transverse which is more difficult for the assessment of the architecture and the distribution of the lamina propria cellular infiltrate. The ideal number of biopsy sections which should be examined in routine practice has not been established. Numbers vary between 2 and 6 in different studies [9, 10]. The diagnostic yield increases though when more sections are examined. It is not clear whether serial sections or step sections from different levels of the sample should be examined. In one comparative study of rectal biopsies, serial sectioning increased the ability to detect focal abnormalities including granulomas compared to step sectioning [11]. In routine practice, step sections may be the most simple procedure. It has been proposed to obtain two to three tissue levels, each consisting of five or more sections. Routine staining with hematoxylin and eosin is appropriate for diagnosis. Special stains, such as immune histochemistry, or other techniques for diagnostic

purposes are not needed routinely. They can eventually be helpful though for the assessment of CD3 positive T lymphocytes (in lymphocytic colitis) or the presence of collagen or tenascin (in collagenous colitis) or for the search of granulomas, using antibodies directed against CD68.

The biopsy samples should be accompanied by clinical information including endoscopic findings as well as the age of the patient, duration of disease, duration and type of treatment, comorbidity, and travel history [5].

2.2 How to Look at a Biopsy

The purpose of the microscopic examination should be to reach a level of diagnosis that allows identification of the etiology of the symptoms or the disease for which the endoscopy is performed. This implies usually that the pathologist has access to the clinical history, information regarding the bowel preparation, and over-the-counter or prescription drug history [4]. Microscopic analysis should however start without looking at this information. The pathologist needs to form a personal opinion. He or she should look first at the number, size, and origin of the samples. This defines the limits of the analysis. When only one sample without submucosa is present, the reliability of the diagnosis may be questionable. At low magnification, it is already possible to see if all specimens are affected by a disease process or not. This will provide an idea of diffuse or discontinuous disease. Multiple samples from different sites can already provide some clues for a diagnosis. Right-sided colitis is more common in Crohn's disease and less usual in ulcerative colitis, unless the patient has been treated with local therapy such as enemas. Sadly, in routine practice, the pathologist has often only biopsies from inflamed areas. Diverticular disease-associated colitis should be considered when biopsies from the sigmoid are involved whereas samples from the rectum and right colon are normal. If only biopsies from the inflamed sigmoid are available, it may be impossible to provide a final diagnosis. Samples could be signed as "inflammatory bowel disease-like features," but diverticular colitis must be considered in the differential diagnosis, especially when the patient is middle aged. Diversion colitis is likely when samples from an excluded rectum are abnormal whereas samples from the colon in transit are normal. For this diagnosis, minimal knowledge of the clinical situation is imperative.

Subsequently, the architecture of the mucosa of the different samples should be assessed. It has been shown that architectural changes can be observed with good reproducibility and that they have good sensitivity and specificity for a diagnosis of IBD [12]. There are however some anatomic variations [3]. Abnormalities in the rectum alone are less useful as they might be a variant of normality. In the rectum, the crypts are usually widely spaced. At higher magnification, it is important to examine also the surface of the specimen and to look for the presence of any abnormality which can include necrotic debris, abundant mucus, and pathogens such as spirochetes, amebae, or crystals such as in kayexalate- and sevelamer-induced colitis [13–15].

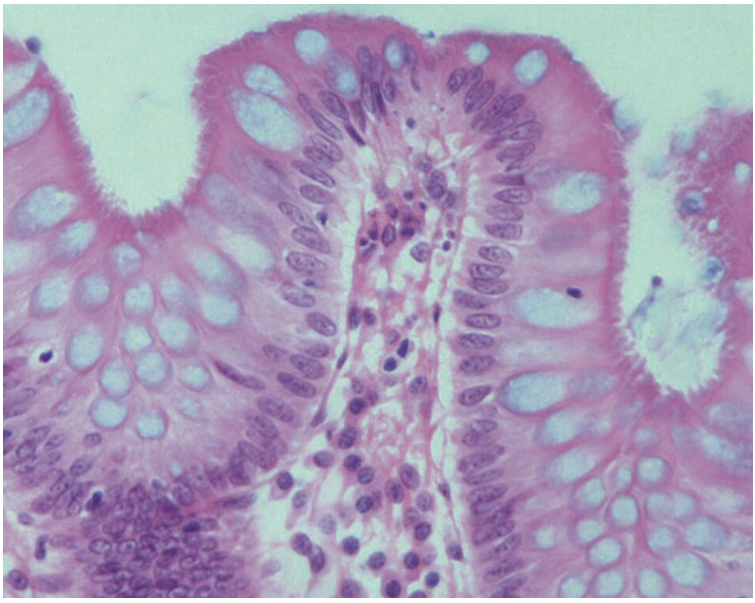

Fig. 2.1 Microphotograph showing a bluish aspect covering the surface indicating the presence of spirochetes forming a false brush border (×40)

Spirochetosis, for instance, is characterized by the presence of a thin, carpet-like layer of spirochetes attached on the colorectal surface epithelium and forming a "bluish" false brush border (Fig. 2.1). The major species is *Brachyspira aalborgi*. Infection is usually asymptomatic and not associated with active inflammation or mucosal injury [16]. *Entamoeba histolytica* infection can be recognized by the presence of trophozoites on the surface (Fig. 2.2). They should not be confounded with desquamated goblet cells. Kayexalate crystals have narrow, rectangular "fish scales" and are violet on routine staining and magenta on periodic acid-Schiff with diastase (Fig. 2.3). Sevelamer crystals (Renagel and Renvela, Genzyme; phosphate-lowering agents) appear as broad, curved, and irregularly spaced "fish scales" with a variably eosinophilic to rusty brown color on hematoxylin and eosin staining (H&E). Periodic acid-Schiff-alcian with diastase staining shows a violet color. Both products can be used in patients with chronic kidney disease. Cholestyramine has to be considered in the differential diagnosis. This compound lacks internal "fish scales," is bright orange on routine staining and variably gray or hot pink on periodic acid-Schiff with diastase, and is unassociated with mucosal injury [17].

The next step is to look at the cytology of surface and crypt epithelial cells to see if they are highly columnar and well differentiated or not. Simultaneously, the distribution, the density, and the composition of the lamina propria cellular infiltrate and the aspect of the stroma are examined. The distribution of the inflammation is another feature that can be assessed with good reproducibility [12]. Finally, the pathologist should look for the presence of blood vessels in the submucosa, and,

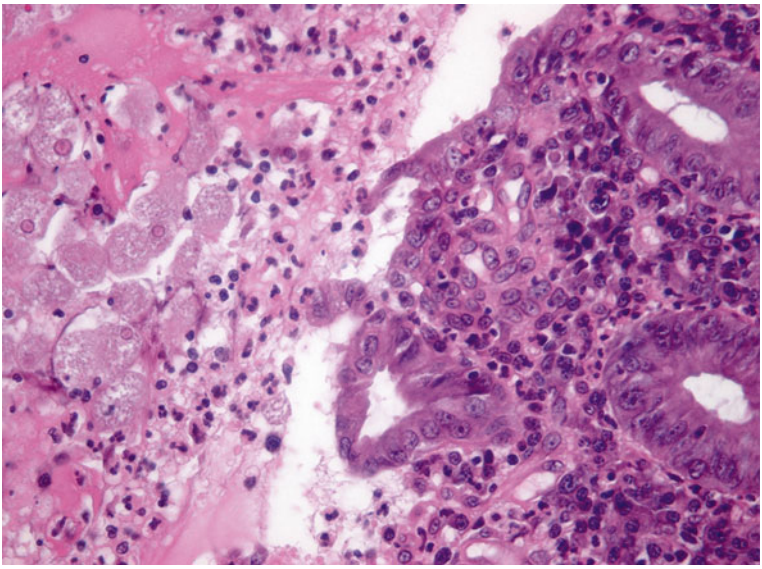

Fig. 2.2 Microphotograph showing the presence of numerous trophozoites of *Entamoeba* covering the surface of the biopsy (×20)

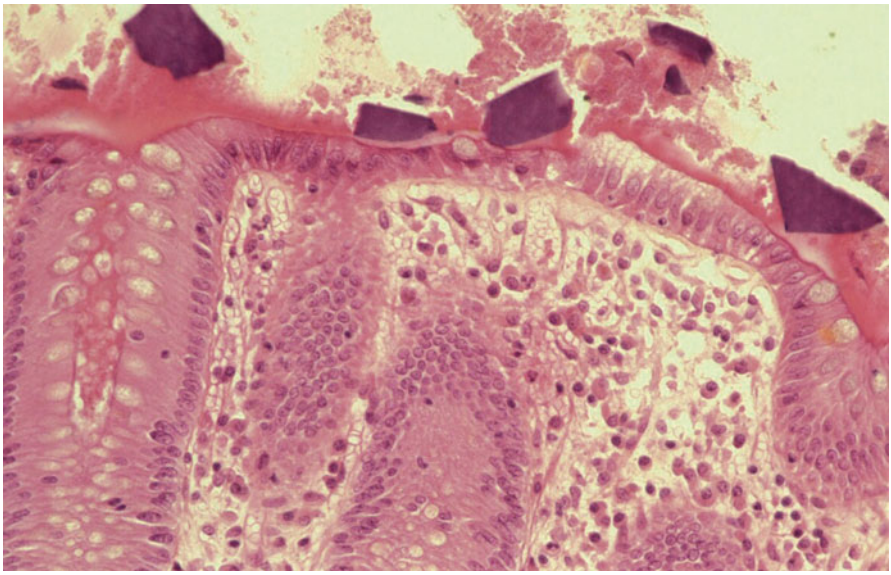

Fig. 2.3 Microphotograph showing the presence of crystals on the surface suggestive of kayexalate (×40)

if present, for the presence of signs of vasculitis or amyloid, and examine also the appearance of the ganglia of the submucosal plexus. Abnormalities should be noted and a preliminary diagnosis should be made, which is then confronted with the available clinical data, such as disease duration, treatment received and the endoscopic findings, the immune status, and the age of the patient. The density of the lamina propria cellular infiltrate may indeed differ according to the immune status of the patient. In transplant patients, patients with human immunodeficiency virus (HIV) infection and patients receiving immune suppression, the inflammatory cell infiltrate may be less prominent. After careful analysis, the findings can be matched with the patient's age and history. The age of the patient may point to some diseases such as diverticular-associated colitis and ischemic colitis which are more common in middle-aged or elderly patients. The presentation of inflammatory bowel diseases may be less characteristic in pediatric patients [5]. Overall analysis of biopsies could be improved by using a checklist for the different items which need to be scored.

2.3 Artifacts

Very often, endoscopic biopsies show some squeeze artifact in the deeper part and partial or complete absence of surface epithelial cells. The latter is usually the result of the biopsy procedure. The artifactual nature of the surface damage can be established by searching for remnant epithelial cells. These are usually well differentiated and highly columnar. When epithelial damage is genuine, remnant epithelial cells appear attenuated and have a darkly staining cytoplasm. This is however more difficult when the mucosa is already damaged by the disease. It may indeed be difficult to distinguish a genuine erosion and loss of surface epithelial cells from artifact-induced damage in samples from severe colitis.

Diagnostic accuracy of colonoscopy depends on the quality of colon cleansing. Bowel preparation includes diet, enemas, high-volume gut lavage, and rectal irrigation [18]. In some occasions, adjuncts are used to improve the results. Currently, preparation is mainly based on oral aqueous sodium phosphate (NaP) solutions and tablets, and polyethylene glycol (PEG) solutions, especially low-volume solutions. These are well tolerated by the majority of the patients [19]. PEG does not alter the histology or at least, the changes are less prominent than with NaP. Endoscopic and histological abnormalities have been reported with NaP and other compounds. A pattern of acute colitis with basal cryptitis and focal colitis has been described following bowel preparation with oral sodium phosphate and bisphosphonate enemas (see also drug-induced colitis). Hyperosmotic or hypertonic enemas may cause sloughing of surface epithelium up to the point that the epithelial cells are completely stripped away. Superficial cells are replaced by young, attenuated cells, migrating from the crypts. Increased apoptosis has also been noted. As a result of

cell loss, increased cell proliferation determined by mitotic counts and immune histochemistry with antibodies against proliferation markers is observed [20]. Neutrophils can be present in the lamina propria. The edematous lamina propria may contain extravasated red blood cells, some of which may be lysed. Mucin release may be prominent. Bisacodyl, a poorly absorbed diphenylmethane that stimulates colonic peristalsis, can be used as an adjunct with PEG or NaP. It may be associated with edema and the appearance of occasional neutrophils beneath the surface epithelium, particularly when administered in the rectum. The changes usually resolve within a week.

Insufflation of air during the endoscopic procedure may induce "pseudolipomatosis" or "mucosal pneumatosis." This is due to small trauma present before or induced by the friction of the instrument against the mucosa. The air used to dilate the lumen and visualize the mucosa may infiltrate the tissue and cause small, clear, bubble-like spaces which resemble adipocytes. This has no clinical implications. Pseudolipomatosis has also been linked to disinfection of the instrument with peroxide agents (peracetic acid or hydrogen peroxide) [21].

In the past, glutaraldehyde has been used for disinfection of endoscopes. This practice has been found to be responsible for acute self-limited chemical colitis appearing within 48 h of colonoscopy or sigmoidoscopy. The morphological features may mimic ischemia [22]. Colonic biopsies reveal vascular congestion, crypt damage, and an increase in the number of foamy macrophages. Lesions may already appear in biopsies obtained during withdrawal of the endoscope. This method of disinfection should not be used anymore nowadays.

Contrast media such as barium sulfate, an inert water-insoluble metallic element used for various radiographic studies, can induce a variety of rare complications including perforation with peritonitis, granuloma formation, ischemic necrosis, "barium" appendicitis, and bezoar or mass formation with subsequent obstruction and/or mucosal injury.

Barium is manufactured with properties to make it more adherent to mucosal surfaces. This adherence leads to clumps which are usually recognizable as whitish crystalline material in aggregates on the surface and occasionally in the mucosa or submucosa. Iodinated contrast media can be responsible for diarrhea because of the osmolarity of the product. They have been associated in rare instances with necrosis of the bowel wall in infants and with cecal perforation in adults. A possible mechanism is a large shift of fluid into the intestine because of the hypertonic nature of the substances.

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Chapter 3
Elementary Lesions of Inflammation

Gavino Faa, Sonia Nemolato, and Karel Geboes

Abstract A diagnosis of the etiology or the type of colitis is usually not based upon a single discriminatory feature but rather upon a combination of "multiple" microscopic features. These should ideally be evidence based and reproducible and have good specificity and sensitivity. Genuine inflammation of the colonic (and small intestinal) mucosa is characterized by changes in the epithelial and lamina propria cell compartments. Both types of changes should be present. Alterations of the epithelial cells can be subdivided in changes of surface epithelial cells, crypt and surface architectural changes, and metaplasia. Typically there is a change of height of lining epithelial cells. In normal mucosa the surface epithelial height exceeds the height of crypt epithelium [1]. The changes occurring in the lamina propria are not a reaction that develops from a zero baseline of leukocytes. Essentially, these changes are characterized by an increase in total cellularity, a more or less prominent redistribution of the infiltrating cells so that the infiltrate may or may not have a similar density throughout the lamina propria, including the basal part and changes in composition. A good understanding of the different lesions characteristic of inflammation will improve the diagnostic results.

Keywords Architectural change • Crypt branching • Crypt distortion • Mucosal atrophy • Crypt atrophy • Crypt regeneration • Cytokine • Magnifying endoscopy • Surface irregularity • Tenascin • Erosion • Ulceration • Restitution • Pyloric gland metaplasia • Metaplasia • Ulcer-associated cell lineage • Mucin depletion • Apoptosis • Paneth cell metaplasia • Lamina propria cellularity • Eosinophils • Granuloma • Lamina propria • Basal plasmocytosis • Eosinophilic colitis • Allergic colitis • Emperipolesis • Epithelioid cell • Basement membrane • Collagenous colitis

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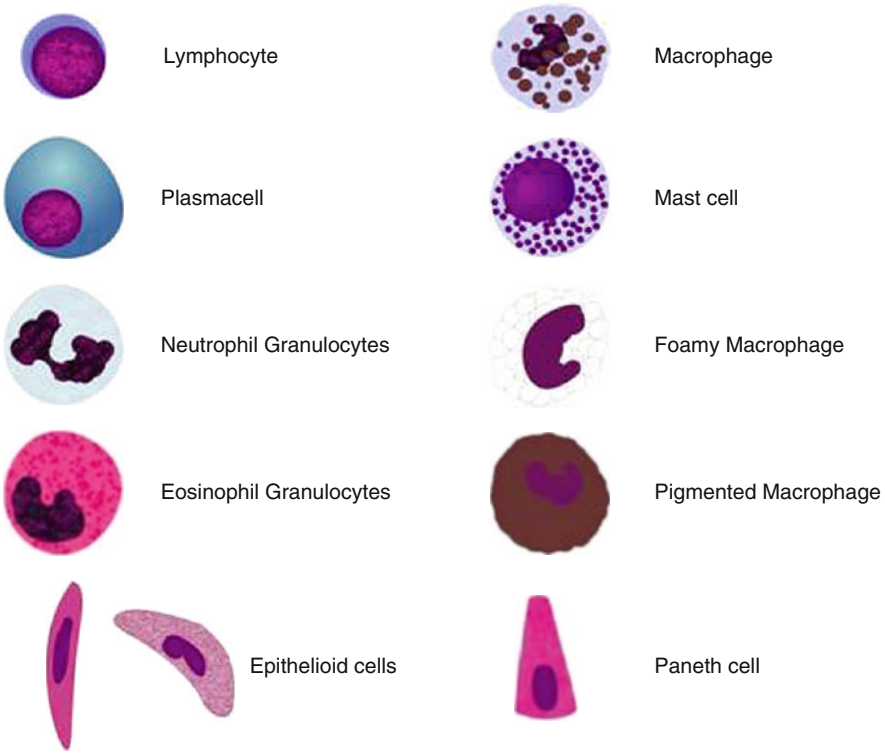


Fig. 3.1 Identification of key cells in the illustrations

Please see Fig. 3.1 for the key to the illustrations.

3.1 Architectural Changes

Crypt branching is characterized by the presence of two or more branched (bifurcated crypts), (vertical or horizontal) in a well-oriented section (Fig. 3.2) [2–5]. If only one crypt is affected, the feature is less specific, particularly in children [3]. The pathogenesis of the feature can be explained by regeneration following previous damage – destruction.

Mucosal or crypt distortion means the presence of irregularities in crypt size (variable diameter) (Fig. 3.3), spacing (Fig. 3.4), orientation (loss of parallelism) (Fig. 3.5), and shape (including branching or cystic, dilated aspect) and separation from the underlying muscularis mucosae (Fig. 3.6) [3–11]. Mild irregularities in orientation are not sufficient.

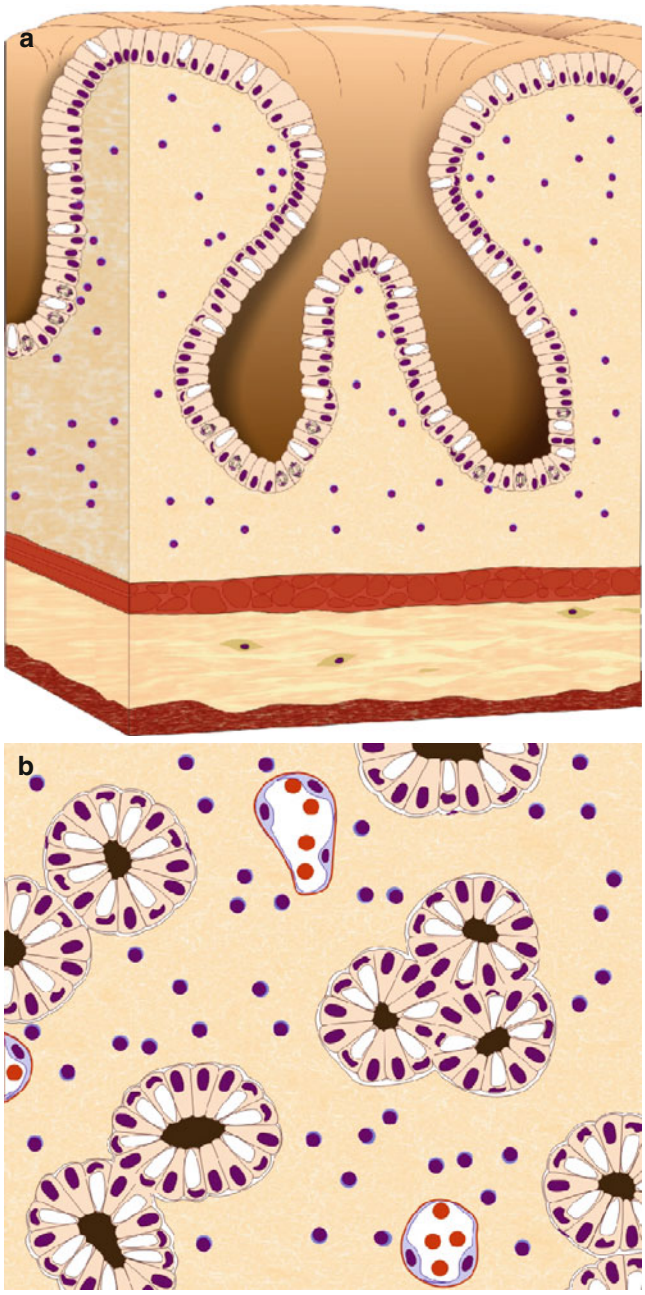


Fig. 3.2 (**a**, **b**) Schematic representation of branching crypts in a perpendicular (**a**) and transverse section (**b**)

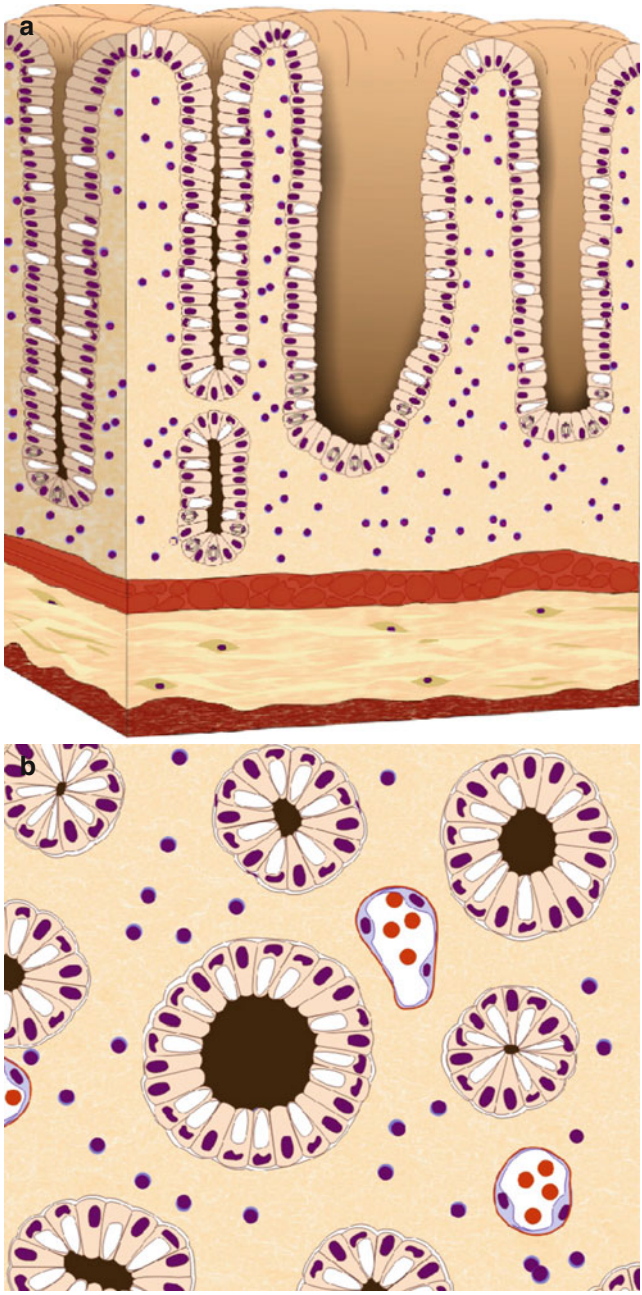


Fig. 3.3 (**a**, **b**) Architectural changes: variability in the cryptal internal diameter in perpendicular (**a**) and transverse sections (**b**)

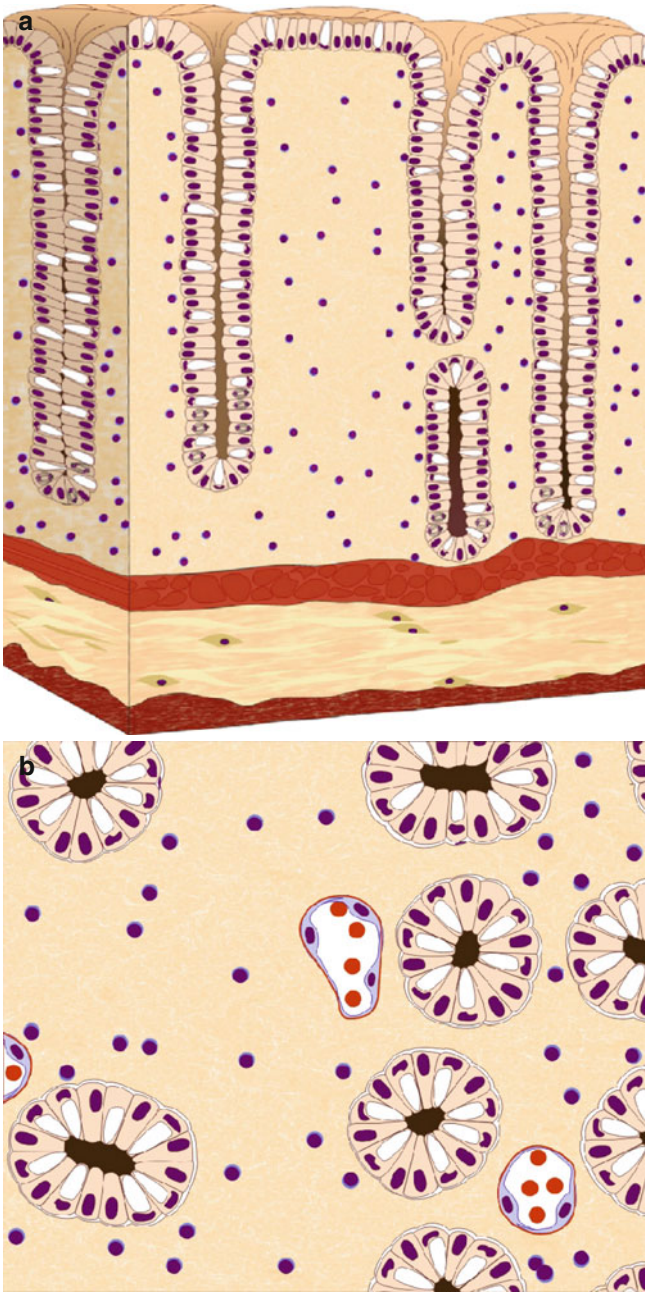


Fig. 3.4 (**a**, **b**) Architectural changes: variability in the intercryptal distance

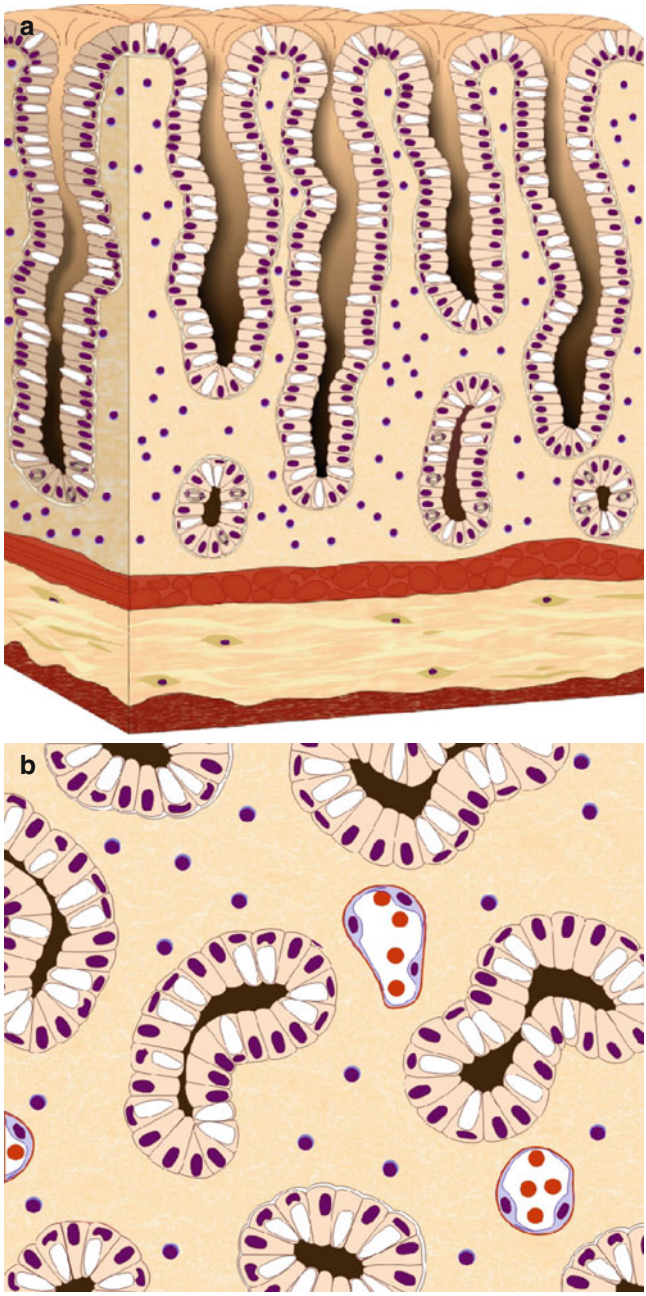


Fig. 3.5 (**a**–**d**) Architectural changes: deformation of crypts and crypt architectural distortion in perpendicular and transverse section (**a**, **b**) and microphotographs (×20 & ×40) of perpendicular sections. In the latter, branching of crypts as well as shortening can be observed

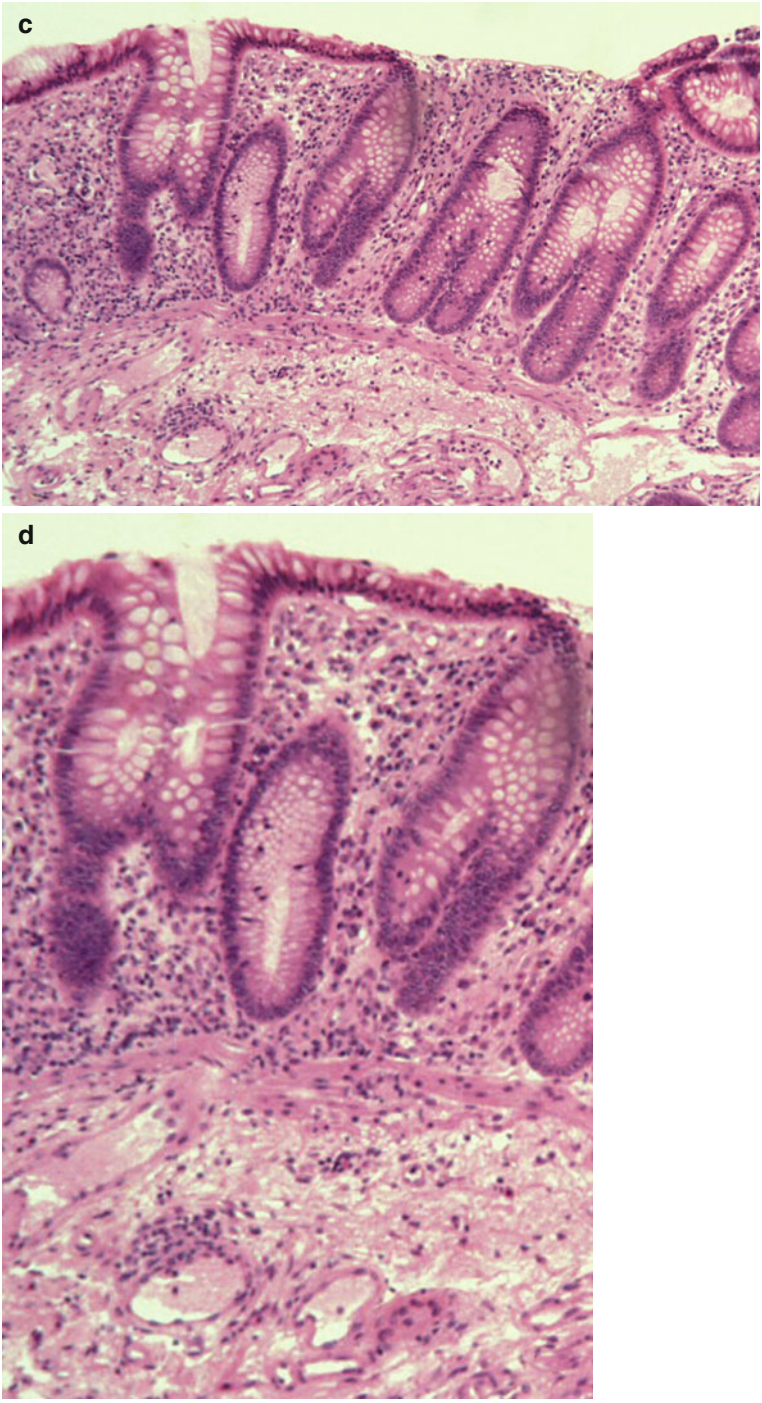


Fig. 3.5 (continued)

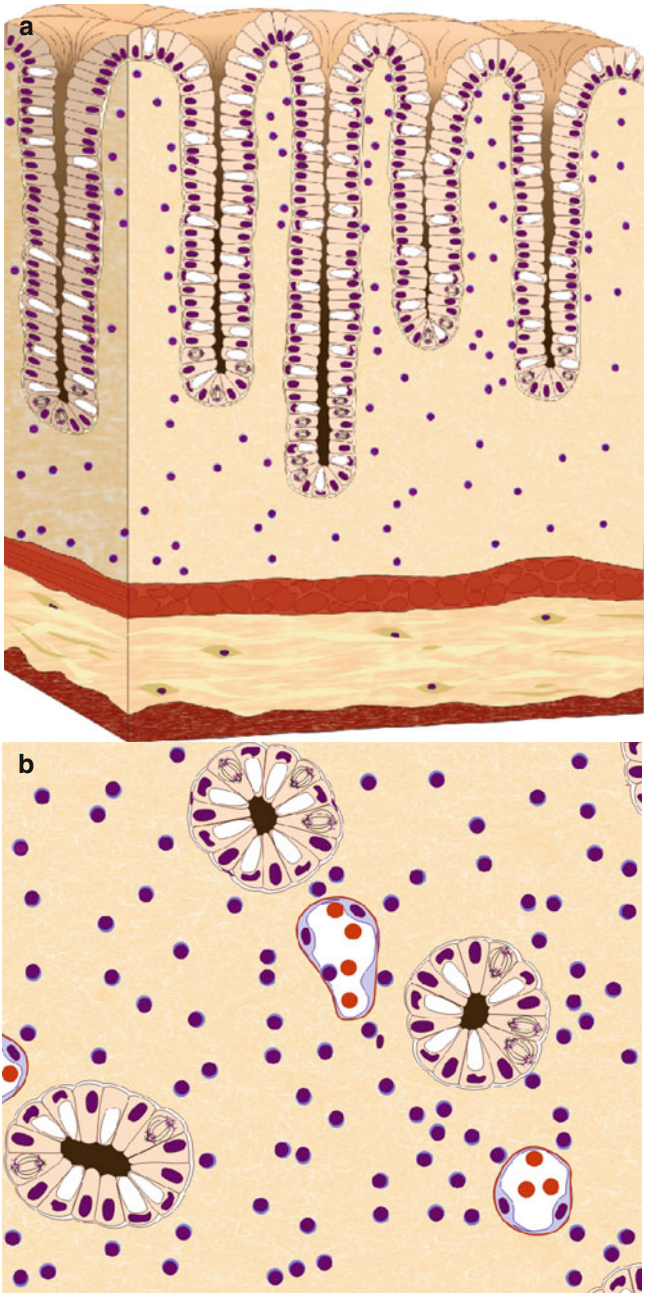
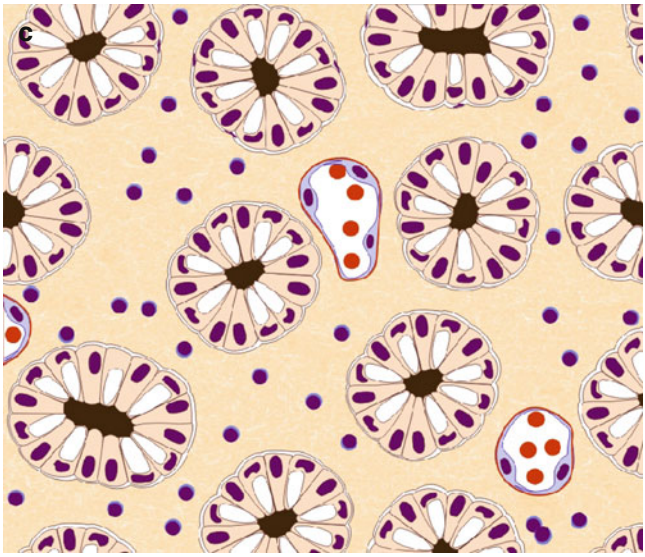


Fig. 3.6 (**a**–**c**) Shortening of crypts. This can be well appreciated in perpendicular sections (**a**) but not in transverse sections (**b**, **c**). The latter show mainly differences in the intercryptal distance

Fig. 3.6 (continued)



Mucosal atrophy–crypt atrophy–loss of crypt density is a combination of thinned-out crypts (loss of crypts – generally increased distance of more than one crypt diameter between crypts) and a general increase in the distance between crypts and the muscularis mucosae (Fig. 3.7) [4–6]. Some authors focus more on the loss of crypts [6] or on the increased distance between the muscularis mucosae and the base of the crypts [9]. Increased spacing may be normal in the cecum and distal rectum [5]. At present it is not clear what size of biopsy is adequate for proper evaluation nor how many levels of the biopsy need to be studied to assess atrophy properly. Perpendicular sections are more suitable for the assessment but transverse sections may already show variability in distance between the crypts and variability in size.

Atrophic microcrypts are lesions characterized by necrosis of epithelial cells of the upper part and the surface and a small, withered, or atrophic appearance. There may be striking cytologic atypia, to the point where care should be taken to avoid overcalling these reactive changes dysplastic [12]. They are characteristic for ischemia or ischemic-type damage.

The pathogenesis of atrophy and architectural distortion can be explained by different mechanisms. If all crypt cells die, crypts are reproductively sterilized and disappear (experimentally within 48 h). However, if one or more clonogenic cell survives the insult, it rapidly proliferates to regenerate the crypt (within 72–96 h experimentally – animals) and subsequently the tissue heals by clonal expansion. The number of crypts that survive and regenerate following a cytotoxic insult correlates well with severity of symptoms in animal models. A number of growth factors have been shown to affect crypt regeneration in murine models [13].

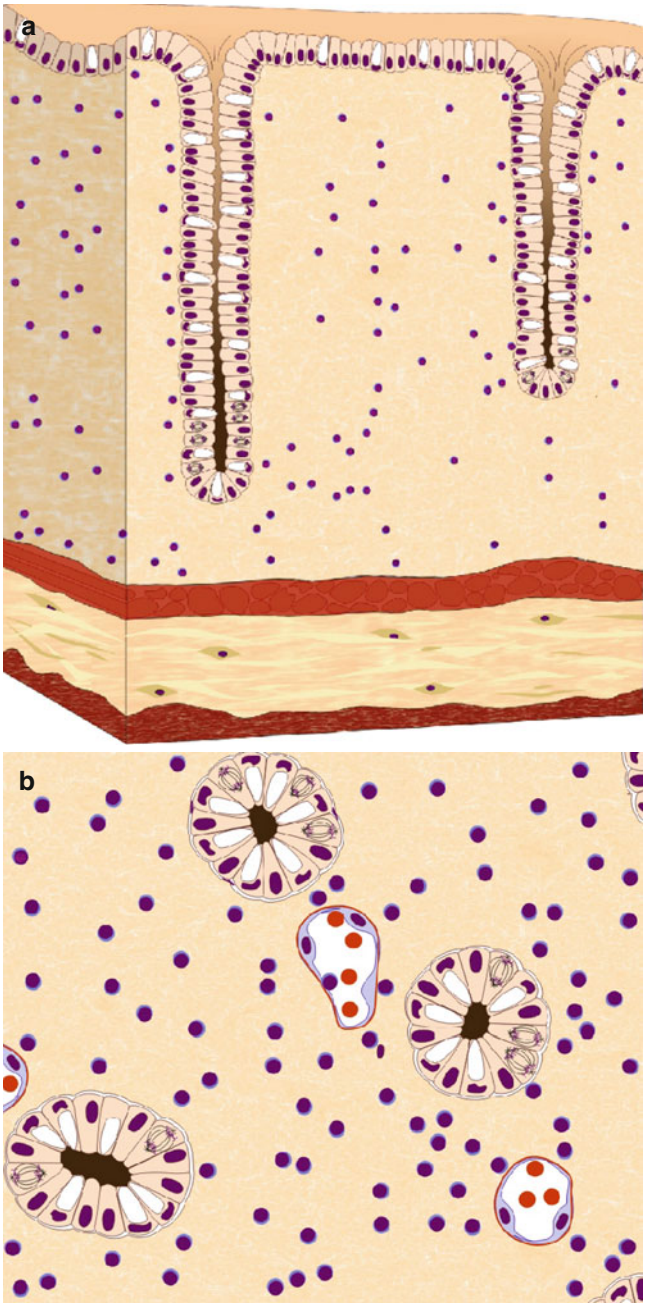
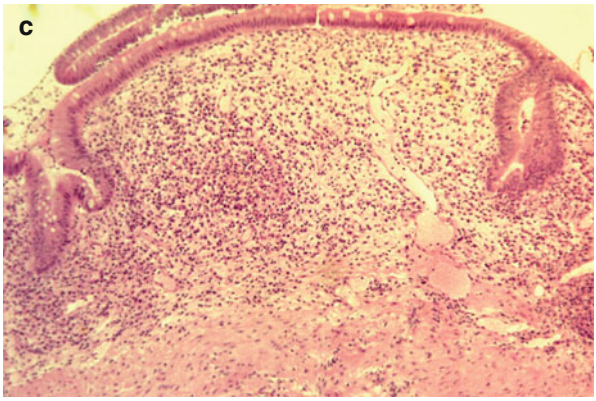


Fig. 3.7 (**a**–**c**) Loss of crypts shown on drawings of perpendicular and transverse sections (**a**, **b**) demonstrating increased distance in between the crypts as compared to normal in the microphotograph (×40)

Fig. 3.7 (continued)



In addition, it has been shown that the subepithelial myofibroblasts of the epithelial crypt sheath are disrupted in the intestinal mucosa of patients with IBD. A loss of myofibroblasts appears to result from the susceptibility of these cells to pro-inflammatory cytokines. Pro-inflammatory cytokines do not affect tenascin-C expression, suggesting that the decrease observed in the inflamed mucosa resulted from myofibroblast apoptosis [14]. Tenascin is an extracellular matrix glycoprotein involved in cell proliferation differentiation and migration during embryogenesis. Fibroblasts and glial cells are the primary cells that synthesize tenascin. In adult tissue it is expressed only in certain areas. In the normal colon mucosa, tenascin appears mainly in a subepithelial position, immediately underneath the intercryptal surface epithelium and around the epithelial cells lining the upper half of the crypts. However, it gains importance again in proliferative processes such as wound healing and tumor development. Crypt architectural abnormalities develop over time. The feature may therefore not be present in biopsies obtained at initial onset. It was observed in biopsies from patients with colitis obtained between 16 and 30 days after onset [3] but not in earlier biopsies and in all biopsies obtained within days after onset in another study [6], but in this study disease onset was defined by loss of blood and not by other symptoms. Crypt distortion and mucosal atrophy may return to normal or remain unchanged during the course of a disease [15, 16].

Various crypt abnormalities can now also be identified in real time with novel currently available endoscopic techniques. With magnifying colonoscopy and methylene blue staining, different grades of "pit patterns" were described in the rectal mucosa of patients with ulcerative colitis on the basis of the size, shape, and arrangement of the pits or glands. Aberrant patterns included grade 2 with rather large, oval, and somewhat irregular pits; grade 3 with pits of various shapes and sizes and irregularly arranged; and grade 4 characterized by dispersed pits varying in morphology and associated with the presence of small erosions. Similar finding have been reported with CLE. In ulcerative colitis, CLE imaging identified crypt abnormalities such as crypt fusion and distortion and dilation of crypt openings, with fluorescein leaks into the crypt lumen [17, 18]. These data confirm previous descriptions using stereomicroscopy.

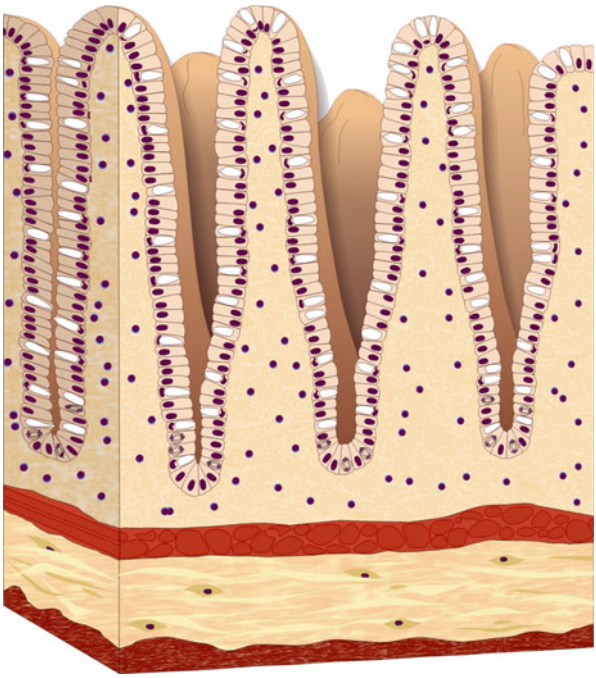


Fig. 3.8 A villiform surface can be induced by widening of the crypts

3.2 Surface Irregularity

Surface irregularity (synonyms: villous surface, villiform surface or features, villous mucosa) (Fig. 3.8) is characterized by a widening of the crypt mouths and lumen giving the mucosal surface a fingerlike appearance [19–21].

3.3 Epithelial Cell Modifications

These include mucosal erosion and ulcerations, changes in shape and size of surface and crypt cells which are essentially flattening of cells or cuboidal appearance, and mucin depletion.

The presence of mucosal erosions and ulcerations (Fig. 3.9) is an important feature for a diagnosis of colitis. An ulceration is a deeper mucosal defect usually characterized by the presence of granulation tissue and/or fibrinopurulent material (Fig. 3.10). An erosion is a more superficial defect (Fig. 3.11). It is often difficult to distinguish an erosion properly from an artifact-induced mucosal damage (due to the biopsy forceps and a friable mucosa).

The presence of flattened or cuboidal cells without nuclear pleiomorphism can be very helpful for this distinction. These cells point to a phenomenon of "restitution" (Figs. 3.12 and 3.13). This is a process capable of restoring the continuity of the epithelial surface. Cells next to the damaged area, usually in the upper part of the crypts,

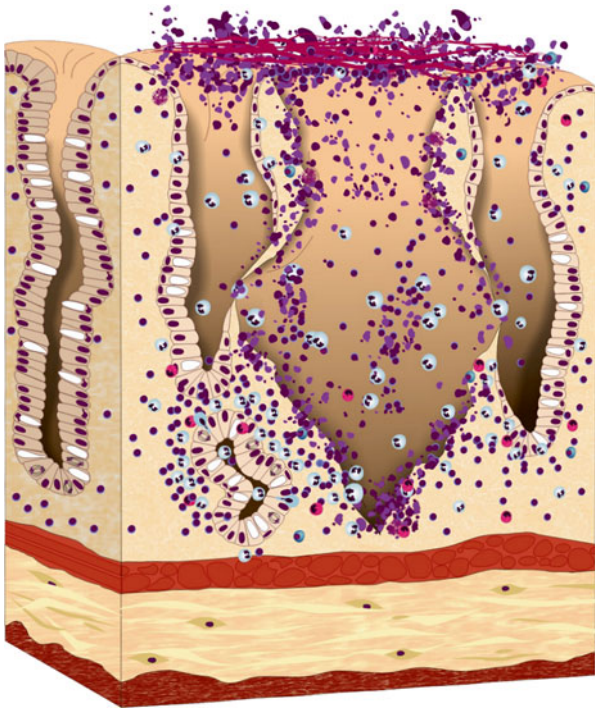


Fig. 3.9 An ulcer is a mucosal defect characterized by loss of glands, often extending into the submucosa or limited to the mucosa (as in this schematic representation)

reorganize their cytoskeletons, create specialized structures known as pseudopodia, and loosen their linkage to the underlying matrix. This enables them to migrate and spread over the damaged area. This process can occur within hours following damage [22]. These cells are metabolically active. Hence, they have a more basophilic cytoplasm. Usually there is a gradual transition from low cuboidal cells in the upper part of the crypts to flattened or attenuated cells on the surface. Mucin depletion is a parameter which can be recognized with good reproducibility (Fig. 3.14). It may partly be due to epithelial cell damage or results from restitution phenomena. Some degree of mucin depletion is not unusual in any type of colorectal inflammation although it is less common in Crohn's disease (except in the edge of mucosal defects). Severe almost total mucin depletion is a specific feature separating UC from Crohn's disease.

Crypts may also show reactive changes. These include a small increase in mitotic figures and an increase of the proliferative compartment. The cells in the lower crypt are becoming elongated and contain an enlarged, basal nucleus. These changes indicate "reepithelialization" and recovery. Apoptosis of crypt epithelial cells may be noted. Apoptosis, derived from the classic Greek word for "dropping off," is a process of programmed cell death. It is characterized by shrinkage of the cells and fragmentation of the nucleus. Apoptotic cells contain scattered karyorrhectic basophilic globular intracytoplasmic debris of apoptotic bodies. Usually apoptosis is focal in nature and occurs in single cells which results in membrane-bound debris of apoptotic bodies in the crypts. This phenomenon has been labeled variously as "exploding crypt cells," "karyolytic body," "apoptotic body," "granular necrosis," and "popcorn lesions" [23]. It is a characteristic feature of graft versus host disease

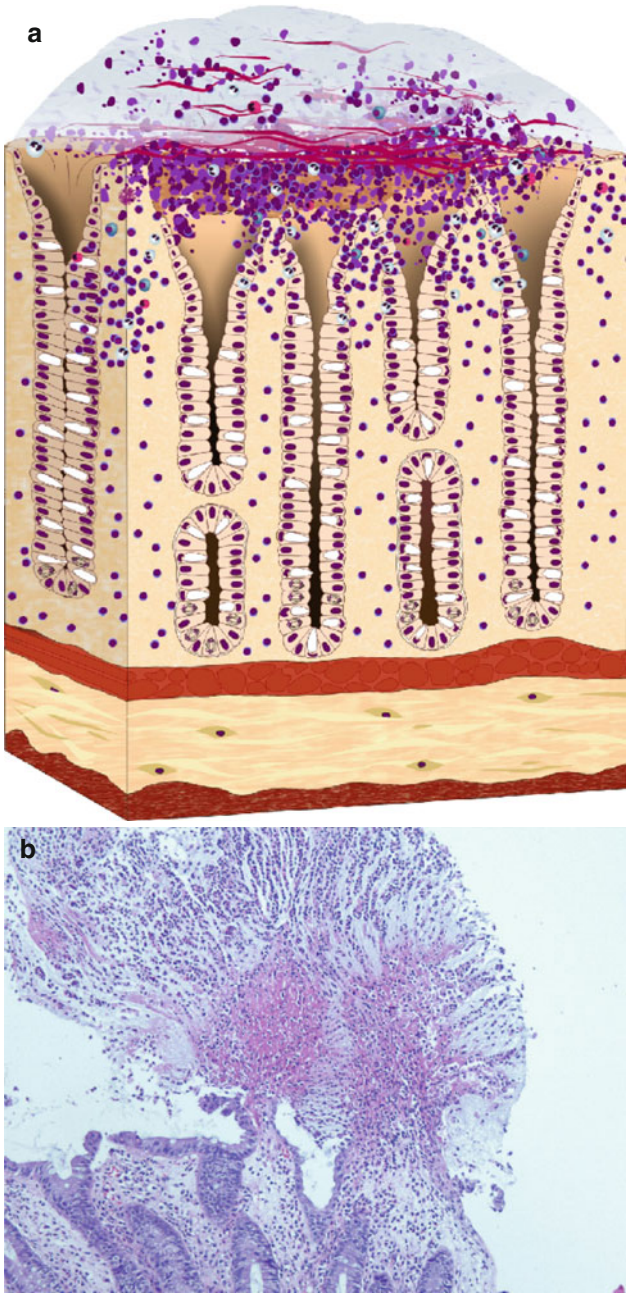
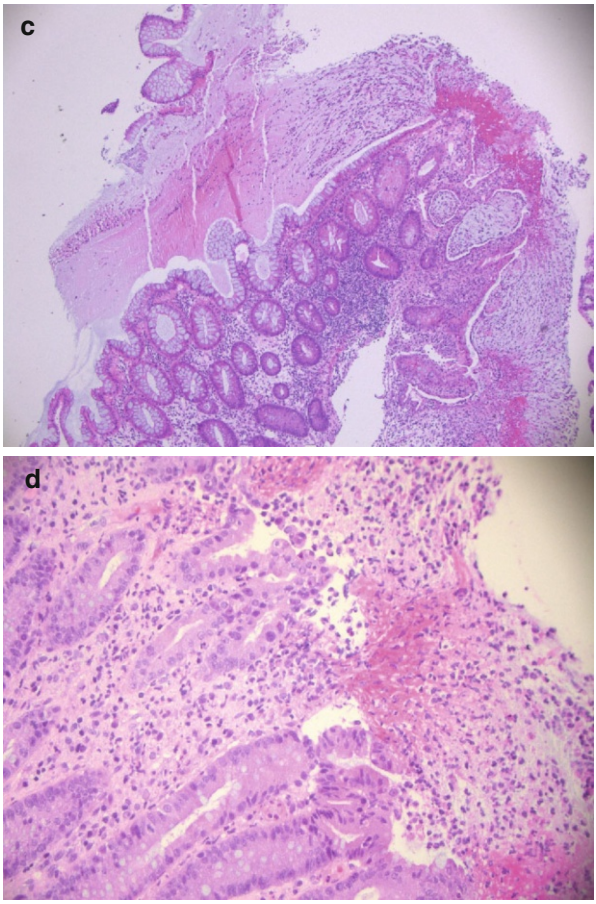


Fig. 3.10 The mucosa can be covered with a pseudomembrane composed of mucus, cellular debris, and inflammatory cells. This is particularly seen in pseudomembranous colitis as illustrated in the schematic representation (**a**) and in the microphotographs (**b**) (small magnification ×5) and (**c**) (×5) and (**d**) (×20)

Fig. 3.10 (continued)



(GVHD) but can also be seen in ulcerative colitis and drug-induced colitis (nonsteroidal anti-inflammatory drugs – NSAIDs), mycophenolate, chemotherapy for cancer). A variant of this are patients with ulcerative colitis, treated with drugs like mesalazine, when apoptosis may be the result of the disease or the drug or both.

In addition "Paneth cell metaplasia" can occur. Paneth cells are not usually present in the colon, except for the cecum and the ascending colon. In ulcerative colitis (and less commonly in Crohn's disease) Paneth cells appear in the crypts distal to the ascending colon. Their presence is thus highly suggestive of IBD, especially ulcerative colitis. In ulcerative colitis, Paneth cell metaplasia is associated with crypt distortion. It is not observed in biopsies obtained during the early onset of the disease. Paneth cell metaplasia is however not a specific feature for IBD or ulcerative colitis. It has been observed in up to 1.9 % in biopsies from non-IBD patients [24].

Metaplasia is defined as a reversible change in which one differentiated cell type is replaced by another differentiated cell type. It is considered to be an adaptive substitution by cells better able to withstand an adverse environment. Pyloric

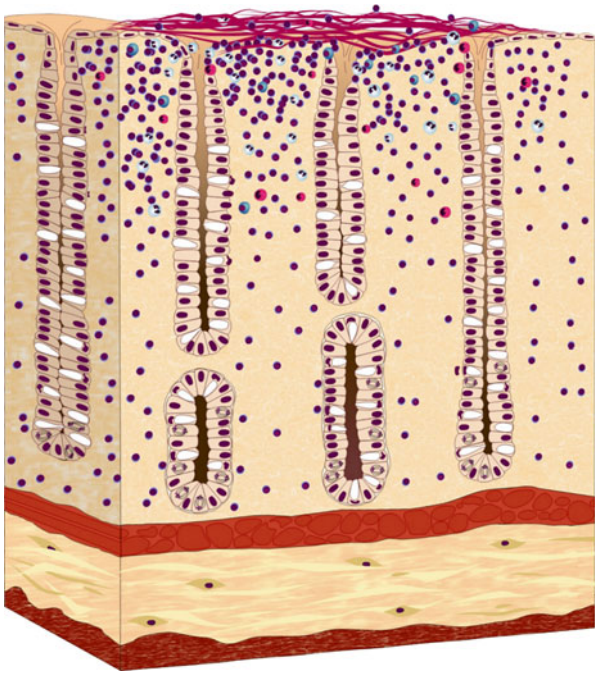


Fig. 3.11 An erosion is limited to the loss of surface epithelial cells and the upper part of the crypts

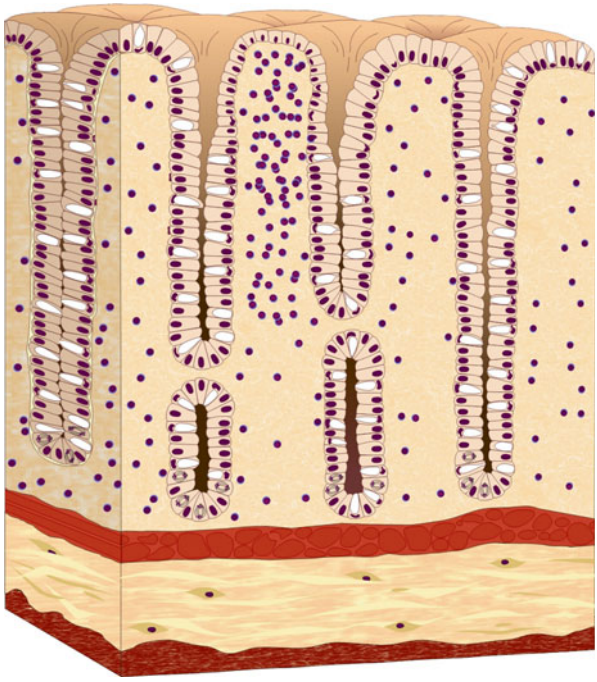


Fig. 3.12 The loss of surface epithelial cells can be compensated early by the appearance of flattened cells on the surface – a phenomenon called restitution. The process can be focal as shown in this drawing

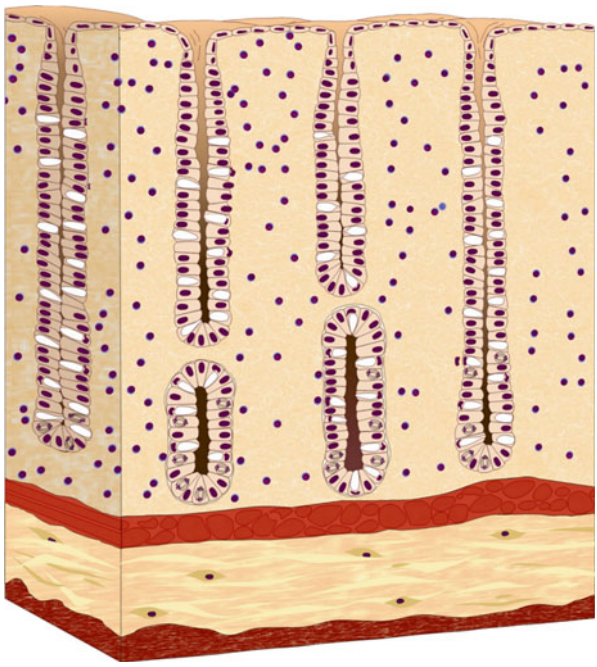


Fig. 3.13 Illustration of diffuse restitution

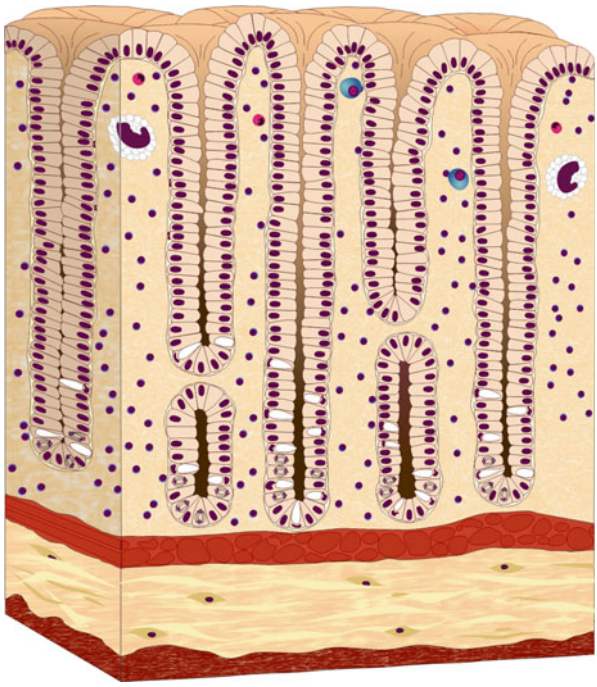


Fig. 3.14 Mucin depletion is characterized by loss of goblet cells and mucin secretion. This is also a hallmark of restitution

gland metaplasia (PGM) (synonyms: pseudopyloric gland metaplasia; mucus gland metaplasia) of the terminal ileum is a feature indicative of chronic mucosal inflammation, commonly related to mucosal ulceration and repair. The lesion can be observed in 2–27 % of ileal biopsies from patients with Crohn's disease. It can also be observed in biopsies from an ileoanal pouch. It is generally accepted that it has not been observed in backwash ileitis associated with ulcerative colitis. It can however occur in other diseases than Crohn's and has been reported for instance in ileal tuberculosis. It is rare in the colon (Fig. 3.15). Using immune histochemistry, lysozyme has been detected in PGM. The development of PGM has been explained by the "ulcer-associated cell lineage (UACL)" a pathway of gastrointestinal differentiation of importance in the natural healing of ulcer disease [25].

Hyperplasia of endocrine, argentaffin cells has been described in ulcerative colitis.

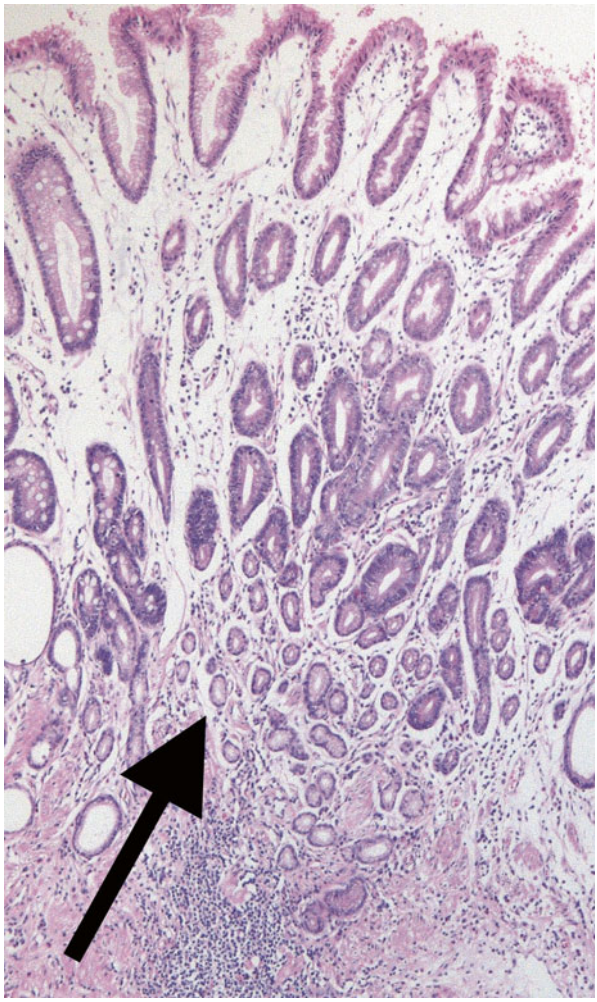


Fig. 3.15 Microphotograph illustrating pseudopyloric gland metaplasia in the colon (*arrow*). This phenomenon is more common in the terminal ileum

3.4 Changes in the Lamina Propria

The increased density of lymphocytes and plasma cells, associated with higher numbers of histiocytes and eosinophils, is a feature of all types of colorectal inflammation. B lymphocytes are transformed into mature plasma cells becoming visible in abundance after 7–10 days following the initial inflammatory response. The increased density has been described as "a subjective abnormal" "infiltrate" [4], a "prominent" increase (assessed by widening of the intercryptal space [26] or "hypercellularity" [6]. The increase is however difficult to assess. Furthermore, increased lamina propria cellularity may be absent in quiescent ulcerative colitis, following treatment or in the natural course of the disease and in immune-suppressed patients [2, 15, 27]. Increased lamina propria cellularity may also persist in "infectious colitis" after appropriate treatment. Associated mild increase of inter-epithelial lymphocytes can be found in postinfectious colitis (Fig. 3.16) [28].

The presence of a predominantly chronic (= mononuclear/lymphocytes and plasma cells) inflammatory cell infiltrate in the absence of epithelial cell alterations or architectural distortion and multiple basal lymphoid aggregates (Fig. 3.17) or plasma cells (Fig. 3.18) immediately above the muscularis mucosae can be seen in a variety of situations.

In the absence of sufficient clinical data or distinctive histological features further classification into specific etiologic types of colitis may not be possible [20, 29]. The presence of (foamy) macrophages (Fig. 3.19) might indicate healing following previous damage or residual colitis [30]. Increase in density and redistribution of the

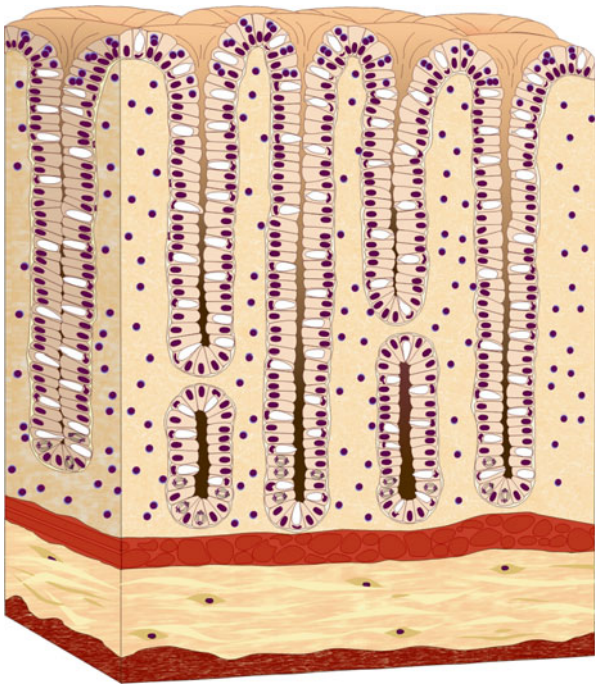


Fig. 3.16 Inflammation can be associated with increased epithelial lymphocytosis. This phenomenon is characteristic for lymphocytic colitis but can occur in other conditions such as a late phase of infectious colitis or chronic idiopathic inflammatory bowel disease

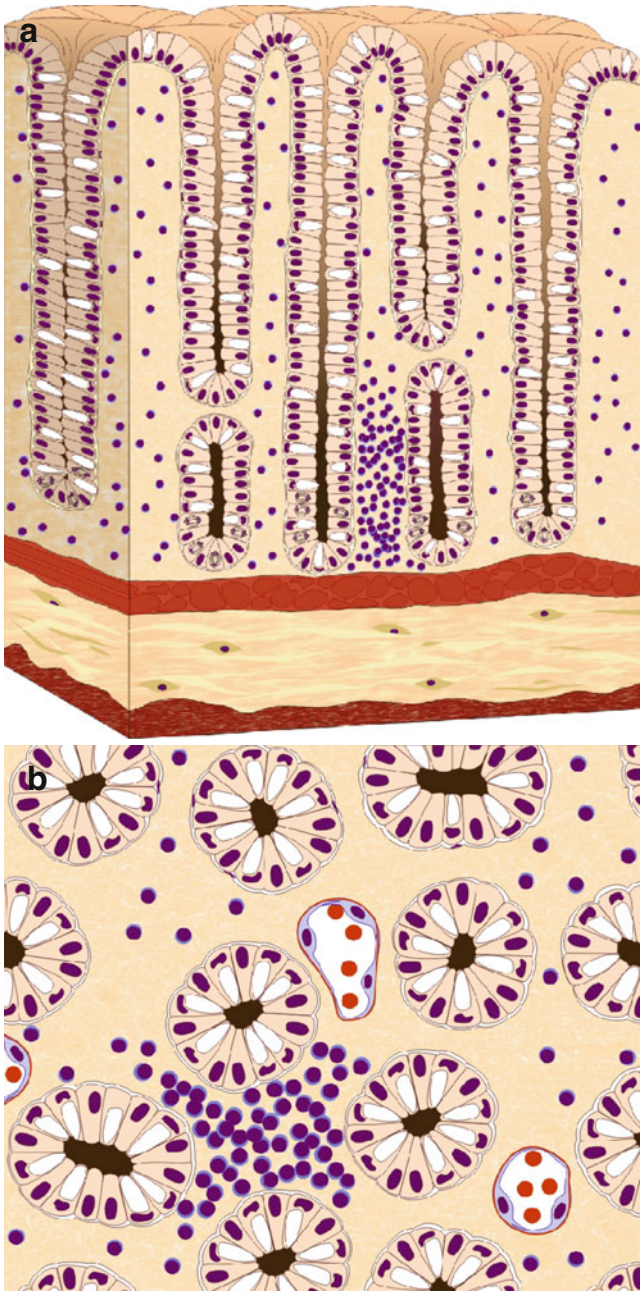


Fig. 3.17 (**a**, **b**) Presence of deep focal aggregates of lymphocytes can be normal or part of inflammation

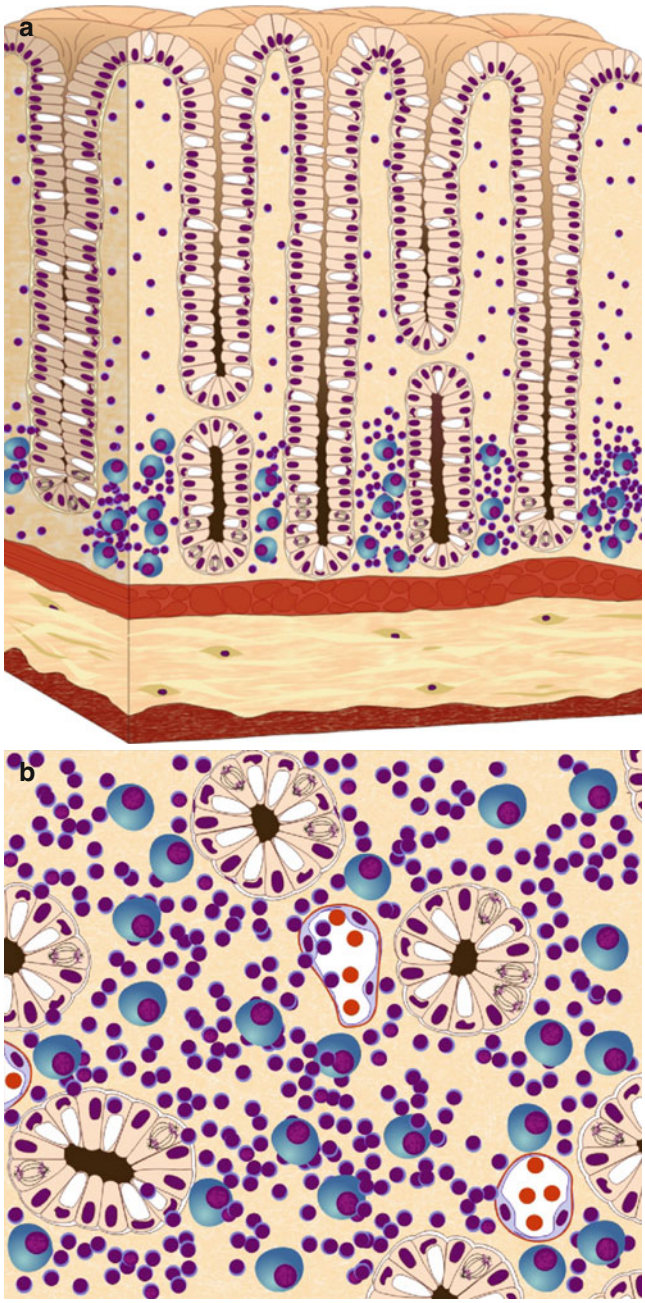


Fig. 3.18 (**a**, **b**) Multiple basal lymphoid aggregates are considered abnormal. They can occur in chronic idiopathic inflammatory bowel disease (and they can be very prominent in diversion colitis)

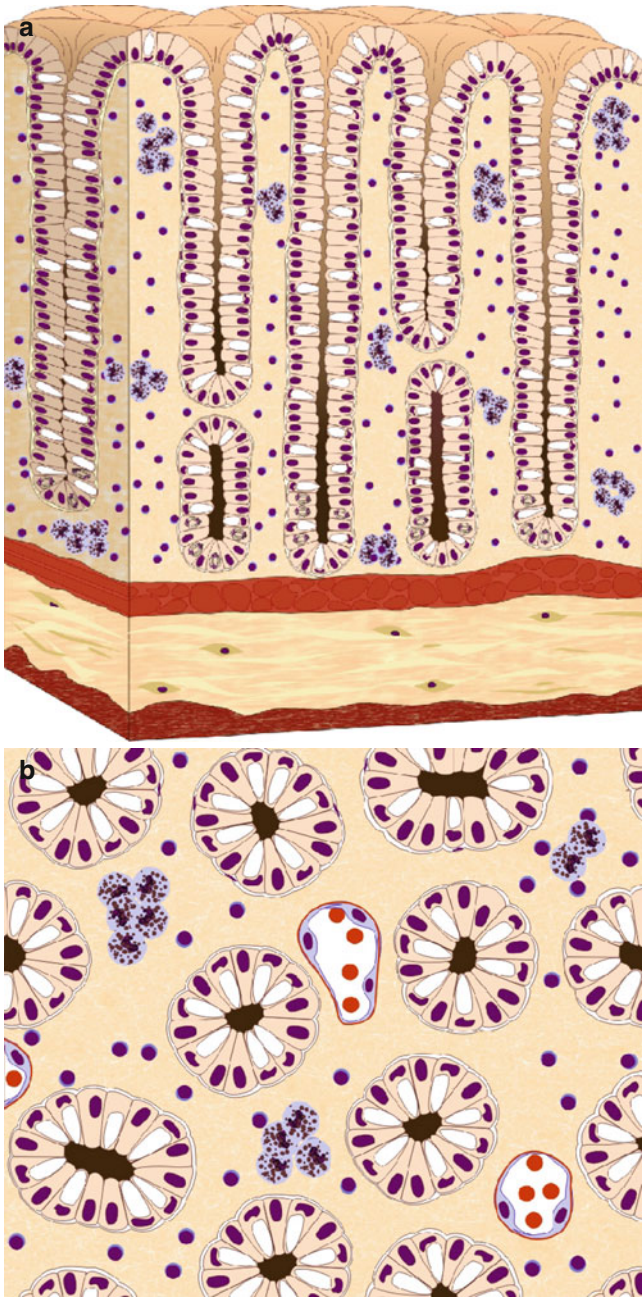
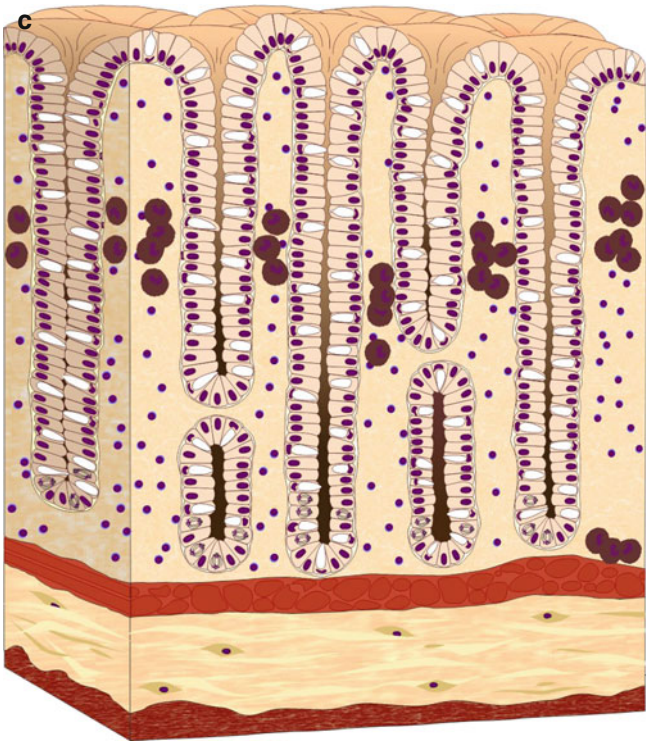


Fig. 3.19 (**a**–**c**) The presence of transmucosal foamy macrophages is a common finding. It has been linked to previous damage (**a**, **b**). Pigmented macrophages are linked to abuse of anthraquinones and epithelial cell apoptosis (**c**)

Fig. 3.19 (continued)



cellular infiltrate could indicate chronic idiopathic inflammatory bowel disease (IBD). The patchy (Fig. 3.20) and diffuse increases (Fig. 3.21), especially when transmucosal (Fig. 3.22), are equally potential indicators of IBD. Such a pattern can be seen in resolving infections, complicated diverticular disease, and drug-induced colitis, but may include Crohn's disease. However, it is impossible to make a positive diagnosis in these circumstances, although in a patient with known Crohn's disease, the lesions may well represent local involvement.

Basal plasmacytosis (synonyms: subcryptal plasma cells [6] plasmacytosis with extension in the base of the mucosa [11], accumulation of plasma cells at the base of the mucosa separating the base of the crypts from the muscularis mucosae [9]) is defined either as the presence of plasma cells around (deep 1/5th of the lamina propria) (Fig. 3.23) or below the crypts, alongside, or penetrating the muscularis mucosae. The lesion can be focal or diffuse (Fig. 3.24) [31]. In a study of full series of colonic biopsies, basal plasmacytosis was present in at least one anatomical segment in 66 % of cases examined for colitis within 4 weeks after the start of the symptoms. It was always present in patients with IBD, whereas it was sparsely found (8.7 %) in patients with other types of colitis. Basal plasmacytosis in biopsies of three or more segments of the colon had more than 80 % probability for a patient to be classified as IBD. With more than 4 segments, the probability of CD was less

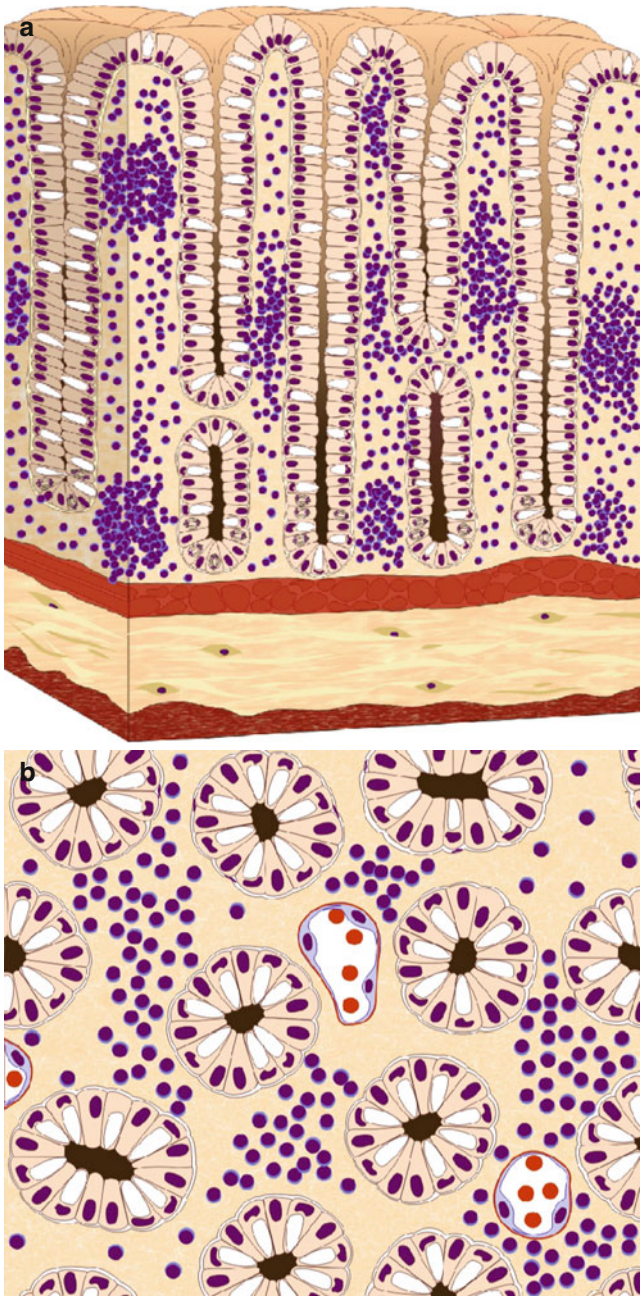


Fig. 3.20 (**a**, **b**) Illustration of the presence of multiple lymphoid aggregates showing a patchy distribution. While these features point to inflammation, they are not specific for a precise condition

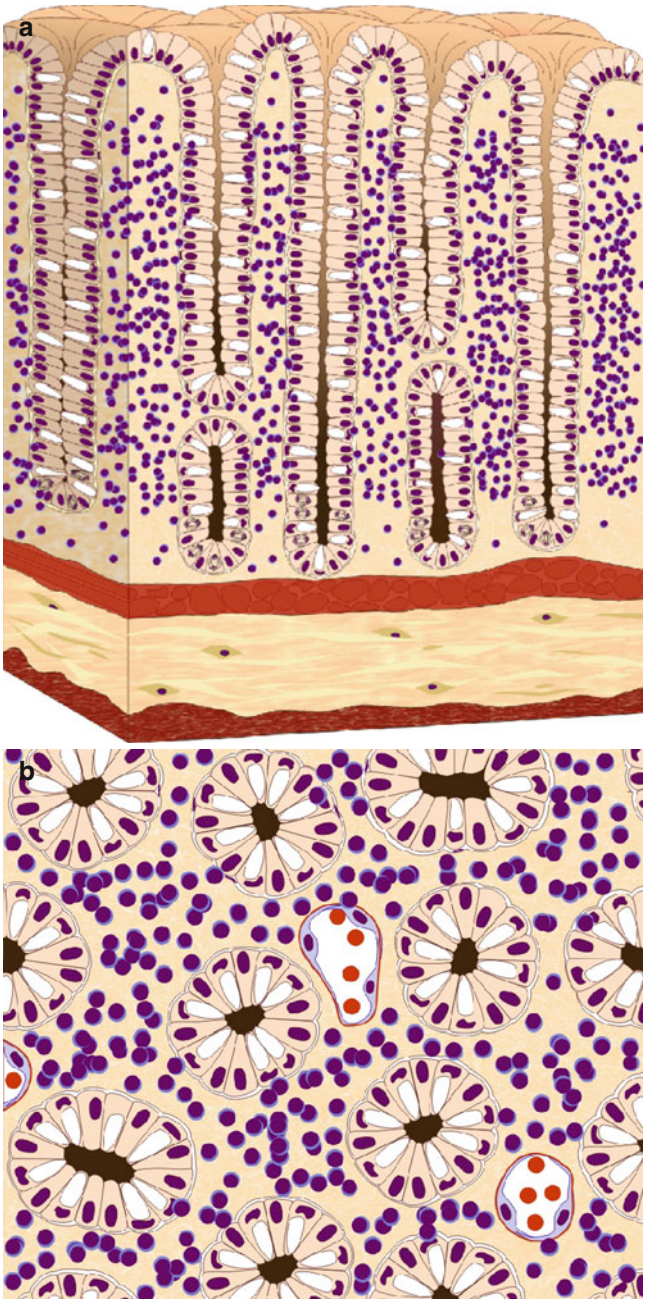


Fig. 3.21 (**a**, **b**) Illustration of lateral diffuse spreading of lymphocytes

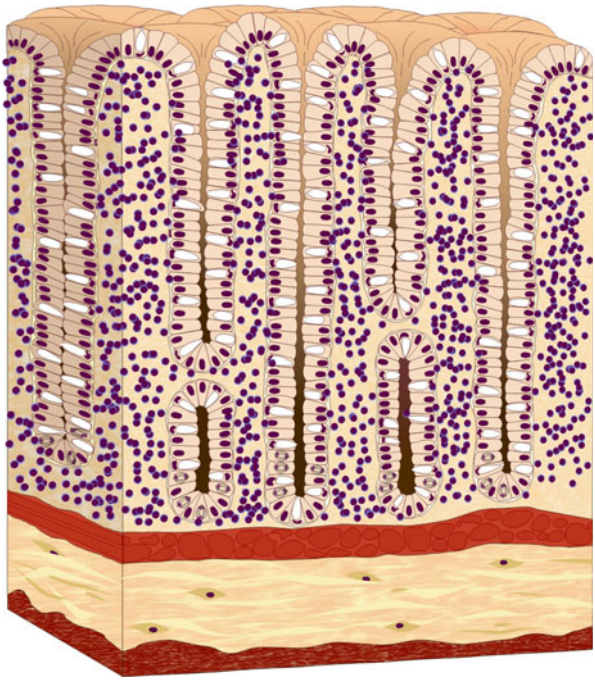


Fig. 3.22 Transmucosal extension of lymphocytic infiltrate

than 20 % and UC was more likely. In CD, the distribution of basal plasmacytosis was more right sided [32]. The subcryptal location of the cells is however not always present [3, 6]. Basal plasmacytosis may vary during the evolution of the disease. In one prospective study looking at the evolution in time of the lesions in patients with IBD, it was noted that focal or diffuse basal plasmacytosis increased from 38 % in the group with an interval of 1–15 days between onset of symptoms and biopsy to 89 % in those who presented in between 121 and 300 days after onset of symptoms [3].

Basal lymphoid aggregates are nodular collections of lymphocytes between the crypt base and the muscularis mucosae without reactive centers (Fig. 3.25). At least two aggregates are needed to be considered abnormal (Fig. 3.26) [2, 15, 16]. Their presence favors a diagnosis of IBD although it is of limited value in early-onset disease [4, 20].

The increase of lamina propria cellularity has been divided by some authors into two categories according to the composition of the infiltrate: an increase in neutrophils alone (Fig. 3.27) or an increase in both round cells and neutrophils (Fig. 3.28). The latter can be called a change in composition of the infiltrate, as neutrophils alone are normally not present. Neutrophils can involve the surface epithelial cells and be associated with surface cell damage and disruption. They can induce cryptitis (Fig. 3.29) with migration of neutrophils through the crypt epithelium and produce

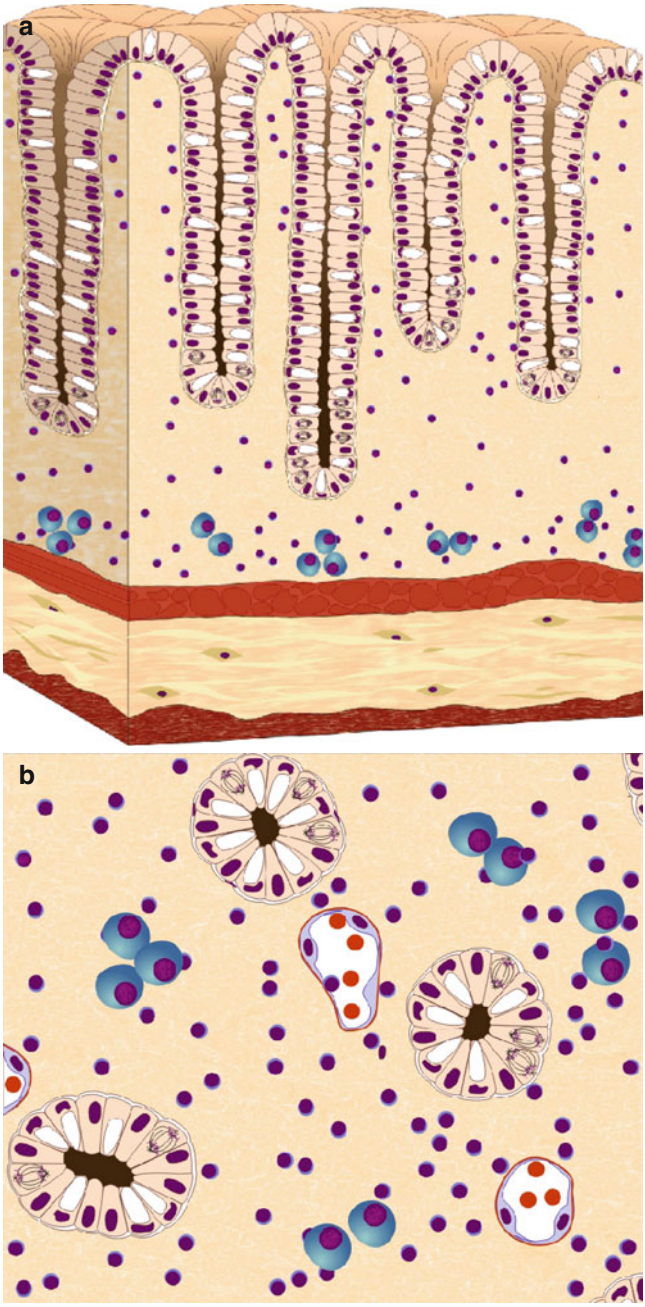


Fig. 3.23 (**a**, **b**) Presence of focal plasma cells in a basal position in a mucosa showing also architectural abnormalities – shortening and loss of crypts

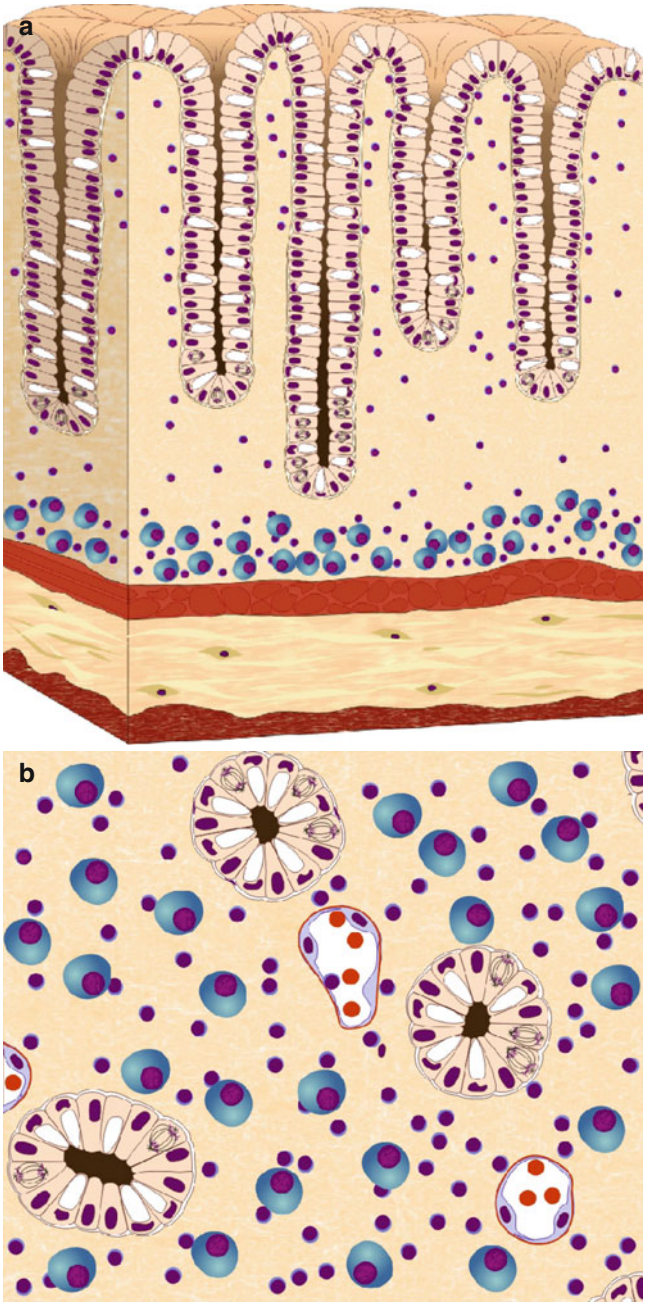


Fig. 3.24 (**a**, **b**) Basal diffuse plasmacytosis illustrated in a drawing of a perpendicular section (**a**). This feature cannot be assessed properly in transverse sections (**b**)

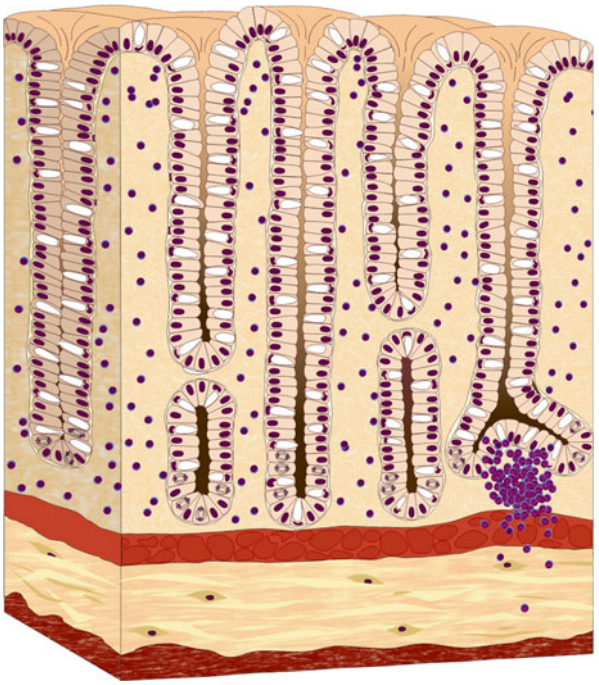


Fig. 3.25 Lymphoid nodules or aggregates can be present in a normal biopsy especially in a basal position. They should not be considered as a manifestation of inflammation

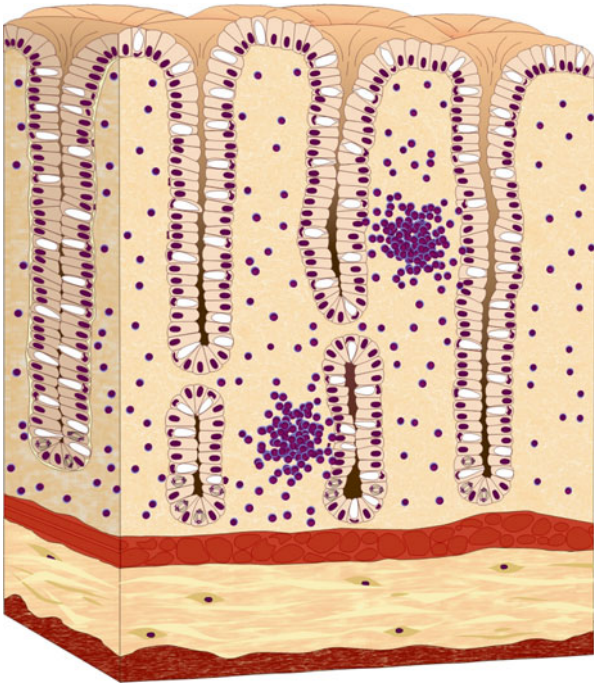


Fig. 3.26 An increase of lymphoid aggregates can indicate inflammation, but on itself it is not a sufficient or reliable feature

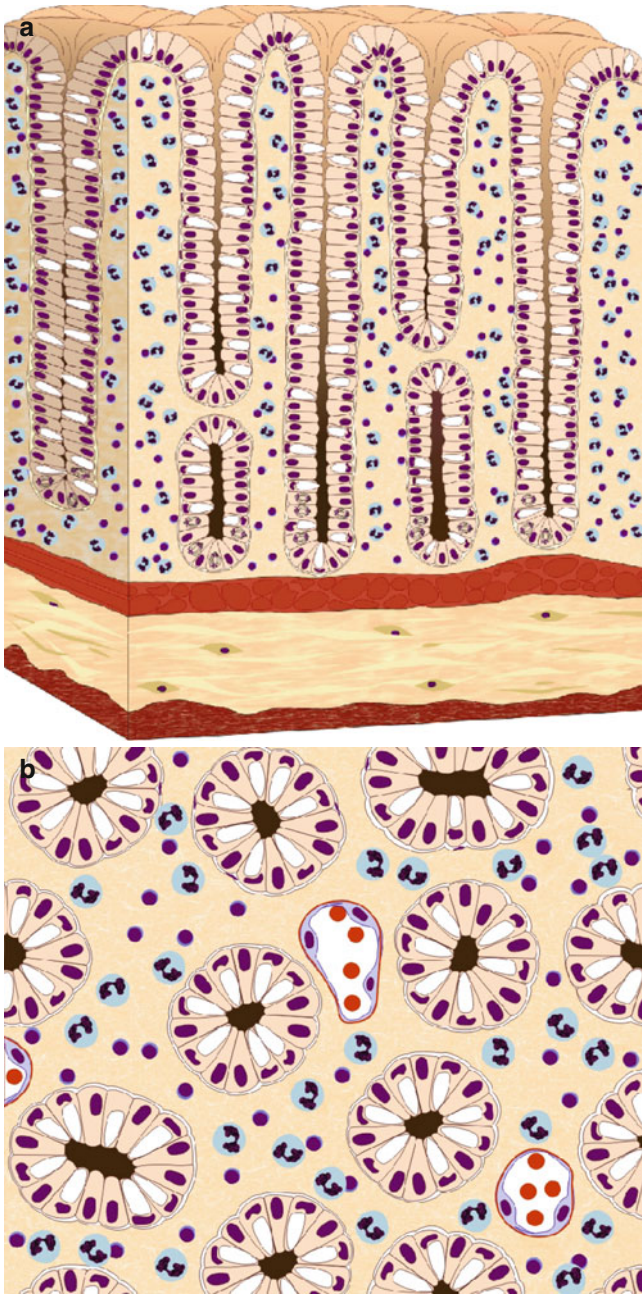


Fig. 3.27 (**a**, **b**) Transmucosal presence of neutrophils. These cells are normally within capillaries. In the lamina propria they indicate active inflammation. Whether an increase of neutrophils within capillaries with signs of margination is also indicating inflammation has not been established although some investigators use this also as a sign

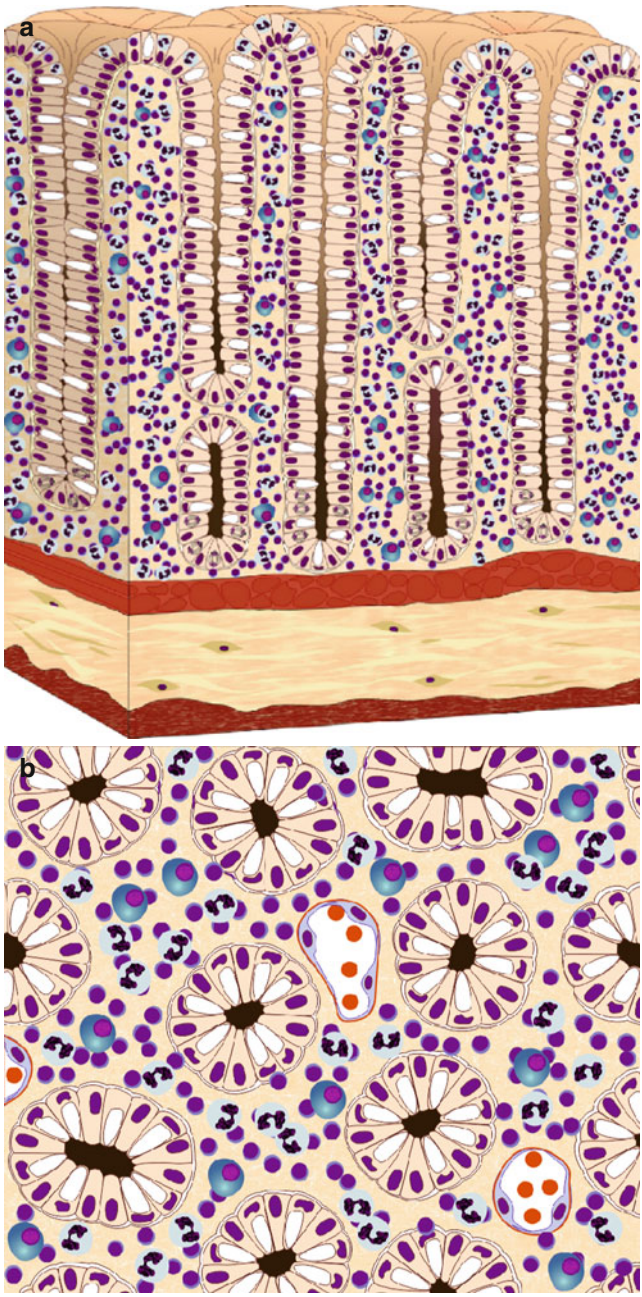


Fig. 3.28 (**a**, **b**) Active inflammation is defined by the presence of neutrophils and plasma cells and epithelial cell alterations

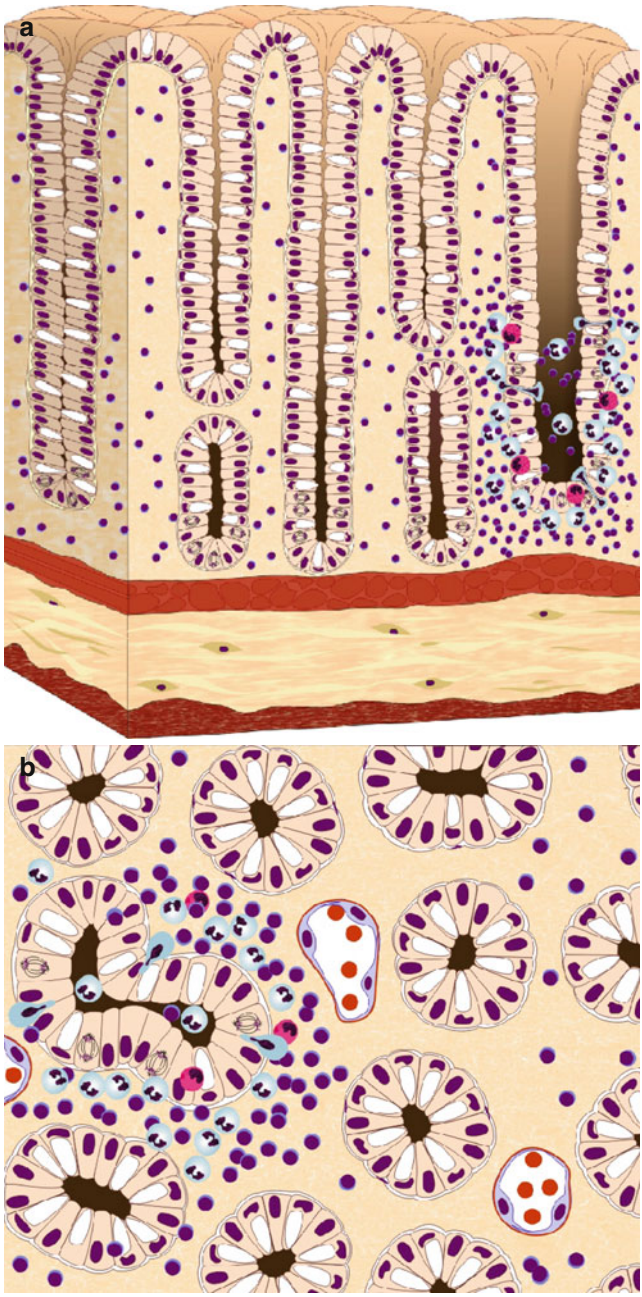
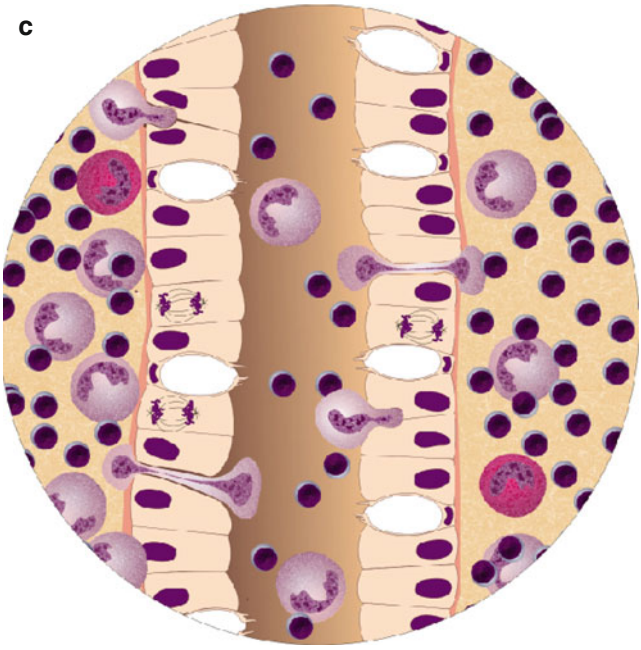


Fig. 3.29 (**a–c**) In active inflammation neutrophils can invade the epithelial cells lining the tubular glands or crypts and induce cryptitis. A detail of this phenomenon is illustrated in drawing c

Fig. 3.29 (continued)



crypt abscesses (Fig. 3.30) and crypt disruption or destruction (Fig. 3.31). General or widespread crypt epithelial neutrophils favor a diagnosis of ulcerative colitis but fewer crypt abscesses and cryptitis can also be present in infectious colitis [6]. Neutrophils are not present in inactive or quiescent disease.

Eosinophils can be part of the increased density of the cellular infiltrate or the increase can be overwhelming in primary eosinophilic colitis (Fig. 3.32). Eosinophilic colitis, also called allergic colitis, is a heterogeneous disorder characterized by the presence of a dense eosinophilic infiltration that can be segmental or diffuse. It may affect children as well as adults. An intraepithelial position of eosinophils is most unusual and a sign of pathology. Three different types of eosinophilic disorders must be distinguished in the differential diagnosis: primary eosinophilic colitis, which belongs to the family of primary eosinophilic gastrointestinal disorders (EGID), secondary eosinophilic colitis including conditions such as celiac disease and IBD, and colitis in the framework of the hypereosinophilic syndrome (HES).

The term "granuloma" was introduced in pathology by Virchow in 1865 to describe well-circumscribed (organized) swellings (spherical structure) found in a number of chronic infectious diseases including tuberculosis and syphilis. He considered these at the time to consist of granulation tissue. Later authors indentified the large swollen epithelial-like cells which they called epithelioid cells. Metchnikoff

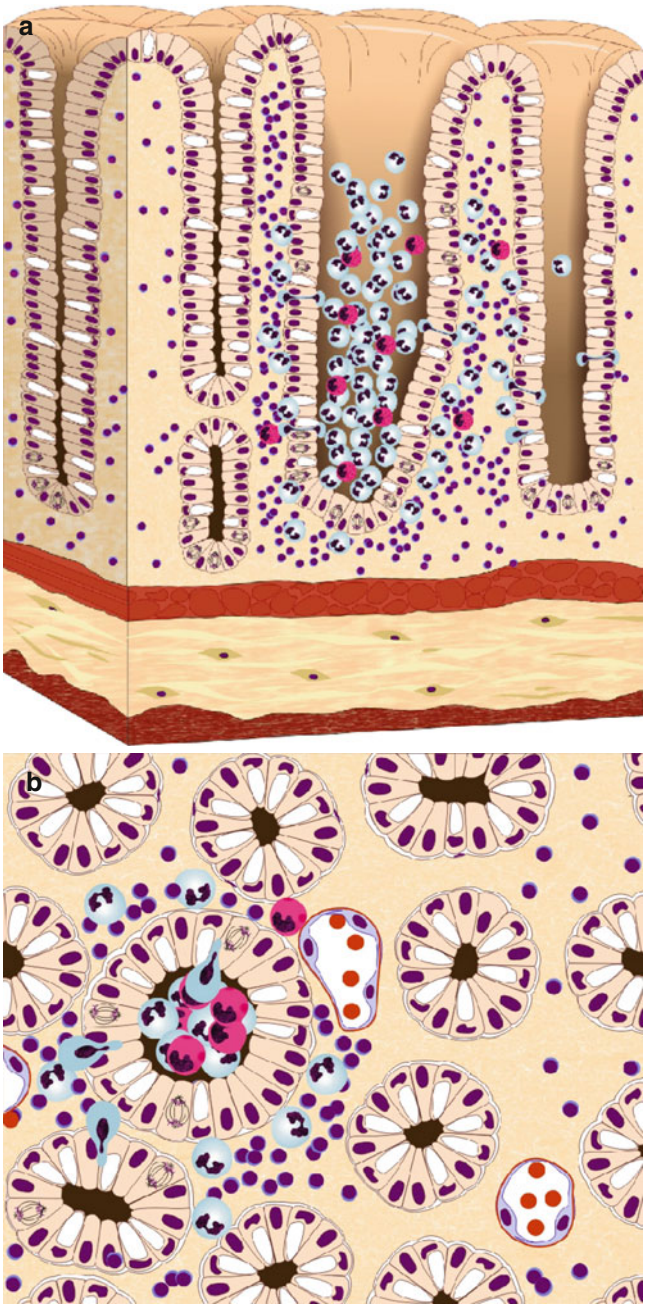


Fig. 3.30 (**a**, **b**) Crypt abscesses are characterized by the presence of neutrophils in the wall and the lumen of the crypts

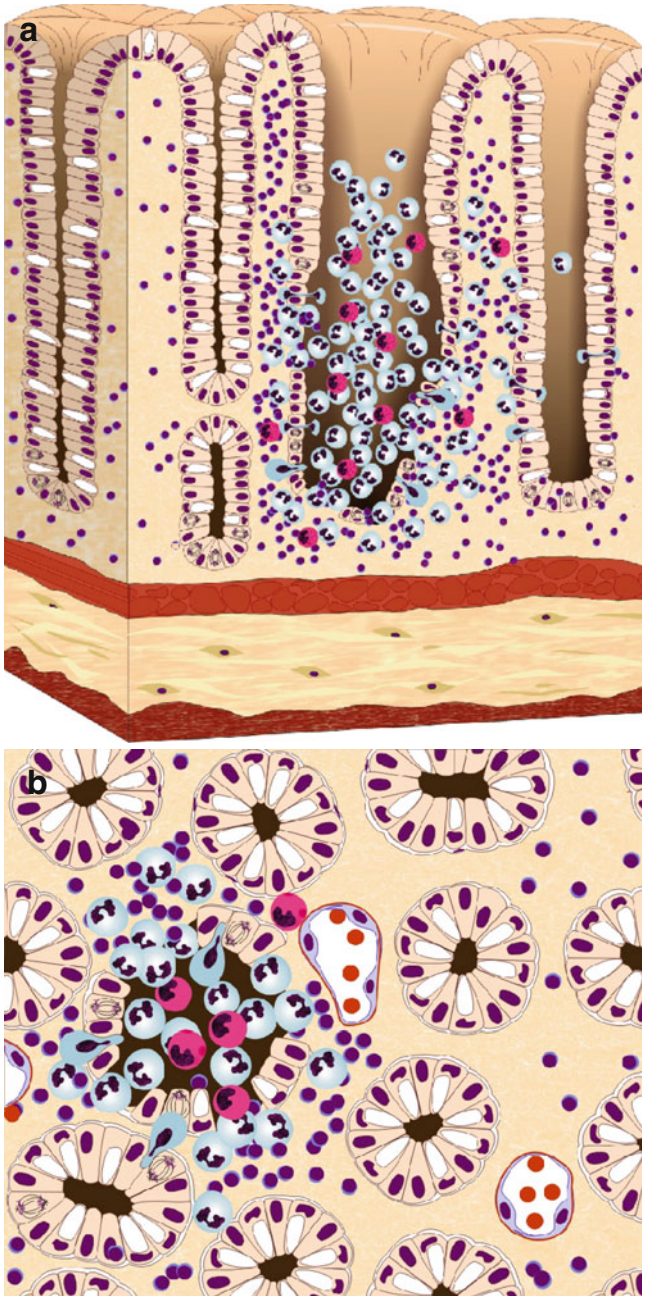


Fig. 3.31 (**a**, **b**) Crypt abscesses can lead to crypt destruction characterized by loss of continuity of the epithelial cells lining the crypts

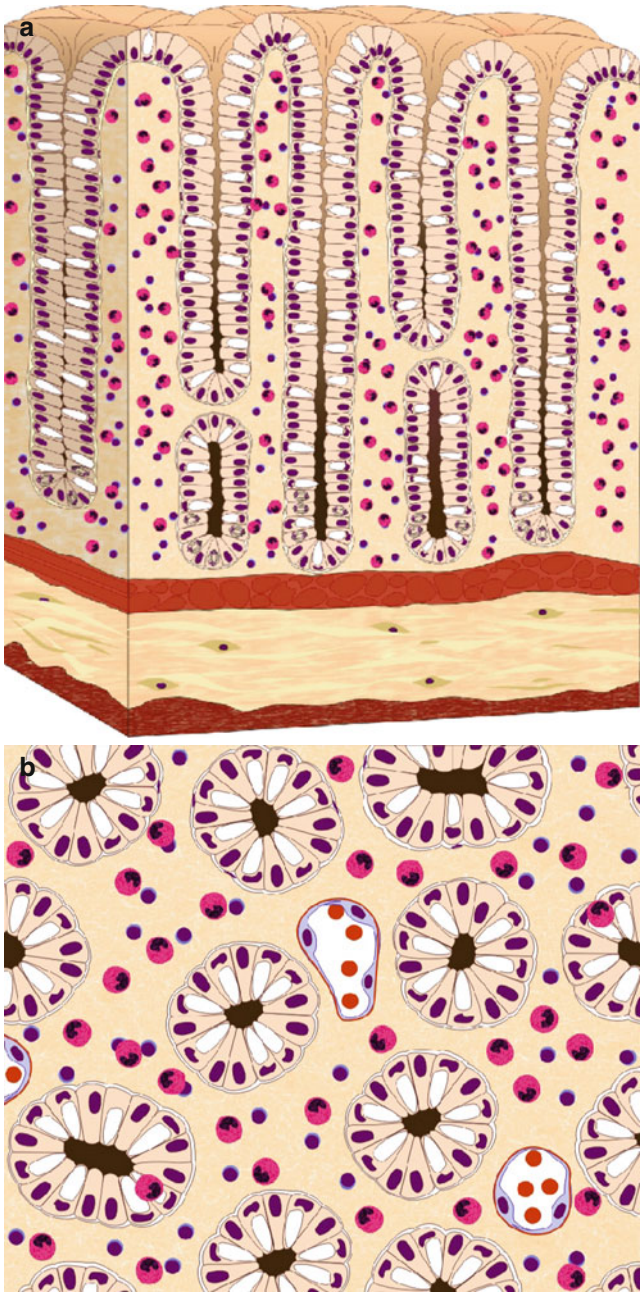


Fig. 3.32 (**a**, **b**) A transmucosal infiltrate of eosinophils can be observed in a variety of conditions including primary eosinophilic colitis and secondary to other diseases such as chronic idiopathic inflammatory bowel disease

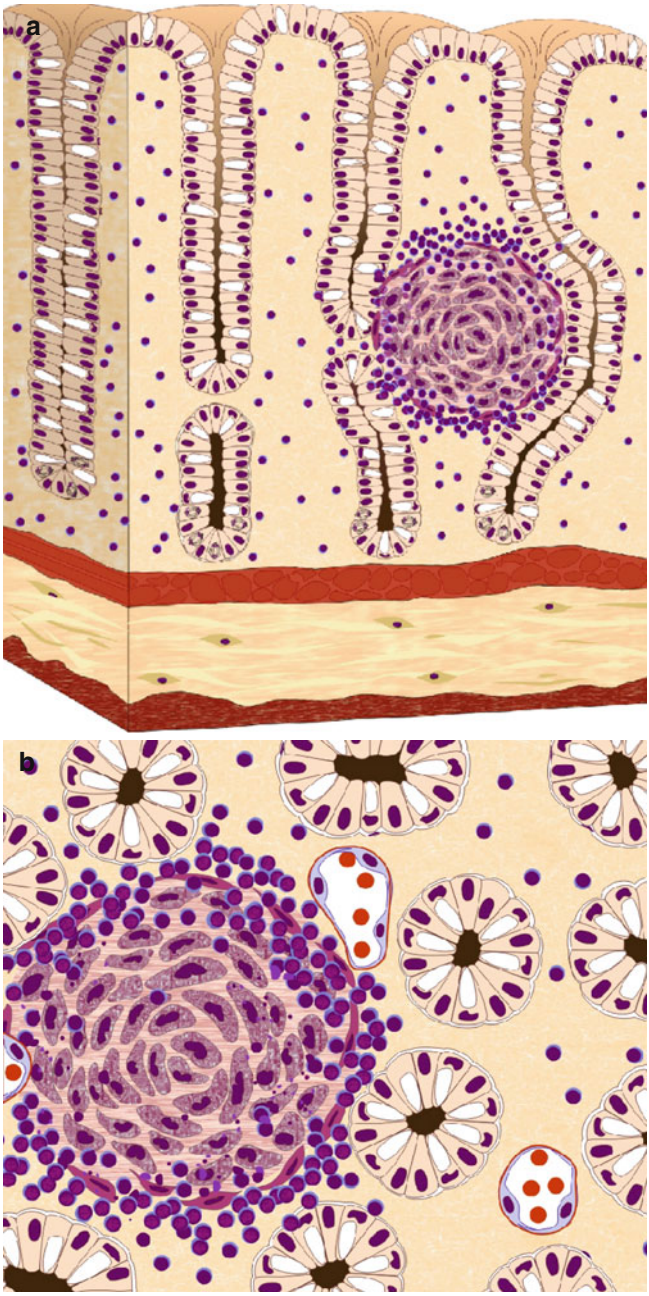


Fig. 3.33 (**a**, **b**) Granulomas are circular lesions composed mainly of epithelioid cells

in 1891 recognized that these were related to the cells that he called macrophages. Currently a granuloma is defined as a focal organized collection of cells of the mononuclear phagocytic series with or without other cell types (Fig. 3.33). They are dynamic structures composed of an organized collection of activated macrophages, including epithelioid and multinucleated giant cells, surrounded by lymphocytes.

Granulomas are observed in a variety of diseases, classically subdivided into immunologic and non-immunologic conditions. Immunologic granulomatous diseases include bacterial infections (mycobacterium, yersinia, leprosy, syphilis), parasitic infections (Schistosoma mansoni), and fungal infections (candida…); a number of conditions of unknown or poorly known etiology such as sarcoidosis and Crohn's disease; certain genetic disorders such as Blau syndrome (and its sporadic counterpart, early sarcoidosis) and chronic granulomatous disease; but also diseases induced by molecules such as beryllium and zirconium. In chronic granulomatous disease, a rare genetic immune deficiency, lesions can occur all over the gastrointestinal tract, but the colon is the most involved site. There are microgranulomas, pigmented macrophages, tissue eosinophilia, and chronic and/or acute inflammation [33]. Non-immunologic granulomas are observed in toxic conditions (silica, talc, starch), nontoxic conditions (plastic beeds) or subsequent to activation of C3 (C = complement) by kaolin. The morphology of granulomas can be variable. They can be compact or loosely arranged and confluent or not. The presence of epithelioid cells is an essential element. Other cells such as neutrophils, eosinophils, lymphocytes, and fibroblasts within or around the lesions are common. In some types, emperipolesis (the presence of an intact cell within the cytoplasm of another cell) can be present. Furthermore, granulomas can show caseating necrosis. Giant cells in granulomas can contain a variety of inclusions such as asteroid bodies (sarcoidosis and foreign body granulomas), Schaumann bodies, Hamazaki-Wesenberg bodies (Sarcoidosis), calcium oxalate, and cholesterol crystals [34]. Granulomas associated with crypt injury are less reliable features for a particular diagnosis as they may be the result of mucus leakage (Fig. 3.34).

Emperipolesis is derived from classic Greek for the description of a phenomenon whereby an intact cell is present within the cytoplasm of another cell. It is a feature of autoimmune hepatitis. Emperipolesis of CD4+ lymphocytes in giant cells can sporadically be found in biopsies from patients with Crohn's disease containing simple, isolated granulomas with subtle lymphocytic coronas and is associated with crystalline inclusions. In contrast, it is an important feature of the Blau syndrome, a condition. associated with gain-of-function mutations in nucleotide-binding oligomerization domain-containing protein 2 (NOD2) [35, 36].

3.5 Stromal Changes

Changes in basement membrane structure have been identified in colonic tissue from patients with collagenous colitis and ulcerative colitis. While collagenous colitis is mainly characterized by thickening of the membrane, in ulcerative

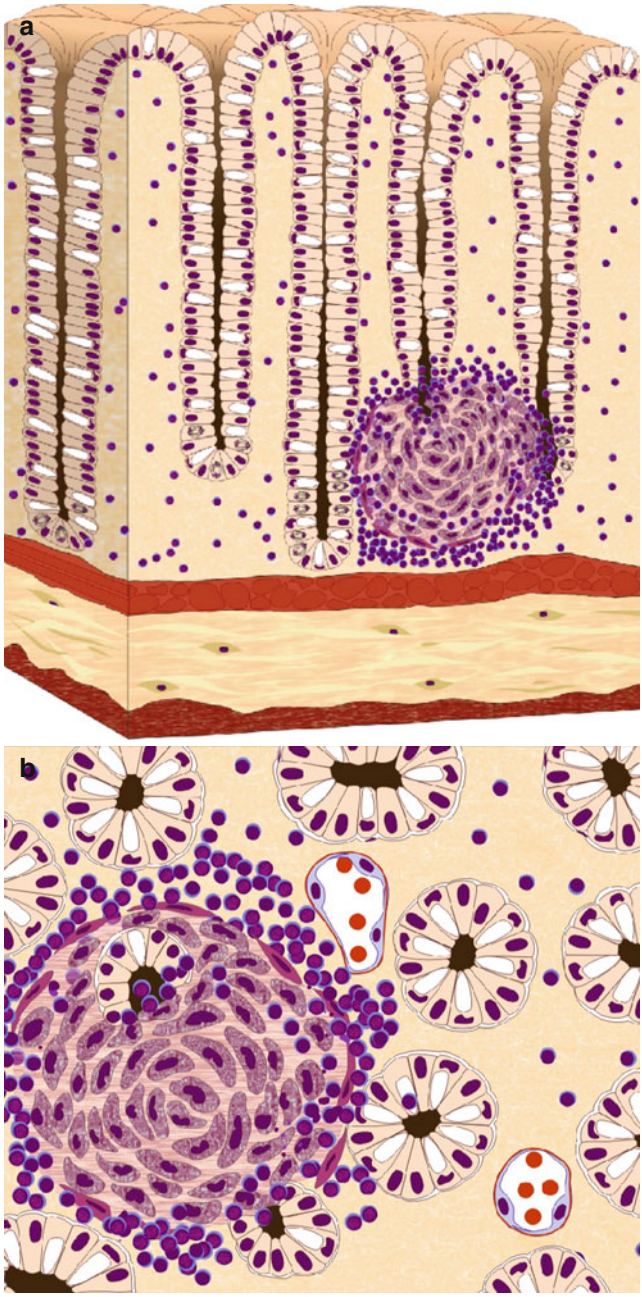


Fig. 3.34 (**a**, **b**) Pericryptal granulomas or granulomas associated with crypt destruction have less diagnostic value

colitis, loss of immune reactivity to laminin in the basement membrane is accompanied by an increase in collagen IV and V expression, ending with pericryptal (Fig. 3.35) or diffuse mucosal fibrosis (Fig. 3.36). These changes paralleled the severity of inflammation within individual patients [37]. Thickening can also be observed in diverticular disease and in biopsies from hyperplastic polyps. Tenascin may also be expressed in both IBD and collagenous colitis. The distribution of this molecule may help for the diagnosis. Whereas tenascin deposits within the intercryptal matrix are found in different forms of colitis, selective subepithelial accumulation of tenascin is mainly observed in collagenous colitis [38].

The muscularis mucosae may become irregular, disappear, or show a diffuse thickening. In the lamina propria which is usually devoid of smooth muscle tissue, ascending muscle fibers can be observed in between the crypts (Fig. 3.37).

The extracellular matrix can show edema or "hyaline changes," which is a term used for the description of a homogeneous, translucent aspect.

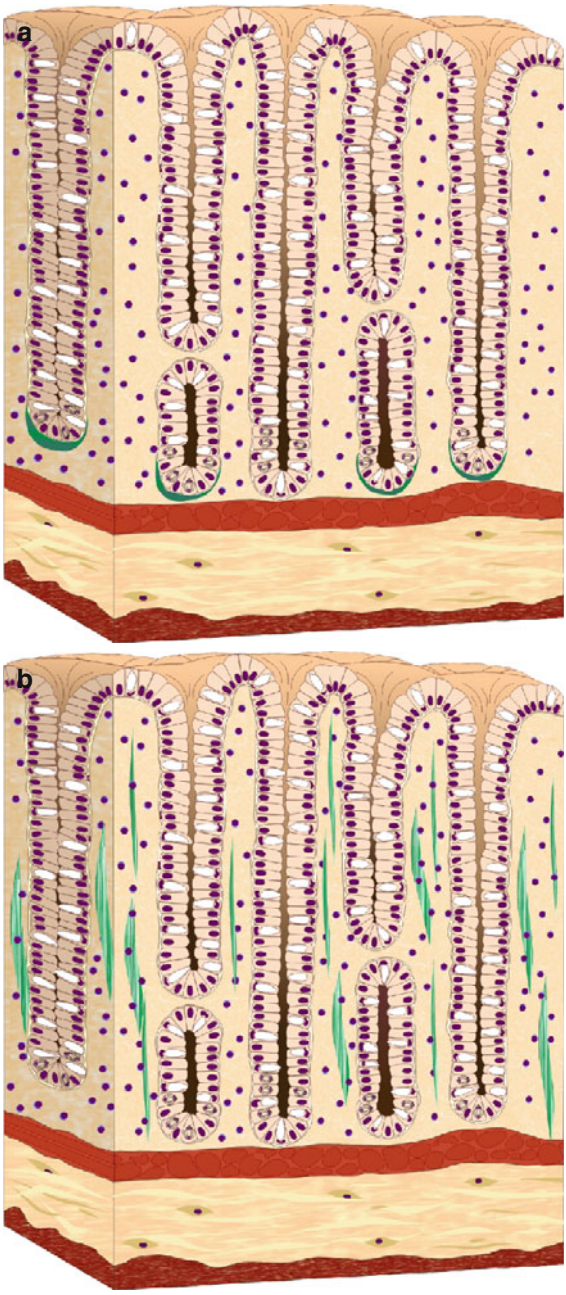


Fig. 3.35 (**a**, **b**) Chronic inflammation can result in or be associated with pericryptal fibrosis (**a**) and mucosal fibrosis

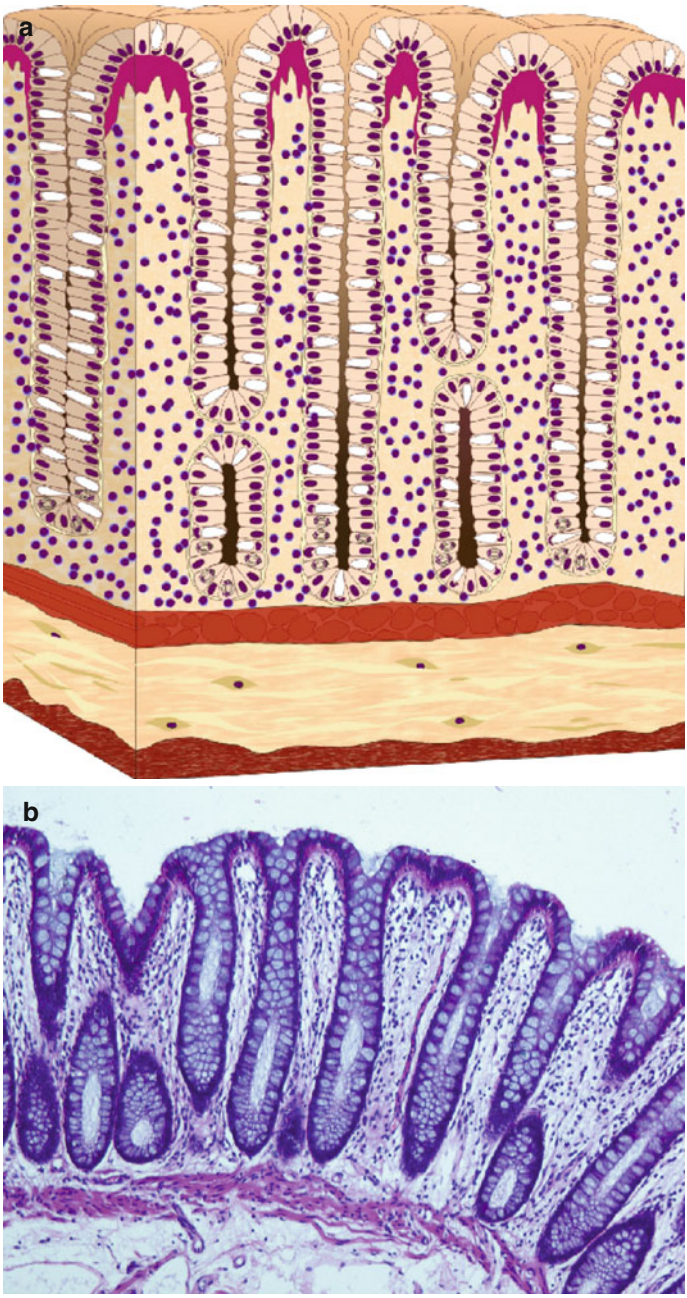


Fig. 3.36 (**a**, **b**) Thickening of the subepithelial layer is illustrated in the drawing (**a**) and the microphotograph (×20) (**b**)

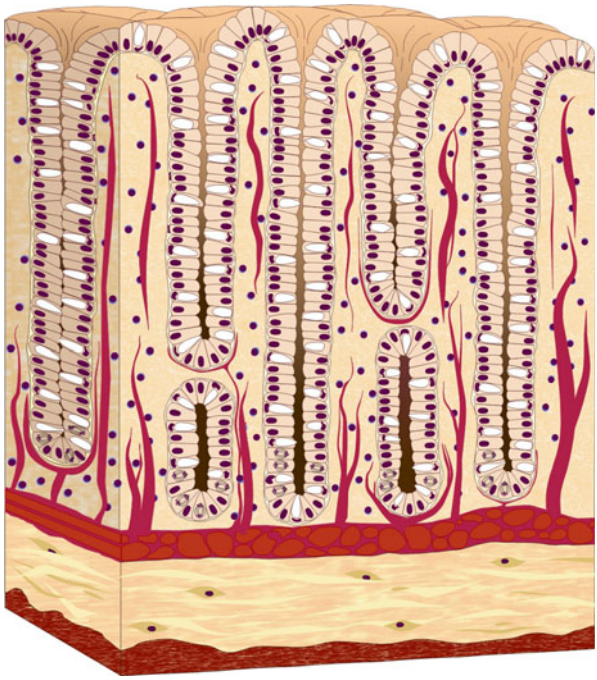


Fig. 3.37 Smooth muscle cells proliferation (in *red*) in the lamina propria. Fibromuscular obliteration of the lamina propria is characteristic for the prolapse syndromes

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Chapter 4
Dysplasia

Karel Geboes, Maria Leo, and Sonia Nemolato

Abstract Ulcerative colitis and Crohn's disease are associated with an increased risk for developing colorectal cancer (CRC). The size of the risk is not exactly known. A cumulative incidence of below 1 % in the first 8–10 years, rising in annual increments of 0.5–1.0 % thereafter to reach 5–10 % after 20 years has been reported. In a population-based study from Canada, Crohn's disease and ulcerative colitis had similar increased risk ratios compared to population controls of 2.6. Independent risk factors for CRC in ulcerative colitis are the duration of the disease and the anatomic extent. Additional risk factors include primary sclerosing cholangitis (PSC), a positive family history or CRC, and the degree of endoscopic and histologic activity. As early as 1949, Warren and Sommers postulated that, like for sporadic CRC, a structural precursor to carcinoma existed in ulcerative colitis [1]. In 1967, microscopic "precancerous" changes were described in the mucosa of colectomy specimens of patients operated for carcinoma in ulcerative colitis [2]. Similar changes were reported in Crohn's disease. The identification of such early lesions, called dysplasia, opens the possibility for early detection and secondary prevention of colorectal cancer with surveillance programs for patients with IBD. This implies however a precise definition of "dysplasia" and identification of reliable criteria for the detection of dysplasia during colonoscopy and microscopy.

Keywords Dysplasia • Ulcerative colitis • Crohn's disease • Dysplasia-definition • Dysplasia-morphologic changes • Dysplasia-diagnosis • Dysplasia-grading of • Dysplasia-histology of • Dystrophic goblet cells • Dysplasia-surveillance • Flat dysplasia • Polypoid dysplasia • DALM • ALM

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4.1 Definition

The morphological term "dysplasia" is derived from classic Greek. The word consists of two elements: "dys" which is "bad" or "wrong" and "plasis" which means "form." The exact meaning is thus "malformation." It was introduced in pathology around 1925. Dysplasia can refer to a malformation that can be identified macroscopically and/or microscopically. A malformation can be a congenital (hereditary or not) or acquired abnormality. In general pathology, dysplasia has been and still is being used both for congenital and acquired malformations. This is also true to a certain extent for gastrointestinal pathology. An example of the latter is "tufting enteropathy," sometimes called "intestinal epithelial dysplasia." This is a congenital pediatric diarrheal disease, characterized by severe malabsorption. It is a genetic disorder with an autosomal recessive inheritance pattern. The disease is caused by defects in the EPCAM (epithelial cell adhesion molecule) gene. Microscopy identifies lesions such as villous atrophy and disorganization of the surface epithelium with focal crowding resembling tufts [3]. An example of an acquired malformation is "vascular ectasia," formerly called "angiodysplasia." If acquired, the nature of the dysplastic transformation can be regenerative (due to healing and repair following damage) or neoplastic (degenerative) [4].

When used for the description of microscopic epithelial changes, dysplasia is often defined as a lesion "in which part of the epithelium is replaced by cells showing varying degrees of "atypia." However, this definition only refers to cytological abnormalities ("atypia"), while "dysplasia" encompasses also changes in architecture and aberrant differentiation [5]. Changes in architecture and cytology such as the appearance of immature cells (altered differentiation) are phenomena that occur during healing and repair. Thus, these regenerative changes may also be considered as dysplasia according to this definition. Yet, these alterations have no clinical consequences.

A more precise definition of "dysplasia" in inflammatory bowel diseases has therefore been proposed by an international "Inflammatory Bowel Disease-Dysplasia Morphology study group." According to this definition, IBD-associated dysplasia is used for lesions showing "unequivocal, non-invasive (i.e. confined within the basement membrane), neoplastic transformation of the epithelium excluding all reactive changes" [4]. This definition stresses the precancerous nature and origin of the lesion. The identification still relies upon the recognition of morphological features resulting from cytological and architectural changes in routinely processed and hematoxylin and eosin-stained sections.

Tumors grow because the homeostatic control mechanisms that maintain the appropriate number of cells are defective leading to an imbalance between cell proliferation and cell death and expansion of the cell population. The lack of growth arrest will prevent normal maturation and differentiation. The morphological changes of neoplastic epithelium will reflect the abnormal proliferation and cell death and abnormal maturation. They affect the nuclei and cytoplasm of cells and the architecture of crypts. Nuclei get first elongated, enlarged, slightly hyperchromatic, and crowded with some stratification. Mitotic figures are common. Further on in the spectrum nuclear stratification is increased. The nuclei get more polymorphic and start to show loss of polarity (long axis of the nucleus not perpendicular to the basement membrane). The cytoplasm shows depletion of mucin as a sign of impaired differentiation

and dark basophilic staining because of accumulation of RNA. The number of crypts increases, and they become irregular. Normal cell maturation from base to surface disappears. Changes in crypt architecture can get more conspicuous and involve branching, budding, and "back to back" orientation. The lesions can thus be arrayed in stages of increasing abnormality. The IBD-Dysplasia Morphology study group of the National Foundation for Ileitis and Colitis classified IBD-associated dysplasia as negative, indefinite, or positive. The latter category is subdivided into low grade and high grade. The two-grade classification appears to be reproducible, although in general the agreement is better for high-grade dysplasia [6].

4.2 Histology of Dysplasia

Overall, the histological features of genuine IBD-associated dysplasia resemble those of tubular adenomas in non-colitic patients and include cytological criteria such as variations in nuclear position, size, and chromatin pattern and architectural crowing and distortion [6, 7]. Crowding of glands may already appear at low magnification and may contrast with the atrophic aspect of the mucosa in quiescent IBD. A villous, hypermucinous mucosa and serrated aspect of glands represents a second type of lesion with increased risk for developing colorectal cancer and is associated with the serrated neoplasia pathway [8].

The grade of dysplasia is determined by the features of the most dysplastic portion. In low-grade dysplasia, the cells are highly columnar but small. They have a dark-staining cytoplasm. The nuclei are enlarged, elongated, and hyperchromatic. They remain in a basal position, largely confined to the basal half of the cell, but, because of the crowding of cells, they are typically stratified, particularly near the base of the crypts [9]. Mitotic figures may be present in the upper part of the crypt and on the surface. The dysplastic process will usually involve the surface epithelium, although cells at the surface may show minimal lesions. They may appear normal except for their large size and their tall, high columnar (non-goblet) shape. Mucin is sometimes present as small mucin droplets similar to those seen in gastric foveolar epithelium. There may be marked reduction in the number of goblet cells and sometimes "dystrophic" or "upside-down" goblet cells appear. These are goblet cells in which the mucin droplet is located in the basal rather than apical portion of the cell (abnormal polarity of goblet cells – mucin below, rather than above the nucleus). Architectural features include thickening of the mucosa due to an increase in number and lengthening of the glands. Furthermore, there is mild distortion of the crypts with budding and increased size. In contrast with the budding that occurs in regenerated mucosa, which is usually associated with a reduced number of crypts, in dysplasia the crypts are increased in number and, therefore, much more closely approximated (Fig. 4.1).

High-grade dysplasia is associated with true stratification of cells and marked distortion of crypt architecture. Cytological changes involve the surface and crypt epithelium. Nuclear stratification extends into the superficial (luminal) parts of the cells. Other criteria include a greater degree of cytological variance, overlapping vesicular nuclei, and loss of nuclear polarity. The nuclei often vary markedly in size, shape, and staining characteristics. Mitotic figures can appear on the surface and peri-crypt fibroblasts

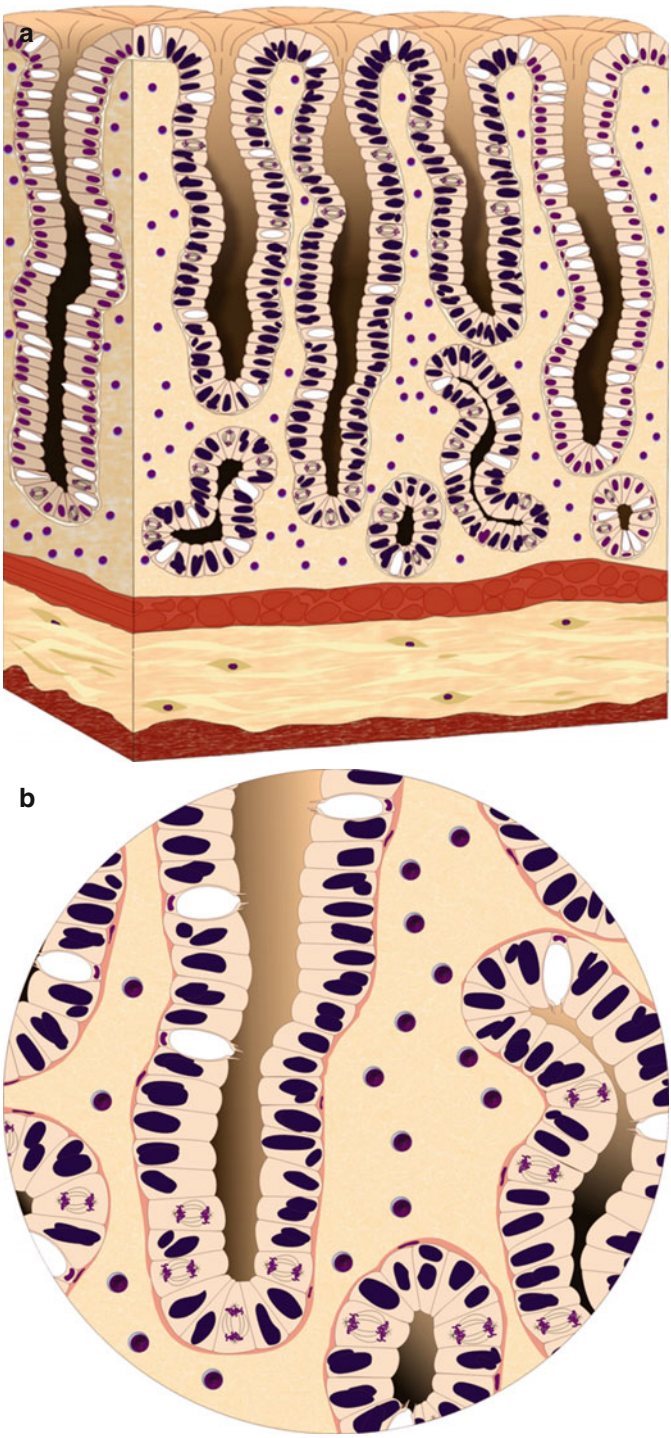

Fig. 4.1 (**a**, **b**) Low-grade dysplasia. The epithelial cells are elongated with an enlarged darkly staining nucleus. However, the shape and size of the cells are generally comparable

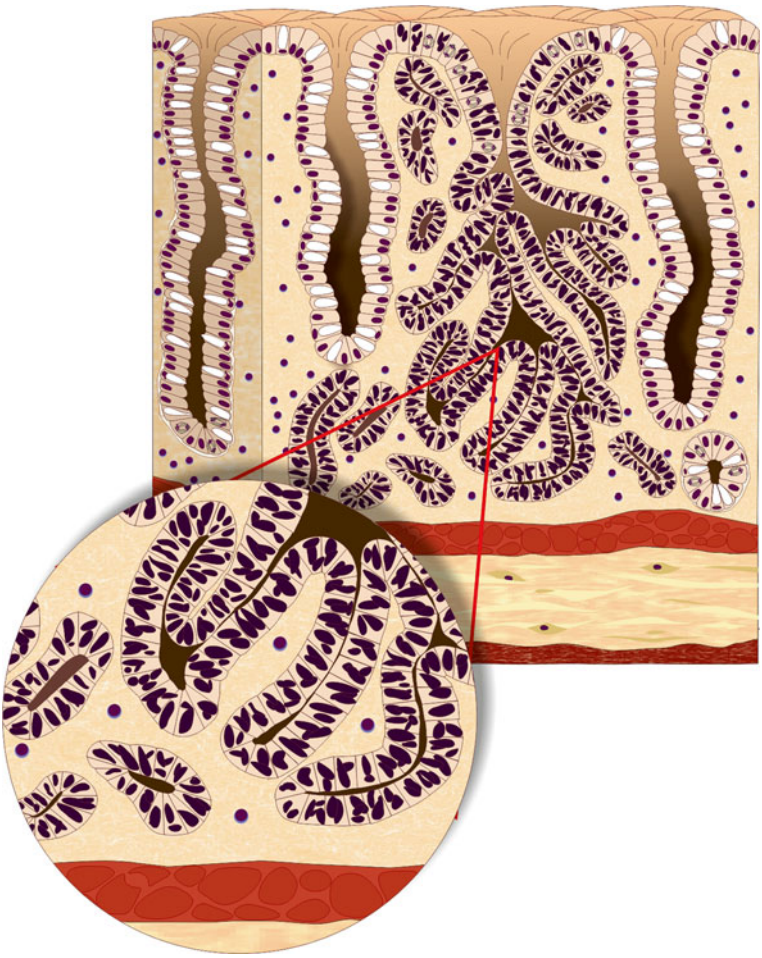

Fig. 4.2 High-grade dysplasia. Both architecture and cytology are more disturbed

become dispersed. Crypts may be tightly packed with branching and lateral budding often yielding a complex architecture (Fig. 4.2). There is intraglandular bridging of epithelium to form a cribriform pattern of back to back glands, and frequently a villiform surface configuration. In general, inflammation is not a prominent feature in dysplasia.

When the mucosa is complete and includes surface epithelium and glands, diagnosis and grading is easier. When both cytology and architecture are highly abnormal, grading of dysplasia is usually straightforward. It is however more difficult when architecture is highly abnormal in a biopsy, whereas cytology is not.

Surveillance procedures for the detection of dysplasia in IBD are preferentially performed during a quiescent phase of the disease. The absence of active inflammation in an area of equivocal atypia is however not a proof of its neoplastic nature. When the diagnosis has to be made on endoscopic biopsy samples, the result may be influenced by sampling error. It has been proposed to take a large number of random biopsies in addition to the biopsies of lesions, in order to improve the detection rate of flat lesions and to find small lesions.

Endoscopy and macroscopic examination of surgical specimens from patients with ulcerative colitis allow to distinguish different types of dysplastic lesions: flat dysplasia and polypoid or elevated dysplasia. Flat dysplasia is the most common lesion. The polypoid lesions are a heterogeneous group originally described as "dysplasia-associated lesion or mass (DALM)" (Fig. 4.3) [10]. Actually a distinction is

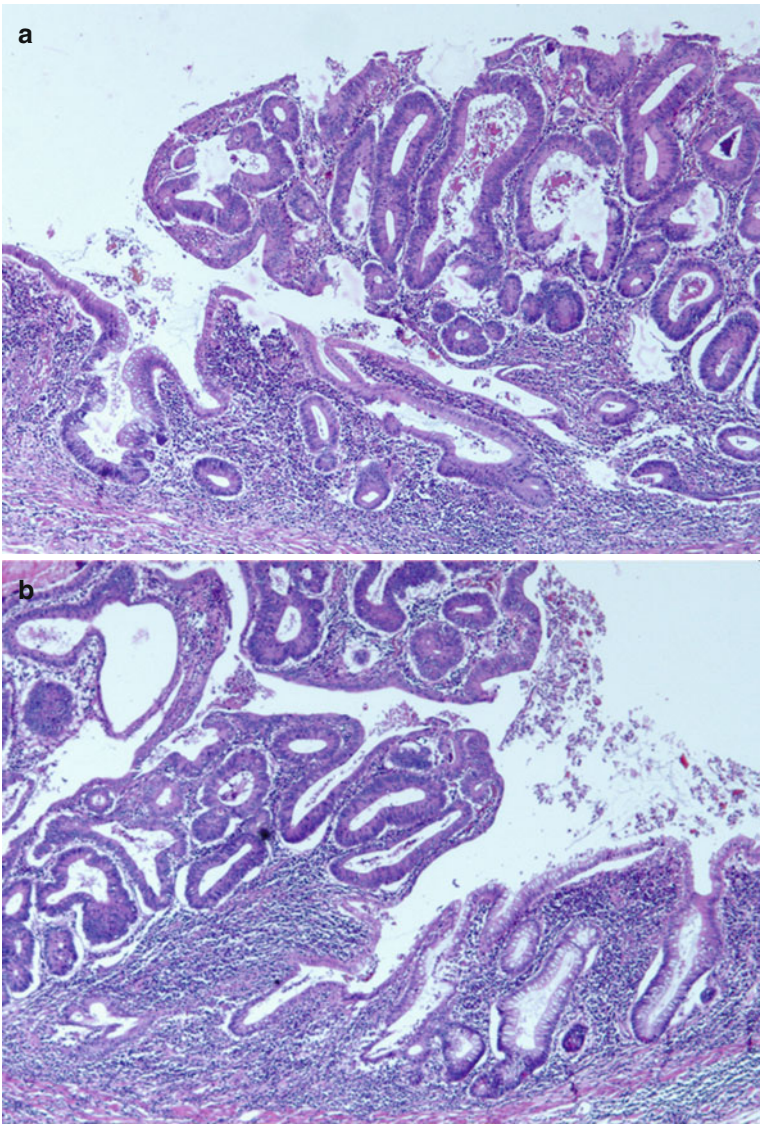

Fig. 4.3 (**a**–**d**) Microphotograph of an elevated – polypoid dysplastic lesion in ulcerative colitis. The flat surrounding mucosa shows features of active inflammation, but the cells are not dysplastic; (**b**, **c**) are higher magnifications showing the cytological atypia (×40); (**d**) is a low-power microphotograph of the elevated lesion

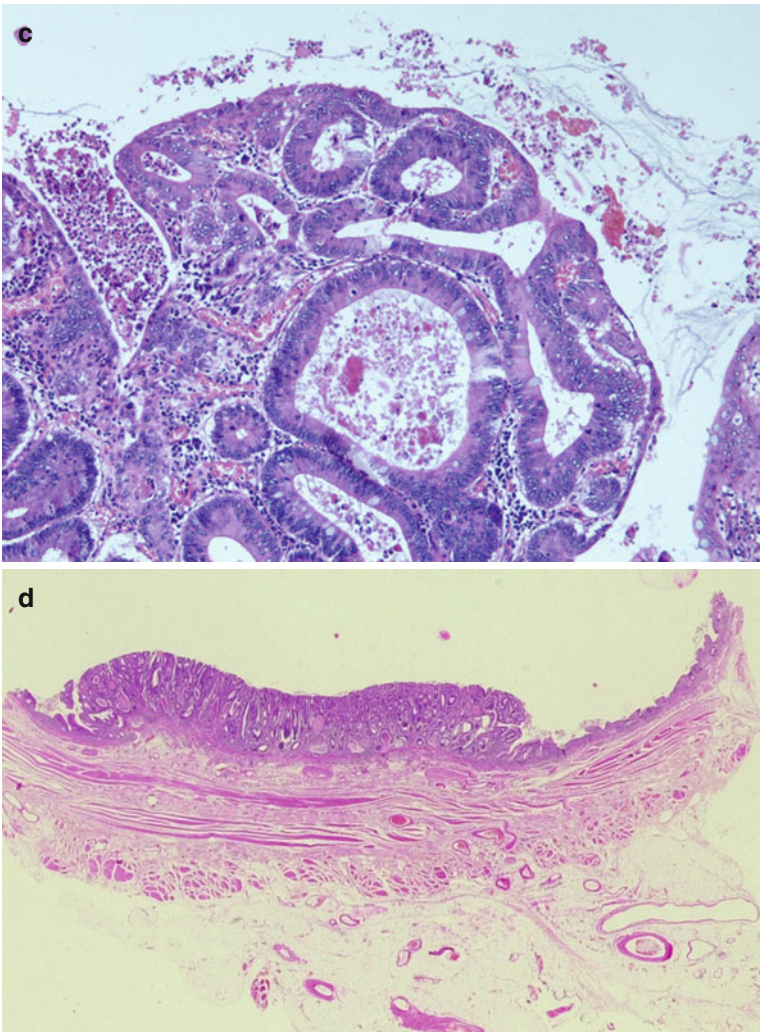

Fig. 4.3 (continued)

made between sporadic adenomas (adenoma-like lesion or mass (ALM) occurring in healthy, non-colitic mucosa and DALM lesions occurring in colitic mucosa). The latter appear in colitic areas. When they are poorly delineated and surrounded by flat dysplasia, they are called "non-adenoma-like DALM or dysplasia" or "NALD." When no surrounding flat dysplasia is present, they are called sometimes "adenoma-like DALM (ALD)." Adenoma-like lesions (ALM) are usually well-circumscribed and small lesions, sometimes with a sessile configuration although a stalk can be present. They can be removed with an endoscopic procedure. This is also possible for ALD lesions. It is thus important to obtain biopsies from elevated lesions and from the surrounding mucosa and send these to the pathology laboratory in

separate recipients or vials. Current surveillance practice recommendations propose to obtain multiple biopsies from the colon of diseased areas and atypical lesions [11, 12]. Modern endoscopic techniques provide however an alternative by allowing targeted biopsies with increased diagnostic yield.

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Chapter 5
Infections

Peter Van Eyken, Clara Gerosa, Daniela Fanni, and Rossano Ambu

Abstract Infections are a major cause of diarrhea and colitis. Usually, the disease is short-lived and biopsies are not necessary. When the diarrhea is prolonged, biopsies can be taken for solving the differential diagnosis with IBD and microscopic colitis. Most cases of bacterial colitis do not present a specific histological pattern. The differential diagnosis relies mainly on the absence of features suggestive for IBD such as architectural distortion and basal plasmacytosis. In rare cases, specific infections can be diagnosed. This is mainly so for chronic infections such as intestinal tuberculosis. In many developing countries it is important to recognize this diagnosis and to distinguish tuberculosis from Crohn's disease. Patients with IBD may also present with bacterial or other superinfections. Pathology is not the appropriate tool to identify this problem.

Keywords Infectious diarrhea • Bacterial colitis • Acute self-limited colitis • Acute infectious-type colitis • Acute self-limited colitis-differential diagnosis with IBD • *Yersinia* • *Campylobacter* • *Salmonella* • *Shigella* • EHEC • *Clostridium difficile* • Mycobacteria • Infections and IBD

Please see Fig. 5.1 for the key to the illustrations.

5.1 Acute Self-Limited Colitis

Infectious diarrhea is usually a short-lived condition characterized by acute (short history, less than 1 week) watery diarrhea or diarrhea with blood or mucus (dysentery). The term "acute self-limited colitis (ASLC)" refers to the histological presentation, which is associated with a rapid spontaneous positive evolution. However,

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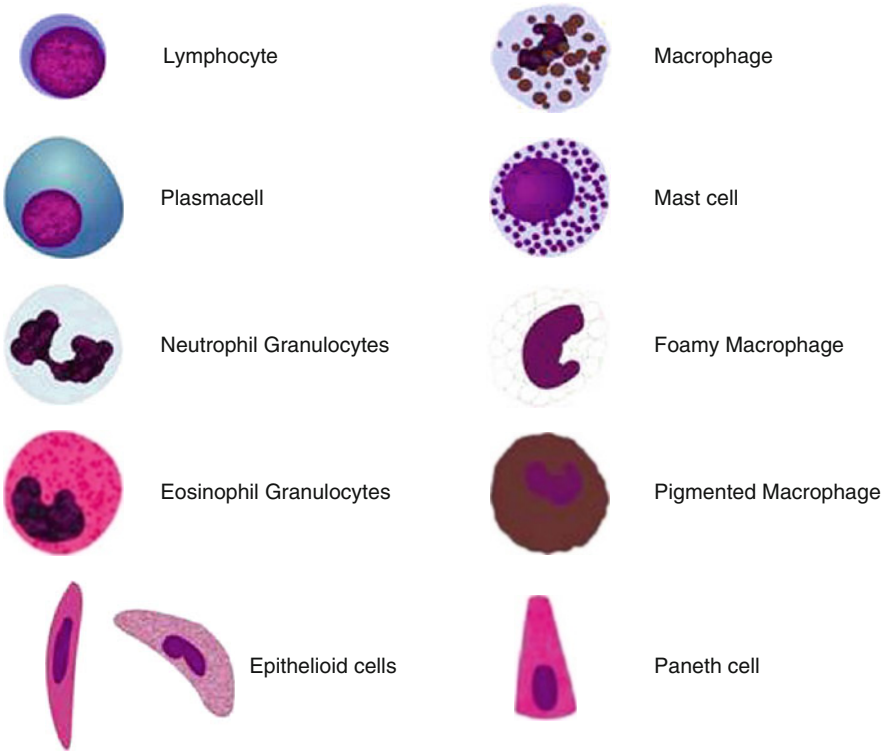

Fig. 5.1 Schematic drawing of the different cell types that may be seen in the lamina propria

in some cases the infection may not be self-limited and even can be fatal. For this reason, the term "acute infectious-type colitis" is also used.

Ileocolonoscopy is only rarely indicated for diagnosis. Watery diarrhea is more often of viral etiology and occurs more commonly in children. Diarrhea with blood is more often of bacterial origin. Production of bloody stools means a mucosal break caused by enteroinvasive bacteria. Acute bloody diarrhea may however begin with watery diarrhea because many bacteria also produce toxins which are not necessarily cytotoxic. Bloody diarrhea is colitis until proven otherwise. Some bacteria can induce either acute diarrhea or acute bloody diarrhea. Stool cultures can confirm the bacterial nature but are often negative. In elderly patients one has to consider diverticular disease, ischemia, malignancy, or a colitis-like picture due to drugs [1]. Drugs are indeed a common cause of diarrhea but less often induce colitis. In a prospective study of 58 patients presenting with colitis examined within 6 weeks of the start of the symptoms, a diagnosis of drug-induced (mainly antibiotics and non-steroidal anti-inflammatory drugs) was made in 35 patients [2]. Whenever more than one person has been acutely ill at the same moment, food poisoning has to be considered, whereas in patients coming from tropical or subtropical countries or in immunocompromised patients, infections are again more likely. A diagnosis of IBD

must be made cautiously in the acute phase of colitis. It should however be considered. Clinical symptoms which might arise suspicion are an insidious onset of the disease and young age. Between 15 and 25 % of patients with IBD have a family history of these disorders. A positive stool culture does not necessarily exclude a diagnosis of IBD. In a series of patients presenting with a first attack of colitis, a positive culture was found in 78 % of the patients with a final diagnosis of infectious colitis, but a positive stool culture was also found in 21 % of the patients eventually developing IBD. Histology of colorectal biopsies may confirm active colitis in patients with acute bloody diarrhea, but the pattern of infectious colitis can be highly variable. It is extremely difficult, if not impossible to recognize the cause of bacterial infections on microscopy. Indeed, the majority of infections (90 %) cause nonspecific mucosal injury.

The spectrum of microscopic features of infectious colitis includes a normal looking biopsy as well as samples showing only edema (Fig. 5.2), samples showing active (presence of neutrophils) inflammation (Fig. 5.3) which can be mild or severe with extensive necrosis and fulminant disease with bowel wall necrosis, and samples showing residual lesions. The majority of infections cause minimal or no inflammatory change. This is seen in infections induced by agents such as toxigenic Vibrio cholerae and Neisseria gonorrhoeae. Other agents can induce a variety of lesions. Enterohemorrhagic *E. coli* (EHEC) infection, for instance, can present five different patterns: normal aspect or mild focal increase in mononuclear cells; focal active colitis; colitis characterized by cryptitis and, less commonly, crypt abscesses with or without neutrophils in the lamina propria; a pseudomembranous colitis-like pattern; and marked edema and hemorrhage in the mucosa or submucosa with microthrombi even in areas away from ulcers and crypt withering causing an ischemic pattern of injury [3–6].

Diarrhea induced by bacteria is the result of two major mechanisms: the production of toxins and the ability of the organisms to invade the intestine. Some strains produce mainly toxins responsible for intestinal secretion without major tissue damage. Infections with Vibrio cholerae and noninvasive *Escherichia coli* are examples of a possibly major secretory diarrhea. *Shigella* species invade enterocytes by a bacterium-directed macropinocytotic process, multiply within the epithelium, and then enter the lamina propria. They may produce apoptosis. Campylobacter organisms produce diarrhea after adhesion to and invasion into the enterocytes. This process leads to loss of function and sloughing of the surface epithelial cells. The organisms are able to invade and replicate in infected epithelia via TLR −2 and TLR −4 receptors (Toll like). They may also produce both an enterotoxin and a cytotoxin damaging the cells. C jejuni organisms seem more enterotoxigenic and probably more virulent than C. coli.

Usually, the microscopic features are a mixture of active and chronic inflammation with some epithelial changes. Active inflammation occurs early in the disease and is characterized by edema and the presence of neutrophils, usually in the upper part of the lamina propria and in the wall of the crypts (usually the upper, more luminal part). The lesions show a focal or patchy distribution. Neutrophils can be numerous or only few. They can invade surface and crypt epithelium and induce

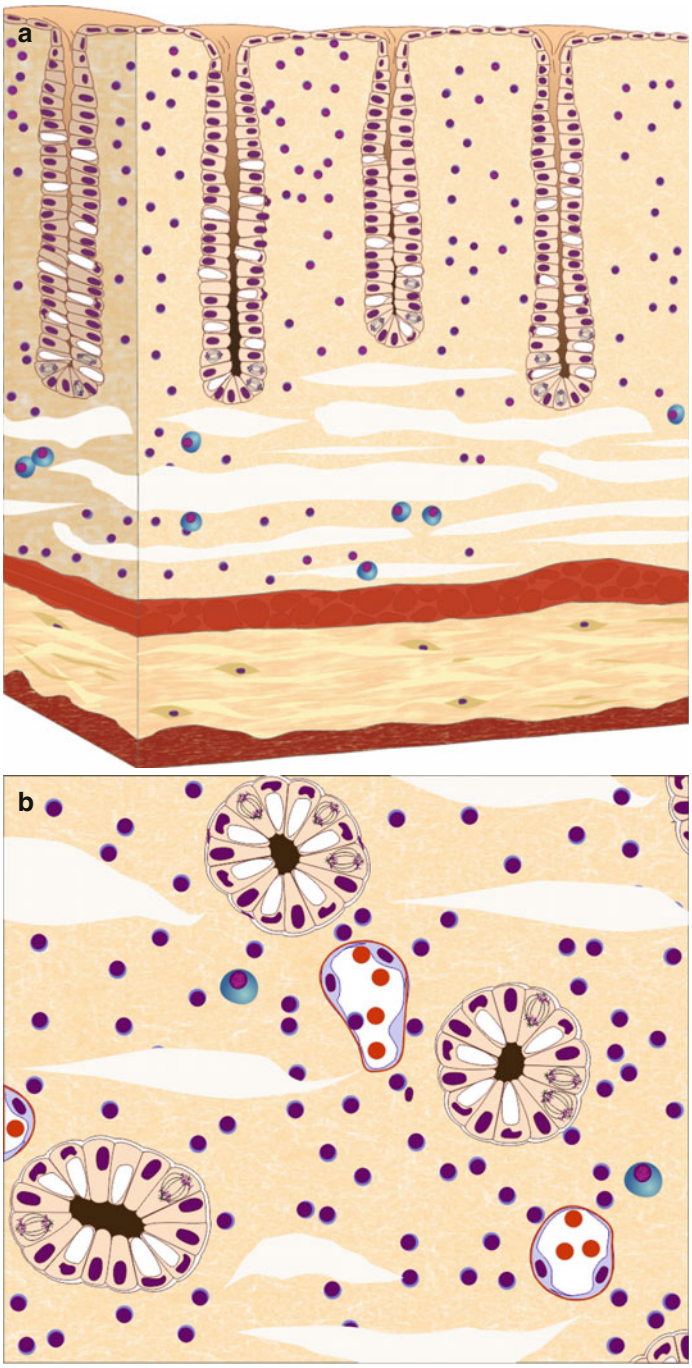

Fig. 5.2 (**a**–**d**) Schematic representation of edema of the mucosa, widening of the intercyptal space, and restitution on the surface in (**a**, **b**); (**c**) is a microphotograph of a biopsy from a patient with proven *Campylobacter colitis* showing edema and epithelial cell damage (×10); (**d**) represents only edema without epithelial alterations which could be due to artifact or a genuine abnormality

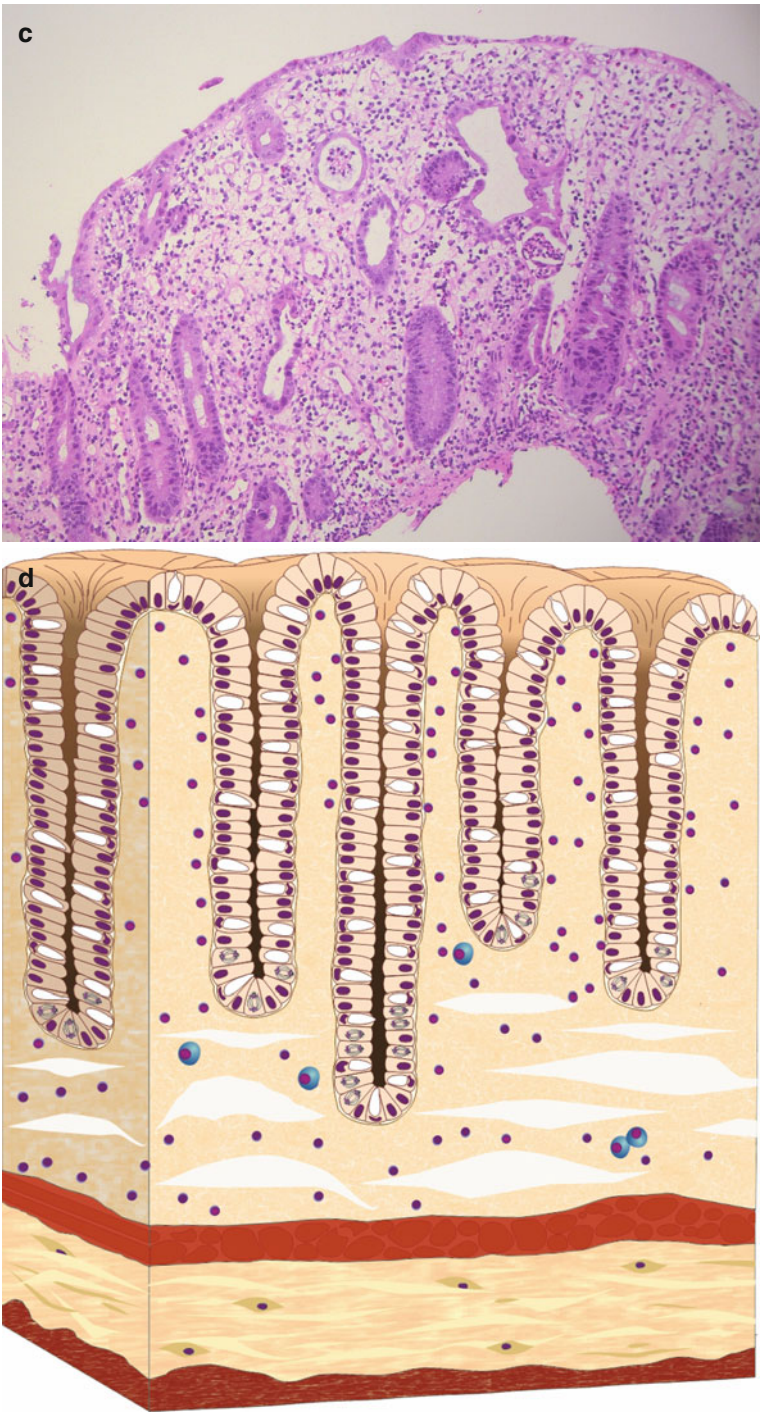

Fig. 5.2 (continued)

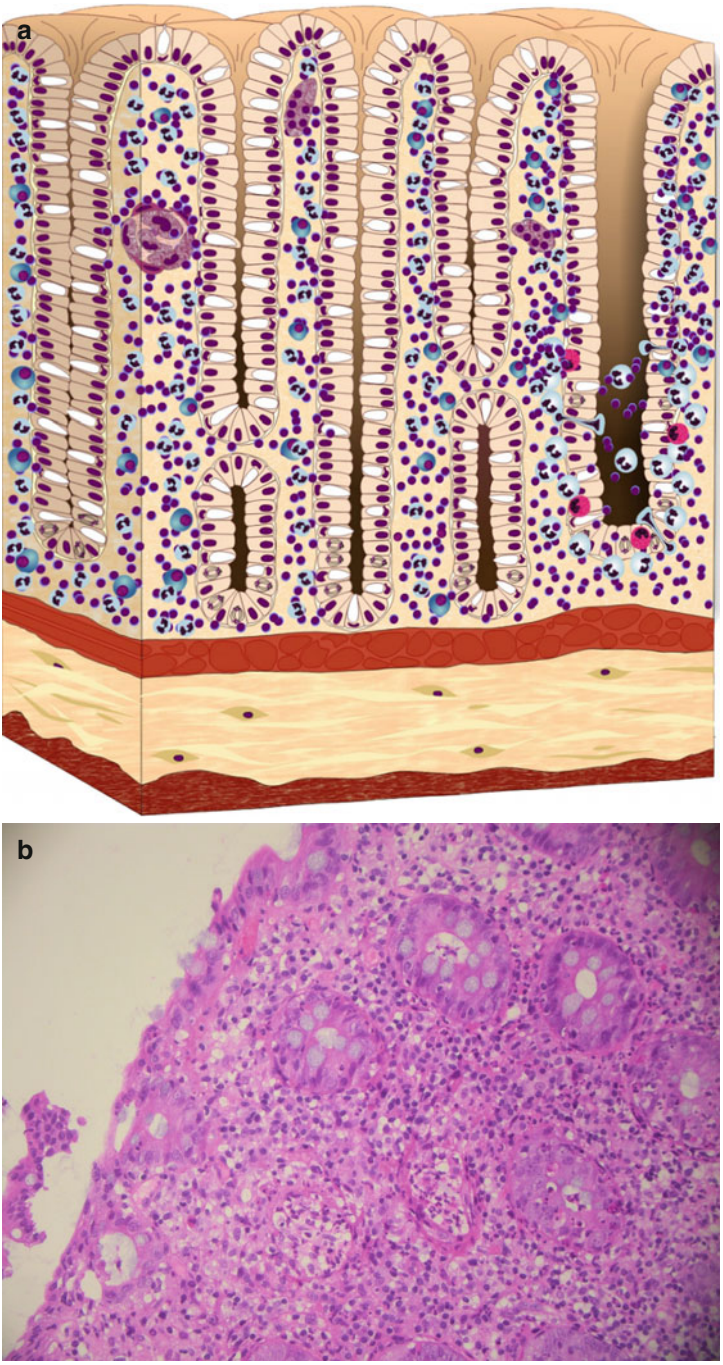

Fig. 5.3 (**a**) Schematic drawing of a case of infectious colitis demonstrating preserved surface and crypt architecture with transmucosal active inflammation, focal cryptitis, and isolated giant cells. (**b**) Microphotograph of a biopsy from a culture-positive bacterial colitis (×20)

erosion, cryptitis, and crypt abscesses. Isolated giant cells can be seen. There is generally no distortion of the architecture. The crypts remain parallel, but they are often smaller at the upper part (string of pearls sign). The surface and crypt epithelial cells may show mucin depletion and can appear flattened or cuboidal. Erosions and ulceration can be present.

An increase of plasma cells can occur 7–10 days after the initial onset of the infection [7]. Increased numbers of IgA- and IgM-containing plasma cells were found in the mucosa in patients with *Campylobacter colitis*, in contrast with active IBD who show increases of IgA and IgG (ulcerative colitis) or IgA, IgM, and IgG (Crohn's disease) [7, 8]. In infectious colitis, plasma cells are not usually located in a basal position. The mononuclear immune reaction is associated with clinical resolution heralded by regenerative changes in the epithelium with mucus depletion and increased mitotic figures in crypt epithelial cells. A mild increase of lamina propria mononuclear cells can persist for months. The presence of some residual surface epithelial damage and increased intraepithelial lymphocytes can sometimes be confused with lymphocytic colitis. However, the clinical context is different enough to usually prevent confusion [9].

It is also possible that some neutrophils persist for longer time, even in occasional crypts. This pattern is called "focal active colitis." The presence of focal active colitis in a patient who does not have a history of chronic inflammatory bowel disease should be interpreted conservatively, as the vast majority of cases turn out to be self-limited. Focal active colitis is more likely to be secondary to CD in pediatric patients. It can also be seen in association with nonsteroidal anti-inflammatory drug (NSAID) use, ischemia, and partially treated UC and as an isolated (incidental) finding in patients undergoing endoscopy to exclude neoplasia. There are no particular features, such as amount, location, or distribution of the inflammation, that correlate with outcome or allow for selection of those at higher risk for inflammatory bowel disease [10, 11].

The distinction between IBD and infective type colitis relies mainly on the absence of features which direct towards a diagnosis of chronic idiopathic inflammatory bowel disease (mainly architectural distortion and basal plasmocytosis). This location is a feature suggestive for chronic idiopathic inflammatory bowel disease, together with architectural abnormalities, which develop later in the course of the disease. Prolonged infection (2–3 weeks) can however be associated with downward expansion of lymphocytes and plasma cells. This expansion is usually not uniform and therefore different from what is seen in ulcerative colitis, although it might mimic Crohn's disease.

5.2 Specific Infections

Some bacteria induce lesions which can be used for diagnostic purposes. The distribution of the lesions is one feature which can be helpful. Several bacteria such as *Yersinia enterocolitica*, *Y. pseudotuberculosis*, *Campylobacter jejuni*, and *Salmonella* species (Fig. 5.4) can induce infections of the small and large intestine

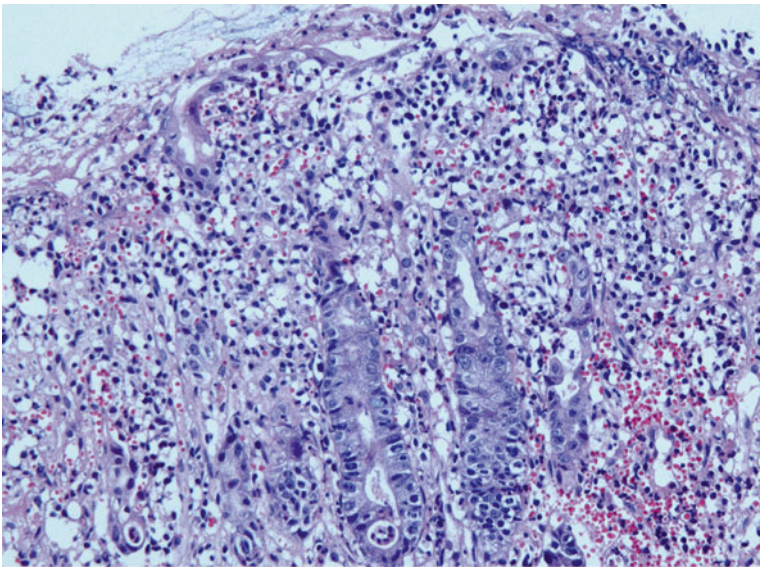

Fig. 5.4 Microphotograph of a biopsy from a patient with *Salmonella colitis* showing surface erosion (×20)

and mimic Crohn's disease. Others, such as *Shigella* species (and enterohemorrhagic *E. coli*), induce infections of the large intestine alone (and may mimic ulcerative colitis). Few bacteria, such as *Clostridium difficile*, lead to specific microscopic features allowing a microscopic diagnosis (see also drug-induced colitis). Three types or grades of *C. difficile* lesions have been described. Type I is the earliest lesion and consists of a superficial inflammatory reaction with subepithelial neutrophils, focal areas of epithelial necrosis, and widening of the crypt opening. This lesion reflects the local epithelial damage occurring on the luminal surface. Type II lesion consists of a well-demarcated group of disrupted and distended crypts containing mucous with neutrophils at their bases. The overlying epithelial cells become flattened and necrotic and are progressively lost. Occasional thrombi are found in superficial mucosal capillaries. Mucous, fibrin, and cellular debris are projected into the intestinal lumen forming a pseudomembrane like a mushroom or volcanic eruptions overlying the necrotic mucosa. The type III lesion is rare and occurs late in the evolution. This lesion consists of complete necrosis with a few surviving glands covered by a membrane of fibrin, mucous, and cellular inflammatory debris. Less characteristic lesions such as focal active colitis with some crypt abscesses have also been described. In the resolving phase, residual glandular irregularity or regenerative changes with pseudopolypoid features may be seen [12].

The enterohemorrhagic strain of *E. coli*, O157:H7, is highly virulent, and only a small number of viable bacteria are required to produce symptomatic infection. The histologic features of enterohemorrhagic *E. coli* can be typically similar to the pattern associated with acute ischemic colitis. The presence of fibrin thrombi within lamina propria capillaries may be a clue to the diagnosis. Viral infections such as

cytomegalovirus infections; some specific bacterial infections such as those due to Mycobacterium tuberculosis or avium; the fungal, protozoal, and helminthic infections can be diagnosed because the pathogenic agents can be detected on histological slides. Some of these are responsible for chronic symptoms.

In patients presenting with persistent or long-standing diarrhea, chronic infections such a Mycobacterium tuberculosis or unusual types of mycobacteria must be considered. Tuberculosis is a granulomatous inflammation that presents as a segmental disease. It most commonly involves the ileocecal region, but it can also be localized in the remainder of the colon and rectum. Unlike the longitudinal serpiginous ulcers of Crohn's disease, tuberculous ulcers tend to be circumferential or transverse. The diagnosis relies upon the presence of necrotizing granulomas with giant cells or of confluent granulomas. Perirectal tuberculosis often presents as anorectal fissures and fistulae containing giant cells, not always associated with granuloma formation. Acid fast stains are indicated, especially in the presence of multiple small or caseating granulomas, but are often negative. Colon tuberculosis may mimic Crohn's disease with stenotic areas, aphthous ulcers, and nodular mucosal changes. The differential diagnosis of cecal tuberculous colitis includes Crohn's disease and yersinia infection [13, 14]. Yersinia may show also stellate foci of necrosis within lymphoid aggregates and aphthous lesions in the area of the appendix and ileocecal valve.

Rectal disease may be a manifestation of sexually transmitted infections. A specific diagnosis must be considered depending upon the clinical information but is usually difficult. Syphilis and lymphogranuloma venereum occur especially in immunodeficiency virus-positive patients. Core features in biopsies are an intense lymphohistiocytic infiltrate with prominent plasma cells and lymphoid aggregates, only mild to moderate acute inflammation, minimal basal plasmacytosis and crypt distortion, and only rare granulomas and Paneth cell metaplasia. Spirochetes can be demonstrated on a Treponema pallidum immunohistochemical stain [15].

5.3 Infections and IBD

Infections can also be responsible for symptomatic relapses of IBD and for complications [16]. The association between *C. difficile* and exacerbations has been studied particularly because of the possible relation with prior antibiotic use in patients with IBD, either for the disease itself or for unrelated infections. The results are controversial and biopsy findings do not reliably detect *C. difficile* infection in ulcerative colitis [17]. Patients with established IBD who present with flare-ups should however be investigated for infections, mainly when the flare-up is atypical in its presentation (bloody diarrhea in a patient with Crohn's disease; non-bloody diarrhea in a patient with ulcerative colitis) or with increased risk for infections (travelling, recent antibiotic use, immunosuppressive therapy). Histology is however not very helpful for this issue except for the detection of some opportunistic infections such as tuberculosis, amoebiasis, and cytomegalovirus [18].

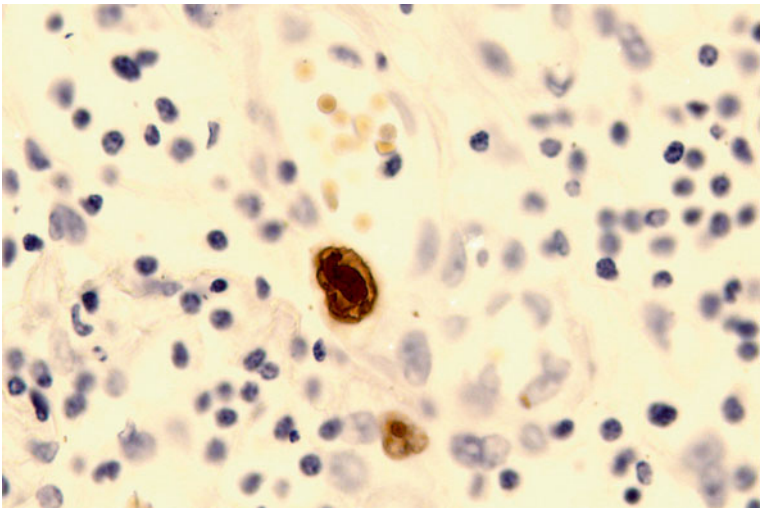

Fig. 5.5 Immunohistochemistry with antibodies directed against Cytomegalovirus shows a positive nuclear staining (×40)

The risk for onset of tuberculosis seems to be high early after the start of treatment with immune modulating agents. Stools for tuberculosis staining and culture should be submitted on anyone at risk for this infection and in those at risk when IBD is considered, corticosteroids should not be started until at least preliminary testing for tuberculosis is negative. Amoebic colitis can mimic Crohn's disease of the colon and ulcerative colitis. IBD patients can also be carriers of amoebae. Since steroids can provoke amoebic activity and even cause fulminant colitis, it is necessary to determine whether or not amoebae are present. Overall, however, the association of amoebic colitis and IBD is rare [19]. Cytomegalovirus infection (CMV) constitutes a special situation. It may be present in the early stage of the disease of ulcerative colitis, but it can also be responsible for relapse of symptoms or cause pouchitis [20]. It has been reported as a cause of refractory IBD. This infection is also responsible for a more severe clinical course and it may cause death if not treated early. Therefore, it has been proposed to always perform rectal biopsies in patients with severe steroid-resistant colitis or fulminant colitis. Histology is the best method for identification of this infection, but should be associated with serologic and PCR studies (Fig. 5.5) [21, 22].

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Chapter 6
Inflammatory Bowel Diseases

Karel Geboes, Maria Leo, Daniela Fanni, and Gavino Faa

Abstract Inflammatory bowel disease (IBD) is a group of chronic idiopathic inflammatory conditions. The two major types are ulcerative colitis (UC) which affects the colon and Crohn's disease (CD) which can involve the whole gastrointestinal tract but is most common in the terminal ileum and colon. There is a genetic predisposition for IBD, and patients with this condition are more prone to the development of malignancy. Further types to be considered are indeterminate colitis (IC) and inflammatory bowel disease unclassified (IBDU). These are essentially "temporary diagnoses" when the difference between UC and CD cannot be established definitely at the time of presentation. IC should be used when examination of surgical samples is available together with clinical, serological, and imaging data, while IBDU is used for patients from whom only endoscopic biopsies are available. CD and UC must be considered in the differential diagnosis of clinically acute colitis because of differences in treatment strategies between infections and IBD. The differential diagnosis is particularly important when the complaints are persisting. Histology plays a key role in the diagnosis. Major diagnostic features are architectural distortion and basal plasmacytosis.

Keywords Inflammatory Bowel Disease IBD • Ulcerative colitis • Crohn's disease • Crypt architecture • Crypt atrophy • Bifid crypt • Crypt distortion • Basal plasmocytosis • Active inflammatory parameters • Non-active inflammatory parameters • Cryptitis • Crypt abscess • Quiescent disease • Inactive disease • Disease activity • Activity score • Histological activity score • Cytomegalovirus CMV •

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Paneth cell metaplasia • Ulceration • Erosion • Mucin depletion • Transmucosal inflammation • Segmental inflammation • Skip area • Transmural inflammation • Fistula • Granuloma • Aphthoid ulcer • Epithelioid cell • Microgranuloma • CARD15/NOD2 • Toll-like receptor • Skip lesion • Focal inflammation • Patchy inflammation • Pseudopyloric metaplasia • Hypercrinia • Indeterminate colitis • IBD unclassified • Effect of treatment • Multistep biopsies

Please see Fig. 6.1 for the key to the illustrations.

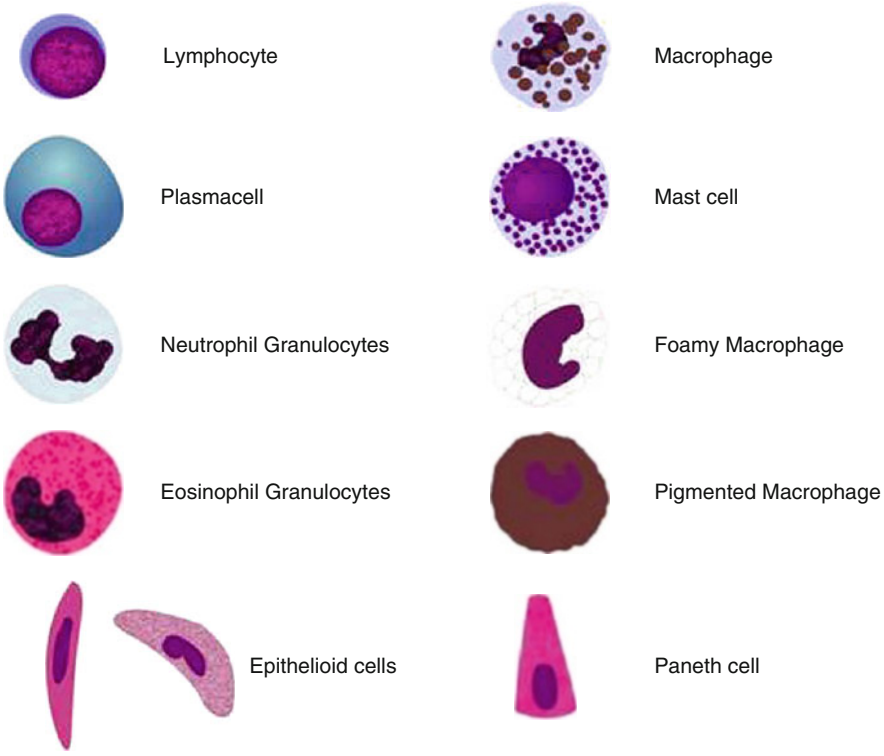

Fig. 6.1 Key to identification of cells in the illustrations

6.1 Ulcerative Colitis

Ulcerative colitis (UC) is a condition of unknown etiology, limited to the rectum and colon. The lesions involve essentially the mucosa and submucosa except for fulminant cases. Microscopy is an important tool for the diagnosis although there are no real microscopic features which are specific for the disease. Indications for a biopsy in patients with a clinical history suggestive for ulcerative colitis are to establish a diagnosis, to solve the differential diagnosis between UC and acute self-limiting (infectious) disease or Crohn's disease, to assess the extent of the disease, to assess the severity of the disease, to exclude coexisting conditions or complications, to monitor therapy, and to detect dysplasia.

The diagnosis of UC relies on a combination of clinical, endoscopic, histological, and serological parameters, and as yet there is no gold standard. The endoscopic pattern is often used as major diagnostic criterion although some infectious diseases may mimic UC. Yet due to this the pathologist often receives only one or of few rectal biopsies and rarely multiple biopsies from different segments of the colon. This is not appropriate for the initial diagnosis because UC can show atypical presentations and Crohn's disease may show features very similar to UC. It is clear that the material provided to the pathologist has an influence on the quality and results of the pathology report. In most cases and certainly in some difficult or atypical presentations, multiple biopsies (including ileal biopsies) of different segments are essential to establish a precise diagnosis [1].

Atypical presentations include especially pediatric patients and patients with primary sclerosing cholangitis (PSC). In early onset disease, few or no diagnostic features may be present, particularly in children. A large proportion of patients with PSC (50–80 %) have pre-diagnosed or concomitant inflammatory bowel disease [2]. The associated IBD is most often UC. The IBD in PSC patients can be clinically mild, rather diffuse and mostly already of long duration. It has been reported that the IBD in PSC might differ in a variety of aspects from IBD without PSC [3–5]. More specifically, a study from the Mayo Clinic pointed to a higher incidence of rectal sparing and backwash ileitis in 71 PSC patients with IBD compared to 142 matched control UC patients [3]. Comparably, a systematic, prospective study of 110 patients from Oslo [4] reported that two thirds of their IBD-PSC patients had no or sparse IBD symptoms and rectal sparing was seen in 65 %. However, such difference was not confirmed in an analogous histopathological investigation [5].

Assessment of disease severity and monitoring of therapy has become increasingly important in recent years. Rectal biopsy has been used for judging therapeutic efficacy since 1966 [6]. Histology may also be useful for the detection or prediction of disease relapse [7]. Persistent disease activity has further also been linked to the development of dysplasia [8].

The microscopic parameters which are used for diagnosis and assessment of severity of the disease can be subdivided into four major categories: (1) structural changes, (2) non-active inflammatory parameters, (3) active inflammatory parameters, and (4) miscellaneous. These parameters allow also an assessment of the severity of the disease as it is a diffuse condition. They make it possible to distinguish between the quiescent form, an inactive form, and active forms.

6.1.1 Structural Changes

This category relates to epithelial and architectural abnormalities and includes the presence of an irregular surface, sometimes called pseudovillous or villiform surface, and the presence of a disturbed crypt architecture. These alterations can be assessed with good reproducibility. They are however not always present. Their appearance depends on the duration of the disease and probably also on the severity. Alterations of the mucosal architecture were present in the first biopsy in about 70 % of the patients examined by Surawicz and Belic [9]. According to some authors it takes 3 weeks for these alterations to develop [10]. Treatment may induce some or complete reversibility [11]. Surface irregularity, especially with development of a villiform pattern, may be so marked in UC that the ratio of villus height to crypt depth may exceed 1/5:1. At this level the change is very specific for UC.

Crypt alterations include crypt atrophy in the form of shortened crypts that become widely separated from the underlying muscularis mucosae, crypt dropout, and prominent crypt budding (branching crypts, bifid crypts). Mucosal atrophy is a combination of crypt dropout 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 inter-cryptal distance and variability of the internal crypt diameter [12].

When using these criteria the pathologist should be aware of the fact that some areas of the rectum and colon may show certain architectural disturbance even in the normal situation. This is the case for the cecal valve and for the distal rectum. In the latter area which is often the site of distal ulcerative colitis or proctitis, architectural abnormalities are normally present and may be aggravated by intercurrent conditions such as mucosal prolapse. Therefore, the pathologist should know the site of origin of the biopsy and be very careful when the biopsy comes from the distal rectum. Accordingly, it is best to evaluate multiple biopsies and to appreciate that only the finding of these structural changes allows a diagnosis of chronic colitis, whereas their absence does not certify that the patient has an acute reversible disorder.

Structural changes in UC are usually widespread and common being present in 57–100 % of the patients. In Crohn's disease they are less common being present in 27–71 % of the patients and the lesions are less diffuse. The widespread or diffuse nature is therefore an important argument for UC. Architectural alterations can however also be seen in some other, less common disorders such as subsequent to

surgery or polypectomy, in mucosa overlying mass lesions such as mural metastases or endometriosis, in diversion colitis, rarely in microscopic colitis, in NSAIDS-induced lesions, and in some forms of chronic infectious colitis such as chronic Shigella dysentery. In most forms of chronic infectious colitis, they are however highly uncommon as shown in a study of schistosomal colitis [13]. Biopsies from patients with infectious colitis show no particular features depending on timing. Crypts remain parallel.

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 [14]. Biopsies were taken before any treatment was given (0–15 days), between 16–30 days, between 1–4 months, and between 4–10 months. It appears that crypt architecture is usually preserved in the early period. Crypt distortion starts in the second period being present in almost 25 % of the patients which eventually have IBD. In the period from 4 to 10 months, almost 75 % of these show crypt distortion. Crypt distortion may disappear again during the natural history of the disease or with therapy. This process takes time. Follow-up biopsies from patients with UC under treatment with immune suppression show that architectural alterations may persist for more than a year, while inflammatory features are decreased within weeks. Architectural abnormalities are thus not a sign of disease activity.

6.1.2 Non-active Inflammatory Parameters

A diagnosis of colitis implies changes in the cellular lamina propria infiltrate. These can be subdivided into a change in density, alterations of the composition, and changes in the distribution. A change in density usually means an increase in number of the lamina propria cellularity. In inactive disease this means an increase in lymphocytes and plasma cells. Similar changes may occur in infections, diversion colitis, and microscopic colitis. In UC the change in density is usually accompanied by a change in distribution. This should be assessed in two directions: lateral and vertical mucosal spreading. UC is characterized by a diffuse lateral and vertical transmucosal increase in density. In acute self-limiting infectious colitis, the increase is usually limited to the upper part of the lamina propria, whereas in UC the whole mucosa is involved. In addition plasmacytosis extending to the mucosal base (basal or basilar plasmacytosis) is common in UC. This feature is usually present in biopsies obtained during the first attack of the disease as well as in biopsies obtained during a flare-up and rarely if ever in samples from infectious colitis [14, 15]. During the first attack of IBD, it is commonly the only finding and may be present as focal plasmacytosis [9, 14, 15]. From 16 days on focal plasmacytosis develops into diffuse plasmacytosis. Focal or diffuse basal plasmacytosis (combined with crypt distortion) is the strongest predictor for the diagnosis of IBD (Fig. 6.2) (occurring in over 70 % of the patients). The presence of a diffuse, transmucosal increase in density of the lamina propria mononuclear infiltrate in one biopsy is thus a good

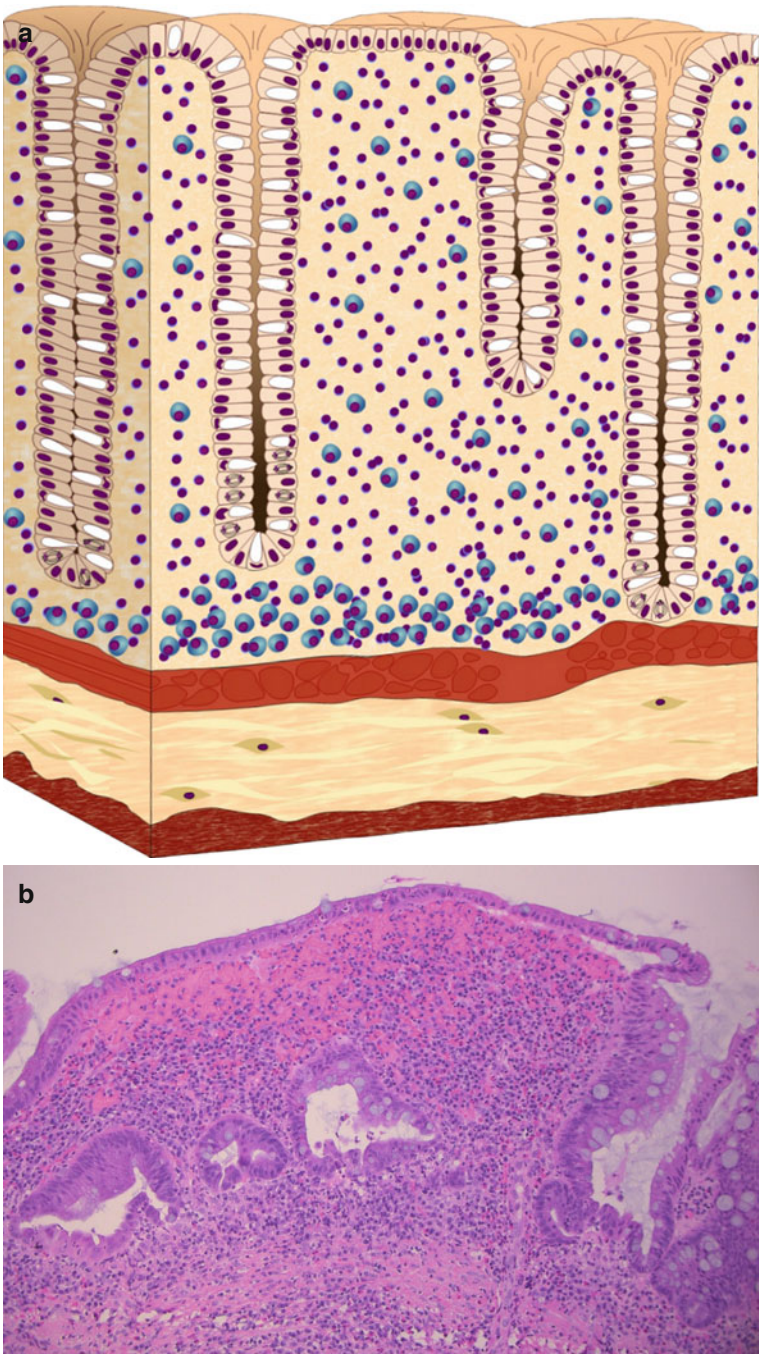

Fig. 6.2 (**a**) Is a schematic representation of inactive IBD with focal restitution and crypt loss and shortening of crypts and basal plasmocytosis. (**b**) Is a low power microphotograph showing mucosal atrophy and diffuse chronic inflammation extending toward the muscularis mucosae; (**c**, **d**) illustrate at higher magnification the crypt architectural abnormalities

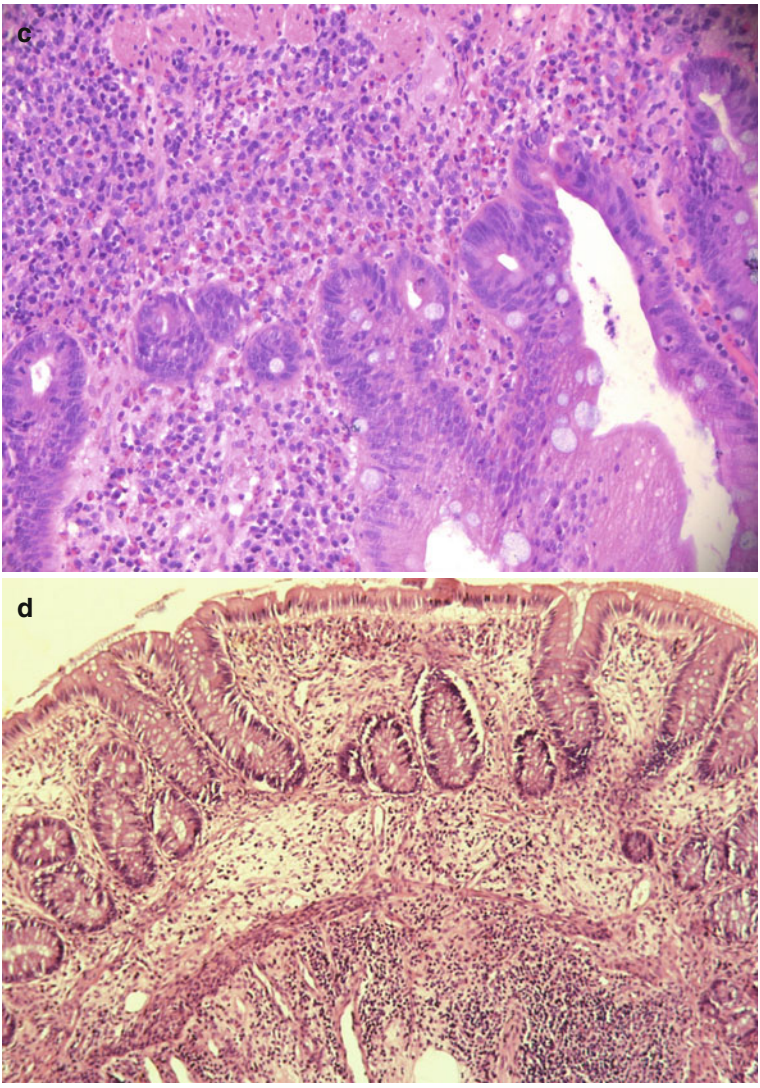

Fig. 6.2 (continued)

feature for making a diagnosis of UC when it is combined with architectural changes. It is however better when two or more biopsies can be evaluated and show the same pattern. Yet even then the diagnosis is not certain and should be reported as consistent with UC, or as "chronic idiopathic inflammatory bowel disease, most probably UC." Some forms of Crohn's disease may indeed show a similar pattern. In fact, up until now there is no reliable gold standard for the diagnosis of either UC or Crohn's disease. In recent years it has become clear that there are subtypes in Crohn's disease. A distinction has been made between inflammatory, perforating,

and stricturing types [16]. A subgroup of Crohn's disease patients where serum pANCA expression characterized a UC-like clinical phenotype has been described. Histopathologic features in these patients were a homogeneous, continuous, predominantly superficial inflammation; crypt abscesses; lack of granulomas; and lack of focality [17]. A test which may be diagnostic for CD is the determination of ASCA (anti-Saccharomyces cerevisiae antibodies).

Although the diffuse, transmucosal increase in density of the lamina propria infiltrate is an important feature of UC, it must be realized also that this may be influenced by therapy especially with the introduction of newer forms of colorectal released steroids and immune suppressives. Even when multiple biopsies are examined the feature may be discontinuous.

In addition to the diffuse increase in density of the lamina propria mononuclear cellular infiltrate there can be also an increase in lymphoid aggregates and follicles. This is a feature which can however also be seen in Crohn's disease and it is even more characteristic for diversion colitis.

6.1.3 Active Inflammatory Parameters

Active inflammatory parameters include the presence of neutrophils within the lamina propria or within epithelial structures such as the surface epithelium, the crypt epithelium (cryptitis), the crypt epithelium and lumen (crypt abscess), and unequivocal epithelial cell damage. Both neutrophils and epithelial damage are used as parameter because the mere presence of neutrophils can be induced by artifacts such as bowel preparation.

Cryptitis and crypt abscesses can lead to crypt destruction. A neutrophil attack of the surface and crypt epithelium may lead to mucosal erosion or ulceration.

Neutrophils in the lamina propria or within the epithelium are not an exclusive feature of UC. Cryptitis and crypt abscesses can be seen in infectious colitis, Crohn's colitis, and diversion colitis. In UC they are generally present in 41 % of the cases, while in CD they are found in 19 % of the cases. The difference thus is mainly of a quantitative nature. In active UC cryptitis and crypt abscesses are usually numerous. This feature can also be assessed with good reproducibility [18]. However, it has been shown that patients receiving treatment (enemas containing steroids or salicylates, oral colon-released steroids, immune suppression, and biologicals) may exhibit improvement in their morphology.

The role of eosinophils is less clear. A prominent presence of eosinophils has been noted repeatedly in ulcerative colitis, especially in the initial phase and mainly in children. There is also significant preclinical-based evidence demonstrating an important contribution for eosinophils in experimental UC [19, 20]. Eosinophils are also particularly present in the resolving phase of UC. The exact meaning of this phenomenon is not well studied. It has been linked to a better clinical outcome, but this has not been confirmed [21]. Some preliminary findings have linked persistent eosinophils also to an increased risk of relapse [22, 23].

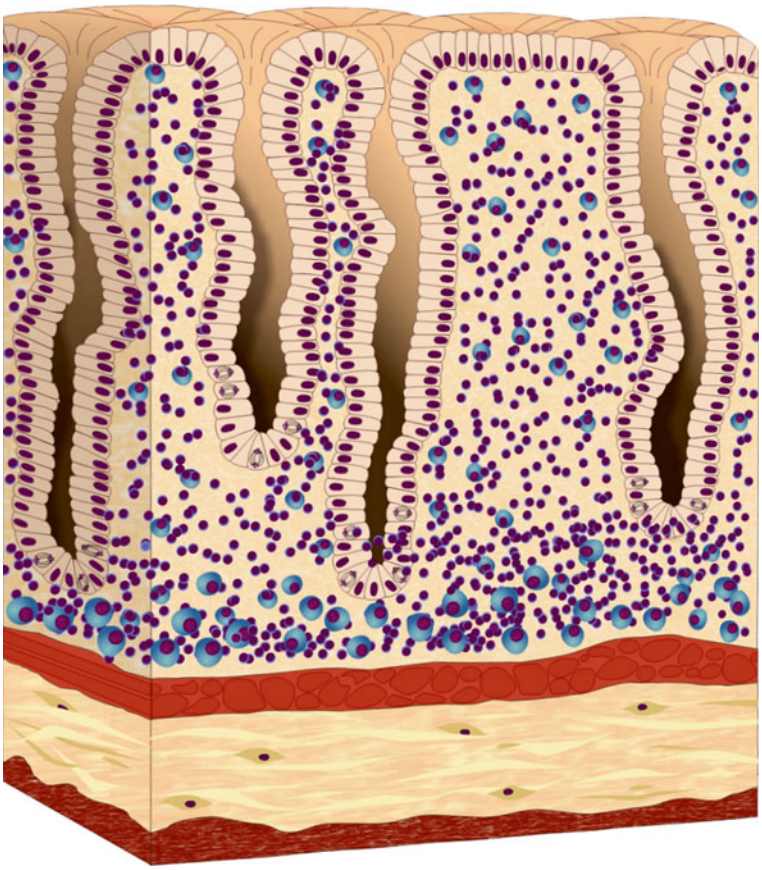

Fig. 6.3 Inactive ulcerative colitis with crypt distortion and diffuse basal plasmacytosis

Basal plasmacytosis should be used not only as a diagnostic feature but also for assessment of disease activity. It is linked to relapse of disease [24, 25]. The density or number of plasma cells also correlates with other histological features of disease activity [26].

Given that the rectum is usually involved, the inflammation is generally mucosal and diffuse, and the rectal mucosa is accessible for histological sampling, rectal biopsy is a potentially useful means of evaluating disease severity in UC [27]. Quiescent disease means the presence of architectural changes without alterations in the intensity and composition of the lamina propria cellular infiltrate (Fig. 6.3). Inactive chronic disease permits the presence of architectural changes (irregular surface and crypt abnormalities) and an increase of lamina propria mononuclear cells. Active disease is defined by the presence of neutrophils in conjunction with epithelial cell damage and (Figs. 6.4 and 6.5). Disease activity can be scored (subjectively) as mild, moderate, or severe. This may be the most appropriate way in routine clinical practice. For clinical trials, several scores for the assessment of histological disease

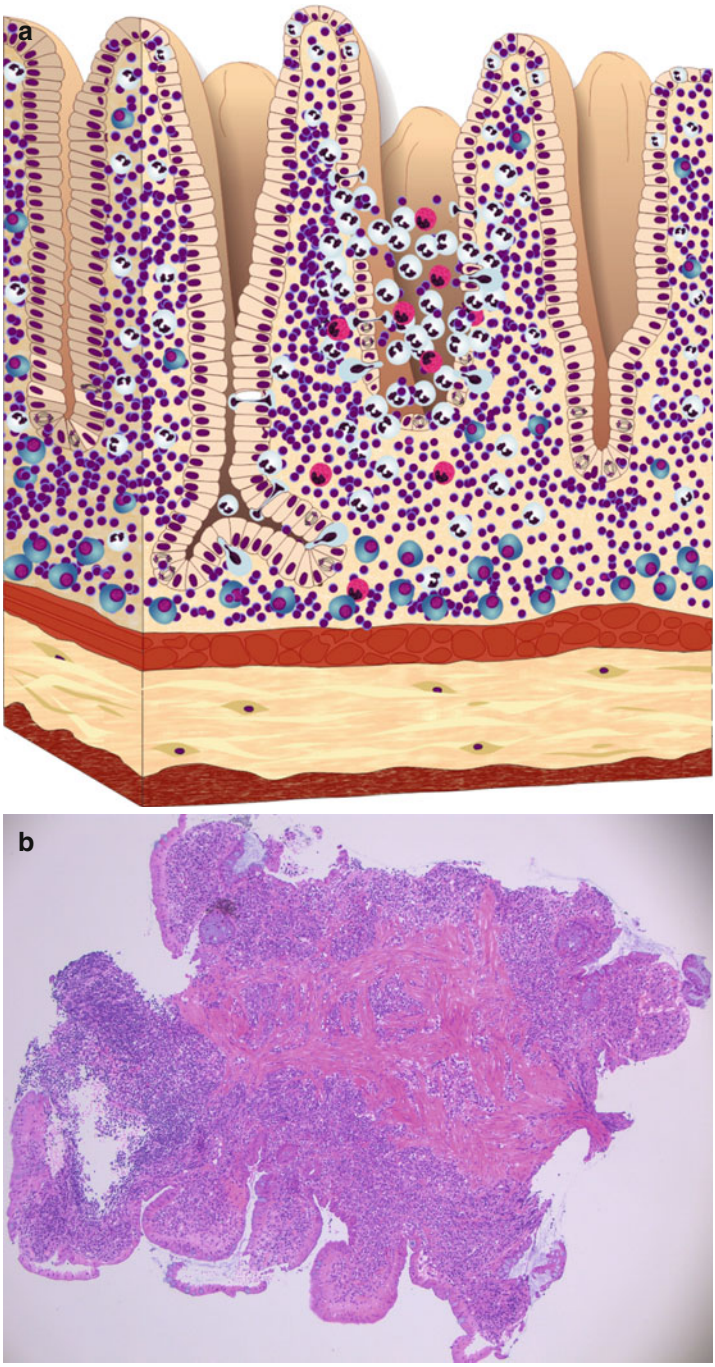

Fig. 6.4 (**a**–**c**) Active ulcerative colitis showing the pseudovillous surface in the drawing (**a**) and the microphotograph (**b**) and cryptitis and crypt abscess in the drawing and at higher magnification (×40) in microphotograph (**c**). This picture also illustrates basal plasmacytosis

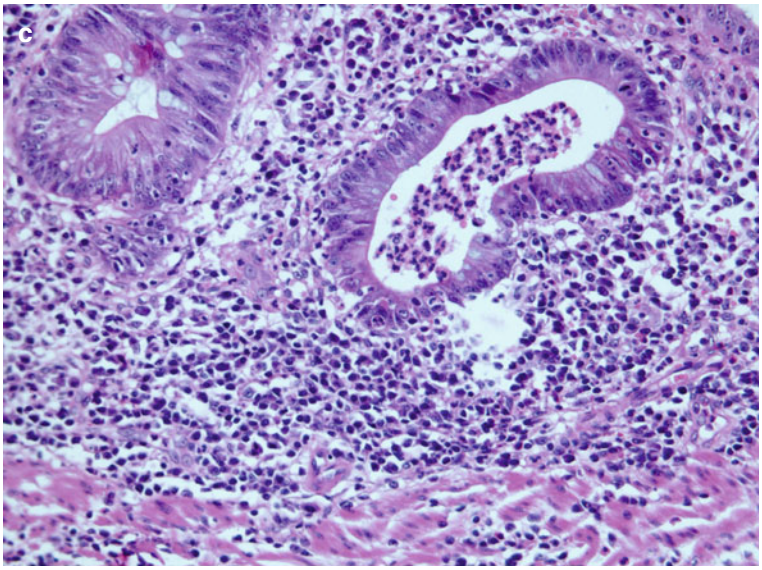

Fig. 6.4 (continued)

activity have been developed. Mucosal inflammation is usually graded by means of a scale composed of different features selected because they have proved sensitive in characterizing the process. Analysis generally relies on the examination of H&E-stained sections of 1 single biopsy. Two or more samples are however more appropriate because it is well known now that treatment can be responsible for variations in disease activity along the colon. Up to 6 samples have been studied, but the optimal number of necessary samples and sections to be examined has not been determined. The reproducibility of the histological activity scores has not been studied extensively, but limited data available show good agreement between different observers for the scores that have been evaluated. A major cause for interobserver differences is the assessment of surface epithelial damage or erosions. The reasons for this are a lack of a uniformly agreed definition and the presence of artifact damage induced by the biopsy procedure in a mucosa that is inflamed (see Chap. 13).

Correlations between histological disease activity and other assessments of disease activity are fair. In general, a good correlation is found between endoscopy and histology, especially when the samples are obtained during active inflammation. However, microscopic features of activity may persist in macroscopically inactive disease [28].

In active ulcerative colitis (and colitis in general), the pathologist should also look for the presence of cytomegalovirus (CMV) infection. CMV is a member of the Herpesviridiae (human herpes virus 4). Serological evidence of infection is observed in 40–100 % of the general population. Following primary infection, usually in childhood or adolescence, CMV persists lifelong. In individuals with appropriate immunity, this persistence of CMV has no clinical impact. Overall, the incidence of CMV infection in IBD is generally between 3 and 5 %. However, in

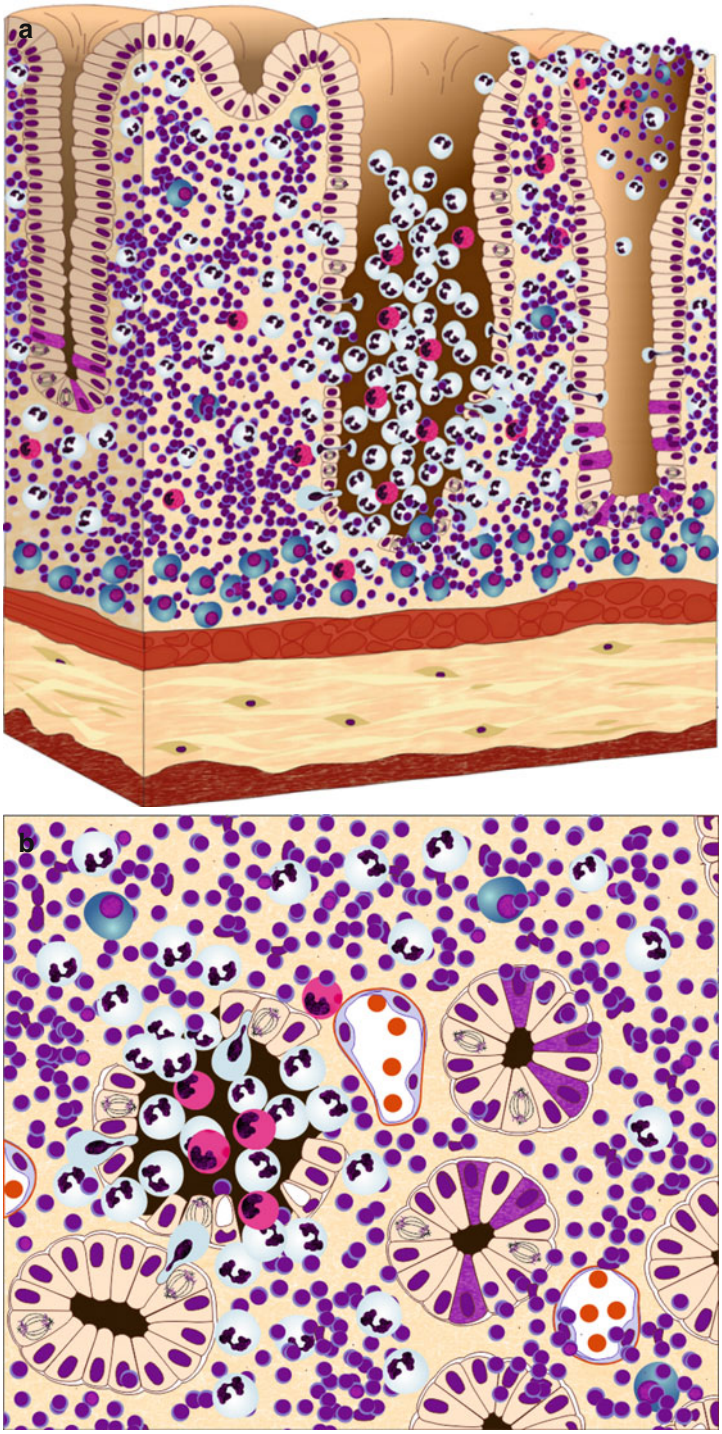

Fig. 6.5 (**a**–**c**) Active ulcerative colitis showing surface erosion, mucin depletion, crypt abscess, and crypt destruction in (**a**, **b**) and basal plasmacytosis in the microphotograph (**c**)

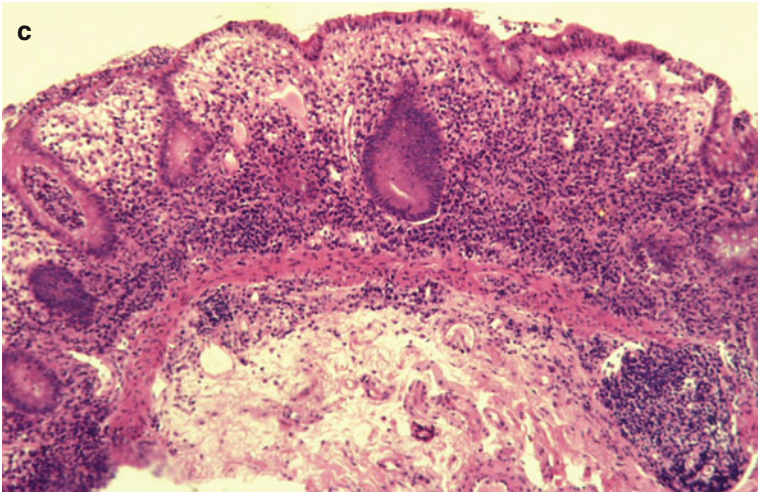

Fig. 6.5 (continued)

patients with steroid resistance, up to 36 % of CMV infection has been reported, especially in resection specimens. The diagnosis is based primarily on the detection of characteristic inclusions in biopsies or surgical specimens. Classical CMV inclusion bodies, the well-known owl eyes due to the characteristic basophilic inclusion surrounded by a clear halo and condensed, irregular chromatin of the nuclear membrane, can be found in granulation tissue of ulcers, especially in endothelial cells but also in stromal cells including fibroblasts and smooth muscle cells. Generally, the specificity for H&E has been reported to be 92–100 %, whereas a much lower sensitivity has been described, ranging from 10 to 87 %. The use of immunohistochemistry can improve sensitivity and specificity. However, appropriate antibodies, namely, antibodies against the immediate early antigen of CMV, should be used. Evidence of extensive CMV infection is of predictive value, as it may lead to a reduction of immunosuppressant and/or antiviral therapy may be given [29, 30]. Semiquantitative statements of immunohistochemistry, reporting the number of infected cells and/or the number of CMV-positive biopsy fragments, may have a predictive value [31].

6.1.4 Other Parameters

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, and Paneth cell metaplasia. The presence of ulcerations is an important feature that can reliably be diagnosed (with sufficient reproducibility). An ulceration is a deeper mucosal defect usually characterized by the presence of granulation tissue and/or fibrinopurulent material. An erosion is a more superficial defect. It may sometimes be difficult to distinguish an erosion properly from an artifact-induced mucosal damage (due to the biopsy forceps and a friable mucosa). The presence of flattened or cuboidal cells can be very helpful for this distinction.

Mucin depletion is another parameter which can be recognized with good reproducibility. It may partly be due to epithelial cell damage and should not be confused with restitution phenomena. Some degree of mucin depletion is not unusual in any type of colorectal inflammation although it is less common in Crohn's disease (except in the edge of mucosal defects). Severe almost total mucin depletion is a specific feature separating UC from Crohn's disease. Paneth cells are not usually present in the colon, except for the cecum where occasional Paneth cells can be seen in the base of the crypts. In UC (and less commonly in Crohn's disease) Paneth cells may occur in the crypts in more distal colonic segments (Fig. 6.6). Their presence is highly suggestive of chronic idiopathic inflammatory bowel disease. The muscularis mucosae is sometimes diffusely thickened.

6.1.5 Ulcerative Colitis in Young Children

Colonic mucosal biopsies from children presenting with new-onset ulcerative colitis show significantly less histologic abnormalities across all pathologic parameters routinely used in the evaluation of colitis because the development of the lesions depends partly upon the duration of the disease. Rectal sparing has been well documented at the initial onset [32]. In samples from children between 1 and 10 years of age, significantly less crypt branching, plasma cells in the lamina propria, cryptitis, crypt abscesses, and epithelial injury are present when compared with samples from adults. Focal colitis and/or absence of chronic crypt abnormalities is observed in initial rectosigmoid specimens in approximately 33 % of patients. In 4–8 % of cases the initial biopsy samples are completely normal. Basal subcryptal plasmacytosis is however already observed in approximately 58 % of the cases in a series of children below the age of 10 years old. In samples from children between 11 and 17 years, similar degrees of crypt architectural distortion and plasma cell infiltrates can be found [33, 34]. These differences can probably be explained by the duration of the disease. It can be concluded that especially in young children, awareness of the disease is important. Basal plasmacytosis is probably the most important histological feature. Discontinuity is common in contrast to what is seen in adults [35]. Mucosal atrophy, widespread architectural abnormalities, and Paneth cell metaplasia are uncommon features in biopsies from young children with ulcerative colitis although in some studies performed at tertiary referal centres a high proportion of Paneth cell metaplasia in the distal colon was found in children with UC and CD. Staining for lysozyme may show abnormal morphology of Paneth cells in CD.

6.1.6 Summary

Overall, the histological diagnosis of UC is based on the combination of widespread crypt architectural distortion and a diffuse transmucosal inflammatory infiltrate with basal plasmocytosis, eventually associated with an active component, causing cryptitis and crypt abscesses. Mucin depletion is less specific, but helpful.

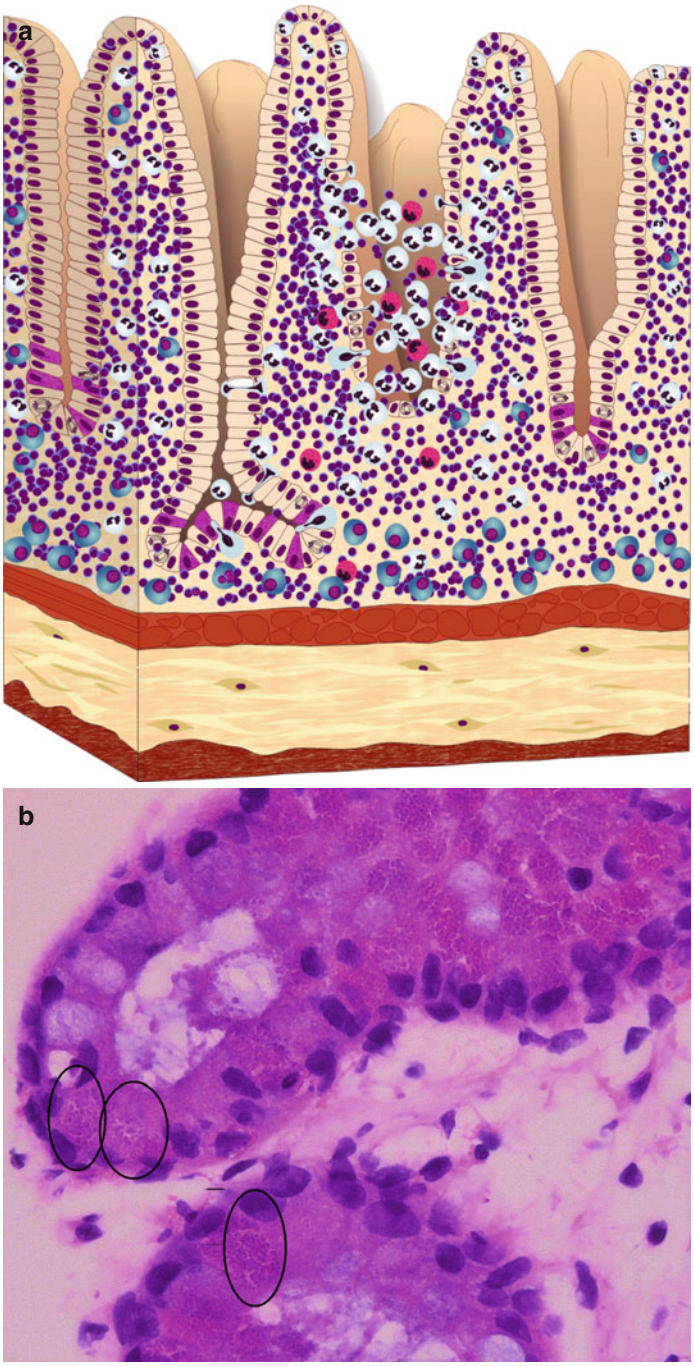

Fig. 6.6 (**a**) Is a drawing of a pattern of active ulcerative colitis with basal plasmacytosis and with Paneth cell metaplasia; (**b**) is a microphotograph of an inactive phase with Paneth cell metaplasia illustrating the supranuclear granules (×40); and (**c**) is a drawing of the same phenomenon

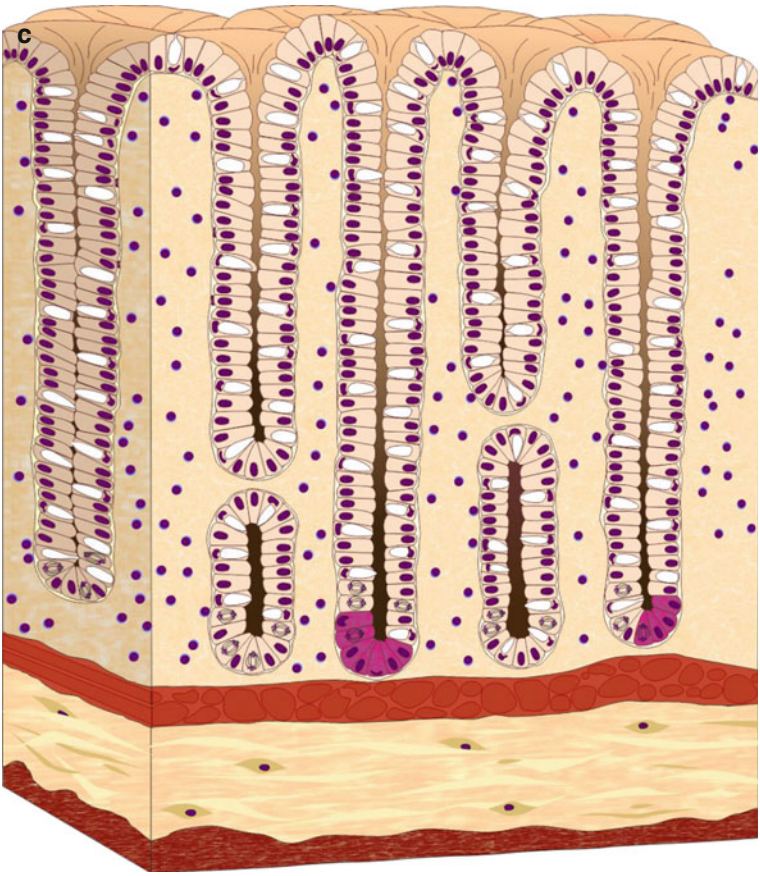

Fig. 6.6 (continued)

A difference in the degree of severity of the lesions along the colon, with more prominent lesions in the distal colon compared with the right colon is a useful additional argument. In children the presentation is often atypical.

Treatment may induce a discontinuous distribution and even some degree of healing [36].

In quiescent disease, the mucosa may show features such as architectural crypt distortion (atrophy and branching) as well as epithelial regeneration, disappearance of basal plasmocytosis, and increased transmucosal cellularity.

A pathology report for ulcerative colitis should also include an assessment of disease activity. A variety of scores has been developed for this purpose, but in clinical practice a distinction between mild, moderate, and severe disease is thus far appropriate [37]. In our opinion severe activity implies the presence of crypt destruction, erosions, or ulcers. Mild activity is more equal to the presence of neutrophils in the lamina propria. Evaluation of mucosal surface damage can be difficult because of confounding factors such as artifacts.

In (severely) active disease, the pathologist should always look for CMV inclusions.

6.2 Crohn's Disease

Crohn's disease is a lifelong inflammatory disease of unknown etiology, probably arising from an interaction between genetic and environmental factors, which can involve different segments of the gastrointestinal tract (Fig. 6.7). The major differences between Crohn's disease and ulcerative colitis are the distribution of the lesions, presence or absence of transmural inflammation, and the ability of Crohn's disease to form fistulas. Crohn's disease is a segmental disease with skip areas that is more prevalent in the proximal colon and ileum, but it can involve the entire digestive tract. A diagnosis of Crohn's disease is therefore most often not based on histology alone but confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and biochemical investigations.

6.2.1 Early Mucosal Lesions

Various types of "early" microscopic lesions have been described in Crohn's disease, mainly in the ileum. They usually occur as focal lesions, in a background of

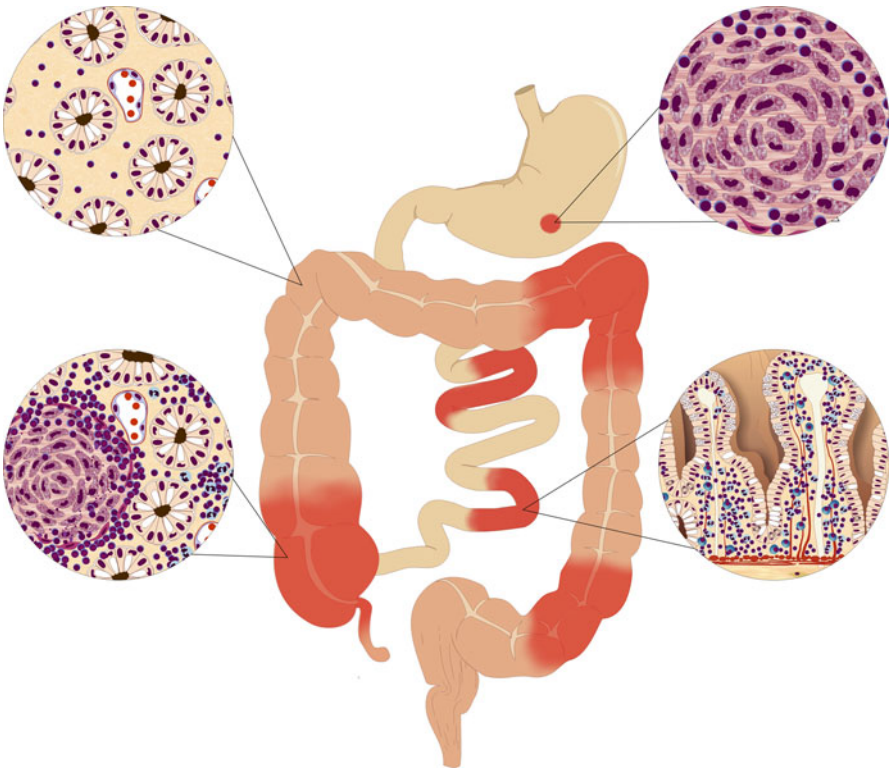

Fig. 6.7 Crohn's disease is a segmental disease: skip lesions can involve the stomach and the ileum and different segments of the colon

normal mucosa in contrast with ulcerative colitis where mainly diffuse epithelial necrosis has been described. Features which are considered to be early lesions include the aphthoid ulcer, epithelial patchy necrosis, or mucosal microulcerations (loss of 1–6 cells) [38, 39]; the occurrence of a naked surface of the dome area overlying a mucosal lymph follicle and loss of M cells [40, 41]; ulcers at the base of crypts with neutrophils streaming into the bowel lumen, leading in a later phase to mountain peak ulcers [42]; and villous abnormalities and damage of small capillaries with subsequent loss of surface epithelial cells (summit lesion) [43]. In general, necrosis of surface epithelial cells is the common element in all these lesions, while crypt epithelial cells seem rarely involved (an exception is the ulcer at the crypt base). Overall, mucosal integrity and barrier function are involved, with alterations of adhesion molecule expression, epithelial apoptosis, and tight junctions [44]. In the summit lesion, microvascular injury may occur before infiltration by inflammatory cells and loss of overlying epithelium [6]. Early vascular lesions have been confirmed, although in most cases, these lesions are associated with inflammation [8]. Overall, biopsies of early lesions do not yield essential diagnostic information and the microscopy of these early lesions is not pathognomonic. An exception to this is the aphthoid ulcer. It is considered to be the initial macrosopic lesion in Crohn's disease. This ulcer has a predilection for the epithelium overlying the lymphoid follicles, although it can occur in other sites with a similar endoscopic appearance. According to some studies, biopsies of aphthoid ulcers more commonly show granulomas, which are diagnostic for Crohn's disease [45–48].

6.2.2 Diagnostic Features: Granulomas

Granulomas in histological sections are a key histological feature of Crohn's disease (Fig. 6.8) [49]. It should however be remembered that granulomas can occur also in other conditions, especially infectious diseases such as tuberculosis but also in Campylobacter and Yersinia colitis and even occasionally in drug-induced colitis [50]. A granuloma is defined as a collection of monocyte/macrophage cells and other inflammatory cells [51]. The macrophages appear as large cells with abundant pale eosinophilic cytoplasm and a large oval nucleus. They are arranged in clusters. Because of this epithelial cell-like morphology, they are called epithelioid cells. According to some authors, a genuine granuloma in Crohn's disease contains five or more epithelioid cells, with or without giant cells. They can be closely packed together and have a sarcoid-like aspect, but a "loose" expanded form of granuloma is more common in Crohn's disease. Central necrosis and caseation should raise the suspicion of tuberculosis. Caseation is however a rare finding and intestinal tuberculosis is more commonly characterized by the presence of multiple and confluent granulomas. Our policy is to do a special Ziehl-Neelsen stain whenever multiple granulomas are present although this is rarely positive. In countries where tuberculosis is still common, this diagnosis should be the first suspect. Giant cells in Crohn's disease granulomas may contain calcified conchoids (Schaumann) bodies [41].

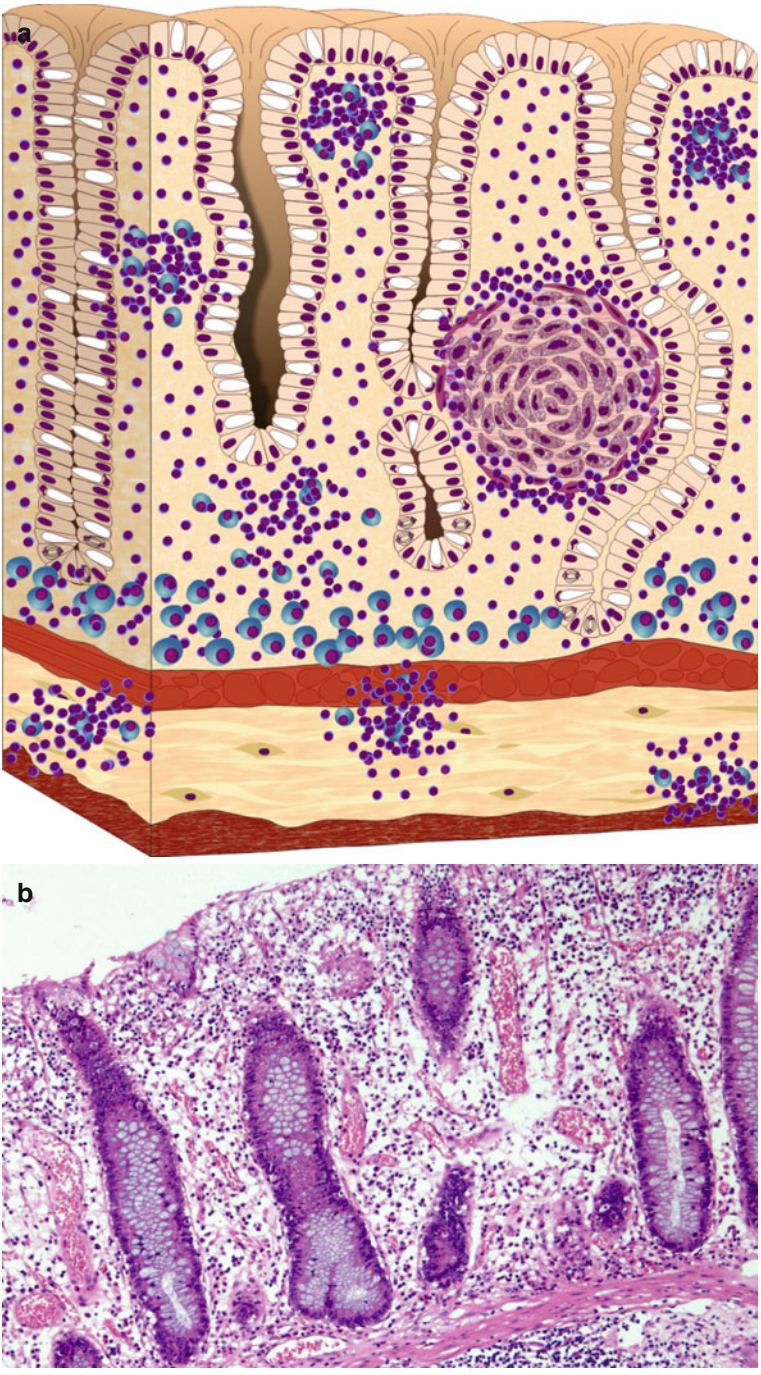

Fig. 6.8 (**a**) Drawing of the microscopic pattern of Crohn's disease illustrating a granuloma and basal inflammation; (**b**) is a microphotograph illustrating a microgranuloma and patchy colitis (×20); (**c**, **d**) illustrate classical compact and loosely arranged granulomas (×40) (**d**)

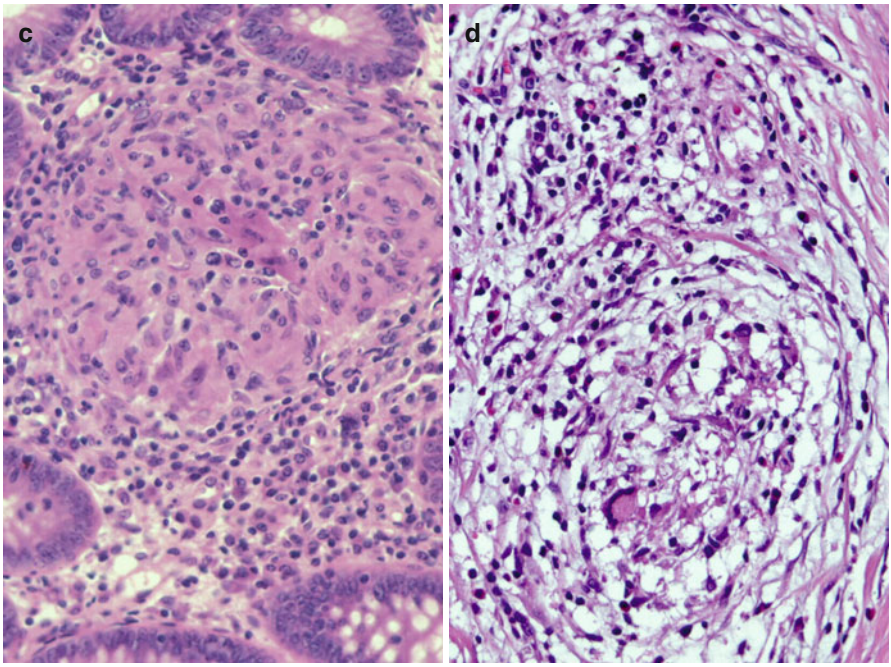

Fig. 6.8 (continued)

Associated inflammatory cells are lymphocytes, usually CD4+ T cells, often showing the expression of CD28, which is a ligand for the B7-related cell surface proteins CD80 (B7-1) and CD86 (B7-2). Immunohistochemical studies have shown that the epithelioid cells may show the expression of MHC class II antigens [52]. Rarely granulomas are seen within a lymphoid follicle. A genuine granuloma should not be confounded with a reactive center in the follicle [53]. More commonly they appear in the periphery of lymphoid aggregates but usually they are not associated with the lymphoid tissue.

The granuloma has to be distinguished from the microgranuloma. This is a lesion which is smaller than the granuloma. It is composed of histiocytes which, like the epithelioid cells, belong to the monocyte/macrophage cells. However, histiocytes are smaller and thus morphologically different from the epithelioid cells in the granuloma. The number of histiocytes in the microgranuloma is smaller than in the granuloma (7–18 vs. 25–90), while the number of lymphocytes is comparable (4–11 vs. 2–15). Microgranulomas are usually situated in the upper part of the mucosa [54]. The frequency of this lesion in Crohn's disease is not well established but seems to vary between 12 and 24 % of endoscopic biopsies obtained in patients with Crohn's disease. The exact meaning of the microgranuloma is still unclear. They seem more common in inactive disease [52]. 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 is defined by the rupture of the epithelial lining and the presence of histiocytes with or without giant cells. While this lesion may be more common in Crohn's disease, it has also been reported in genuine ulcerative colitis [55, 56]. Its diagnostic value is therefore limited.

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 [57, 58]. However, granulomatous inflammation can occur in oral mucosa. When it occurs in oral and vaginal labia, in association with cranial nerve VII and other autonomic nerve disorders and possibly segmental enterocolonic inflammation, it is referred to as the Melkersson-Rosenthal syndrome.

The frequency of finding granulomas in Crohn's disease 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 and 82 % and for endoscopic samples the frequency varies between 3 and 56 %. The highest numbers are observed in children, both in surgical series (82 %) and in endoscopic series. In pediatric Crohn's disease, the incidence of granulomas is twofold compared to adults, but it is reduced after the second year of the disease. The lowest number comes from a surgical series composed of older patients [59–64]. In general, granulomas are more common in the distal colon and rectum [49]. Granulomas are as common in Crohn's disease 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 [45].

The number of examinations can influence the frequency of detection of granulomas. A granuloma was found in 23 % of the patients in whom one colonoscopy was performed and 47 % in whom four colonoscopies were done. The number of samples varied between 2.5 ± 1.4 for one colonoscopy and 8.0 ± 1 for four. It seems however more appropriate to increase the number of biopsy samples per procedure rather than to increase the number of examinations. The practice of taking more than one biopsy during colonoscopy increases the yield clearly. For 1–6 biopsy samples the frequency varies between 11 and 47 %. Six biopsy samples seem an optimal number. When multiple serial sections are examined in the pathology laboratory, the frequency of detection further increases to 50 % [48].

The ideal number of biopsy sections which should be examined in routine practice is not established, but numbers vary between 2 and 6 in different studies [65, 66]. The diagnostic yield increases when more sections are examined. It is not clear whether serial sections or step sections from different levels of the sample should be examined. In one comparative study of rectal biopsies, serial sectioning increased the ability to detect focal abnormalities including granulomas compared to step sectioning [29]. In routine practice, step sections may be the most simple procedure.

It has been proposed to obtain two to three tissue levels, each consisting of five or more sections. Routine staining with hematoxylin and eosin is appropriate for the diagnosis.

While the diagnostic value of the granuloma in Crohn's disease is generally accepted, its clinical and prognostic significance remains unclear. Several studies have examined the relation between the presence of granulomas and prognosis assessing the postoperative recurrence rate, clinically, at endoscopy or the risk of a new surgical intervention. Postoperative recurrence can indeed be a clinical recurrence, which means the reappearance of symptoms after complete resection of macroscopic disease or a morphologic recurrence defined as the appearance of new lesions or both. The results are conflicting. In 8 of 14 studies the presence of granulomas had no influence upon the outcome. In 3 series recurrence was diminished and in 3 other series recurrence rate was increased [46, 62, 67–69]. A variety of other histological features has also been studied for the prediction of postoperative recurrence. These include macroscopic and/or microscopic inflammation of the section margins, the severity of the inflammation, remaining small intestinal lesions, and inflammation of the enteric nervous system in the resection specimen. The latter feature may have a potential predictive value.

The presence of granulomas has been associated with the need of surgical resection, but not immunosuppressive therapy [70], and although they occur more often in young patients, they are not related to polymorphisms of the CARD15/NOD2 (CARD = caspase recruitment domain-containing protein) and Toll-like receptor 4 genes [71, 72]. The R702W polymorphism of the CARD15/NOD2 gene has been found to be associated with the stricturing phenotype of Crohn's disease and the presence of intestinal granulomas [73]. There may be also an association with smoking, a risk factor for Crohn's disease. Smoking has immune modulating effects on mucosal inflammation including reducing antigen presentation and activation of T-helper lymphocytes.

6.2.3 Other Diagnostic Features

It has been suggested that the diagnosis of Crohn's disease 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 [74]. It has also been shown that, although the degree of mimicry with ulcerative colitis may be high, the presence of aphthoid ulcers, fissuring ulcers, transmural inflammation, fistulas, lymphangiectasia, fibrous stricturing, and neural changes is predominantly a feature of Crohn's disease [75]. Six of the features proposed in the second statement can however not be detected on endoscopic samples. Features that can reliably be assessed on endoscopic biopsies with good reproducibility and diagnostic sensitivity are focal (discontinuous) chronic (lymphocytes and plasma cells) inflammation, focal crypt irregularity, focal cryptitis, and ileal lesions [76].

A diagnosis of Crohn's disease on endoscopic samples of the colon therefore relies heavily on the identification of microscopic features of IBD, present in a discontinuous or focal distribution. These features have been examined in a number of studies of rectal biopsies [77–79], colorectal biopsies [80], and surgical specimens [81]. Most of the studies have been performed in adults. Only a limited number of features have acceptable sensitivity, specificity, and predictive value and are sufficiently reproducible. Lesions that favor Crohn's disease other than epithelioid granulomas are discontinuous (=focal) or segmental distribution of crypt atrophy and crypt distortion together with focal or patchy inflammation and mucin preservation in the epithelium at an ulcer edge and the presence of mixture of normal samples (skip lesions) and inflamed samples in a set of biopsies obtained in the same area [82, 83].

Focal inflammation is defined as a small collection of inflammatory cells in an otherwise normal mucosa. 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 ulcerative colitis in long-standing disease or following treatment, but it is important when samples are obtained for the initial diagnosis in untreated patients.

Disproportionate submucosal inflammation can occasionally be seen in endoscopic biopsies. It consists of a heavy submucosal infiltrate with a relatively normal overlying mucosa. This pattern is also suggestive for Crohn's disease while in ulcerative colitis, inflammation is usually "proportionate" or more intense in the mucosa. It should not be confused however with a large solitary lymphoid nodule or multiple small lymphoid aggregates.

Distinguishing Crohn's disease from ulcerative colitis may be different in children and adolescents [84]. Discontinuous inflammation and variable density of infiltration prevail in children, while a diffuse type of infiltration is more common in Crohn's disease in adults. Granulomas are more common in children being present in 26 % of the biopsies and 42 % of the patients. The incidence of granulomas is reduced after the second year of illness and after the 16th year of life [47]. Another feature which helps to distinguish Crohn's disease from ulcerative colitis is the presence of neuronal changes. These changes are however only rarely observed in endoscopic biopsy samples because of the superficial nature of the latter.

Ileal biopsies have rarely been included in studies examining microscopic features. The presence of ileal lesions is however another key lesion which allows discrimination (Fig. 6.9) [85, 86]. Important diagnostic microscopic features 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 (Fig. 6.8), active chronic inflammation, and the presence of granulomas. Edema and marked lymphangiectasia can be present. A disturbed villous architecture was found in 84 % ($n=74$) of 88 patients with Crohn's disease in a series of 257 patients presenting with clinical and radiological signs of IBD. Hypercrinia, the presence of an increased number of goblet cells covering the villi, was another important feature favoring Crohn's in the same series. This was also true for pseudopyloric gland metaplasia

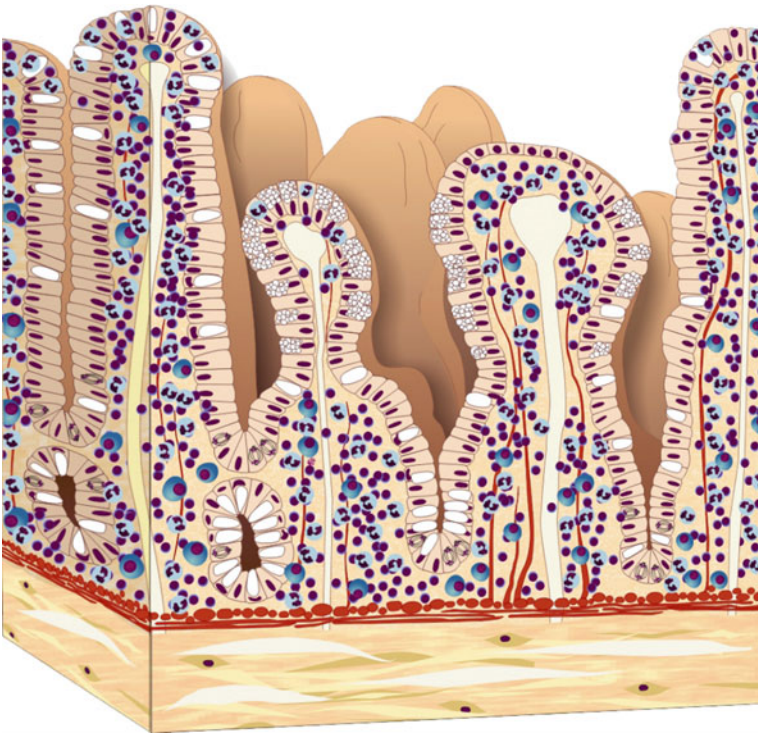

Fig. 6.9 Drawing of an ileal biopsy. The pattern shows irregular villi

(mucoid metaplasia, pyloric metaplasia) which is however a nonspecific feature as it is related to ulceration. The cells in pyloric metaplasia share many features of pyloric and Brunner's glands. The regular acinar glands have a coiled tubular neck and therefore the entire neck is rarely seen in a single section. They have a number of terminal branches that are given off at right angles to the neck, so that they are usually seen in cross section. The glands are lined by low clear or pale-staining columnar cells containing indistinct neutral mucin granules. The nuclei appear oval or round and are located near the base of the cell. The glands develop from the base of intestinal crypts where they extrude and proliferate downward, ramifying in the lamina propria to form a new gland. The gland then generates a duct that penetrates the surface where it carries out secretions and also supplies cells to cover the surface.

The presence of "isolated active ileitis" presents a diagnostic challenge. It may be a feature of Crohn's disease, but it may also be the result of an infection, of drugs, or an associated deeply situated lesions such as endometriosis. The pathology results must be correlated with the clinical data such as age, gender, the presence of fever, and biochemical signs of inflammation or malabsorption [87].

6.2.4 The Value of Multiple, Multistep Biopsies

The contribution of stepwise biopsies for the diagnosis of either Crohn's disease or ulcerative colitis has received little attention in the literature. Most studies have focused on single rectal biopsies. The presence of a discontinuous inflammation in stepwise biopsies has a low discriminating value in adults because it can be found in approximately 30 % of patients with long-standing ulcerative colitis, but it works in children and in patients with a short history of the disease [82]. The presence of an inflammatory infiltration with decreasing intensity from cecum to rectum favors a diagnosis of Crohn's disease [84]. In combination with ileal biopsies, multiple colonic biopsies are therefore useful and recommended for the diagnosis. In general it is known that for the initial diagnosis, analysis of a full colonoscopic biopsy series, rather than a single rectal biopsy, produces the most reliable diagnosis of Crohn's disease. A correct diagnosis can be reached in approximately 70 % of the cases [88, 89]. The findings have been confirmed in children. In children with IBD, diagnostic accuracy of rectosigmoid histology was 0.4524. For ileocolonic biopsies, diagnostic accuracy was 0.7619 [90]. Therefore, it has been proposed to take "multiple" biopsies from 5 sites of the colon (including the rectum) and the ileum. Multiple biopsies imply a minimum of 2 samples of each site.

6.2.5 Disease Activity: Effect of Treatment

As in ulcerative colitis, disease activity is defined by the presence of neutrophils and epithelial damage. In Crohn's disease, however, neutrophils are frequently focally present. They may affect a few crypts in one area, and although a crypt abscess or ulcerated crypt may be at the center (Fig. 6.10), numerous neutrophils tend to remain in the lamina propria. The intense crypt tropism so characteristic for ulcerative colitis is uncommon. Therefore, lamina propria neutrophils outside capillaries are already a marker of active disease.

Microscopic assessment of disease activity with endoscopic biopsies is difficult if not impossible in Crohn's disease because of the segmental and transmural character of the disease. Yet several scoring systems have been designed and even used in clinical trials. The scores are usually based on the microscopic analysis of multiple biopsies from different segments [91]. The scoring systems can be used in association with endoscopy. One of the current goals of treatment in Crohn's disease is indeed to obtain mucosal healing, a result that is assessed with endoscopy. The correlation between endoscopic findings and indices of disease activity and the microscopic scores is variable [52]. This reflects the fact that mucosal biopsies are not necessarily representative of the entire inflammation and that clinical features are not always reliable indicators of disease activity at the tissue level. In some studies there is however a good correlation [92, 93].

Fig. 6.10 Drawing of the pattern of active Crohn's disease showing an epithelioid granuloma and a crypt abscess

6.2.6 Summary

The diagnosis of Crohn's disease on endoscopic biopsy samples is based on the finding of focal abnormalities in architecture and inflammation with or without granulomas, especially when the lesions are predominantly in the right colon. When ileal disease is simultaneously present, the strength of the diagnosis is increased.

Because of the discontinuous nature of the disease, it is important to study multiple step sections of multiple biopsies from different segments of the colon.

During the follow-up of the patients, and at initial diagnosis, it is advisable to assess disease activity because mucosal healing is one of the goals of treatment. Endoscopic biopsies are however less appropriate for this goal because of the transmural and focal character of the disease. In specimens showing active disease, the pathologist should also look for CMV inclusions.

6.3 Indeterminate Colitis: Inflammatory Bowel Disease Unclassified

The morphological diagnosis of ulcerative colitis and Crohn's disease can be difficult during the initial onset. The lesions characteristic for ulcerative colitis are only established after a certain period of time which is usually several weeks to months [10, 14]. This is supported by the data obtained in young children [32]. It is also supported by the finding that patients with distal ulcerative colitis have often a patchy involvement of the proximal colon on endoscopy and/or histology. It may also explain why a correct diagnosis may be difficult also in patients presenting with (acute) fulminant colitis [94]. Labels such as "indeterminate colitis (IC)," "uncertain colitis," "inflammatory bowel disease unclassified (IBDU)," "CIBD unclassified," and "chronic idiopathic inflammatory bowel disease NOS (not otherwise specified)" are used in the literature for patients presenting with chronic colitis without a definitive diagnosis.

The term "indeterminate colitis (IC)" was originally used by surgical pathologists for cases of severe colitis showing either "overlapping features" between ulcerative colitis and Crohn's disease or "data, insufficient to make a decision" [94]. Macroscopically one finds extensive ulcerations, involvement of transverse and right colon, with usually diffuse disease (less severe in the distal colon). Microscopy confirms extensive ulceration with a sharp transition to normal adjacent mucosa and multiple V-shaped ulcers lacking surrounding inflammation. Overlapping features are described as "severe mucosal and wall involvement" [95], none aggregated transmural inflammation [95], fissures reaching the muscularis propria, and a discontinuous pattern [95, 96]. The overlapping features are also recognized in cases with non-severe chronic disease, deep mural lymphoid aggregation and diffuse mucosal disease with normal ileum; non-necrotizing granulomas in lymph nodes and diffuse mucosal disease with normal ileum; anal fistula and diffuse mucosal disease with normal ileum [97, 98].

When the term was introduced, colonoscopy was not yet widely available. Among pathologists, there continues to be a preference to limit the use of the term to the gross and microscopic description after examination of colectomy specimens. However, over the years the definition has been broadened to include endoscopic features, histology, radiology, and even serologic findings. This has caused confusion because there was no longer a uniformly accepted definition. It has been proposed therefore to limit now the term of IC to those cases where surgical resection specimens are available and use "IBD unclassified (IBDU)" for those patients for which only endoscopic biopsies can be examined [99, 100].

The trend to use IC for patients who seem to have IBD but who cannot be readily called UC or CD is still more marked in children than in adults. It has been suggested that upper gastrointestinal (GI) endoscopy with biopsy could solve the differential diagnosis. Whether this is correct remains unclear. The presence of focally enhanced gastritis is not an appropriate marker, as it can occur in both Crohn's disease and ulcerative colitis, even in children, although it is more frequent in Crohn's

disease [101]. The upper GI pathology further tends to resolve, being less common in adults (6–12 %) compared with children (20–75 %) [102, 103]. So it is in some ways "sympathetic" with early disease. Video capsule endoscopy revealing small bowel pathology may be helpful [104]. Histology confined to the colon showing acute and chronic inflammation with architectural changes does not allow definite classification of CD or UC. At present, there are no clear guidelines concerning the number of biopsies needed or the number of sections required for histological evaluation.

In children, however, 4–23 % of new-onset cases present with an equivocal diagnosis. In 2005, a 12-year prospective population-based study included 509 cases of childhood inflammatory bowel disease (7.2 % of all IBD cases): 367 CD, 122 UC, and 20 IC (4 %). The diagnosis of IC was based on a history of chronic colitis compatible with either CD or UC [105]. In another study published the same year, including 202 patients, a diagnosis of IC was made in 45 patients (9.8 % of all IBD cases). The median age was 13 years compared to 14 years for UC and CD. The diagnosis remained the same in seven patients (3.5 %) [106]. The percentage of cases diagnosed as IC among the initial diagnosis of IBD in children varies between 4 and 23 % [10–12]. IC seems thus more prevalent at younger age, especially in the very young. Patients diagnosed with IBD before the age of 2 years were equally affected with UC (31 %), CD (36 %), and IC (33 %). UC was more prevalent among those in the 3- to 5-year group. IC declined progressively with increasing age, being present in 9 % of the 13- to 17-year-old patients [104]. Among pediatric patients with IC, approximately 60 % are ultimately reclassified as UC or CD [105–107]. Reclassified cases are more often UC.

As for surgical series, the definition used for the diagnosis of IC in pediatric patients is not always clear. Imprecision in diagnosis may relate to lack of or insufficient clinical imaging, or endoscopic data or to issues regarding histological variables. In an attempt to clarify the issue, a "pediatric" working party proposed that "Indeterminate colitis can only be diagnosed after a full diagnostic work-up" [108]. In general, the pattern in children confirms data from studies in adults showing that the problem is more common soon after the onset of the disease. For many patients a definite diagnosis is reached subsequently. A small number remains unclassified. While there are microscopic features available for the analysis of resected colons and a diagnosis of IC, there are however no such features for endoscopic biopsies [7, 109, 110]. Therefore, a diagnosis of IBDU is preferred when only endoscopic biopsies are available. Both IC and IBDU are "temporary diagnoses." Scheduled follow-up procedures at 1 and 5 years for reconfirmation of diagnosis and disease activity should be performed.

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Chapter 7
Treatment-Related Diseases

Karel Geboes, Maria Leo, Clara Gerosa, and Peter Van Eyken

Abstract A variety of conditions may develop as an adverse event or within the context of specific types of treatment such as radiation treatment for cancer, some types of surgery, and stem cell or solid organ transplantation. While the microscopic aspect of a colon biopsy may suggest the diagnosis, clinical information is extremely useful because other conditions may mimic certain patterns, or the lesions secondary to the treatment may not be entirely specific. Surgery is sometimes performed in order to divert the fecal stream. Indications for such a procedure can be variable and include, among others, Crohn's disease, collagenous colitis, and acute abdominal conditions such as obstruction and perforation. The interpretation of the lesions can be difficult depending on whether the patient has established inflammatory bowel disease before the procedure or not. In patients with IBD, the differential diagnosis between diversion colitis and IBD may be difficult and rely partially on the study of samples of the non-diverted segment.

Keywords Radiation-induced colitis, acute • Radiation-induced colitis, chronic • Diversion colitis, graft-versus-host (GVHD), acute • Graft-versus-host (GVHD), chronic • Cord colitis • Hematopoietic stem cell transplantation • Apoptosis • Solid organ transplantation • Mycophenolate

Please see Fig. 7.1 for the key to the illustrations.

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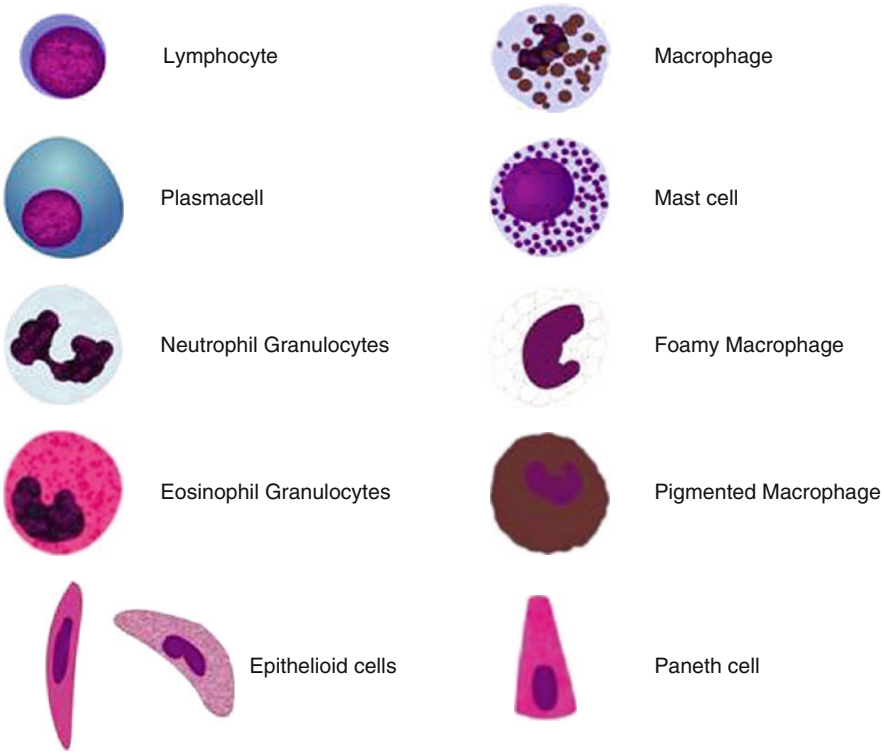

Fig. 7.1 Identification of cell types in the illustrations

7.1 Radiation-Induced Colitis

"Radiation-induced damage" can be subdivided into two distinct conditions: acute irradiation injury (mucositis) and chronic radiation damage. There is indeed a direct toxic effect, responsible for the acute injury, and then an indirect effect which is mainly due to progressive vascular damage and fibrosis, responsible for the late effects [1]. Acute intestinal injury induced by ionizing radiation is directly related to the dose and frequency at which radiation is given. Acute radiation causes DNA (deoxyribonucleic acid) damage. The rapidly dividing progenitor cell populations in intestinal crypts are particularly sensitive to this effect. Concomitant chemotherapy, blocking DNA synthesis, may aggravate the process. Cell division may stop, and an increase in apoptosis will occur, while migration of epithelial cells out of the crypts is not inhibited [2]. The loss of epithelial cells can therefore still induce "restitution." Goblet cell numbers increase transiently between 24 and 48 h after irradiation (while goblet cells appear to be preferentially spared during chemotherapy). Free radical damage, induced by radiation, will further affect epithelial and subepithelial cell populations with disruption of cell-cell and cell-matrix interactions, epithelial denudation, and impaired epithelial integrity (Fig. 7.2). There is also a marked reduction of intestinal trefoil factor messenger RNA (ribonucleic acid) [3].

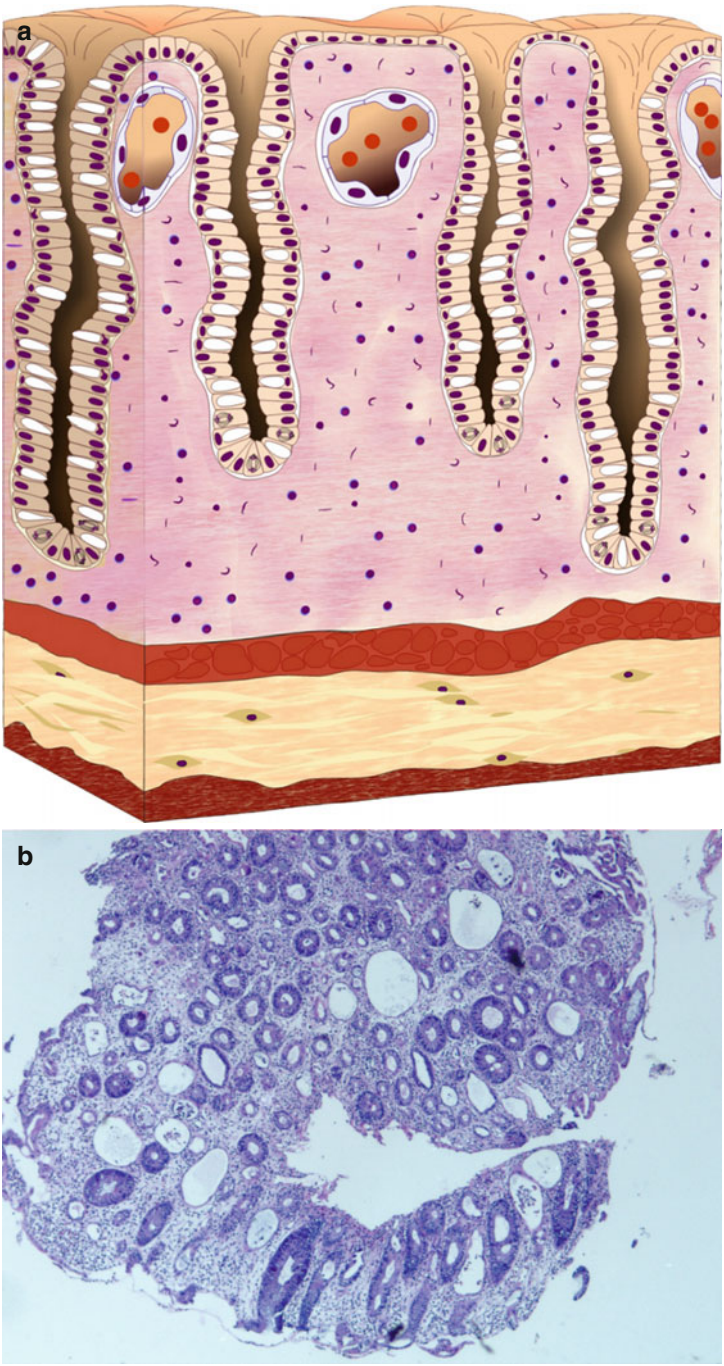

Fig. 7.2 (**a**–**d**) Schematic representation of chronic radiation damage in (**a**) showing superficially dilated vessels (often thick walled) in a fibrotic stroma; (**b**) is a microphotograph of radiation rectitis (×10); (**c**) is a transverse section showing fibrosis of the stroma and dilated vessels; (**d**) is illustrating the epithelial damage occurring during acute irradiation

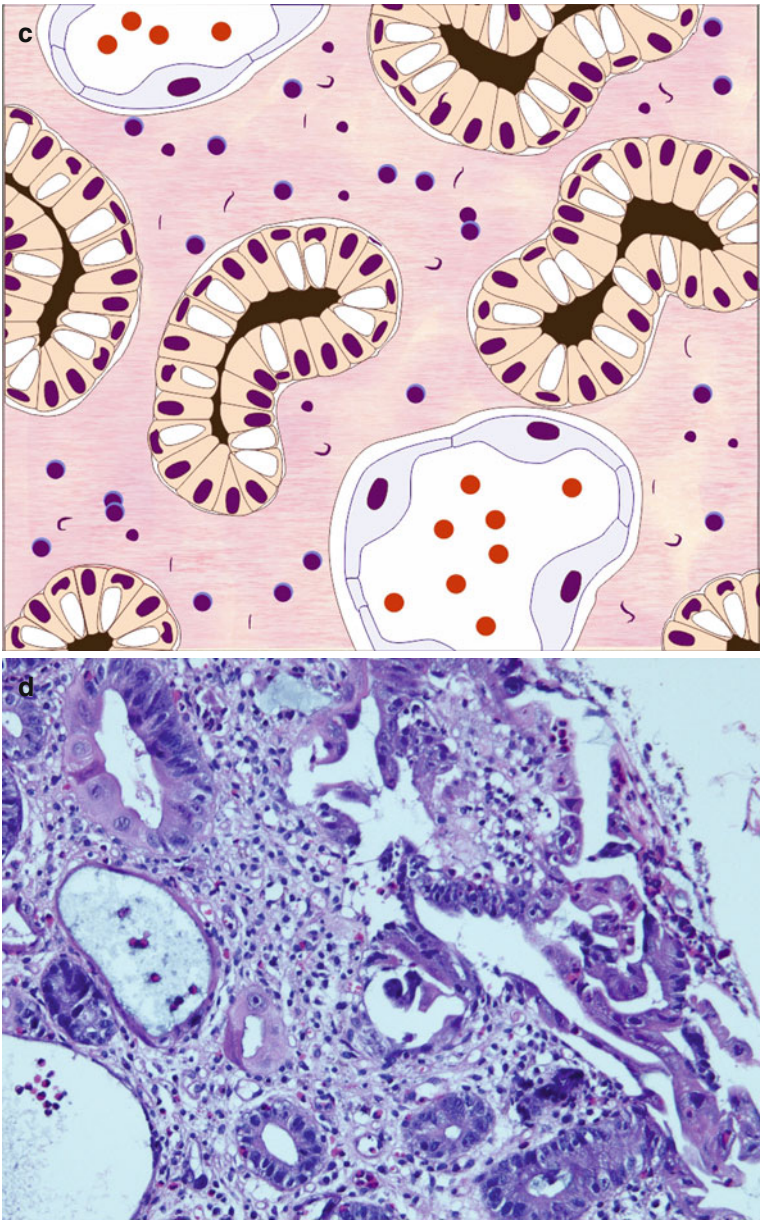

Fig. 7.2 (continued)

The loss of epithelial integrity can trigger a rapid influx of immune and inflammatory cells into the lamina propria.

Aggressive therapies can induce extensive cell loss leading to an almost complete breach of barrier integrity. This can lead to bacterial invasion and colonization

and inflammation. Factors predisposing to intestinal mucositis are an impaired immune status, intestinal damage, high endogenous levels of proinflammatory cytokines, and the presence of pathogens or opportunistic infections [4].

Significant cellular proliferation restarts at around 3–4 days after the onset of therapy. This leads to the restoration of functional crypts and increased crypt numbers. Goblet cell numbers may return to normal at around 4–7 days post-therapy. Paneth cells may be spared during therapy.

Delayed damage is the result of repetitive epithelial, stromal, and vascular lesions. It is an indolent process that can occur 3 months after therapy completion or up to 30 years later. Epithelial lesions include atrophy, delayed necrosis generally resulting from ischemia, and atypia of epithelial cells. Stromal alterations include necrosis, fibrosis, presence of atypical fibroblasts, and lack or paucity of cellular inflammatory reaction. Capillaries are often dilated, with prominent endothelial cells, and rarely thrombosis. Small-sized arteries and arterioles show subendothelial, intimal, or adventitial fibrosis, hyalinization of the media (dense, acellular, acidophilic collagenous material), and accumulation of lipid-laden macrophages in the intima.

The histological pattern of short-term preoperative irradiation therapy is thus generally characterized by severe mucosal inflammation with crypt abnormalities. The surface epithelial cells are absent or attenuated. Crypts show a slit-like or slightly dilated lumen lined with flattened epithelial cells. Crypt epithelial cells may show bizarre nuclear atypia. This may be confusing and wrongly lead to a suspicion of dysplasia. The number of apoptotic bodies is increased. The distance between the crypt base and the muscularis mucosae is generally increased. Decreased crypt numbers or small residual crypts are usually present in areas with severe inflammation. The inflammatory infiltrate is diffuse and transmucosal in distribution. It is composed of a mixture of eosinophils, lymphocytes, plasma cells, and histiocytes. Eosinophils may be present in between the surface epithelial cells or induce cryptitis and crypt abscesses. Aggregates of histiocytes, plasma cells located basally, and increased numbers of intraepithelial lymphocytes are usually not detected. The submucosa shows no or only minor changes (fibrosis) [5].

The most common clinical presentation of chronic radiation changes is radiation proctitis. Endoscopic biopsies show a combination of mucosal atrophy and telangiectatic thick-walled capillaries (which should have at least the diameter of a normal crypt). The capillaries may be separated from the lumen by only one layer of columnar epithelium. Rarely platelet thrombi may be present. The remaining crypts are distorted and frequently show budding. Mucin depletion in epithelial cells tends to be moderate or marked. Nuclei are often larger than the normal, and atypical features such as nuclear stratification may be present (Fig. 7.3). Paneth cell metaplasia can be occasionally be seen. In addition, both Paneth and argentaffin cells may have an excess number of granules, and they may be present on the wrong side of the nucleus. The loose areolar tissue of the lamina propria and submucosa is replaced and thickened by homogeneous masses of collagen and fibroblasts. Fibroblasts are characteristically enlarged, and nuclei and nucleoli become enlarged and prominent. The cytoplasm tends to be basophilic. Submucosal glands can rarely be found as a sequel to irradiation therapy [6].

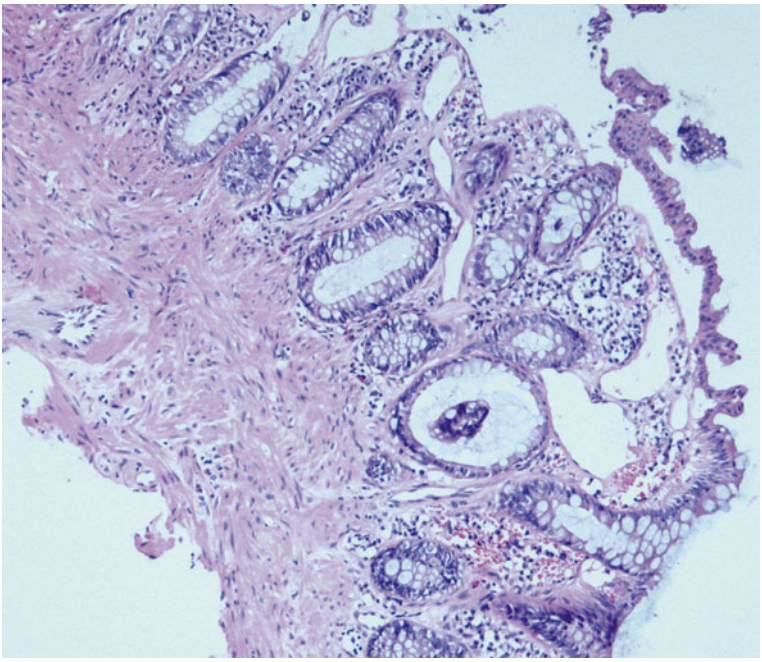

Fig. 7.3 Microphotograph illustrating chronic radiation damage, characterized by fibrosis of the lamina propria, architectural distortion, mild epithelial damage, and dilated vessels in the upper part of the lamina propria (×5)

7.2 Diversion Colitis

Diversion colitis is a chronic inflammatory process that develops in segments of the colon and rectum after surgical diversion of the fecal stream. The pathogenesis is not precisely known. The condition is thought to result from a deficiency of essential short-chain fatty acids (SCFAs) normally produced by fecal bacteria from fermentation of dietary starch. SCFAs, predominantly acetate, propionate, and n-butyrate, are derived from anaerobic bacterial metabolism of unabsorbed dietary carbohydrates. They are absorbed from the lumen by a combination of simple diffusion and ion exchange and oxidized by colonocytes in the preferred order of butyrate, propionate, and then acetate. They are the preferred nutrients of colonocytes, and essential for maintaining mucosal integrity. Most patients with diversion colitis are asymptomatic. However, patients may complain of mucoid or bloody discharge and abdominal pain. Endoscopy may reveal mucosal erythema, friability, nodularity, and ulceration.

In an excluded or diverted, previously normal, rectum mild inflammation is already apparent at 3 months [7–10]. When continuity is restored, the changes disappear completely within 3–6 months. Histological abnormalities show a spectrum of changes ranging from mildly active to severe colitis, but usually the lesions are

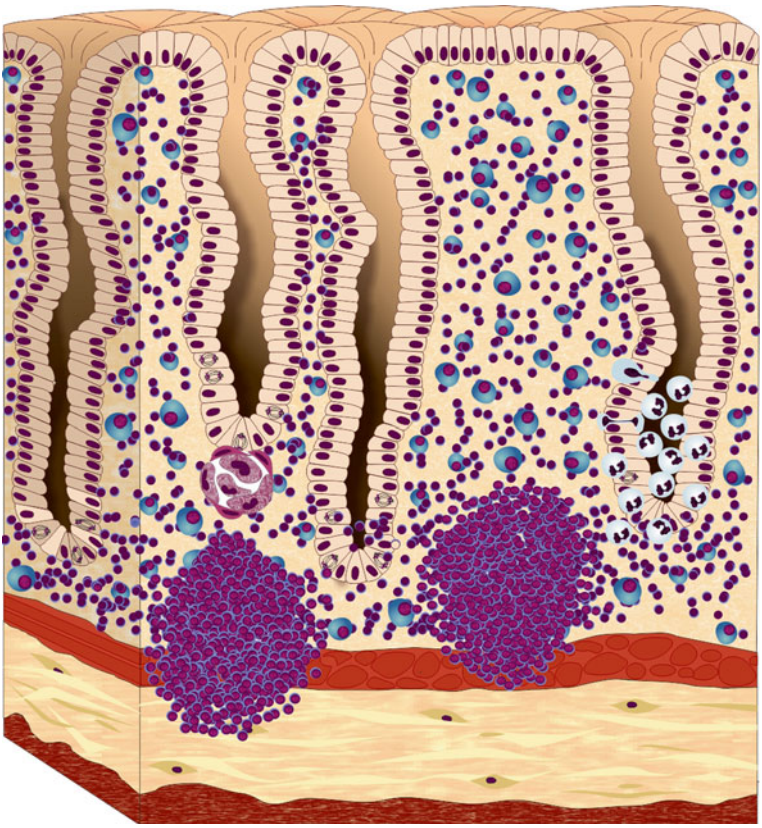

Fig. 7.4 Diversion colitis is characterized by dense diffuse or patchy basal lymphoid hyperplasia, and crypt distortion, crypt abscesses, and atrophy can be present

mild and nonspecific. The cellular infiltrate in the lamina propria is increased in density. It is mainly composed of plasma cells with smaller numbers of lymphocytes, macrophages, and eosinophils. It is confined to the mucosa but may extend to the upper submucosa. The distribution is mostly diffuse but can be patchy. Neutrophils are observed in approximately 50 % of the patients. The active inflammation is usually mild with occasional crypt abscesses (Fig. 7.4). Mucin granulomas can be observed. Mild crypt distortion, atrophy, and branching can be present. Erosions, mucin depletion, reactive hyperplasia of crypts, and Paneth cell metaplasia are uncommon but can be seen. The surface may become ulcerated [11]. Patchy or diffuse lymphoid hyperplasia characterized by prominent lymphoid aggregates with germinal centers involving the lower part of the mucosa and/or submucosa is an important, be it less frequent, feature. The prominent follicular hyperplasia resembles somewhat to what can be seen in the appendix mucosa and allows a correct diagnosis of diversion colitis (Fig. 7.4).

Several 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 ulcerative colitis, the differential diagnosis is difficult and may be virtually impossible. Histological features favoring diversion colitis may be a 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 [11, 12]. 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 [13, 14]. While these features would suggest a diagnosis of Crohn's disease, 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 [14]. In general it seems that the condition worsens in ulcerative colitis, while diversion is favorable in Crohn's disease. In routine practice, it is extremely helpful to have samples from the excluded rectum and the remaining colon (if still present) for comparison.

7.3 Graft-Versus-Host Disease and Cord Colitis

Graft-versus-host disease (GVHD) is a common, potentially life-threatening complication of allogenic hematopoietic stem cell transplantation. Donor T cells may identify the patient cells as nonself and induce a reaction which is not countered by the patient's own immune system. Gastrointestinal GVHD frequently involves the colon.

The "cord colitis syndrome" is considered as a variant complication of hematopoietic stem cell transplantation occurring in patients when the umbilical cord blood is used. It is clinically and histopathologically distinct from acute GVHD. Cord blood transplantation is associated with an increased risk of infection because of delayed immune reconstitution due to the infusion of naive immune cells with the graft. Clinical information is important for the diagnosis of these conditions. The differential diagnosis includes infections, ischemia, drug toxicity, and conditioning regimens such as irradiation.

Acute GVHD is clinically characterized by an abrupt onset of severe watery diarrhea and lesions in the ileum and colon [15, 16]. The rectum can be spared. The optimal site for diagnostic biopsies is the distal colon. Histology shows crypt cell apoptosis which may be focal and mild or extensive (Fig. 7.5). Cell degeneration is mainly located at the base of the crypts. Several variations for the minimum criteria for a diagnosis of acute GVHD, in the absence of confounding features due to infections or conditioning, have been proposed. For a diagnosis consistent with GVHD disease, it was needed to have at least one apoptotic body per biopsy piece, or the total number of apoptotic bodies should at least be equal to the number of pieces, or scattered apoptotic bodies should be present in more than 1 crypt. However, none of these variations specify the number of serial sections that should be examined. Because GVHD may be patchy, it has been proposed to examine between 8 and 20 serial sections [17].

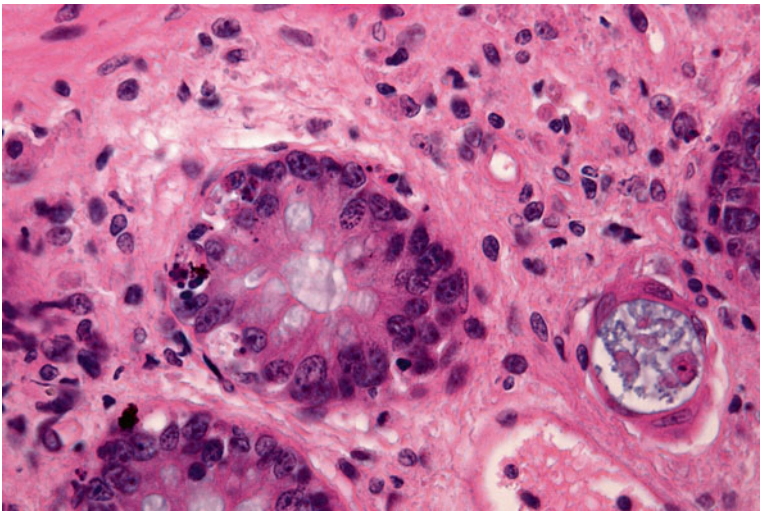

Fig. 7.5 Microphotograph from a biopsy obtained for evaluation of graft-versus-host disease showing crypt epithelial cell apoptosis (×40)

In more severe cases, the epithelial necrosis extends to involve the whole crypt with crypt cell degeneration (resulting in loss of crypts), crypt dilation, and crypt abscess formation. Eosinophils contribute to the injury. Infiltration is variably scant or heavy with destruction of glands and crypt abscesses. Other features are crypt abnormalities (including crypt size variation, crypt dilation, and irregular crypt distribution), reduced mucosal thickness, the presence of muciphages in the lamina propria, an increased microvessel network, and focal fibrosis, and reactive changes in the surface epithelium with mucin depletion. Endocrine cells are usually spared, and inflammation is minimal. In advanced cases, there may be extensive ulceration. The lesions following conditioning or preparation of the patient are usually more diffuse, while acute GVHD is usually more focal. GVHD in the colon can be mimicked by cytomegalovirus colitis or mycophenolate-induced colitis [18].

Four categories have been used for the diagnosis of GVHD. They are not GVHD, possible GVHD, consistent with GVHD (synonymous with probable, favor, or suggestive), and GVHD (yes, without equivocation). Consistent with GVHD applies when there is clear evidence of GVHD with mitigating factors such as small sample, recent chemotherapy or radiation, unequivocal evidence of CMV infection, and rare apoptotic bodies [17]. Severity and prognosis of GVHD are determined by clinical grading supported by histopathological findings. Grades I and II are mild forms, while grades III–IV can be life-threatening. Colonic biopsies may however underestimate the grade and are not entirely without risk because of possible thrombocytopenia [19].

In chronic GVHD the intestinal mucosa is usually less affected. Microscopy usually reflects the duration of the disease. Lesions include destruction of glands, ulceration, or fibrosis of the mucosa and submucosa, lymphoplasmacytic inflammation and Paneth cell metaplasia [17].

Giant cells can occasionally be observed in GVHD.

Cord colitis is a diarrheal disease of uncertain etiology and pathogenesis although a bacterial origin, possibly an as yet unknown pathogen is considered as a probable cause. Biopsies of the stomach and colon may reveal granulomatous inflammation, consisting of scattered ill-defined aggregates of epithelioid histiocytes, with associated mild neutrophilic inflammation and mildly increased epithelial cell apoptosis. In the colon, the granulomatous inflammation can be associated with surface epithelial injury (including surface erosions) and contained occasional multinucleated epithelioid giant cells, but crypt architecture is preserved, and there is no basal lymphoplasmacytosis. Paneth cell metaplasia in the distal colon has been reported [20, 21].

7.4 Colitis and Solid Organ Transplantation

The frequency of colonic complications following solid organ transplantation varies between 2 and 7 % of the patients. The majority of cases presenting with colitis are due to ischemia or infections with viruses such as CMV and human herpesvirus 6, bacteria such as *Clostridium difficile*, or, on rare occasions, parasitic infections such as schistosomiasis. The incidence of ischemic colitis in renal transplant patients varies from 0.3 to 3.15 % and is approximately 1 %. Less common types of colitis that have been reported following transplantation include eosinophilic colitis (associated with the use of tacrolimus (FK506)-based immunosuppression), collagenous colitis, ulcerative colitis, and Crohn's disease. Tacrolimus increases intestinal permeability which will lead to increased systemic exposure to allergenic peptides, and it inhibits interleukin-2 production resulting in an imbalance between Th1 (h = helper) and Th2 cells, possibly contributing to the development of allergic disease. It is suggested that children are more susceptible because of the immaturity of their immunity and intestinal permeability. The symptoms of patients improve with food restriction treatment and replacement of tacrolimus by cyclosporin A. The immunosuppressive agent mycophenolate mofetil (MMF) may induce patterns that mimic self-limited colitis, graft-versus-host disease, or Crohn's disease leading to diagnostic difficulties. Overall, the association between inflammatory bowel disease, organ transplantation, and immunosuppressive therapy is rare. An exception to this is ulcerative colitis after orthotopic liver transplantation. De novo ulcerative colitis was observed in 4 of 314 liver-transplanted patients in one series and in 3 of 120 patients in another series [22–24]. In biopsies from patients with colitis and solid organ transplantation, inflammatory features are often less prominent.

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Chapter 8
Ischemic Colitis

Peter Van Eyken, Daniela Fanni, and Clara Gerosa

Abstract The large bowel accounts for roughly half of all episodes of gastrointestinal ischemia. Three major manifestations of ischemic injury to the colon can be distinguished: massive bowel infarction (gangrenous colitis), hemorrhagic enterocolitis, and ischemic colitis (nongangrenous colitis). Ischemic colitis, usually due to subacute colonic ischemia, is the most common form. The disease can be reversible or irreversible. It affects mainly elderly, but younger patients can also show features of ischemic colitis in particular situations. It occurs on the mucosal side (ulceroinflammatory pattern) or transmural (cobblestoning and strictures). Histology shows a characteristic picture with variable cell necrosis, minimal inflammation, and hyalinization of the stroma.

Keywords Ischemia • Ischemic colitis • Reperfusion injury • Bowel infarction • Hemorrhagic enterocolitis, gangrenous colitis

Please see Fig. 8.1 for the key to the illustrations.

Generally, the mucosa of the gastrointestinal tract receives half of the intestinal blood flow, while the muscularis propria, although accounting for half of the mass of the wall, receives only 30 %. The mucosa is therefore more vulnerable to hypoxia. Local regulation of the mucosal vasculature is an important mechanism for the prevention of ischemic damage. Prolonged ischemia results in a variety of cellular metabolic changes causing ultimately degeneration of cells. Intestinal epithelial cells are more sensitive because of their differentiated phenotype. Hypoxia causes membrane degeneration leading to altered permeability and diminished activity of ATPase (adenosine triphosphatase)-dependent ionic pumps. This induces disturbed osmoregulation and an influx of fluid into epithelial cells with subsequent hydropic degeneration. Lysosomal rupture will increase damage. In most cases, loss of blood flow is however not complete, and even in occlusive disease, much of the mucosal injury develops

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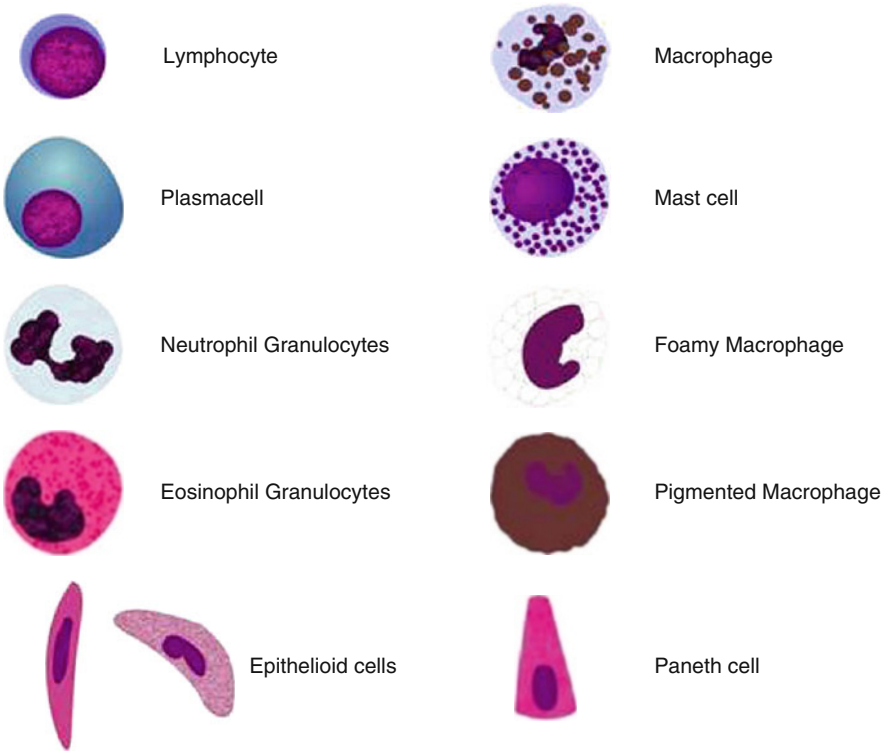

Fig. 8.1 Identification of cell types appearing in the illustrations

after a period of hypoperfusion, that is, when normal perfusion and oxygenation have been more or less restored. This is called "reperfusion injury." Reperfusion damage is mediated by "free radical formation," inflammation, and exhaustion of antioxidant defense mechanisms. The toxic reactive oxygen species (ROS) are potent oxidizing and reducing agents that directly damage cellular membranes by lipid peroxidation. In addition, they stimulate leukocyte activation and chemotaxis. Ischemia is therefore characterized by cell necrosis and mild inflammation.

Three major types of colonic ischemia can be distinguished: massive bowel infarction (gangrenous colitis), hemorrhagic enterocolitis, and ischemic colitis (nongangrenous colitis). The latter type accounts for the large majority of the cases. Massive bowel infarction results from occlusive or nonocclusive vascular insufficiency, usually in association with small bowel infarction. Hemorrhagic enterocolitis is a variant of nonocclusive mesenteric ischemia, with lesions confined to the mucosa and submucosa, occurring usually in severely debilitated elderly. Ischemic colitis is usually due to subacute colonic ischemia. The disease can be reversible or irreversible [1, 2]. It occurs most frequently in the elderly, but an increasing number of younger patients are being identified. It affects both genders in an equal way [3].

In the normal human, the rate of blood flow in the colon is the lowest in the gastrointestinal tract. Colonic ischemia occurs when the blood flow is temporarily

diminished in patients who already have a preexistent impaired blood flow because of arterial or venous thrombi, low flow states, diseases of the small vessels, or an elevated intraluminal pressure caused by a colonic obstruction. Older patients with cardiovascular disorders; patients on various medications such as antihypertensive treatment; people taking drugs, e.g., cocaine; patients with obstructing lesions of the colon such as carcinomas or diverticulitis; and patients with coagulation disorders are at risk. Colonic ischemia can occur in young people after prolonged physical exertion, e.g., long-distance running and following anorexia behavior. Colonic ischemia is frequently observed after aortic or cardiac bypass surgery [2, 4, 5].

The clinical presentation does not always correlate with the degree of ischemia. Colonic ischemia comprises a spectrum of disorders: (1) reversible colopathy (submucosal or intramural hemorrhage), (2) transient colitis, (3) chronic colitis, (4) stricture, (5) gangrene, and (6) fulminant colitis [2, 6].

The histological changes range from mild edema (Fig. 8.2) and hemorrhage to transmural destruction. About 50 % of patients develop some degree of necrosis, followed by granulation tissue, scarring, and fibrous structuring (Fig. 8.3).

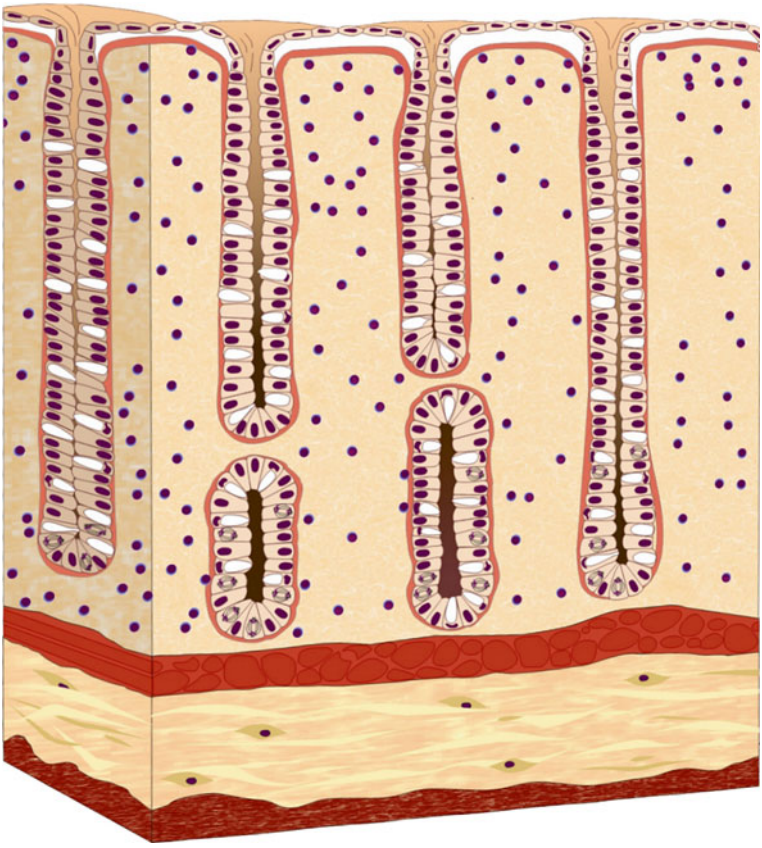

Fig. 8.2 Drawing illustrating the earliest manifestation of ischemia with lifting of the surface epithelial cells and edema

Vascular injury affects the mucosa first. The earliest changes are mucosal congestion and hemorrhage, followed shortly afterward by lifting of the surface epithelial cells and coagulative necrosis of the surface and crypt epithelium [7]. The deep portion of residual glands may persist. In a later or more severe stage, one may still see the ghost outline of the gland crypts, but the entire epithelium is sloughed, and one may then see crypt spaces devoid of epithelium. (Similar changes may occur in an autolyzed bowel, although without the hemorrhage.) This change may result in pseudomembranes composed of necrotic mucosa, fibrin, and blood. Usually however necrosis spares the base of the crypts and muscularis mucosae. The residual glands become more closely spaced due to lamina propria "collapse." They appear as small atrophic micro-crypts lined by irregular cells with darkly staining cytoplasm and variable nuclei. Damage of the stroma such that the normal loose connective tissue is replaced with a dense eosinophilic matrix is responsible for hyalinization of the lamina propria. This is a specific and sensitive marker, which is almost characteristic for genuine ischemia [3]. Capillary microthrombi can occur, and inflammation is minimal, especially in early lesions.

The major differential diagnosis for ischemic colitis is *Clostridium difficile-induced* pseudomembranous colitis. Full-thickness mucosal necrosis, diffuse microscopic distribution of pseudomembranes, and hyalinization are more common in ischemia. In genuine *Clostridium difficile*-associated pseudomembranous colitis, neutrophils are more common, the upper part of the crypts is dilated, and necrosis is mainly present in the upper half of the mucosa [8].

In the healing phase of ischemic colitis, granulation tissue becomes prominent. When necrosis is limited to the mucosa, the bowel is capable of complete resolution without scar formation. However, often, the mucosa regenerates but remains atrophic, with shortened and branched crypts. Paneth cell metaplasia and endocrine cell hyperplasia are occasional findings. Hemosiderin-laden macrophages may be found in the scarred tissue. They have been described as a hallmark of ischemia [9], but, in our experience, this is uncommon. The healing stage of ischemic colitis may thus resemble quiescent inflammatory bowel disease because of the persisting architectural changes. The age of the patient and his or her previous history can help to solve the differential diagnosis.

In ischemic colitis, the submucosa and muscularis propria are markedly widened initially by edema and granulation tissue, which is later replaced by fibrous tissue without the fibromuscular obliteration which is commonly observed in Crohn's disease. Fibrosis may result in stricture formation. Sometimes the submucosal fibrosis extends into the mucosa, frequently in a diffuse manner. This finding may be a useful pointer in the biopsy diagnosis of (healed?) ischemic colitis.

Occasionally cholesterol crystal embolization can be seen. Cholesterol emboli result from the release of cholesterol crystals from ulcerous atherosclerotic plaques. Gastrointestinal involvement occurs in about a third of cases, but is usually asymptomatic. Limited ischemic bowel necrosis, occasionally with subsequent stricture formation, can however occur [10].

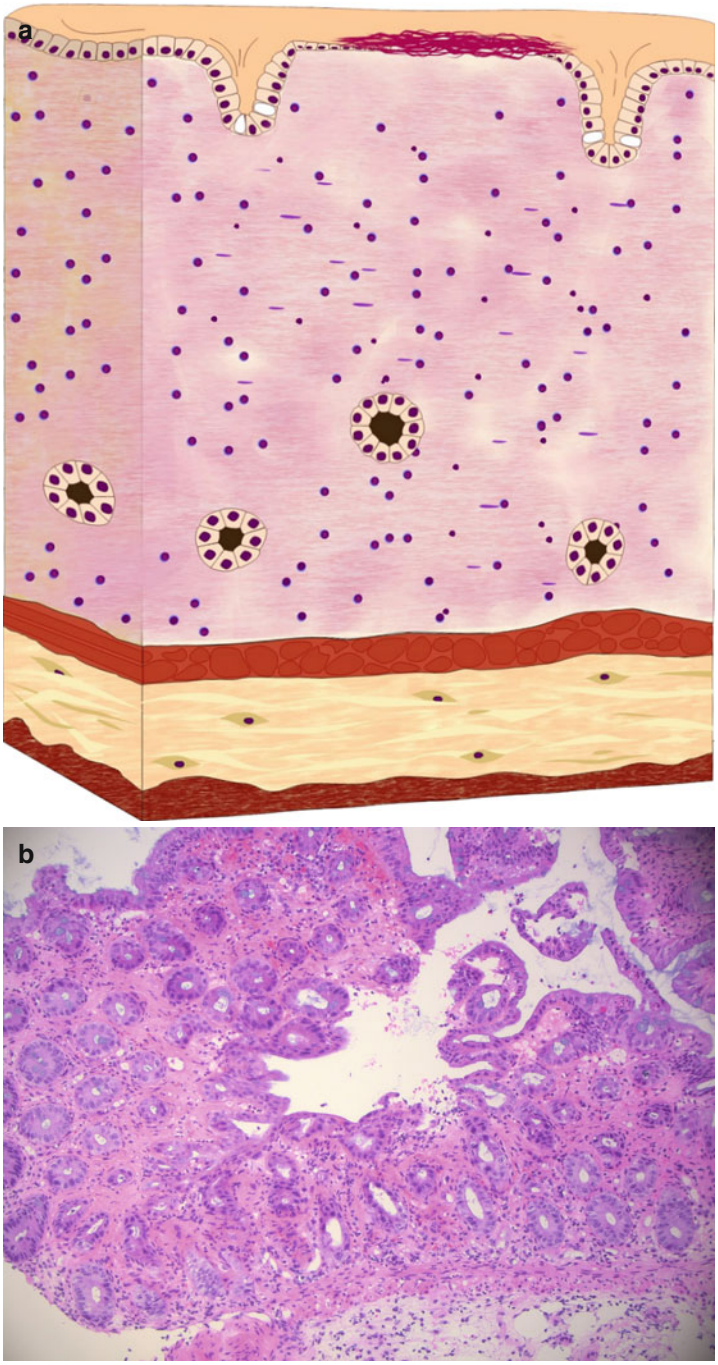

Fig. 8.3 Drawings (**a**, **c**) illustrating loss of crypts, microatrophic crypts, and hyalinization of the stroma. The same phenomena are observed in the microphotographs (**b**, **d**) and are characteristic for ischemia (×10 & ×20)

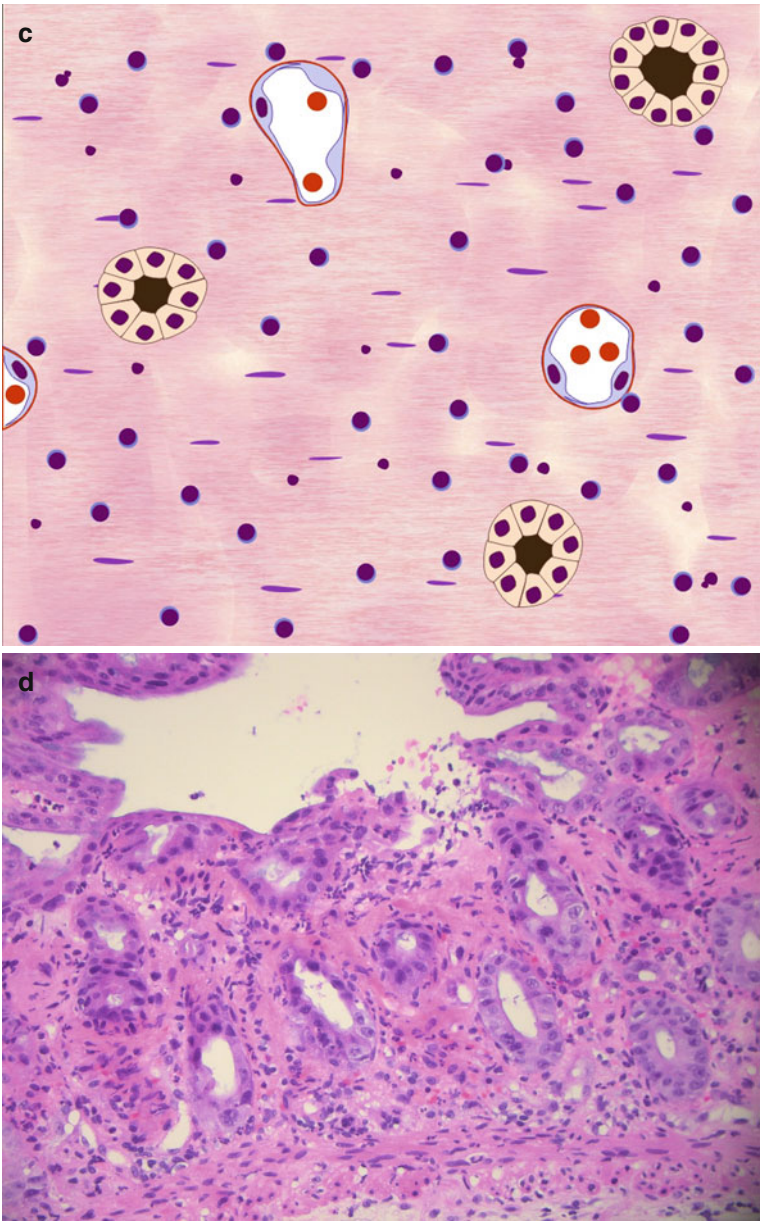

Fig. 8.3 (continued)

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Chapter 9
Diverticular Disease-Associated Colitis

Sonia Nemolato, Daniela Fanni, Clara Gerosa, and Rossano Ambu

Abstract Diverticular disease-associated colitis is characterized by the presence of features of chronic inflammation such as distortion of the architecture and an increase of inflammatory cells which may be associated with basal plasma cells and even granulomas. The lesions are however limited to the sigmoid and should not be diagnosed as either ulcerative colitis or Crohn's disease. For a precise diagnosis, it is essential to know the site of origin of the biopsy.

Keywords Diverticular disease • Diverticulitis • Diverticular disease-associated colitis

Diverticular colitis is a term used to describe a pattern of active chronic inflammation limited to the sigmoid or left colon segments that harbor diverticula. Synonyms are "diverticular colitis," "crescentic colitis," "segmental colitis," and "sigmoiditis." The term refers to the occurrence of luminal mucosal inflammation of the sigmoid, whether or not there is evidence of inflammation within and/or around the diverticula themselves (diverticulitis) [1]. Evidence of diverticular colitis is observed in approximately 25 % of sigmoid colonic resection specimens of middle-aged patients [2]. The condition is often asymptomatic, but endoscopy can reveal mucosal hyperemia, edema, and erosions, especially on the crescentic folds in the sigmoid and rectal sparing. In symptomatic cases, rectal bleeding and/or diarrhea and passage of mucus can be present. The pathogenesis remains uncertain but is probably multifactorial involving mucosal ischemia, and mucosal prolapse. It has also been suggested that diverticular colitis may be related to increased exposure to intraluminal antigens and toxins due to relative stasis. Mucosal biopsies of this condition show features varying from mild inflammation with edema and telangiectasias through mucosal prolapse changes to florid chronic active inflammatory changes including a distorted crypt architecture and basal plasmacytosis, closely mimicking IBD, particularly ulcerative colitis (Fig. 9.1). The proximal and distal colonic mucosa is

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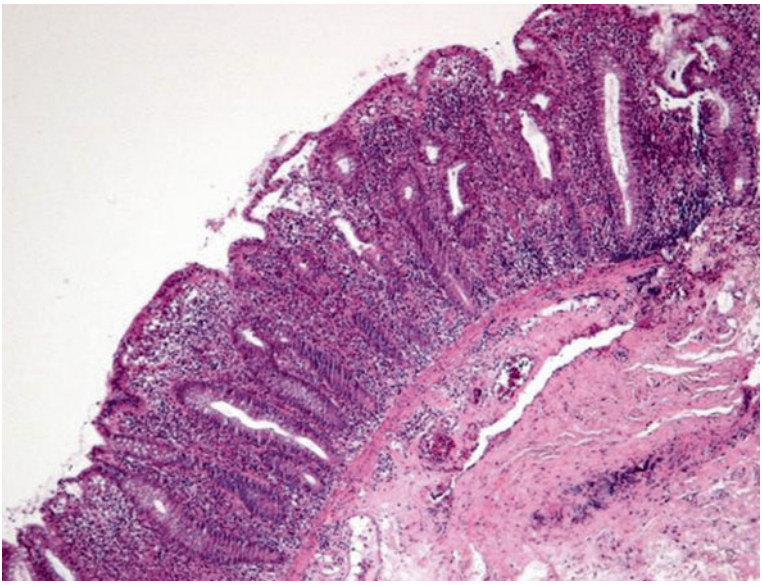

Fig. 9.1 Diverticular-associated colitis can mimic the pattern of ulcerative colitis showing diffuse transmucosal inflammation (×20)

usually normal. For a correct diagnosis, it is therefore essential to study biopsies from the inflamed segment and from proximal and distal areas. The relation of the inflammatory reaction with genuine ulcerative colitis is unclear. Overall, it seems that diverticular disease-associated chronic colitis will precede the onset of conventional ulcerative proctitis and colitis in only a minority of cases [2].

Complicated diverticular disease may also induce changes that are virtually indistinguishable from classical Crohn's disease affecting the sigmoid colon. All three of the diagnostic lesions of Crohn's disease, transmural inflammation, fissuring, and granulomas have been observed. In fact, most cases of putative dual diagnoses (Crohn's disease and diverticulitis) merely represent complicated diverticular disease alone [3, 4]. This does not mean that Crohn's disease and diverticular disease cannot coexist. Concomitant diverticular disease can be observed in more than 50 % of elderly patients with Crohn's disease [5]. However, the diagnosis of coexistent disease can only be proposed when collateral evidence such as ileal involvement supports a diagnosis of Crohn's disease.

Similar features of architectural abnormalities and either superficial or deep mucosal mixed inflammation can also be observed in biopsies from the colon and rectum obtained in elderly patients (>80 years old) without a previous history of IBD. This type of colitis in those patients may equally be due to a combination of vascular and infectious factors.

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Chapter 10
Eosinophilic Colitis

Karel Geboes

Abstract Eosinophilic gastrointestinal disorders (EGID) form a heterogeneous group of diseases, which are classified according to the site of involvement and to the depth of infiltration of the different layers of the gut. The prevalence of these diseases decreases toward the distal part of the gastrointestinal tract. Since its first description by Kaijser in 1937, approximately 300 cases of eosinophilic gastroenteritis have been published. The diagnosis of primary EGID is based on the presence of gastrointestinal symptoms, on histology showing eosinophilic infiltration, usually with eosinophils in an intra epithelial position, and on the exclusion of secondary causes of eosinophilia such as drugs, malignancy, or inflammatory bowel disease. Peripheral eosinophilia is not necessary for the diagnosis.

Keywords Eosinophilic colitis • Primary eosinophilic gastrointestinal disorders • Hypereosinophilic syndrome • Secondary eosinophilic colitis

When a pathologist is faced with a dense eosinophilic infiltration in the mucosa of the colon which is either segmental or diffuse, he/she has to consider three major possible conditions: primary eosinophilic colitis, which belongs to the family of primary eosinophilic gastrointestinal disorders (EGID); secondary eosinophilic colitis; and colitis secondary to the hypereosinophilic syndrome (HES). Primary eosinophilic colitis occurs in infants and adults. In infants, it usually presents as a mild self-limited proctitis. In young adults, it is usually mild self-limited colitis. Clinically, it may be associated with the classical hallmarks of EGID including peripheral eosinophilia (in the range 5–35 %) and functional abnormalities. Synonyms available in the literature are "allergic colitis (proctitis or proctocolitis" and "milk-protein proctocolitis"). The disease may affect primarily the mucosa or the serosa or may be transmural. Mucosa-predominant disease results in diarrhea, while transmural disease may be associated with obstruction, volvulus, intussusceptions, and even perforation. Secondary eosinophilic colitis is observed in a variety of diseases such

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as idiopathic inflammatory bowel disease (IBD), drug-induced colitis, and parasitic and helminthic infections including schistosomiasis, *Strongyloides stercoralis*, and *Enterobius vermicularis*. Drugs involved include gold salts, rifampicin, antiplatelet agents, tacrolimus, and naproxen (see drug-induced colitis). Other associations include connective tissue disease (scleroderma, dermatomyositis, polymyositis), vasculitis (Churg-Strauss), systemic mastocytosis as well as allogenic bone marrow transplantation, and the rare Tolosa-Hunt syndrome characterized by headache, ophthalmoplegia, and cranial nerve palsies [1, 2]. The differential diagnosis with HES can be solved easily because of the clinical characteristics of the syndrome. Classically, patients with the HES have markedly increased levels of blood eosinophilia (>1,500 μl) persistent for at least 6 months, clonal eosinophilia, and involvement of multiple organs. Two distinct subcategories of clonal eosinophilia have been identified: chronic eosinophilic leukemia, NOS (not otherwise specified), and myeloid/lymphoid neoplasms. In HES, the gut is rather an innocent bystander with eosinophils infiltrating various sites [3].

The diagnosis of primary eosinophilic colitis is based on endoscopic biopsies demonstrating hypereosinophilia and on the absence of any other primary disorder that may cause secondary eosinophilic infiltrates. Eosinophils in the stools are also suggestive of eosinophilic colitis. For the pathologist, it is thus essential to have clinical information and to be informed about associated diseases.

The precise etiology of primary eosinophilic colitis is unclear. There is an interaction between genetic and environmental factors. Approximately, 75 % of affected young patients have a history of allergy or atopy. Cow's milk and soy proteins are the foods most frequently implicated in the infantile form, although the condition has been reported in infants exclusively breast-fed or given protein hydrolyzed formulas. The disease is most probably due to the exposure to food allergens, causing a mixed IgE and non-IgE allergic reaction. Mast cell accumulation and degranulation in colonic tissue have been reported which supports the role of IgE in eosinophilic colitis. Furthermore, the reaction may induce a Th2-related immune response. Less is known about the potential causes of the adult form. Food-related anaphylaxis is uncommon [4]. Eosinophilic colitis of infancy is usually a benign disease. On withdrawal of the offending protein, gross blood in the stools usually resolves within 72 h. The vast majority of patients are able to tolerate the culprit food by 1–3 years of age. The prognosis for eosinophilic colitis at lager age is generally good.

Eosinophilic colitis is limited to the colon, but primary and secondary eosinophilic infiltration of the colon may also occur as part of a larger condition which is then called enterocolitis or gastroenterocolitis. Endoscopy of the colon may be normal or reveal edematous mucosa with a loss of the normal vascular pattern, erythematous spots, and even superficial ulcerations. Changes can occur throughout the colon but tend to more prominent in the ascending colon and rectum.

Diagnostic criteria for primary eosinophilic colitis include the presence of sheets or aggregates of eosinophils in the lamina propria and muscularis and of focal aggregates of eosinophils in the (crypt) epithelium (Fig. 10.1). The lesions can be associated with epithelial damage such as erosions and crypt abscesses. For the colon, most authors propose a diagnostic cutoff of 20–35 eosinophils per high-power field

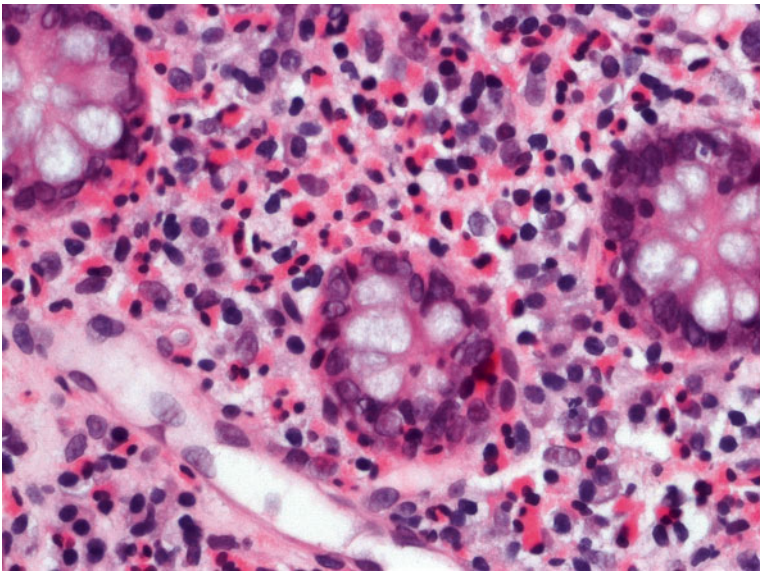

Fig. 10.1 Eosinophilic colitis is characterized by the presence of numerous eosinophils in the lamina propria and in an intraepithelial position (×40)

(HPF), while others suggest an increase of over 60 eosinophils for 10 HPF at 40× particularly in the left colon. The eosinophils can be present as focal aggregates or more diffuse in the lamina propria and muscularis mucosae [5]. Increased mucosal eosinophilia is seen in the absence of histopathological abnormalities suggesting IBD (no distortion of crypt architecture, no basal plasmacytosis, nor a significant increase of neutrophils/mononuclear cells or prominent intestinal tissue damage). They can be present as focal aggregates or more diffuse in the lamina propria and muscularis mucosae [5]. The mucosal architecture is usually normal. Crypt distortion in association with mucosal eosinophils has occasionally been noted in Churg Strauss vasculitis.

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Chapter 11
Microscopic Colitis

Vincenzo Villanacci and Marianna Salemme

Abstract The term "microscopic colitis" refers to a particular clinical-pathological entity, whose pathogenesis is still unknown, and includes two different entities named collagenous colitis (CC) and lymphocytic colitis (LC). The diagnosis is based on a correlation between clinical information and specific histological features. A correct pre-analytical phase, characterized by detailed clinical data and adequate sampling of the different segments of the colon and the ileum, is of paramount importance in the evaluation of these diseases; the latter is particularly important because the morphological findings may be patchy and not continuous.

Histologically, the normal mucosal architecture of the crypts is usually well preserved; in CC, there is a typical thick (>10 mμ) amorphous hyaline eosinophilic band immediately beneath the superficial epithelium of the mucosa, with an irregular, jagged aspect of the lower edge and inflammatory features in the lamina propria.

The histological diagnosis of LC is based upon a diffuse increase of intraepithelial T lymphocytes (IELs) (>20 IELs per 100 epithelial cells) in the superficial epithelium without associated thickening of the subepithelial collagen band accompanied by an increase of lamina propria inflammatory cells.

Sometimes, the histological pattern can show an overlap between CC and LC with features of both being present. Besides, both entities can present some so-called atypical forms and a particular variant, named microscopic colitis incomplete (MCi), is characterized by the presence of clinical features of microscopic colitis without the morphological criteria necessary for a diagnosis of lymphocytic or collagenous colitis. Most patients with microscopic colitis require some form of anti-inflammatory therapy; histologically, few patients show a complete restitutio ad integrum of the colonic mucosa, even though there is a complete clinical remission.

Keywords Collagenous colitis • Lymphocytic colitis • Thick collagen band • Trichrome stain • Lamina propria cellular infiltrate • Increased intraepithelial T lymphocytes • Immunohistochemistry • Atypical forms • Microscopic colitis "incomplete"

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11.1 Definition

The term "microscopic colitis" refers to a particular clinical-pathological entity characterized by three elements:

(A) A clinical history of chronic watery (non-bloody) diarrhea
(B) A normal or almost normal endoscopic appearance of the colon
(C) A peculiar histopathological pattern

Histologically, microscopic colitis can show features of two separate entities: collagenous colitis (CC) or lymphocytic colitis (LC) [1].

The first description of microscopic colitis was published in 1976 by Lindstrom, which described a new pathological entity named collagenous colitis characterized by chronic watery diarrhea, normal endoscopy of the colon, and histologically the presence of a thick collagenous band (over 10 mμ) underneath the surface epithelium in the colonic mucosa [2].

Four years later, the first description of what is now known as lymphocytic colitis was published by Read [3] in a series of 27 patients with chronic diarrhea and histologically the presence of minimal chronic inflammation with a particular feature that was highlighted in subsequent studies [4], which is a marked increase (over 20/100 epithelial cells) of intraepithelial T lymphocytes (IELs) in the superficial epithelium.

In 1986, two groups of investigators [5] showed that the demographic characteristics, the symptoms of the patients, and the response to treatment were similar rather than different for both conditions, proposing the term microscopic colitis for both entities, a term important to remember, valid only from the clinical and endoscopic point of view but not histologically.

11.2 Pathogenesis

The pathogenesis of microscopic colitis is still unknown [1]. Different studies [6] focused on smoking as an important factor for the development of both forms of microscopic colitis, by induction of secondary inflammatory reaction. A recent study [7] suggests a possible IL-6-174 gene polymorphism association with both types of microscopic colitis, mechanism supported by the increase of IL-6 serum concentration in CC as compared with LC, but today an important role seems to be due to drug abuse in particular nonsteroidal anti-inflammatory drugs (NSAIDs) [8].

Gunther et al. [9] studied collagen accumulation in CC, highlighting impaired fibrinolysis rather than increased fibrogenesis as being involved in the pathogenesis of the disease; in particular, connective tissue growth factor (CTGF) and TGF-1β (a stimulator of fibroblast) might be important in the process, as their expression is markedly increased in CC.

Some authors [10] suggested a possible involvement of colonic hormones (serotonin) in the pathogenesis of LC, supported by the high density of chromogranin A immunoreactive endocrine cells in colonic mucosa.

11.3 Procedures

The diagnosis of microscopic colitis is based on a correlation between clinical information and specific histological features. For this reason, a correct preanalytical phase is of paramount importance. It should include detailed clinical data such as the age of the patient and duration of the disease together with the type and duration of any drug treatment that the patient received, if this occurred. Furthermore, an adequate sampling of the different segments of the colon (including the rectum) and the ileum (a minimum of two biopsies for any segment) is necessary.

In fact, in microscopic colitis the morphological findings may be patchy and not continuous; for this reason, not all segments of the large bowel may be affected to the same extent, causing significant variation between specimens sampled from different regions of the large bowel or even within a single biopsy specimen. As a consequence, rectal biopsy alone appears to be insufficient for making the diagnosis of microscopic colitis and sampling within the range of sigmoidoscopy may not be adequate. Thus, it is advisable to take multiple biopsy samples throughout the whole colon, a minimum of two for each segment of the colon, which should be submitted, preferably, in separate containers [1].

This recommendation is in the line with the recommendations put forward by Yantiss and Odze [11]: for "optimum detection," these authors recommend to perform full colonoscopy with two or more biopsies each from the right, transverse, descending, and sigmoid colon, in addition to sampling of all endoscopically visible abnormalities.

Sections are routinely prepared and stained with hematoxylin and eosin; special stains such as trichrome and Van Gieson stains and immunohistochemical stains with antibodies directed against tenascin, CD3, and CD8 T lymphocytes are recommended.

11.4 Histology

In biopsies from patients with microscopic colitis, the normal mucosal architecture of the crypts is usually well preserved. The surface epithelium may show degenerative and/or regenerative changes, such as vacuolization, flattening, and mucin depletion [12]. Damage to the surface epithelium is usually more pronounced in collagenous colitis [13]. Detachment of surface epithelial cells from subepithelial collagen is a characteristic finding.

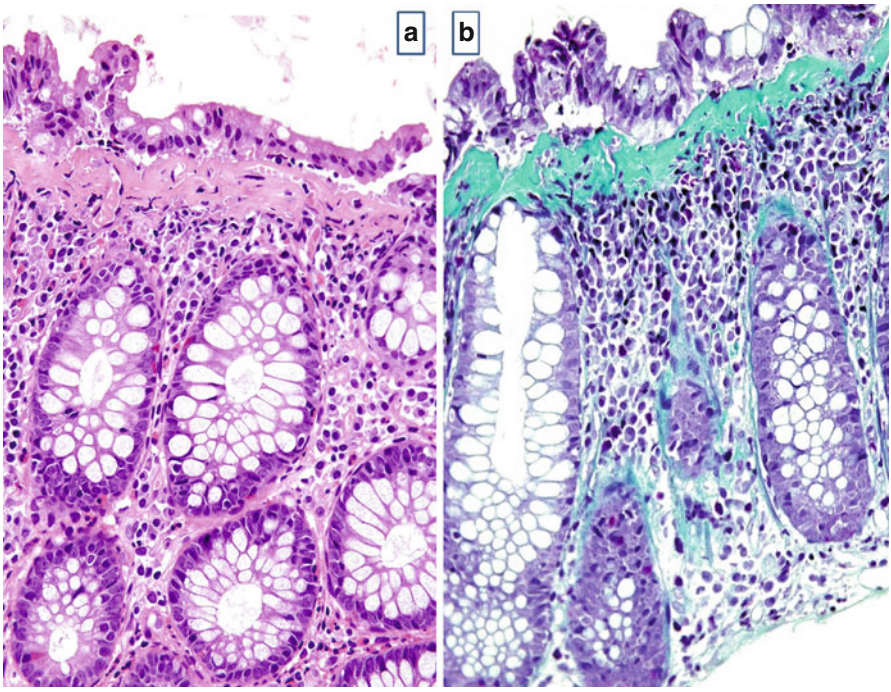

Fig. 11.1 Microphotograph of a biopsy of collagenous colitis: the subepithelial collagen table is markedly thickened and irregular. **(a)** The thickening is confirmed by special trichrome stain. **(b)** The density of the cellular infiltrate in the lamina propria is clearly increased

The diagnosis of CC on routinely hematoxylin- and eosin-stained sections is based on the presence of a thick amorphous hyaline eosinophilic band immediately beneath the superficial epithelium of the mucosa. This layer has an irregular, jagged aspect of the lower edge. The thickness is >10 mμ. Its presence is associated with inflammatory features in the lamina propria [1] (Fig. 11.1).

The most important elements for the assessment of the collagen band are the thickness and the irregularity.

The average thickness of the normal subepithelial collagen table is approximately 3 μm [14, 15]. There is still no real consensus among pathologists as to how thick the collagenous band should be and about the "ideal method" for the assessment of the thickness of the collagen band (histological estimate, conventional measurement using a calibrated micrometer scale or semiautomatic micrometer measurements). However, in most studies, a thickness more than 10 μm is considered to be diagnostic for CC. A common pitfall for the diagnosis is the misinterpretation of the basement membrane as collagen deposition in poorly oriented, tangentially sectioned biopsy sections. A trichrome stain is a useful ancillary technique because it allows the identification of the presence of collagen.

It is important to keep in mind that the collagen deposition can be patchy in distribution and thickness can be highly variable along the length of the entire colon;

in some studies, the increase of the collagenous band appeared to be more prominent in the right colon compared with the left colon [13]. Besides, although the collagen band is usually amorphous, capillaries and fusiform cells can be found within the material [16].

Several studies have shown that the collagen band consists predominantly of type VI collagen and tenascin. The latter is a glycoprotein involved in organogenesis and reappears in matrix remodeling during active inflammation and healing. The fusiform cells usually present within the collagen matrix have ultrastructural features consistent with activated pericrypt myofibroblasts [17].

Thickening of the collagen band can be seen in other conditions such as ischemia, diverticular disease, mucosal prolapse, diabetes, and curiously hyperplastic polyps. In these conditions, however, the inflammatory changes necessary for the diagnosis of CC are not present. Amyloid colitis can also show the presence of thickened eosinophilic material underneath the surface epithelium. This can be identified with specific stains such as Congo red.

CC is an inflammatory disorder and for this reason, inflammatory features are an essential component of the diagnosis. The density of the lamina propria cellular infiltrate is overall increased with a loss of the normal predominance in the upper part and increased numbers of plasma cells and lymphocytes around the crypt bases. The composition of the infiltrate is usually changed. Eosinophils may be markedly increased and are sometimes seen infiltrating crypt and surface epithelium together with T lymphocytes. Neutrophils are often present and may induce cryptitis and occasional crypt abscesses [1].

The histological diagnosis of LC is based upon a diffuse increase of intraepithelial T lymphocytes (IELs) (>20 IELs per 100 epithelial cells) in the superficial epithelium without associated thickening of the subepithelial collagen band accompanied by an increase of lamina propria inflammatory cells [1] (Fig. 11.2). The exact number of intraepithelial lymphocytes needed for the diagnosis of LC is not determined. The required number varies between 10 and 20 per 100 surface epithelial cells (normal number = 4 – 10). In the study by Lazenby et al. [4], there was an average of 24 lymphocytes per 100 surface epithelial cells. In general, a number of more than 20 intraepithelial lymphocytes are considered as diagnostic for LC. There is no tendency for prominent increase in a particular segment of the colon although inflammation may be less prominent in the left colon. Immunohistochemical analysis shows that the increased IELs retain the normal CD3-/CD8-positive T-suppressor cell phenotype.

LC is considered an inflammatory disorder; therefore, the increase of IELs is associated with surface epithelial injury. While plasma cells are numerous, the predominant cell type in the lamina propria and in crypts is that of T lymphocytes [18].

Obviously, the diagnosis of LC should be made in conjunction with clinical, endoscopic, and histological findings. Resolving infections, drug reactions, and also an early manifestation of celiac disease can lead to similar features, such as increased epithelial lymphocytosis, epithelial injury, and lamina propria inflammation, and in particular, in cases of LC, the exclusion with serological tests (TtG) of celiac disease is mandatory.

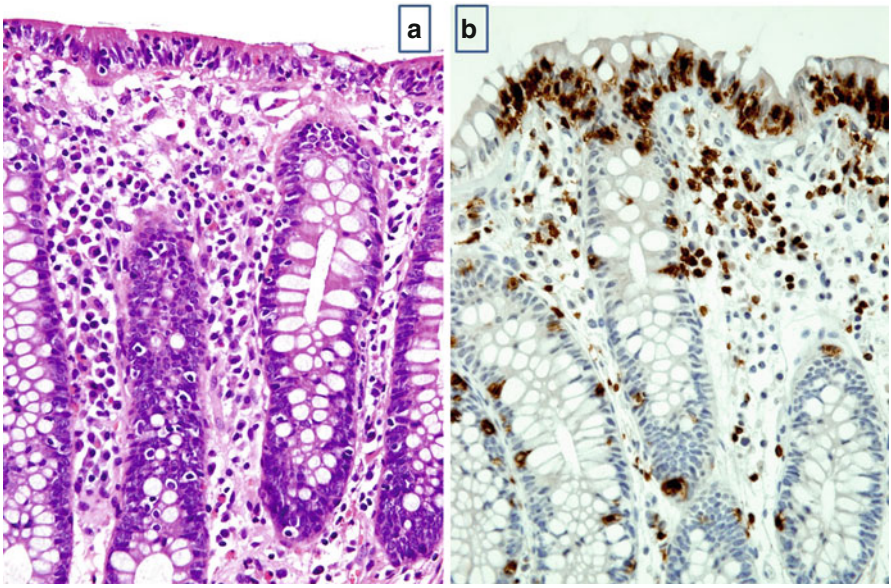

Fig. 11.2 Microphotographs of the classical pattern of lymphocytic colitis. The increased epithelial lymphocytosis **(a)** is confirmed with immune staining using antibodies against CD3 **(b)**

11.5 Pitfalls

Sometimes, the histological pattern can show an overlap between CC and LC with features of both being present [1]; this has been reported in up to 30 % of patients in some series [19, 20]. Besides, it is important to remember that features of both CC and LC can be present simultaneously with some biopsies showing a pattern of lymphocytic colitis and others that of collagenous colitis and that a patient can present with one form of the disease and subsequently develop the other type [1]. Another important aspect is that both entities can present some so-called atypical forms as evidenced in the following scheme of Chang (Fig. 11.3) [21].

11.6 Microscopic Colitis "Incomplete"

A particular variant of microscopic colitis is named microscopic colitis incomplete (MCi). This entity is characterized by the presence of clinical features of microscopic colitis without the morphological criteria necessary for a diagnosis of lymphocytic or collagenous colitis.

Histology shows an increased inflammatory infiltrate in the lamina propria and an abnormal collagenous band <10 μm or an increased number of IELs <20 per 100 epithelial cells. Some authors [22] have tried to analyze clinical-pathological

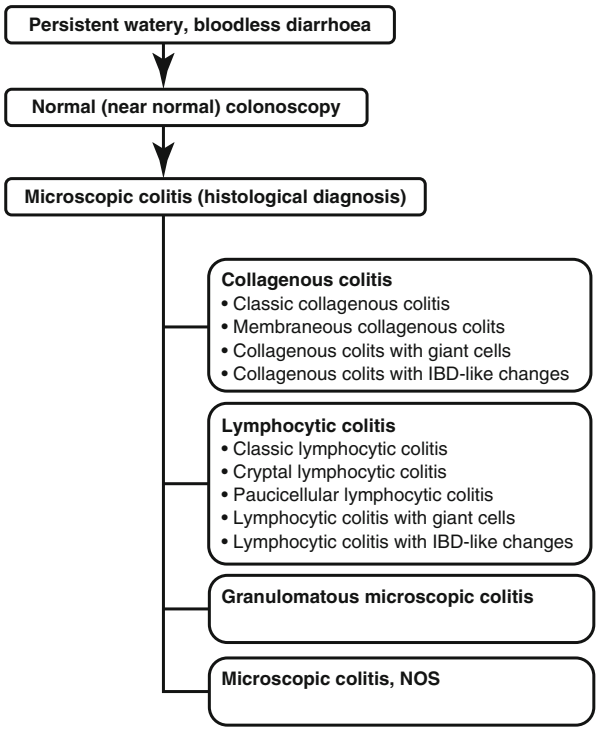

Fig. 11.3 Scheme of Chang et al. [21]

features of patients with a diagnosis of MCi, finding that a significant subgroup of cases with MCi had in fact LC or CC. Also, the majority of described MC patients with a primary not diagnostic endoscopy had chronic inflammation or MCi in their biopsies, supporting the concept that patients with incomplete signs of MC or MCi should probably be included with the established MC subgroups and should be examined further.

The histological diagnosis MCi could thus be the pathologists' contribution to reduce the risk of missing patients with a treatable cause of chronic diarrhea, and in the near future, it is necessary to plan prospective therapeutic trials of patients with this particular diagnosis.

11.7 The Influence of Treatment

Some patients with microscopic colitis have a spontaneous clinical remission, while others respond to simple over-the-counter antidiarrheal agents. Most patients, however, require some form of anti-inflammatory therapy (steroids and/or 5-aminosalicylic acid compounds) or imunosuppressants. From the histological point of view, in few patients undergoing follow-up biopsies, there is a restitutio ad integrum of the colonic mucosa, even though there is a complete clinical

remission. However, a standardized follow-up plan still not exists; in this context, the clinician has an important role to guide the better clinical-pathological approach for each single case.

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Chapter 12
Drug-Induced Colitis

Vincenzo Villanacci and Marianna Salemme

Abstract Drug-induced injury of the gastrointestinal tract is a relatively frequent though usually underestimated event, whose pathogenesis is based on different mechanisms.

The term "drug-induced colitis" at present does not identify a "real" nosological entity, because usually the diagnosis of this condition is based on clinical and endoscopic features, in the absence of clear histopathological findings.

The clinical presentation can be classified into two forms: an acute pattern with either prominent ischemia, constipation, or acute diarrhea and a more chronic pattern with chronic diarrhea that appears a long time after the start of drug therapy.

The histological manifestations are different, ranging from inflammation to ischemia, ulceration, or strictures, in some cases mimicking other pathological entities with different etiology.

In particular, the morphological features can be classified into different patterns: the inflammatory pattern (including hemorrhagic and pseudomembranous colitis, "microscopic colitis," ulcerative colitis-like pattern, and Crohn's disease-like pattern), the ischemic pattern, and the group of specific patterns (such as fibrosing colonopathy, apoptotic colopathy, and "pseudomelanosis or melanosis or pseudolipofuscinosis coli").

It is also important to remember that some drugs can induce duodenal villous blunting with consequently malabsorption.

Finally, the hemorrhagic manifestations of anticoagulants on the GI tract are analyzed.

Keywords Diarrhea • Inflammation • Active infectious type colitis • Pseudomembranous colitis • Microscopic colitis • IBD-type colitis • Ischemic-type colitis • Apoptotic colopathy • Enteropathy • Hemorrhage

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12.1 Epidemiology and Definition

Diarrhea is a frequent side effect of drugs, accounting for about 7 % of all adverse effects [1]. In a series of 5,669 patients treated with lansoprazole, the prevalence of diarrhea was 4.1 % [2]. In a series of 11,541 patients treated with pantoprazole, the major adverse advent and reason for stopping was diarrhea (106 pts) [3]. More than 700 drugs have been implicated. Those most frequently involved are antimicrobials, laxatives, magnesium-containing antacids, lactose- or sorbitol-containing products, NSAIDs, prostaglandins, colchicine, antineoplastic agents, anti-arrhythmic drugs, and cholinergic agents. The mechanism by which the diarrhea is induced can be variable and may affect the small intestine, the large intestine, or both. Diarrhea is not the only symptom which can be part of the clinical presentation of drug-associated diseases of the small and large intestine although is probably the most common manifestation. Drugs like galantamine, a competitive acetylcholinesterase inhibitor used for symptomatic treatment of Alzheimer disease, can be responsible for abdominal pain, nausea, and vomiting without obvious injury because of the influence of the drug on gastrointestinal (GI) motility [4]. Constipation is also a side effect of many frequently prescribed medications. A search of pharmacologic agents yields more than 280 products from a variety of classes listing constipation as an adverse event in more than 3 % of treated patients [5]. Other adverse effects of drugs on the small and large intestine include malabsorption, hemorrhage, intestinal obstruction, ulcerations, and ischemia. Colon ischemia is the most common form of ischemic injury.

Drug-induced injury of the gastrointestinal tract is a relatively frequent though usually underestimated event [6, 7], due to several factors, but first of all the lack of knowledge of the side effects of drugs, whose use and often abuse are dramatically increasing. The incidence of drug-induced colitis is not precisely known. In France, 80 cases were reported to the "Centre de Pharmacovigilance" for the period 1984–1994. Reports in the literature are usually limited to cases or small series.

The term "drug-induced colitis" at present does not identify a "real" nosological entity, because usually the diagnosis of this condition is based on clinical and endoscopic features, in the absence of clear histopathological findings. The diagnosis of drug-associated disease of the small and/or large intestine is therefore not simple. The GI tract can be normal or show inflammation, ischemia, ulceration, or strictures. In the large intestine, inflammation can be classified as "active - infectious-type colitis" including "pseudomembranous colitis," "microscopic colitis," or even as "IBD-type colitis" and "ischemic-type colitis." The diagnosis is essentially based on clinical suspicion and the awareness that a patient is taking drugs. A pattern of ischemic-type colitis in a young immune-competent patient is uncommon and should arouse suspicion. Age is an important element to suspect a drug-related disease (NSAIDs are more commonly taken by elderly).

From the clinical point of view, the diagnosis of drug-induced colitis relies upon the presence of chronic or bloody diarrhea and the following elements that demonstrate a correlation between drug use and the onset of colitis [8, 9]: (A) establish a temporal relationship, (B) link with withdrawal or rechallenge of the suspected drug, (C) ensure that the onset of colitis cannot be explained by an underlying

Table 12.1 Drug-induced pathology of the large intestine

Erosions and ulcers	NSAIDs, KCl
Strictures	KCl, pancreatic enzyme replacement
Microscopic colitis	PPIs, ticlodipine, ranitidine, simvastatin, carbamazepine, paroxetine, sertraline, penicillin V, Cyclo 3 Fort, NSAIDs
Pseudomembranous colitis	Antibiotics, PPIs, chemotherapy
Neutropenic colitis	Cytosine arabinoside, cisplatin, vincristine, adriamycine, 5-FU, mercaptopurine
Malakoplakia	Corticosteroids
Perforation	Contrast media
Sigmoid diverticular perforation	Corticosteroids, NSAIDs
Ischemic colitis	Digitalis, diuretics, ergotamine, cocaine, Kayexalate, glutaraldehyde, sumatriptan, γ-interferon, dopamine, methysergide, NSAIDs, following angiography (trauma to vessel wall or embolization)
Focal active colitis	NaPO4, NSAIDs
Epithelial atypia mimicking dysplasia cyclosporin	
Apoptosis	NSAIDs, NaPO4, anthraquinones, 5-FU, irinotecan
Hemorrhages and hematomas (intramural and retroperitoneal)	Anticoagulants

disease or other known drug effect, and (D) estimate the certainty of the association. The presence of these clinical features is particularly important because the absence of a strong clinical suspicion index may erroneously lead to a diagnosis of irritable bowel syndrome or unspecified colitis.

Endoscopically, in most cases of drug-induced colitis, there are "normal" colonoscopy findings; however, it is important to remember that this "lack of visible lesions" does not necessarily imply microscopic/histological normality.

The clinical presentation of drug-induced pathology of the large intestine can schematically be subdivided in two major patterns: an acute pattern with either prominent ischemia, constipation, or acute diarrhea which appears during the first few days of treatment and a more chronic pattern with chronic diarrhea lasting more than 3 or 4 weeks and which can appear a long time after the start of drug therapy. Both can be severe and poorly tolerated. The microscopic spectrum ranges from benign without microscopic lesions on hematoxylin- and eosin-stained sections over mild edema to fulminant colitis and severe lesions including extensive necrosis. Other abnormalities which can also be induced by drugs in the small and large intestine are hemorrhages and hematomas and microscopic features such as mimics of dysplasia and epithelial apoptosis (Table 12.1).

12.2 Pathogenesis

Several mechanisms are involved in the pathogenesis of drug-induced small and large intestinal symptoms and injury (Table 12.2). Some drugs cause injury by a physical event: simple entrapment of a pill in the mucosa. In the colon, this is a rare

Table 12.2 Mechanisms involved in drug-induced ischemia, diarrhea, and colitis

Ischemia
Embolization – thrombosis
Vascular spasm
Vascular compression
Vasculitis
Low blood flow
Hypercoagulation, platelet aggregation
Ulcerations and strictures
Inhibition of prostaglandin synthesis (NSAIDs)
Direct toxicity (potassium chloride)
Hemorrhage (anticoagulants)
Diarrhea
Secretory diarrhea
Shortened transit time
Osmotic diarrhea
Colitis
Toxic injury
Immunological injury
Allergic reactions
Impairment of cell proliferation
Vascular impairment
Promotion of infections
Bacterial overgrowth

event, but it has been observed in the presence of strictures. Anticoagulants can be responsible for hemorrhages. Many drugs can either reduce the splanchnic flow or act as toxic agents or as mediators of an immunologic reaction. A variety of drugs can induce several abnormalities. Antibiotics such as erythromycin, a motilin agonist, can promote diarrhea through interference with the enteric nervous system and smooth muscle or by bacterial overgrowth or both. Predisposing factors for drug-induced injury are local lesions such as strictures and associations of drugs (drugs which delay peristalsis such as neuroleptics and NSAIDs). The effect of some drugs may be increased or decreased by other drugs, depending on which symptoms and injury become apparent or not. Cyclosporin A can influence P-glycoprotein-mediated multidrug resistance and by this mechanism increase cytotoxicity of some drugs like the anticancer drug etoposide. The chemotherapeutic agent Irinotecan, a selective inhibitor of topoisomerase I, often causes severe diarrhea with delayed onset (probably by a secretory mechanism with an exudative component). Its GI toxicity is exacerbated by cisplatin, which by itself has no known GI toxicity [10, 11].

Often two or more mechanisms are present simultaneously, but in many situations, the exact mechanism is not clearly established. For NSAID enteropathy, a two-phase process has been proposed. A phase 1 oxidative stress would be followed by phase 2 attack of aggressive luminal mediators and inflammatory cells. Support for a phase 2 by luminal bacterial products such as endotoxin comes from animal

experiments of antibiotic attenuation of NSAID enteropathy. The initial event could be triggered by "adduct formation" of reactive drug metabolites and enterocyte macromolecules [12]. These adducts, formed within enterocytes, could lead to ulcers. Some drugs can induce toxic injuries. These can be identified because they can be reproduced in animals and they show a dose-related effect and a standard lesion. Therefore, this type of lesions is less common. In contrast, immunologic injury is typically not regular and not reproducible.

Many of the deleterious effects of drugs are initiated by damage to the mucosal epithelial cells, either directly or mediated by vascular insufficiency. Hypoperfusion deprives the involved bowel segment of oxygen and nutrients leading to tissue hypoxia and cell death. Oxygen is of central importance in the mechanisms of cell injury. Lack of oxygen causes injury by reducing oxidative phosphorylation (decrease of ATP levels). Reperfusion injury accounts probably for most of the histologic and macroscopic damage, especially when the ischemic period is short. During reperfusion, neutrophils appear in the tissue and release reactive oxygen species. The free radicals can induce lipid peroxidation, leading to membrane injury and increased permeability. Some free radicals contribute to tissue damage indirectly by causing vascular smooth muscle contraction and influencing mucosal blood flow. Following membrane injury, the influx of calcium from outside and mobilization of calcium within the cell can accelerate membrane damage by activating enzymes. Proteases derived from lysosomes may attack intracellular and extracellular structural proteins, cell adhesion molecules, and also activate procollagenase leading to further cell and tissue injury. Vascular lesions include hemorrhages related to treatment with anticoagulants or drug-induced thrombocytopenia and ischemia because of vascular thromboses, nonocclusive mesenteric ischemia (NOMI), toxic vascular injury, drug-induced (hypersensitivity) vasculitis (usually generalized), and reduced splanchnic flow caused by cardiovascular drugs or hypovolemic agents.

Promotion of infections is the result of many antibiotics, chemotherapeutic agents, and immunosuppressive therapy.

Anthraquinone laxatives and chemotherapeutic agents can cause increased apoptosis. Chemotherapeutics may induce crypt hypoplasia in the small and large intestine or they can have a direct toxic effect on actively replicating epithelial cells. Histology may show minor abnormalities limited to an increase in number of mitotic figures in the crypts or expansion of the proliferative compartment to the upper third of the crypts.

Drug-induced damage in the colon includes also effects on preexisting disease as well as de novo disease. With regard to preexisting disease, NSAIDs have been associated with complications of diverticular disease, such as hemorrhage, perforation, and fistulous tract formation. Standard NSAIDs and selective COX2 (cyclooxygenase) inhibitors have also been linked to flaring of chronic idiopathic inflammatory bowel diseases as well as to triggering a first episode. Intravenous cyclosporin can promote villous transformation and epithelial regeneration in ulcerative colitis. These histological changes may mimic dysplasia [13]. In the following review on histological patterns, more detailed information is provided for specific drugs.

12.3 Histology

The pathologist should try to give to the clinician a correct indication concerning possible drug-related damage to the gastrointestinal tract [14], particularly in the colon, based on some simple histological findings. From the morphological point of view, drug damage in the colon may display different features, in some cases mimicking other pathological entities with different etiology. The spectrum of drug-induced colitis comprises inflammatory features which are usually nonspecific but can be similar to or mimic specific diseases and ischemic patterns. The following review provides an overview of older and more recent descriptions of drug-induced colonic injury.

12.3.1 Inflammatory Patterns

In a prospective study of 58 adult patients presenting with acute inflammatory diarrhea, drug-induced colitis was diagnosed in 35 cases. The main drugs implicated were antibiotics and NSAIDs [15]. Antimicrobials are responsible for 25 % of all cases of drug-induced diarrhea. The disease spectrum ranges from normal to hemorrhagic and pseudomembranous colitis. The term pseudomembranous colitis has been used for the diarrheal syndrome following antibiotic use, mostly secondary to infection by *Clostridium difficile* (see also infectious colitis) [16]. Three histological patterns have been described [17] (see chapter on infectious colitis). Currently, there are also cases without the presence of pseudomembranes but with positivity for *Clostridium difficile* toxin, in particular in patients receiving immune suppressive therapies [18].

A pattern of acute colitis has been described following treatment with laxatives such as bisphosphonate enemas and bisacodyl; with carbamazepine and isotretinoin, a vitamin A analog; and with mefenamic acid, diclofenac, naproxen, and pirprofen (NSAIDs) [15, 19–23]. Bisacodyl may be associated with edema and occasional neutrophils immediately beneath the surface epithelium. Hyperosmotic fleet enemas may cause mucin depletion and sloughing of surface epithelium. Neutrophils can be present in the lamina propria; the changes usually resolve within a week. Hypertonic saline enemas equally induce epithelial damage and sloughing of cells, which are replaced by young flattened cells, migrating from the crypts, showing mucin depletion. With isotretinoin, aphthoid ulcers and hyperemia have been noticed in the distal colon. Histology showed focal neutrophils in the superficial lamina propria and adjacent crypts without architectural distortion [21]. It has been proposed that nearly 10 % of newly diagnosed inflammation in the colon results from NSAIDs [24]. The histological lesions vary and include a thinned mucosa with edema, mucosal hemorrhages, irregularity of the crypts which may be increased in height, and ulcers with loss of smooth muscle fibers of the muscularis mucosae. NSAID-related ulcers occur mainly in the right colon. They are more common in elderly patients. A median age of 67 years with a median duration of

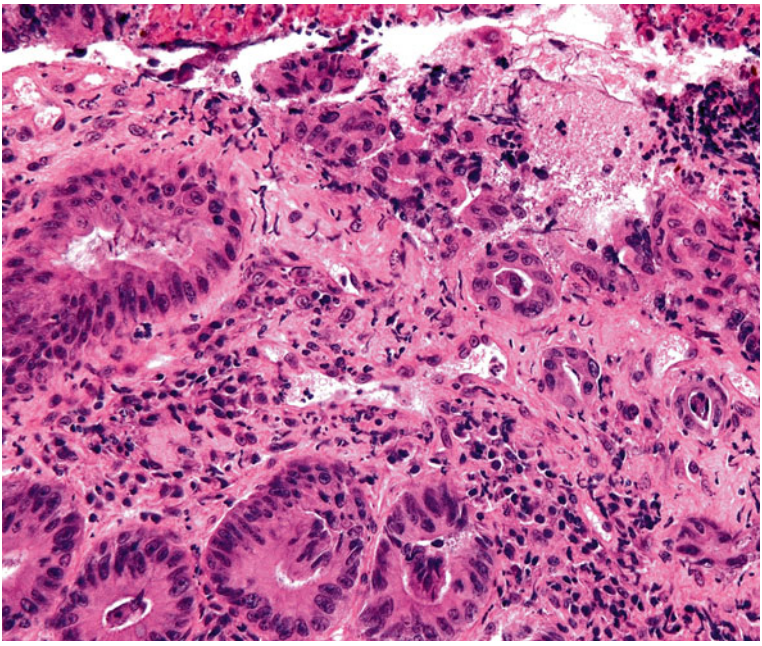

Fig. 12.1 Microphotograph of a biopsy from NSAIDs induced ulcer showing necrotic material, overlying paucicellular granulation tissue, and reactive glands (×40)

NSAID exposure of 3 months and a range of 2 days to 12 years have been reported [25]. Diaphragm-like strictures have also been observed in the ascending colon [25]. NSAID-mediated inhibition of prostaglandin synthesis is the major toxic mechanism responsible for the injury (Fig. 12.1).

A so-called ulcerative colitis-like pattern was reported with gold salts (also related to microscopic colitis), diclofenac (NSAID), and aminoglutethimide (an antineoplastic agent), but the morphological description is not always accurate [26–29]. Gold salts have been used for treatment of rheumatoid arthritis. The lesions observed in relation with these drugs, which are now only rarely used, are highly variable. Diarrhea is a frequent side effect, possibly through increased permeability. There may be a relatively long latent period between the start of treatment and onset of symptoms. The gross appearance of the colon in gold-associated colitis may show diffuse inflammation or may be limited to the rectum. There may be areas of hemorrhage, interspersed with focal punched-out ulcers and deep penetrating ulcers. The terminal ileum may have a cobblestone aspect. The microscopy varies from a severely ulcerated mucosa, a mucosa with minor architectural abnormalities and a heavy neutrophilic infiltrate, to prominent eosinophilia in small and large intestine.

A Crohn's disease-like pattern with granulomas has been reported with diclofenac, naproxen, and clofazimine (with clofazimine, crystals can be demonstrated in the granulomas). A Crohn's disease-like pattern without granulomas was observed with other NSAIDs and immunosuppressive treatment (mofetil) [25, 30, 31].

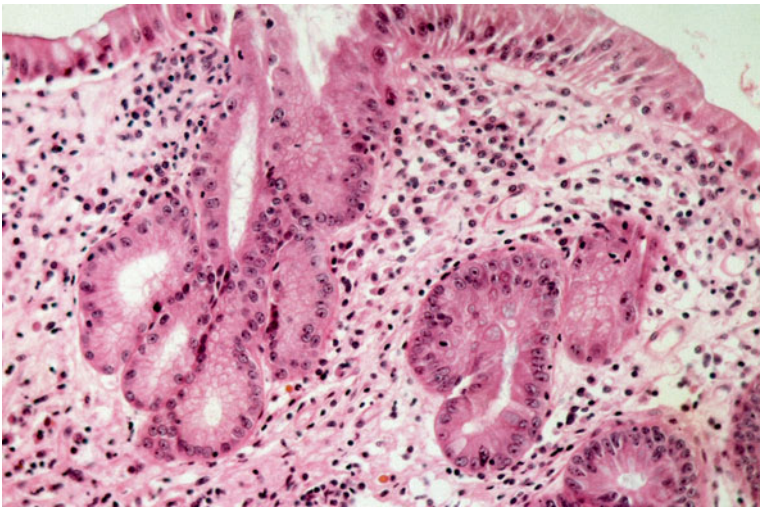

Fig. 12.2 Microphotograph of a biopsy from a patient with renal transplant, treated with mycophenolate and presenting with chronic diarrhea. The architecture of the mucosa is severely distorted but inflammation is minimal (×20)

Mycophenolate mofetil inhibits inositol-monophosphate dehydrogenase (IMPDH) which is needed for the guanine synthesis in B- and T-lymphocytes. Experimentally, it has been shown to impair colonic healing [32]. A graft-versus-host-like pattern has also been described with mofetil [33] (Fig. 12.2).

"Microscopic colitis" is a clinical-pathological entity or syndrome. The primary symptom is watery (non-bloody) diarrhea, and the course of disease is variable with alternating episodes of remission and relapse. "Collagenous colitis" and "lymphocytic colitis" are the two major conditions associated with the syndrome (see microscopic colitis). The lymphocytic type of microscopic colitis has been described following several types of drugs including proton pump inhibitors, H2 receptor antagonists (histamine 2), ticlopidine, NSAIDs, veinotonics, and others (Table 12.3). Some drugs such as ticlopidine and Cyclo 3 Fort can even induce lymphocytic colitis and villous atrophy in the ileum or small intestine [34–38]. Upper small intestinal villous atrophy and lymphocytic colitis have also been associated with NSAIDs and olmesartan, a drug used for the treatment of hypertension [39]. The collagenous type of microscopic colitis has been observed with the proton pump inhibitor lansoprazole [40]. A relation with NSAIDs has also been proposed. A scoring system for the identification of drug-induced microscopic colitis has been proposed [26]. As the etiology of lymphocytic and collagenous colitis can be multifactorial, a possible relation with drugs should be examined in each case. For the drug-related forms, it is often sufficient to stop the offending agent to resolve completely the clinical–pathological picture.

Isolated case reports describe drug-induced colitis in association with fever, rashes, and eosinophilia (isotretinoin, penicillamine, clofazimine, a drug used in the treatment of leprosy, acyclovir, and sulfasalazine). Drug reaction with eosinophilia and systemic symptoms (DRESS) has been noted with antiepileptic drugs such as phe-

Table 12.3 Conditions associated with lymphocytic colitis

Enteric infections
Gluten
Autoimmune diseases
Drugs
Alpha-glucosidase inhibitor (diabetes)
Acarbose
Anticoagulants
Ticlopidine
Clodipogrel
H2 receptor antagonists
Ranitidine
Cimetidine
Proton pump inhibitors
Lansoprazole
Cholesterol lowering agents
Simvastatin
Antiepileptic drugs
Carbamazepine
Anti Parkinson drug
Levodopa benserazide
NSAID
Piroxicam beta cyclodextrin
Anti-serotonin agent
Oxetorone
Angiotensin II receptor antagonist
Olmesartan
Selective serotonin reuptake inhibitors
Sertraline
Paroxetine
Antiandrogenic
Flutamide
Phlebotonic drugs
Flavonoid extract (daflon)
Cyclo 3 Fort, Cirkan
Vinburnine
Ferrous sulfate (Tardyferon)
Antipsychotic
Clozapine (collagenous colitis)

nytoin and lamotrigine and may include gastrointestinal involvement. These manifestations, which are considered as allergic reactions, are generally reversible after withdrawal of the drug although severe cases with toxic megacolon have been observed. Active colitis with a clear increase of eosinophils in the mucosa is observed also after the use of psychotropic drugs (carbamazepine), aspirin, chlorpropamide, methyldopa, and ticlopidine. In methyldopa-related colitis, the disease remitted when the drug was stopped and in some patients rechallenged and invoconfirmed the

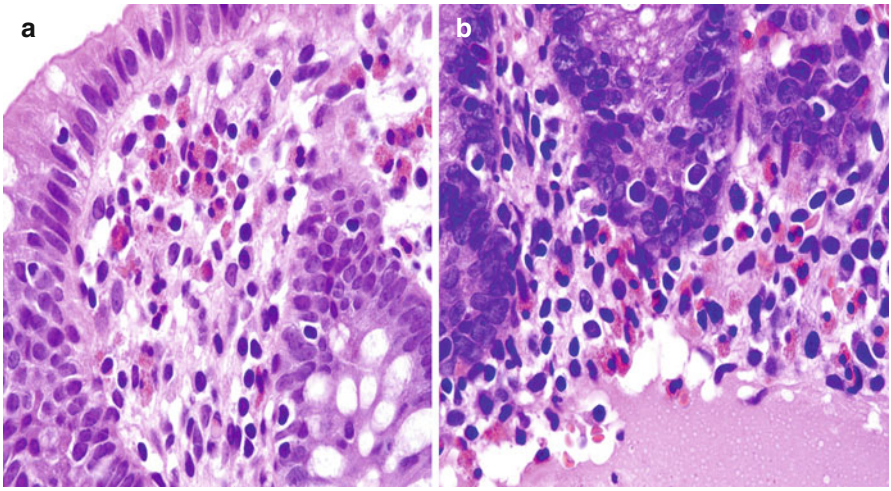

Fig. 12.3 Microphotograph of biopsies with prominent eosinophils obtained in the left colon from a patient presenting with diarrhea. The presence of these features in the left colon must help to consider drug-induced disease. Eosinophils are present both in the upper (**a**) and lower (**b**) lamina propria

relationship [41]. Eosinophilic colitis has also been observed in transplant patients treated with tacrolimus. This has been linked to increased intestinal permeability. It is important to keep in mind that left-sided mucosal eosinophilia is a clue for diagnosing drug-related colitis [42–44] Eosinophilic drug-related colitis must be differentiated from the "classic" form of eosinophilic colitis which is in general an expression of allergic conditions particularly in children, on the basis of clinical (lack of bloody or non-bloody diarrhea and of peripheral eosinophilia) and endoscopic findings (Fig. 12.3).

Steroids and other immunosuppressive agents may unleash opportunistic infections such as cytomegalovirus (CMV) or reactivate tuberculosis, in immune deficient patients (transplants) and in predisposed patients (inflammatory bowel disease) [45]. Gold salts might have a similar effect in predisposing to CMV infection [6]. Neutropenic colitis or enterocolitis, ileocecal syndrome, and typhlitis are all labels for a syndrome with bowel-wall necrosis, occurring during the treatment of hematologic malignancies but also during aplastic anaemia and cyclic neutropenia. It is in fact usually an infection occurring in a patient with neutropenia [46, 47].

Potassium chloride can be responsible for strictures which are usually broader than those related to NSAIDs.

12.3.2 Specific Patterns

Fibrosing colonopathy, strictures, and increased colonic wall thickness are observed in children with cystic fibrosis and adults exposed to large doses of high strength pancreatic enzyme supplements [48].

Apoptotic colopathy, characterized by an increase in apoptotic bodies in the cryptal epithelium (greater than 5 per 100 crypts) has been observed with 5-fluorouracil, irinotecan, cyclosporin, colchicine, diclofenac sodium, mefenamic acid (NSAID), ticlopidine, ranitidine, and sodium phosphate bowel preparation [49–51]. Apoptosis of surface epithelial cells is noted with some laxatives (anthranoids). Apoptotic bodies may be very common. In samples from patients undergoing 5-FU (fluorouracil) therapy up to 100 apoptotic bodies per 100 crypts were present. A challenge with the drug might induce or re-induce the typical apoptotic lesions.

Clofazimine can induce crystal-storing histiocytosis. The crystals are red in frozen sections and appear as clear spaces in routinely processed sections [52, 53].

Colchicine is an alkaloid with antimitotic activity. Pathology is the result of loss of cellular renewal coupled with a selective depression of intestinal enzyme activity. Metaphase mitoses, epithelial pseudostratification, and loss of polarity have been described in colchicine toxicity [54]. Lesions are more common in patients with renal failure and usually not limited to the GI tract.

"Pseudomelanosis or melanosis or pseudolipofuscinosis coli" is the result of long-term use and abuse of anthraquinone-containing laxatives. This is a common asymptomatic condition that is characterized by the presence of a lipofuscin-type pigment in the macrophages of the lamina propria of the large bowel (including the appendix). The laxative drugs involved in the pathogenesis of this phenomenon belong to the contact laxatives. The active compound is released from the prodrug in the cacum by bacteria. Therefore, the small intestine is never involved. The accumulation of pigmented macrophages starts in the right colon. When the intake of the drug is prolonged, gradually the whole colon will be involved. The pigmentation is reversible. The active drug binds to surface epithelial cells and promotes apoptosis of these cells. The cell remnants (with the drug metabolites) are engulfed by the macrophages, and this produces the typical color. The epithelial cell damage is usually associated with mild mucosal inflammation. Macroscopically, the presence of the macrophages induces a dark brown, grayish, or black discoloration, in a lizard-like pattern, of the colonic mucous membrane. Typically neoplastic lesions such as adenomas do not contain the pigment (Fig. 12.4). Other products linked with melanosis coli are cholagoga and weight-reducing preparations containing substances with an anthranoid structure [55]. The relation between the laxatives and melanosis coli has however been questioned, and the pigmentation has been attributed to apoptosis by itself [56]. Several studies of environmental factors in colorectal cancer have analyzed the influences of constipation and cathartics. A meta-analysis of 14 published case-control studies revealed statistically significant risks for colorectal cancer associated with both constipation and the use of cathartics for both sexes [57]. The pooled odds ratios and their 95 % confidence intervals were 1.48 (1.32–1.66) for constipation and 1.46 (1.33–1.61) for the use of cathartics. In a retrospective study of 2,277 patients (mean age 52.9 years), no association could be found between melanosis coli and colorectal cancer. However, the association of melanosis coli and colorectal polyps was statistically significant as expressed by a relative

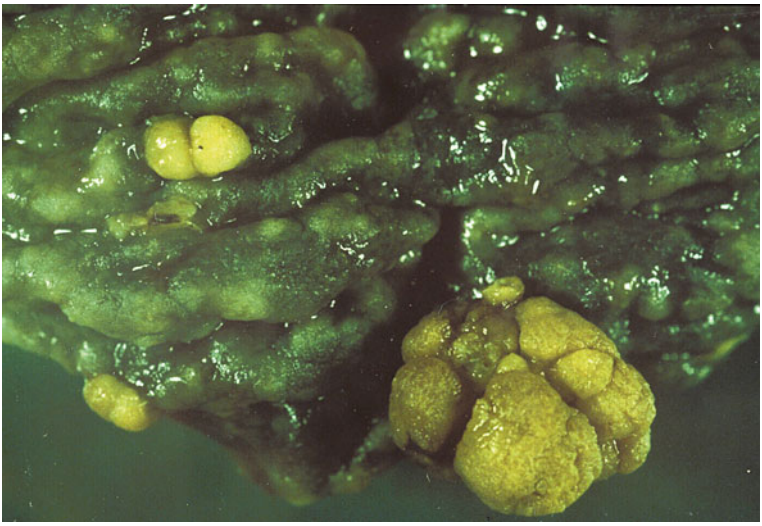

Fig. 12.4 Macrophotograph of a colonic specimen showing black coloration of the mucosa due to anthraquinone abuse, while adenomas are unstained

risk of 2.19 [58, 59]. The relation between cancer and contact laxatives could be explained by the induction of damage of surface epithelial cells with increased loss and subsequent increased proliferation. In humans, anthraquinones given orally or by colonic lavage induce indeed an increase in colonic epithelial cell proliferation. There is however no shift in the proliferative compartment from the distal part of the crypts towards the surface, neither in animal experiments nor in studies on human samples [60]. It is at present not yet clear if laxatives and especially those containing anthraquinones have an influence upon the colorectal cancer risk.

Kayexalate-sorbitol (sodium polystyrene sulfonate) is given as an enema or orally for the treatment of hyperkalemia. It has been reported to induce intestinal necrosis in uremic patients. Necrosis is observed in endoscopic and surgical specimens of the stomach, small intestine, and colon. The mechanism of the mucosal damage is unclear. Experimental evidence suggests that the sorbitol component of the drug, rather than Kayexalate itself is involved in the pathogenesis of the necrosis. Sorbitol is metabolized by colonic bacteria to short-chain fatty acids. If the concentration of these acids exceeds the patient's absorption capacity, osmotic entrance of fluid into the gastrointestinal lumen occurs with subsequent necrosis. It has indeed been shown that rats receiving enemas of Kayexalate in water developed no lesions, while 6/10 rats receiving sorbitol enemas showed transmural colonic necrosis. Nevertheless the lesions induced by Kayexalate can be recognized through the presence of characteristic Kayexalate crystals [61]. It must be remembered that other resins besides Kayexalate are used clinically. For instance, Questran (cholestyramine) is an orally administered resin which binds to bile acids. The histology induced by Questran is very similar to that of Kayexalate, except that Questran tends to be more opaque. With acid fast stains, Kayexalate crystals are more maroon while Questran is more pink [62].

12.3.3 Ischemic Patterns

12.3.3.1 Illicit/Controlled Drugs

The use of cocaine and related products has been associated with mesenteric thrombosis, perforation, and visceral ischemia in the lower GI tract. Vascular complications can occur by five mechanisms: (1) direct vasoconstriction through a channel-dependent mechanism independent of endothelium; (2) indirect vasoconstriction via norepinephrine release; (3) direct vasoconstriction from cytokine concentration alteration through activation of platelets, neutrophils, and endothelial cells; (4) indirect obstruction or thrombosis caused by direct endothelium injury; and (5) endothelium-dependent vasorelaxation from a resistance or inability to respond to G-protein-mediated releasing agents such as acetylcholine. Cocaine-associated enterocolitis usually presents within 3 days of cocaine use. Inflammatory or ischemic changes are most common in the proximal colon. The major presenting complaint is abdominal pain. Colonoscopy can show ulcers, mucosal edema, or ischemic changes. Biopsies show findings consistent with ischemia [63, 64].

Case reports have described the occurrence of colon ischemia in association with several amphetamines, including dextroamphetamine, methylphenidate, and methamphetamine, commonly known as "speed," "crank," "ice," or ecstasy." Their mechanism of action is that of a sympathomimetic, causing vasoconstriction by the release of neurotransmitters [65, 66].

12.3.3.2 Immune Modulator Agents

Colonic ischemia has been reported in patients treated with interleukin-2 (IL-2) in combination with interferon, which has been linked to the development of colonic ischemia also as a single agent. Ischemia was noted predominantly in the ascending colon. Histopathology revealed thrombi in capillaries and venules. The exact mechanism is not known but IL-2 is characterized by episodes of transient hypotension. In addition, it induces greater levels of tumor necrosis factor alpha and interferon gamma, which have thrombogenic effects [67, 68]. Colonic ischemia has also been associated with solumedrol and azathioprine [69].

12.3.3.3 Ergot

Ergot compounds are generally safe, but in some instances, colitis with bowel wall necrosis and perforation or strictures have been recorded. There are case reports describing colon ischemia in association with ergot alkaloids. There are also reports of patients who took increasing doses of methysergide maleate for migraine and presented with postprandial pain for several years that had gradually increased in intensity. Arteriography carried out because of symptoms and an abdominal bruit showed a long, tapering stenosis of the superior mesenteric artery, with complete occlusion just distal to the origin of the ileocolic artery [70, 71]. The use of

ergot drugs in suppositories can cause localized ulcers of the rectum and anal canal that resemble those seen in solitary ulcer syndrome, but the lesions heal promptly after stopping the drug. However, histology does not show the fibromuscular obliteration of the lamina propria observed in the solitary ulcer. Similar ulcers as well as strictures can be observed with suppositories containing analgesics (dextropropoxyphene, paracetamol) [72]. Suppositories containing ergotamine have also been associated with fistulae although anorectal ergotism is a rare complication [73, 74].

12.3.3.4 Diuretics

Diuretics have been implicated in the development of both nonocclusive mesenteric ischemia and colonic ischemia. The proposed mechanism is twofold: loss of fluid which results in mesenteric vasoconstriction and greater venous capacitance and lower peripheral vascular resistance which leads to greater limb flow and a "steal syndrome" reducing mesenteric blood flow. Reported clinical manifestations range from hematochezia to colonic gangrene and strictures mimicking carcinoma.

12.3.3.5 Oral Contraceptives

In the older literature, there have been reports of women taking oral contraceptives who developed a focal and segmental colitis with aphthoid ulcers on a background of normal mucosa and rectal sparing. Biopsies showed focal, nonspecific ulceration on a background of a normal mucosa. Cessation of oral contraceptive use resulted in prompt relief of symptoms and healing. A similar report followed administration of depot synthetic progesterone. These reports suggest that local intestinal ischemia might have occurred in at least some of these patients [75–77].

12.3.4 Ischemic Colitis

Colon ischemia is a clinicopathological condition that comprises a spectrum of disorders from reversible and transient colitis to fulminant colitis. In younger (and elderly) patients, medication must seriously be considered as a predisposing factor. Drugs that can mimic ischemic disease include penicillin, neuroleptics, nonselective NSAIDs and selective COX-2 inhibitors (rofecoxib, meloxicam), the migraine headache medication naratriptan and sumatriptan succinate, a serotonin-1 (5-hydroxytryptamine[1]) receptor agonist, alosetron hydrochloride, a potent selective 5-hydroxytryptamine[3] receptor antagonist used for the treatment of diarrhea predominant irritable bowel syndrome, some hormonal drugs such as flutamide (antiandrogenic), and chemotherapeutic agents [5, 78–84]. The frequency of colitis induced by neuroleptics is estimated to be 1 case for 2,000 patients [79].

Involved classes include tricyclic antidepressants, phenothiazines, and barbiturates. The relationship between the drug and ischemia is however not always clear, and the mechanism of the ischemia induced by drugs is also not always precisely known. Sumatriptan may induce vasopressor responses that are distinct from the cranial circulation. For nonselective NSAIDs, an effect upon the isozymes COX-1 and COX-2 has been proposed. These isoenzymes catalyze the conversion of arachidonic acid to eicosanoids, which play a role in the platelet-vessel wall interaction. Thromboxane, the major COX-1 product of arachidonic acid metabolism in platelets, causes platelet aggregation and vasoconstriction. Biopsies from cases with drug-induced ischemic colitis show a pattern characterized by erosions, small shrunken abortive crypts (micro crypts), hyaline stroma, little inflammation, and lamina propria hemorrhage which is indistinguishable from other ischemic conditions (apart, perhaps, from a slightly higher increase of the eosinophilic infiltrate). The diagnosis must therefore be suspected in patients of relatively young age in whom the relationship with the incriminating drug may be frequently ascertained [85, 86].

12.3.5 Duodenal Villous Blunting and Enteropathy

Two important drugs that can induce duodenal villous blunting with consequently the development of a malabsorption syndrome are ipilimumab and olmesartan.

Ipilimumab is a humanized IgG1 antibodies against CTLA-4 (Cytotoxic T-Lymphocyte Antigen) (a negative regulator of T-cell antitumor response), and it is used in the treatment of different cancers such as melanoma, prostate, kidney, and ovarian cancer. The adverse effects of this drug on the gastrointestinal tract are several, ranging from toxicity affecting the stomach, the small intestine, and the colon. Oble et al. [87] reported clinical and histological findings of 5 patients who developed severe panenteritis after injection of a-CTLA-4 mAbs (monoclonal antibodies). The most important clinical sign was diarrhea, followed by abdominal pain, nausea, vomiting, and fever. The endoscopic findings were variable, ranging from normal to diffusely erythematous and ulcerated mucosa. From the histological point of view, distinct morphological features were lymphoplasmacytic expansion in the lamina propria, intraepithelial lymphocytosis (CD3+, CD4+ and CD8+), villous blunting, increased apoptosis, and cryptitis, leading to different clinicopathological entities such as gastritis/enteritis/colitis (autoimmune gastroenteritis-like) and lymphocytic colitis.

Olmesartan is an angiotensin II receptor antagonist used for treatment of hypertension. Diarrhea is a common adverse effect of this drug, but recently Rubio-Tapia et al. [88] described severe spruelike enteropathy related to this medication. The authors analyzed 22 patients taking the drug with unexplained chronic diarrhea and weight loss; celiac disease was ruled out in all cases by conventional methods of serology and the absence of clinical response to a gluten-free diet. Intestinal biopsies showed both villous atrophy and variable degrees of mucosal inflammation in

15 patients, with marked subepithelial collagen deposition (collagenous sprue) in 7. All patients had clinical improvement after suspension of the drug, and histologic recovery or improvement of the duodenum was confirmed in all 18 patients who underwent follow-up biopsies.

12.4 Anticoagulant-Associated Hemorrhage and Hematoma

Although thrombolytic agents clearly have the potential to cause GI hemorrhage, few cases have been documented. The vast majority occur as a complication of standard anticoagulant therapy. Hemorrhage due to anticoagulants most frequently takes the form of an intramural or submucosal hematoma. However, while 1–7 % of patients taking anticoagulants will suffer a bleeding complication each year, overall, intramural hematoma of the intestine is a rare complication of [89]. The most common site is the small bowel; in one series, 9 % were duodenal, 59 % jejunal, 25 % ileal, and 7 % in the large bowel [90].

12.5 Conclusion

At the end of this chapter, we think that it is important to remember a consideration of Chandrasoma: "Many of these conditions, when encountered in biopsy or surgical resection specimens, usually receive nonspecific pathologic diagnoses. Careful clinical correlation and the knowledge of dosages and temporal relationship of drug usage is required by the pathologist to even attempt to reach the conclusion that the pathology is caused by drug toxicity: unfortunately, this information is rarely available to the pathologist" [91].

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Chapter 13
Solitary Rectal Ulcer Syndrome

Rossano Ambu and Karel Geboes

Abstract Solitary rectal ulcer syndrome is a benign condition of the rectum caused by mucosal prolapse. Common clinical symptoms are constipation and red blood loss per anum. The endoscopy can show a variable picture of erythema, a shallow ulcer, or even polypoid lesions. The histology is characteristic. The rectal mucosa shows crypt distortion, reactive epithelial cells, and typical fibromuscular obliteration of the lamina propria. Inflammation is usually mild. This lesion should not be misdiagnosed as neoplasia.

Keywords Solitary rectal ulcer syndrome • Inflammatory cloacogenic polyp • Proctitis cystica profunda • Inflammatory cap polyp • Prolapse • Fibromuscular obliteration

13.1 Definition and Pathogenesis

The "solitary rectal ulcer syndrome (SRUS)" is an uncommon benign rectal disorder characterized by a spectrum of clinical presentations and variable endoscopic and microscopic findings. It was first described by Cruveilhier in 1829. The term "solitary ulcers of the rectum" was introduced by Lloyd Davies in the late 1930s. It is the major form of mucosal prolapse syndromes. Other types are polypoid lesions such as proctitis or rectitis cystica profunda (the localized form of colitis cystica profunda) and inflammatory cloacogenic polyp due to prolapse close to the anal canal and polyps occurring in association with diverticular disease such as inflammatory cap polyps [1].

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The pathogenesis of SRUS has not been completely clarified yet. Mucosal prolapse is the most important factor. The most likely mechanism is a descent of the perineum and a paradoxical or abnormal contraction of puborectal muscle in the pelvic floor during straining or defecation, resulting in mucosal prolapse. Another theory suggests that abnormal defecation could result from abnormal pressure gradients produced by the external anal sphincter generating a high intrarectal pressure [1]. The postulated mechanism responsible for rectal prolapse in most cases seems to be excessive straining efforts during which high intra-abdominal pressure might force the anterior rectal mucosa firmly into the contracting puborectalis muscle. The mucosa would be strangulated, causing poor blood flow, venous congestion, edema, mucosal ischemia, and eventually ulceration [2, 3]. Prolapse close to the anal canal may lead to florid polypoid lesions. Most probably, the pathogenesis of SRUS is related to the coexistence of multiple factors, including direct trauma and local ischemia.

In one study, it has been suggested that SRUS has the potential to progress to malignancy [4]. Loss of hMLH1 gene (MutL homolog) expression was demonstrated in several cases of SRUS in another study underlining the possibility of neoplastic progression [5]. However, no causal relationship has been established yet between SRUS and neoplastic lesions such as adenoma and adenocarcinoma until now.

13.2 Clinical Presentation

Men and women are affected equally, with a small predominance in women. SRUS has been reported in a wide age range (15–85 years) including children and the geriatric age group, but few reports of SRUS have been described in young children [6]. The clinical presentation is variable, but constipation, mucous discharge, rectal bleeding, and abdominal pain are the most common symptoms. In children, the condition usually presents with rectal bleeding, mucous discharge, prolonged straining, tenesmus, and localized pain in the perianal area [7]. SRUS often remains unrecognized for years. The correct diagnosis is usually delayed approximately 5–7 years after the clinical onset. This delay may be responsible for the scarcity of pediatric cases [8]. Clinical examination may reveal an anal fissure in up to 30 % of the patients. Endoscopy plays a major role in the diagnosis. Endoscopic features are highly variable with hyperemia, ulcerative lesions in up to 78 % of the patients, or single or multiple polypoid lesions in 25–30 % of the patients. Therefore, the term “SRUS” might not be appropriate as in fact the lesions are not always solitary, nor are they always ulcerative. If an ulcer is present, it is usually located on the anterior wall of the rectum and the distance of the ulcer from the anal margin varies from 3 to 10 cm. Ulcers may range from 0.5 to 4 cm in diameter but are usually 1–1.5 cm. They are shallow and covered by a white, gray, or yellowish slough (Fig. 13.1). The adjacent mucosa may appear granular or nodular. Anorectal manometry, electromyography, and defecography can help to confirm the diagnosis. Anorectal manometry and electromyography provide information about anorectal inhibitory reflex, pressure profiles, defecation dynamics, and rectal compliance. Defecography or defecating proctography is a radiological test that records

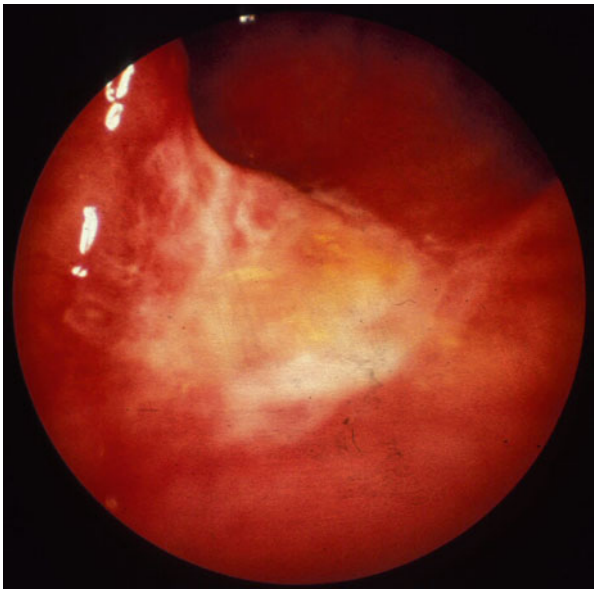

Fig. 13.1 Endoscopic picture of a shallow solitary rectal ulcer

anorectal anatomy and pelvic floor motion. In SRUS patients, this test frequently reveals several abnormalities, including intussusception, rectocele, and internal prolapse [8]. Several studies have also shown the value of anorectal ultrasound in assessing internal anal sphincter thickness, which is increased in patients with SRUS.

13.3 Histopathology

During endoscopy, biopsies should be obtained from abnormal- and normal-looking mucosa. The histopathology of SRUS has been well described in 1969 [9]. Routine staining is sufficient to reach the diagnosis. Special staining for fibrosis or immune histochemistry for the detection of smooth muscle fibers can sometimes help. The histological pattern is characterized by the presence of a superficial ulceration (in most cases) and the occurrence of crypt distortion, surface serration, and fibromuscular obliteration of the lamina propria with the presence of vertically oriented smooth muscle fibers and bundles in between the crypts. The muscle fibers are in continuity with the muscularis mucosae, which is often thickened (Figs. 13.2 and 13.3). The ulceration, when present, is usually limited to the mucosa. The ulcer base is covered with necrotic cells and granulation tissue. Crypts may be dilated and the distance in between the crypts can vary. Some crypts may show a particular triangular form (diamond-shaped crypts), but this is not always present [2]. The epithelial cells of the surface and upper part of the crypts may appear cuboidal with basophilic staining cytoplasm and loss of goblet cells. Less frequently, they are well differentiated. The proliferative compartment of the crypts

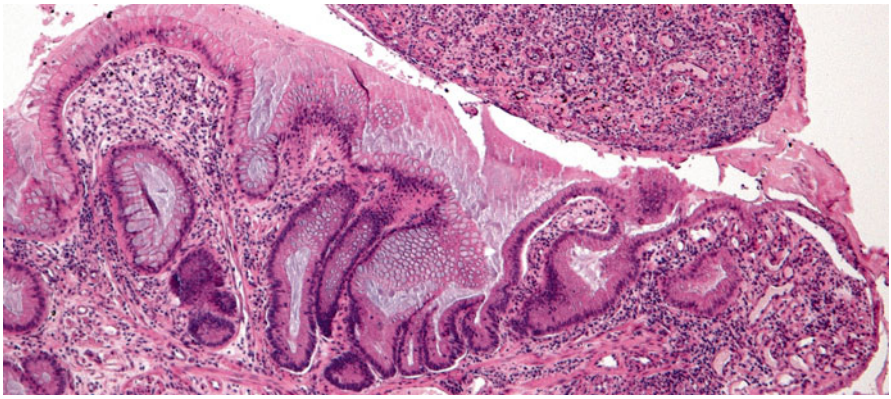

Fig. 13.2 Histopathology shows necrotic material overlying the mucosal surface. In the mucosa, granulation tissue can be seen on the right and smooth muscle fibers are prominent overall (×20)

Fig. 13.3 Drawing illustrating the different histological characteristics of solitary rectal ulcer

may be enlarged. The fibromuscular obliteration of the lamina propria is the most significant change. It is an early feature and has been reported in 93 % of patients [10, 11]. It is however not always present and may lack in very early cases. Fibrosis

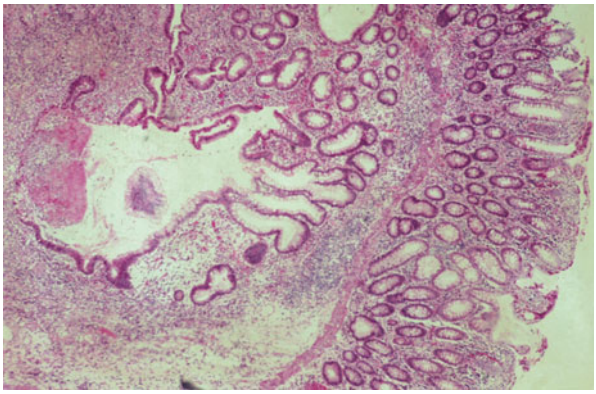

Fig. 13.4 Microphotograph illustrating misplacement of dilated glands (×20)

of the lamina propria and vascular ectasia with congestion are also considered as typical lesions of SRUS, having been found in 95 % of the patients in various studies. Vascular thrombosis and fibrin deposition are less common [12]. Misplacement of mucus-filled or empty but dilated glands in the submucosa, probably as a result of repetitive ulceration and healing, may lead to a polypoidal appearance on macroscopic examination (Fig. 13.4). In general, the density of the lamina propria cellular infiltrate is not or mildly increased.

The inflammatory cloacogenic polyp (proctitis cystic profunda, myoglandular polyp) is generally the result of mucosal prolapse closer to the anal canal. It is usually a rounded polypoid lesion, composed of hyperplastic thickened rectal-type mucosa with smooth muscle fibers in between the crypts and anal transitional or squamous epithelium overlying fibrous tissue. The surface may be ulcerated. The epithelium can look atypical and sometimes, displaced glands are present in the submucosa.

Inflammatory cap polyps are usually found in the rectosigmoid. They may be multiple. The histology is characterized by the presence of tortuous, elongated crypts, usually lined with attenuated epithelial cells, with a densely inflamed lamina propria. The surface is ulcerated and covered with a grayish cap. The etiology is unknown, but the lesion has been linked to prolapse [13].

Some of the histological changes occurring in SRUS, including crypt distortion, can make it challenging to differentiate SRUS form IBD. However, the absence of cryptitis, of crypt abscesses, and of granulomas, the presence of fibromuscular obliteration, and the absence of lesions in biopsies obtained proximal to the rectal abnormalities, associated with the different clinical setting, can help to differentiate between the two conditions. Localized rectal or anal ulcers can also be caused by the abuse of drugs, such as suppositories, and local trauma. A major differential diagnosis is also neoplasia or malignancy of the rectum. Crypt distortion, misplacement of crypts, and the reactive features of epithelial cells may raise suspicion of neoplasia. To avoid such a misdiagnosis and reach the correct diagnosis of SRUS, it is therefore imperative for clinicians, endoscopists, and pathologists to keep this entity in their differential diagnosis, even in the absence of an ulcer at endoscopy.

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Chapter 14
The Role of Biopsies in the Treatment of Colitis: Scoring of Disease Activity

Karel Geboes

Abstract The development of new drugs fortunately leads to a better disease control and often to remission. Many clinical trials are usually needed before a new drug can be released. The aim of the trials is to show efficacy and safety of the drug, by defining different clinical endpoints such as clinical and endoscopic remission and by registration of adverse events. Histology is one of the elements which is used in clinical trials for the assessment of the efficacy of a drug, most often as a secondary endpoint. For this purpose, scoring systems have been developed for the measurement of disease activity. They rely usually on a combination of various histological features. While they are not designed for routine practice, the underlying concepts may be useful in daily practice because the features used correlate with disease activity and predict relapse.

Keywords Clinical trial • Score • Disease activity • IBD • Microscopic colitis

In routine pathology, biopsies of the colon are mainly used for diagnostic purposes. However, it has been shown that treatment can influence greatly the pattern of inflammation in biopsies from patients with IBD [1]. This phenomenon was already observed decades ago. Therefore, the Oxford group headed by Dr. Truelove proposed to use histology as a tool for the assessment of drug efficacy for UC [2]. The authors designed a stepwise three-grade scale (no inflammation, mild to moderate inflammation, and severe inflammation) and showed that histological activity was observed in more than half of the patients in clinical remission and in 37 % of biopsies taken from endoscopically normal mucosa. Since then several histological methods have been used including cell counts and scoring systems. While cell counts can confirm the elimination of active inflammation, it is also a time-consuming process [3]. Over the years, a variety of scores has been developed for

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the assessment of disease activity in IBD. These are either divided in different steps or grades of severity or designed as numerical systems in which different lesions are scored for severity, and the final score is the sum of all these scores. The latter system may be more interesting for Crohn's disease because this is a segmentary disease.

Currently, for ulcerative colitis, 19 scores can be identified. They have been used in clinical drug trials in 88 studies [4]. The initial histological indices for Crohn's disease were based on UC scoring systems. Binder established the first stepwise score in 1970. The first numerical approach by Ward and Webb was developed in 1977 [5]. Initially, these scoring systems did not receive widespread recognition. Crohn's disease is indeed a segmentary disease. Treatment options and endoscopic and radiologic modalities for imaging the involved intestine were limited at the time; therefore, assessment of histological disease activity was not a high priority. This approach changed gradually with the spread of colonoscopy. In 1998, the global histological activity score (GHAS) was developed [6]. This numeric scoring system is more extensive than other scoring systems and has been used in several clinical trials. Scoring systems are now often used in clinical trials. While they are not appropriate for routine pathology, the underlying concepts are important and several features should be mentioned in routine pathology reports, because these features correlate with prediction of relapse and the course of the disease.

In the various scores disease activity is assessed on hematoxylin and eosin-stained sections. Immune histochemistry is not normally needed although it can be helpful for the study of some particular features. Staining has been used for tenascin for a better assessment of healing, for matrix metalloproteinases for activity, and for particular subtypes of lymphocytes and other markers, usually in studies with biological agents [7–9]. In UC, usually at least two biopsies are required. Scoring, in my opinion, should be performed on the sample which is most severely involved. For Crohn's disease, multiple specimens from different parts of the colon (and ileum) are needed. For optimal scoring, ideally, good-quality biopsy samples are needed. These can best be obtained with disposable biopsy forceps with elongated (oval) cups. Sections should be 4–5 μm thick and properly stained. Optimally sections should be cut perpendicular to the mucosal surface (ideally from well-oriented biopsy samples) to allow evaluation of the distribution of the inflammatory infiltrate including basal plasma cells. The histological features which should be assessed include architectural distortion; the cytologic aspect of epithelial cells; the presence, distribution, and density of lymphocytes and plasma cells; the presence of neutrophils and eosinophils; and the occurrence of epithelial damage (erosions, ulcers, crypt destruction). Architectural distortion is mainly a feature of chronicity or chronic repetitive damage (see also Chap. 2, elementary lesions). It may therefore not reflect disease activity, but it is useful to see if the mucosa becomes normal or not following treatment. Assessment of the cytology of epithelial cells is mainly based upon the size and staining qualities of the cells. Flattened or cuboidal surface and crypt epithelial cells, with darkly stained basophilic cytoplasm, correlate with previous damage and repair. An increase of plasma cells correlates with disease

activity and persistent basal plasmacytosis correlates with disease relapse. Correlation of the histopathologic stage of disease activity with the isotypes and numbers of immunoglobulin-containing cells in the lamina propria demonstrated highly significant (P less than 0.001) increases in the mean numbers of IgG- (18-fold), IgA- (twofold), and IgM- (sixfold) containing cells in specimens from patients with active inflammatory bowel disease as compared with control specimens [10–12]. Neutrophils are key elements for disease activity. They are normally not present in the mucosa outside capillaries. The survival time in the lamina propria is limited although it can be prolonged by inflammatory cytokines, and they secrete products such as matrix metalloproteinases which can induce tissue damage. Neutrophils are also related with relapse [13]. The potential role of eosinophils is more complex. They are normally present in the lamina propria, and the numbers are influenced by environmental factors (see also Chap. 1, the normal mucosa). They are most probably involved in tissue repair and remodeling, but they are potentially toxic by the release of MBP (major basic protein), EPO (eosinophil peroxidase), and ECP (eosinophil cationic protein). Some studies have also shown a relationship with relapse in UC [14]. Many authors consider these cells as part of chronic inflammation. Erosions can be identified by the presence of fibrin and neutrophils, and by the actual loss of epithelial cells with adjacent flattened cells and/or focal stripping of flattened or cuboidal cells with adjacent inflammation. An ulceration is defined by the presence of granulation tissue. The different features are combined in the various scores that have been developed. In other words there is no single item which defines disease activity. Examples are given in Tables 14.1 and 14.2. None of these systems have however been validated, interobserver and intra-observer agreement must be tested, and histological remission has not been defined unequivocally. Interobserver agreement is most probably within acceptable limits if the lesions are well defined and pathologists are trained [15]. Histological remission in UC can best be defined most probably by the absence of neutrophils and plasma cells, but in Crohn's disease, not being a mucosal disease, such a definition may not be appropriate.

Scoring of disease activity is important for the assessment of the treatment but also for prediction of relapse (correlating particularly with active inflammation and basal plasmacytosis) and because disease activity correlates with the development of dysplasia [16]. Scoring should allow also to assess "microscopic mucosal healing." Endoscopic "mucosal healing" is currently considered as an endpoint in different clinical trials [17]. It does however not necessarily reflect microscopic quiescent disease, as already shown by the original study of Truelove and Richards [2]. On the other hand, endoscopic healing in UC is associated with longer periods of remission and lower rates of colectomy. Histological healing may even be a better endpoint. Therefore it will however be necessary to validate scoring systems.

Assessment of therapy has also been used in clinical trials for microscopic colitis. Treatment with budesonide induces a significant decrease of the lamina propria infiltrate in collagenous colitis, while the mean thickness of the subepithelial collagen table remained unchanged [18]. Histological remission was also described in lymphocytic colitis [19].

Table 14.1 Examples of scoring systems for ulcerative colitis

Riley Index

	None	Mild	Moderate	Severe
Acute inflammatory infiltrate (polymorphonuclear cells in lamina propria)	0	1	2	3
Crypt abscesses	0	1	2	3
Mucin depletion	0	1	2	3
Surface epithelial integrity	0	1	2	3
Chronic inflammation (round cells in lamina propria)	0	1	2	3
Crypt architectural irregularities	0	1	2	3

Geboes score

Grade 0 Structural (architectural change)	
No abnormality	0.0
Mild abnormality	0.1
Mild or moderate diffuse or multifocal abnormalities	0.2
Severe diffuse or multifocal abnormalities	0.3
Grade 1 Chronic inflammatory infiltrate	
No increase	1.0
Mild but unequivocal increase	1.1
Moderate increase	1.2
Marked increase	1.3
Grade 2 Lamina propria polymorphonuclear cells	
No increase	2A.0
Mild but unequivocal increase	2A.1
Moderate increase	2A.2
Marked increase	2A.3
Grade 3 Neutrophils in epithelium	
None	3.0
< 5 % crypts involved	3.1
< 50 % crypts involved	3.2
> 50 % crypts involved	3.3
Grade 4 Crypt destruction	
None	4.0
Probable—local excess of neutrophils in part of crypt	4.1
Probable—marked attenuation	4.2
Unequivocal crypt destruction	4.3
Grade 5 Erosion or ulceration	
No erosion, ulceration, or granulation tissue	5.0
Recovering epithelium+adjacent inflammation	5.1
Probable erosion—focally stripped	5.2
Unequivocal erosion	5.3
Ulcer or granulation tissue	5.4

Table 14.2 Global histology activity score (GHAS) for Crohn's disease. To be applied separately for ileum and colon

1 : Epithelial damage	
Normal	0
Focal	1
Extensive	2
2 : Architectural changes	
Normal	0
Moderate (< 50 %)	1
Severe (> 50 %)	2
3 : Mononuclear cells in lamina propria	
Normal	0
Moderate increase	1
Severe increase	2
4 : Polymorphonuclear cells in lamina proria	
Nomal	0
Moderate increase	1
Severe increase	2
5 : Neutrophils in epithelium	
Surface	1
Cryptitis	2
Crypt abscess	3
6 : Erosion or ulceration	
No	0
Yes	1
7: Granuloma	
No	0
Yes	1
Number of biopsies affected (*n* = 6 or more)	
None	0
Equal or less than 33 %	1
Between 33 and 66 %	2
More than 66 %	3
Each variable is scored independently. The total score is the sum of all individual scores (max = 16)	

In the future it is likely that the role of histological analysis for the evaluation of treatment and clinical course of a disease will become as important as the diagnostic role of the biopsy in the management of patients with colitis.

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Index

K. Geboes et al. (eds.), *Colitis: A Practical Approach to Colon Biopsy Interpretation*, DOI 10.1007/978-3-319-08028-4