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

K. Geboes, MD, PhD (✉)
Department of Pathology, KULeuven, Gasthuisberg, Leuven, Belgium

Department of Pathology, UGhent, Ghent, Belgium
e-mail: karel.geboes@skynet.be

M. Leo • S. Nemolato, MD
Department of Pathology, University of Cagliari, Cagliari, Italy
e-mail: marialeo@medicina.unica.it; sonianemolato@libero.it

K. Geboes et al. (eds.), *Colitis: A Practical Approach to Colon Biopsy Interpretation*, DOI 10.1007/978-3-319-08028-4_4

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

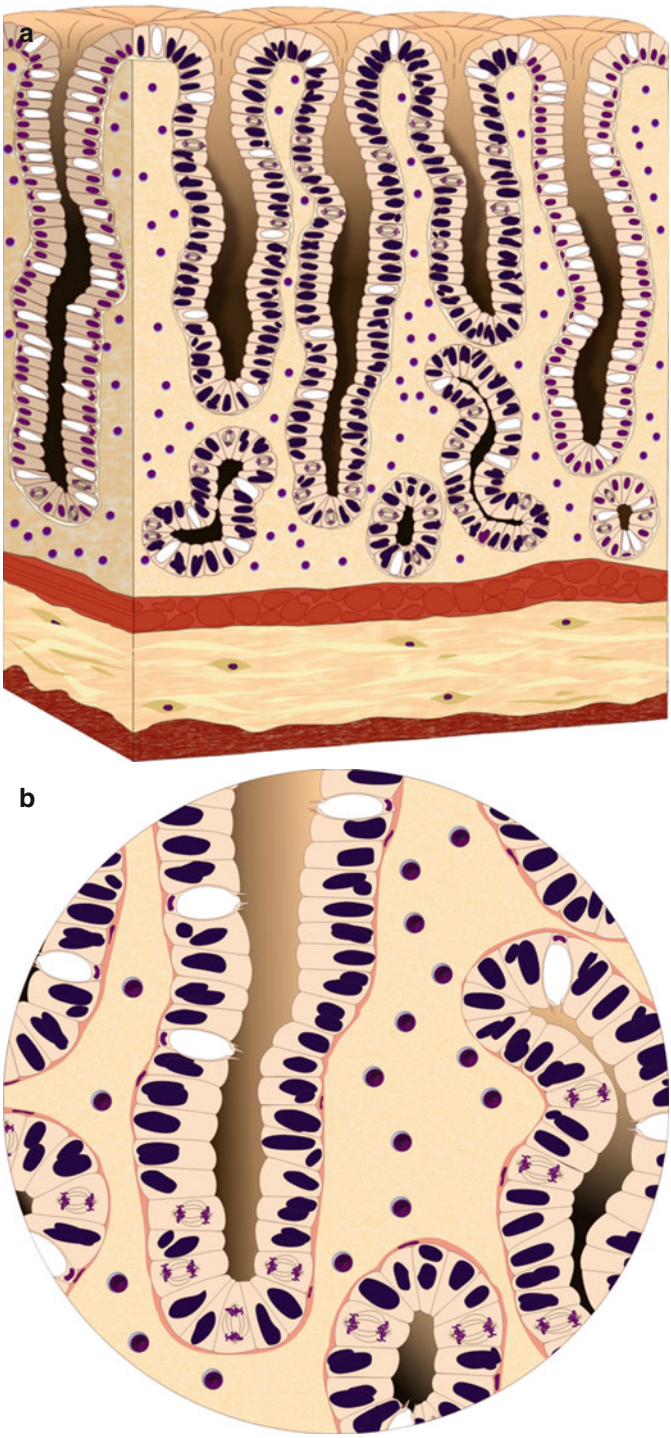

Fig. 4.1 (**a**, **b**) Low-grade dysplasia. The epithelial cells are elongated with an enlarged darkly staining nucleus. However, the shape and size of the cells are generally comparable

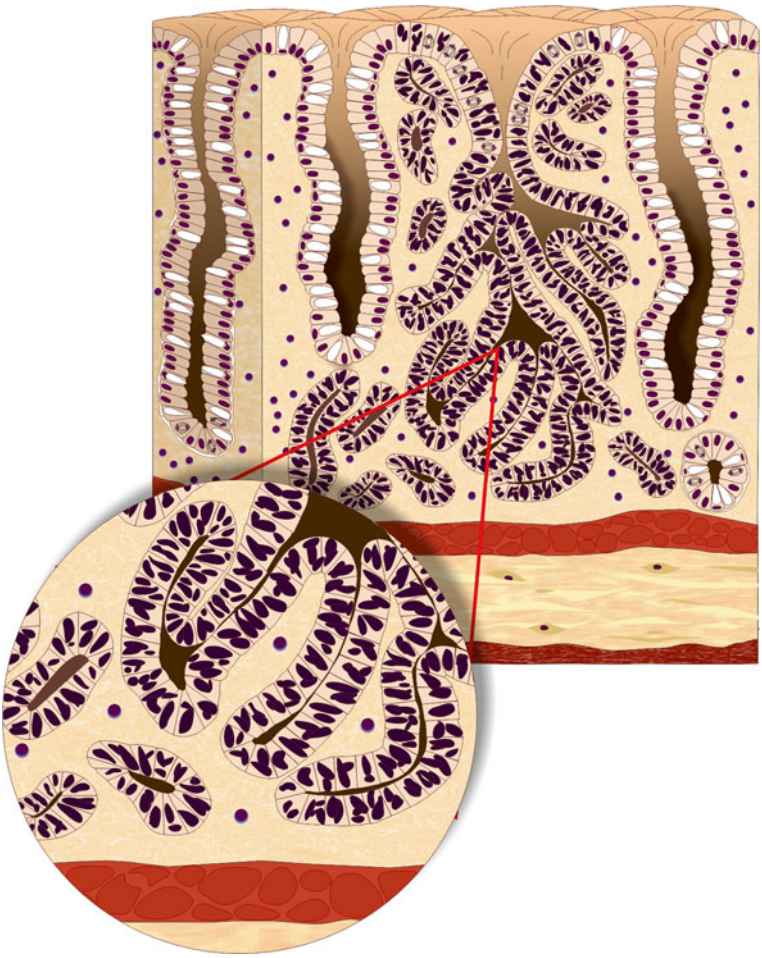

Fig. 4.2 High-grade dysplasia. Both architecture and cytology are more disturbed

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

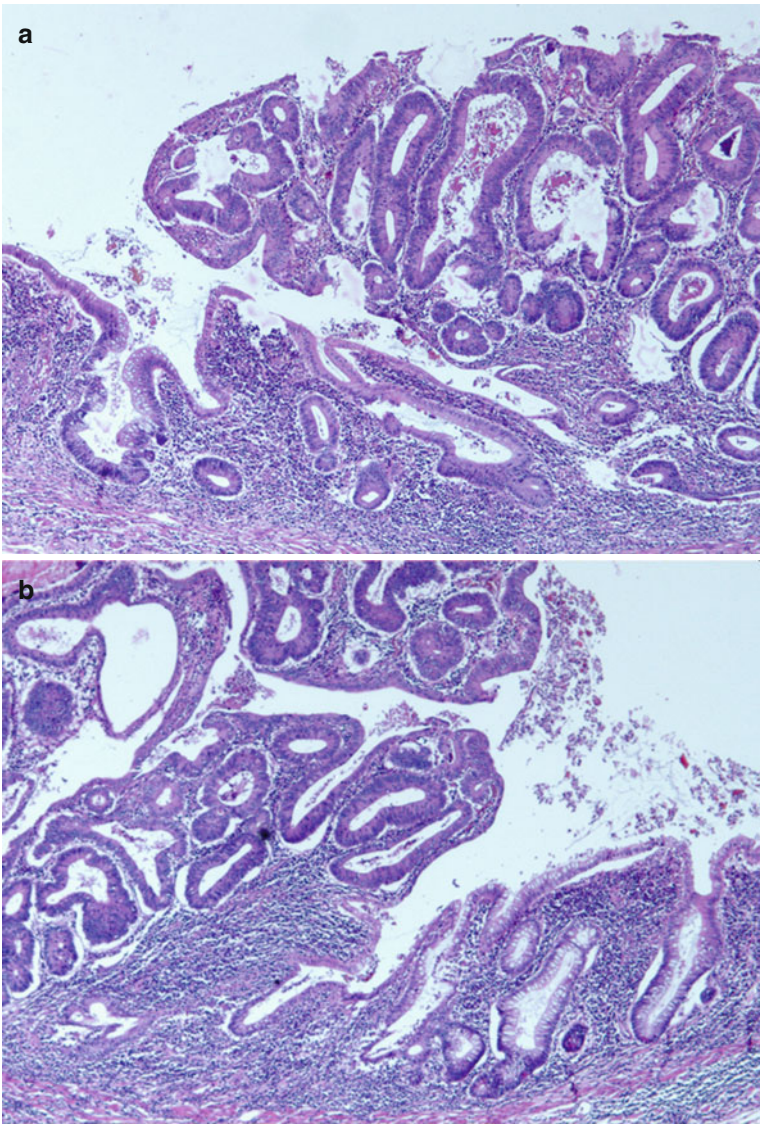

Fig. 4.3 (**a**–**d**) Microphotograph of an elevated – polypoid dysplastic lesion in ulcerative colitis. The flat surrounding mucosa shows features of active inflammation, but the cells are not dysplastic; (**b**, **c**) are higher magnifications showing the cytological atypia (×40); (**d**) is a low-power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

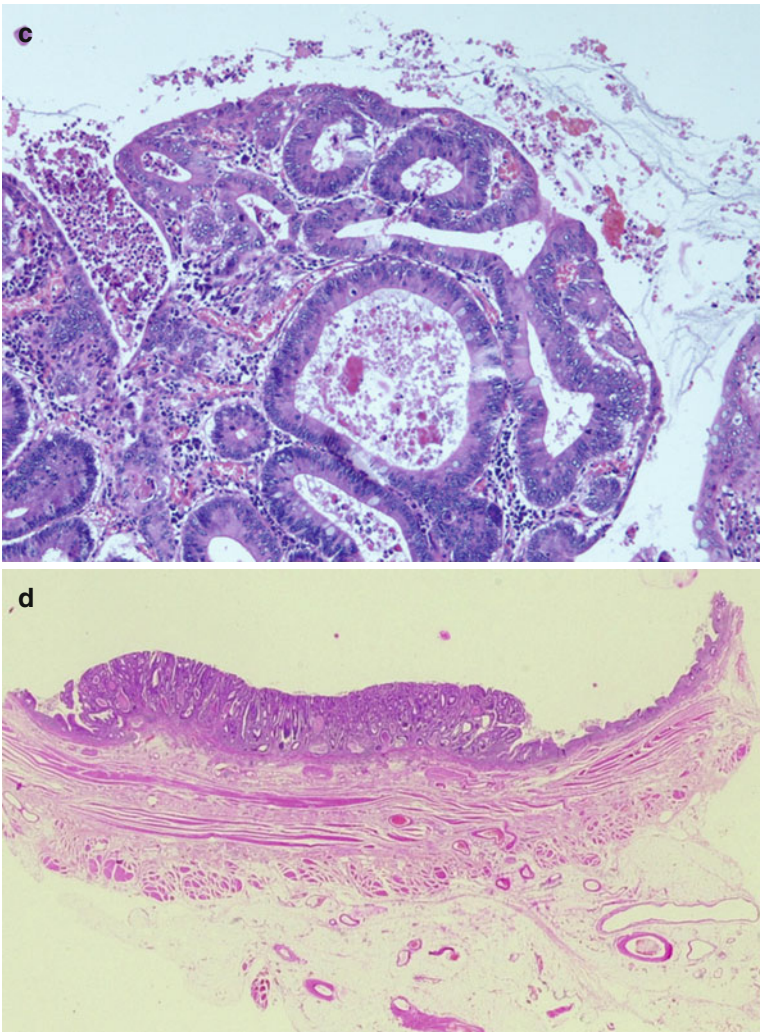

Fig. 4.3 (continued)

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.

References

1. Goulet O, Salomon J, Ruemmele F, et al. Intestinal epithelial dysplasia (tufting enteropathy). Orphanet J Rare Dis. 2007;2:20–6.
2. Geboes K, Rutgeerts P. Dysplasia in inflammatory bowel diseases: definition and clinical impact. Can J Gastroenterol. 1999;13:671–8.
3. Tannock IF, Hill RP. Glossary. In: Tannock IF, Hill RP, editors. The basic science of oncology. 3rd ed. New York: McGraw-Hill; 1998. p. 497.
4. Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Hum Pathol. 1983;14:931–68.
5. Batts KP, Haggitt RC. Dysplasia in ulcerative colitis and Crohn's disease: clinical pathology and current surveillance methods. In: Targan SR, Shanahan F, editors. Inflammatory bowel disease, from bench to bedside. Baltimore: Williams & Wilkins; 1994. p. 631–42.
6. Itzkowitz SH, Harpaz N. Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. Gastroenterology. 2004;126:1634–48.
7. Blackstone MO, Riddell RH, Rogers BHG, et al. Dysplasia-associated lesions or mass (DALM) detected by colonoscopy in longstanding ulcerative colitis. An indication for colectomy. Gastroenterology. 1981;80:366–74.
8. Ensari A, Bosman FT, Offerhaus GFA. The serrated polyp: getting it right! J Clin Pathol. 2010;63:665–8.
9. Rosenstock E, Farmer RG, Petras R, et al. Surveillance for colonic carcinoma in ulcerative colitis. Gastroenterology. 1985;89:1342–6.
10. Rubin CE, Haggitt RC, Burmer GC, et al. DNA-aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. Gastroenterology. 1992;103:1611–20.
11. Kiesslich R, Fritsch J, Holtmann M, et al. Methylene-blue aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology. 2003;124:880–8.
12. Harpaz N, Polydorides AD. Colorectal dysplasia in inflammatory bowel disease. Arch Pathol Lab Med. 2010;134:876–95.