Inflammatory bowel disease-related dysplasia: evolving diagnostic and therapeutic paradigms

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Abstract

Patients with inflammatory bowel disease show an excess colon cancer incidence and mortality. Colonoscopy with biopsies represents the most robust strategy for decreasing the risk of malignancy. Targeted biopsies of lesions identified on a high-resolution endoscope and chromoendoscopy is now believed to be a more efficient means of detecting dysplasia, and random biopsies do not increase the yield of neoplasia. In clinical practice, the diagnosis of dysplasia is based on a constellation of changes that include cytologic, architectural and maturational abnormalities. Morphologically, most dysplasia is of the adenomatous type. The distinction of low-grade dysplasia from reactive epithelial changes remains a significant and sometime an insurmountable problem. Although p53 immunohistochemistry has been proposed as a biomarker for dysplasia, positive staining reactive conditions significantly limits its utility as a marker of dysplasia. The advent of high resolution endoscopes and chromoendoscopy allows for the visualization of the vast majority of dysplastic lesions, leaving only a minority of lesions are endoscopically invisible. Advances in screening and endoscopic resection techniques now permit conservative management of endoscopically visible dysplastic lesion, including some cases of high-grade dysplasia.

Keywords dysplasia; inflammatory bowel disease; p53

Introduction

While the increased risk of cancer in patients with inflammatory bowel disease is widely acknowledged, over the last decade its become increasingly apparent that the extent of the risk may have been over-estimated, a consequence of the bias introduced by the study of referral center cohorts. A recent Danish population based study found no excess risk of cancer in ulcerative colitis.[1] This may well be a consequence of better surveillance, more robust control of inflammation, as well as use of agents such as 5-aminosalicylates, a potentially chemopreventive agent. On the other hand, a recent study from Northern California found excess colon cancer incidence and mortality in patients with inflammatory bowel disease.[2] Regular colonoscopy with biopsies represents the most robust strategy for decreasing the risk of malignancy.[3–6]

Until recently, multiple random biopsies from diseased/previously diseased colon was the standard of care. There is however increasing evidence that targeted biopsies of lesions identified on a high-resolution endoscope represents a more efficient means of detecting dysplasia, and random biopsies do not increase the yield of neoplasia.[7,8]

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Stratification of risk in IBD

The degree of cancer risk is modulated by several factors including the extent of colitis, duration of disease, the presence of primary sclerosing cholangitis, and the severity of inflammation: these features assist in stratifying risk and guide the management of patients. Patients with pancolitis and primary sclerosing cholangitis are at the highest risk of malignancy, while patients with isolated proctitis are at no additional risk of cancer. Thus, patients with proctitis do not require cancer surveillance while those with primary sclerosing cholangitis and pancolitis are placed on an accelerated screening protocol. The severity of microscopic inflammation over time has also been shown to be an independent risk factor for colorectal neoplasia among patients with ulcerative colitis.[9]

Diagnosis of dysplasia

Endoscopic appearance

Endoscopically the appearance is highly variable and includes nodules, plaque-like lesions, a filiform appearance, as well as stricture formation (Figure 1a and b).

Histology

Colonic biopsies are grouped into five categories: negative for dysplasia, indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia and invasive carcinoma. A revised Vienna classification is used in many centers in Europe.[10] The classification and criteria for dysplasia in inflammatory bowel disease were proposed by Riddell and colleagues in 1983.[11]

Intra- and inter-observer variability in the interpretation of biopsy specimens for dysplasia in inflammatory bowel disease is well documented, even among experienced gastrointestinal pathologists.[12,13] In general, levels of agreement are highest for the category of high-grade dysplasia and for biopsy specimens considered negative for dysplasia, but are lowest at the lower end of the spectrum (e.g., indefinite for dysplasia versus low-grade dysplasia).

Defining dysplasia

Dysplasia, also referred to as intraepithelial neoplasia, is a preneoplastic lesion that puts the patient at a high risk of invasive carcinoma, both at the site of biopsy and other sites within the diseased organ. Dysplasia is defined as unequivocally neoplastic epithelium confined to the basement membrane. This definition has little practical value since evaluating the basement membrane and defining 'unequivocally neoplastic' represent significant and sometimes insurmountable challenges. In clinical practice the diagnosis of dysplasia is based on a constellation of changes that include cytologic, architectural and maturational abnormalities. Cytologically, dysplastic cells are characterized by nuclear stratification, cellular crowding, as well as hyperchromatic and enlarged nuclei (Figures 2 and 3). Common architectural abnormalities include small glandular profiles, irregularly shaped glands, glandular crowding, crypt budding

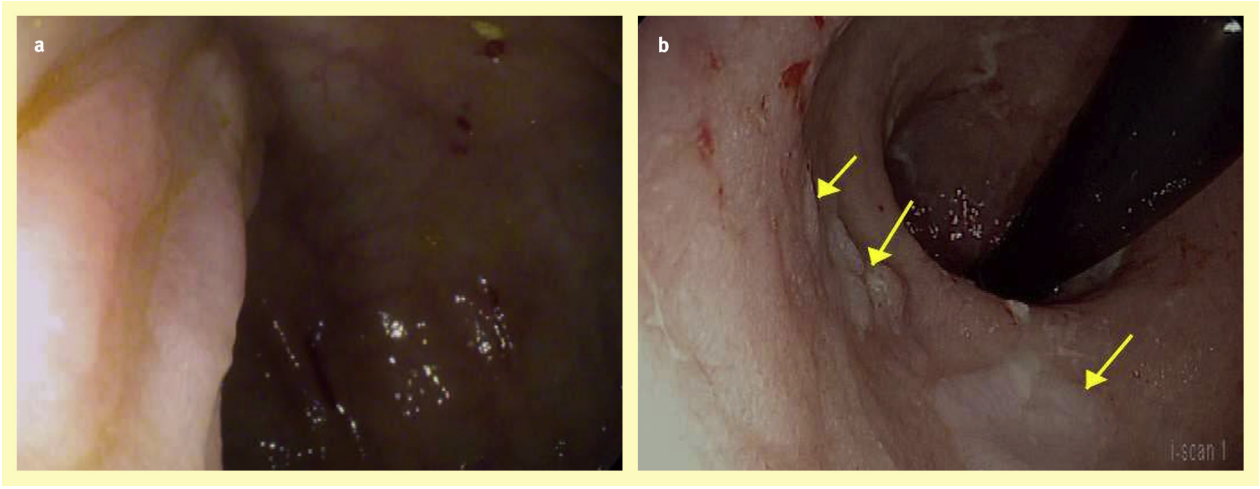

Figure 1 (**a** and **b**) Endoscopically visible dysplasia arising in inflammatory bowel disease (arrows).

and cribriforming, the presence of back-to-back glands with varying degrees of stromal extinction, and a villiform surface (Figures 4 and 5). It should be noted that severe architectural changes are typically seen only in high-grade dysplasia.

The lack of maturation represents a key feature that distinguishes a reactive process (also see below) from dysplasia. Within normal colonic epithelium, proliferation is confined to the crypt base. It is notable that stem cells are identified at the bottom of the crypt and proliferative activity is noted immediately above this region — thus Ki67 positive cells are confined to the bottom 1/3rd of the crypt. This contrasts with the location of stem cells and the proliferative zone in the stomach — situated in the higher regions of the mucosa. The colonic cells above the crypt base show progressively smaller nuclei and differentiate into goblet cells, absorptive and endocrine cells. This pattern of acquisition of terminally differentiated cells is often referred to as maturation. Dysplastic epithelium often lacks maturation, instead 'proliferative-type' epithelium is identified within the upper 1/3rd of the crypts, and more significantly, on the surface epithelium. While lack of maturation distinguishes dysplasia from reactive epithelium, it should be noted that the expanded proliferative zone may extend into the upper half of the crypt in regenerative states (Figure 6). Furthermore, it should be recognized that the length of the crypts may be significantly reduced in cases with marked regenerative changes — as is often found adjacent to an ulcer. In this scenario the proliferative zone may extend extremely close to the surface epithelium, as a result only subtle (or rarely none) evidence of maturation may be evident

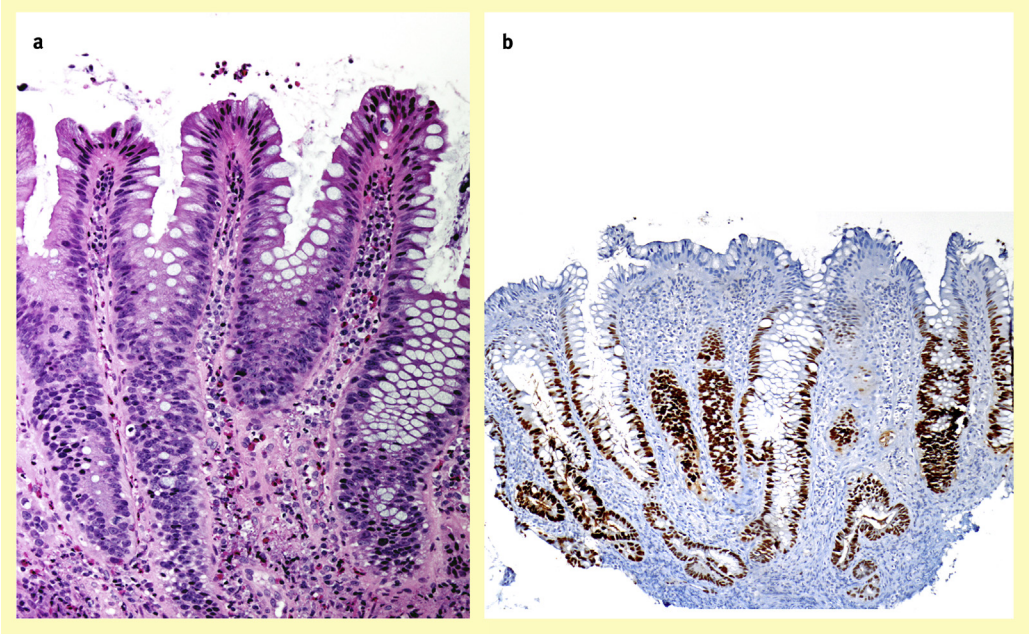

Figure 2 Ulcerative colitis with low-grade dysplasia. The image shows lack of maturation. However, the polarity of the cells is preserved (**a**). Immunohistochemistry performed on this case show strong reactivity for p53. The reactivity extends to the upper half of the crypts (**b**).