Classification and diagnosis of colorectal dysplasia in inflammatory bowel disease

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Abstract

In patients with ulcerative colitis or Crohn colitis, the risk for dysplasia and colorectal cancer increases with disease duration, and early detection by surveillance colonoscopy has been the mainstay for preventive treatment. For these diseases in which the clinical management relies heavily upon pathologic interpretation, the diagnosis and grading of dysplasia remains inherently challenged by interobserver variability. This diagnostic challenge is coupled with new developments in endoscopic techniques resulting in relatively rapid shifts in terminology and changes in the macroscopic classification of dysplastic lesions. This article provides pathologists with an update on the preferred macroscopic classification, details the histologic features of dysplasia and utility of immunohistochemistry, and provides a historical context for outdated terminology.

Keywords Crohn; dysplasia associated lesion or mass (DALM); histology; immunohistochemistry; immunohistochemistry; inflammatory bowel disease (IBD); invisible dysplasia; pathology; polypoid dysplasia; ulcerative colitis (UC)

Introduction

Patients with ulcerative colitis (UC) or Crohn disease (CD) have an increased risk of colorectal cancer (CRC) which is directly associated with disease duration. Most cases of CRC are believed to arise from dysplasia, and therefore surveillance colonoscopy is the standard for detection of these precursor lesions. Colonoscopic sampling to evaluate for dysplasia is two-fold, including (1) targeted biopsies to sample visible or "polypoid" mucosal abnormalities and (2) extensive random biopsies to identify invisible or "flat" dysplasia. This endoscopic distinction between visible polypoid and invisible flat dysplastic lesions is of particular clinical significance because polypoid lesions can be safely resected endoscopically, whereas treatment for flat dysplastic lesions historically required colectomy. The current US guidelines recommend biopsying at least 32 random samples from all segments of the colon as the foundation of endoscopic surveillance.[1] However, the body of literature supporting these recommendations is from older investigations performed when most dysplasia was diagnosed on random biopsies of colonic mucosa.[2] With the arrival of video endoscopy, chromoendoscopy and newer endoscopic technologies, researchers now report that most dysplasia arising in inflammatory bowel disease (IBD) is visible rather than invisible, thus changing the way we classify and treat dysplasia in IBD. This article details the current preferred terminology for macroscopic classification of dysplasia in IBD and reviews the issues related to histopathologic diagnosis.

Risk of neoplasia

The risk of neoplasia is directly related to the duration of disease and extent of colonic inflammation. However, the exact magnitude of risk for colorectal neoplasia conferred by IBD is difficult to quantify due to biases and methodological errors. For example, earlier studies implicating UC included higher proportions of patients with more severe disease, whereas later population-based studies likely underestimated the true risk by including more patients with left sided disease or who had undergone colectomy. Regardless, there is at least unanimous agreement in the literature that, compared to the age-matched general population, there is an increased risk of 3–5 fold. A widely cited comprehensive meta-analysis of 116 studies involving almost 55,000 patients with UC with age-stratified data has estimated that the probability of developing CRC is 2% after 10 years, 8% after 20 years, and 18% after 30 years following diagnosis.[3] More recent studies report lower incidence rates suggesting that the widespread use of maintenance therapy with anti-inflammatory chemoprophylaxis agents, such as 5-ASA, and surveillance colonoscopy is leading to overall decreased risk for CRC.[4]

In UC, there is well established data showing that the extent of disease and duration of disease are directly related to the risk for neoplasia. For example, 80% of CRC in UC occurs in patients with pancolitis or extensive colitis (inflammation extending proximal to the hepatic flexure).[5] Whereas left-sided UC results in intermediate risk, there is minimal risk with ulcerative proctitis.[6] The mean interval to CRC in all groups is 20 years, with an average age of CRC diagnosis at 45 years, approximately 15–20 years younger than the general population.[6] Of note, patients with synchronous primary sclerosing cholangitis have a substantially higher risk of CRC with an incidence of 10%, 33%, and 40% at 10, 20, and 30 years after diagnosis of UC respectively.[7]

There is less data on the risk of CRC in patients with CD, as early studies failed to account for effects of early colectomy or evaluate cases with colitis as a separate risk group. Several recent studies suggest that given a similar duration and extent of disease, the relative risk of colon cancer is similar in CD and UC (2.64 and 2.75, respectively, in one study), even without factoring in the effect of early colectomy.[8,9] Cohorts of patients with comparable extensive colonic involvement of CD and UC have similar cumulative incidence of CRC: 8% in CD and 7% in UC at 22 years following onset of symptoms.[10] However, unlike UC, CD confers an increased risk of adenocarcinoma in the excluded segments of bowel and small intestine.

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Macroscopic classification of dysplasia

The historical DALM

The first descriptions of "polypoid" lesions in UC were reported in 1959 in a retrospective study of 17 carcinoma specimens, and in nine cases these lesions were indistinguishable from adenomas.[11] Following this description, other retrospective studies also described adenoma-like dysplastic lesions in UC that were grossly visible or elevated, and the term "DALM" (dysplasia associated lesion or mass) was coined in 1981.[12] In the defining study of 112 UC patients, DALMs were associated with invasive carcinoma in 58% of cases, and therefore were considered a strong indicator for colectomy.[12] Thus, colectomy became the widespread standard of care when a DALM was encountered regardless of the macroscopic appearance.

Over time, it became apparent that DALMs portend unequal cancer risk based upon their endoscopic appearance, which is widely heterogeneous. For example, the lesions may appear as a plaque, strictured lesion, broad-based irregular mass, discrete sessile nodule, or polyp.[13] Consequently, it was suggested that the gross appearance and association with involved segments were critical features to determine appropriate therapy. For example, studies in the late 1990's indicated that DALMs arising in areas involved by colonic inflammation should be considered an indication for colectomy.[14] By comparison, in areas unaffected by colitis, polypectomy alone was considered appropriate so long as the lesions were considered "adenoma-like", meaning they were grossly discrete, well-defined, sessile or pedunculated polyps resembling sporadic adenomas.[13] Follow-up studies have confirmed that adenoma-like DALMs could be adequately treated with polypectomy and continued endoscopic surveillance.[15,16] As a result of these studies, three distinct categories of DALM evolved:

- Sporadic adenoma: A polyp that resembles an adenoma both endoscopically and histologically and is outside areas of colitis
- UC-associated adenoma-like polypoid dysplasia: A lesion that resembles an adenoma both endoscopically and histologically and is located in areas of colitis
- UC associated non-adenoma-like dysplasia ("true DALM"): An elevated or flat lesion that is irregular and broadly-based, or forms a mass and is located in areas of colitis.

These distinctions became important for treatment, as both of the adenoma-like lesions could be treated by polypectomy alone, whereas the non-adenoma-like lesion was considered a "true DALM" requiring colectomy.

As the field evolved, terminology such as "polypoid dysplastic lesion", "polypoid dysplasia", and "flat dysplasia" came into favour, replacing the term DALM, which was saddled by its misleading historical association with colectomy. The ensuing years brought evolution of endoscopic techniques such as video endoscopy, chromoendoscopy and endoscopic mucosal resection which improved the detection and removal of previously imperceptible lesions. Consequently, we now recognize that the principal factor in managing patients with raised dysplastic lesions is whether the dysplasia is completely resectable by endoscopic techniques. Furthermore, expert consensus recommendations now suggest that even flat lesions, so long as they are endoscopically visible, can be treated by endoscopic resection to avoid colectomy.[17] This has led to the current recommended macroscopic classification of lesions in IBD below.

Endoscopically invisible dysplasia

To avoid confusion, experts in the field recommend refraining from use of the term "flat dysplasia", as this term is now commonly used among endoscopists to describe macroscopically visible but minimally elevated (<2.5 mm) lesions in the gastrointestinal tract. Rather, use of more descriptive terms such as "macroscopically invisible" or "endoscopically invisible" is encouraged for endoscopists.[17] Invisible dysplasia is therefore defined as dysplasia identified on random (non-targeted) biopsies of colon mucosa without a discretely visible lesion (Figure 1).[17] The histologic confirmation of invisible dysplasia warrants surgical intervention.

Endoscopically visible dysplasia (historically: DALM)

International consensus recommends that terms like dysplasia associated lesion or mass (DALM), adenoma-like, and non-adenoma-like should be abandoned. Instead, experts suggest dividing visible lesions into "endoscopically resectable" and unresectable categories. The term endoscopically resectable applies to a lesion that (1) has identifiable distinct margins, (2) appears to be completely removed on visual inspection after endoscopic resection, (3) is confirmed to be completely removed by histologic examination, and (4) is surrounded by histologically confirmed nondysplastic mucosa immediately adjacent to the resection site (Figure 2).[17] Patients with lesions fulfilling these criteria may be followed with close surveillance. By contrast, patients with lesions not considered endoscopically resectable require surgical intervention.

Microscopic classification of dysplasia and morphology

It is widely accepted that cancer in IBD progresses in a stepwise fashion from inflammation through dysplasia and carcinoma, and that epithelial dysplasia is the most important marker for increased risk of malignancy. Epithelial dysplasia in IBD is defined as unequivocally neoplastic alterations of the intestinal epithelium restricted within the basement membrane.[18] In general, the morphologic features of IBD-associated dysplasia show similarities to sporadic adenomatous polyps, including alterations in nuclear, cytoplasmic, and architectural characteristics. Nuclear atypia is common and is characterized by hyperchromasia, increased nuclear to cytoplasmic ratio, nuclear crowding with overlapping or stratification, and alterations in shape such as exaggerated elongation (pencil-shaped nuclei) or loss of nuclear polarity (round nuclei). Clumped nuclear chromatin and multiple nucleoli may also contribute to the nuclear atypia, as does a characteristic lack of surface maturation. The most common cytoplasmic alterations include mucin depletion and hypereosinophilic tinctorial changes. Excessive goblet cell mucin, dystrophic goblet cells, and endocrine or Paneth cell metaplasia can also be found, although these features are much less common. Architecturally, dysplastic crypts tend to show crowding with scant intervening lamina propria, irregular crypt budding, cystic change, cribriforming, or tubular and villiform growth patterns.