Neoplasia Without Dysplasia

Lessons From Barrett Esophagus and Other Tubal Gut Neoplasms

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Context.—Classic pathology teaching emphasizes that neoplastic lesions of the gastrointestinal tract are characterized by architectural and cytologic abnormalities that distinguish it from normal tissue. Recent studies suggest that many important—and in some cases clonal—molecular abnormalities that lead to dysregulation of cell proliferation and differentiation (neoplasia) occur before morphologic expression of dysplasia.

Objective.—To summarize the biologic and pathologic features of preneoplastic conditions of the tubal gut that reveal evidence of neoplastic alteration, but without the traditional morphologic features of dysplasia, in order to provide guidance on how to identify these lesions. Particular attention is given to Barrett esophagus, a chronic inflammatory condition in which early molecular and morphologic events that drive carcinogenesis are best understood.

Data Sources.—Selected references and abstracts were obtained by a PubMed (US National Library of Medicine) search by using the search headings neoplasia, preneoplasia, dysplasia, adenoma, serrated polyps, and Barrett’s esophagus between the years 1980 and 2009.

Conclusions.—Many types of lesions throughout the tubal gut fulfill the most basic and classic principles of a neoplastic precursor lesion but lack conventional morphologic evidence of dysplasia and/or maintain the capacity for cell differentiation and maturation. All of these lesions, such as squamous dysplasia of the esophagus, dysplasia in Barrett esophagus, and hyperplastic/serrated polyps of the colon, represent early neoplastic precursor lesions but without conventional histologic features of dysplasia. It is important for pathologists to be aware of these lesions, both for diagnostic and prognostic purposes, but also so that future studies can be performed with regard to risk stratification of patients.

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This review will focus on preneoplastic conditions of the tubal gut that reveal molecular or biologic evidence of neoplastic alteration, but without the traditional morphologic features of dysplasia, and will provide some guidance regarding how to identify these lesions. Particular attention is given to BE, a chronic inflammatory condition in which early molecular and morphologic events that drive carcinogenesis are best understood.

DEFINITIONS

There is a lack of consensus regarding the definition of the term neoplasia, and often the definition depends on the purpose or context in which it is used. The simplest definition of a neoplasm is an abnormal growth of tissue without physiologic function. However, other more scientific definitions of neoplasia also include criteria for hyperproliferation, independence from initial growth signals, destruction of the normal organization of the tissue, disruption of functional coordination with normal tissue, and formation of a distinct mass. Some propose that a neoplasm must show a definite increased risk of progression to cancer. Although not specifically indicated in the definition of neoplasia, most authorities would also require that neoplastic cells show expansion of clones of cells with reproductive or survival advantage over competitor cells in the microenvironment.

The term dysplasia is defined as histologically unequivocal neoplastic epithelium confined to the basement membrane. In contrast, the World Health Organization defines an intraepithelial neoplasia as a lesion characterized by morphologic changes, including architectural and cytologic, that result from clonal alterations in genes, with a predisposition for progression to invasion and metastasis. Unfortunately, demonstration of histologically identifiable “unequivocal” neoplastic tissue is often problematic, as indicated in this review. Nevertheless, for the purpose of this article, the term dysplasia is defined by the presence of either cytologic and/or architectural features of neoplasia, as defined above.

BARRETT ESOPHAGUS

It is well known that cancer in BE develops via a stepwise process that begins with gastroesophageal reflux disease (GERD)—induced damage to the squamous epithelium, then proceeds through various stages of columnar metaplasia, low- and high-grade dysplasia, and, ultimately, carcinoma. Traditional pathology teaching emphasizes that, to establish a diagnosis of dysplasia in BE (and, in fact, anywhere in the columnar-lined tubal gut), dysplastic changes must involve the full length of the crypt and surface epithelium, without evidence of surface maturation. This has always been based on the rather anecdotal belief that unequivocal neoplasia does not retain the capacity for normal crypt cell dynamics, such as increased cellular differentiation and decreased proliferation as cells migrate toward the luminal surface of the mucosa. Thus, up until recently, the significance of dysplasia-like cellular atypia limited to the basal portions of crypts, but without involvement of the upper (luminal) half of the crypts and surface epithelium, has been considered “reactive” in nature and represents a controversial aspect of dysplasia pathology. This concept has recently been challenged by the demonstration that dysplasia may, in fact, be limited to the crypt bases in the early stages of neoplastic progression in BE (Figure 1, A through C) and in other chronic inflammatory disorders such as chronic gastritis and IBD (see below).

In a recent study by Lomo et al., patients with BE— who were part of a cohort of 206 high-risk patients with dysplasia-like atypia limited to the basal crypt compartment (prevalence rate, 7%) and with histologic evidence of surface maturation—were evaluated for the clinical, pathologic, immunohistochemical, and molecular features of disease. Clinically, patients with “crypt dysplasia” were similar to those with conventional, full-length crypt dysplasia. However, a significantly higher proportion of patients with BE who had crypt dysplasia also showed evidence of conventional low- or high-grade dysplasia (87%), and/or adenocarcinoma, in biopsies taken elsewhere in the patient’s esophagus, from either the same or prior endoscopic procedure. Crypt dysplasia also showed an increased proliferation rate and a significantly higher prevalence rate of molecular abnormalities, such as aneuploidy and loss of heterozygosity of TP53, in comparison to controls. This article showed, for the first time, that dysplasia may be detected at an early stage of development when it is limited to the crypt bases and placed doubt on the theory that early in situ neoplastic lesions cannot undergo surface maturation. Two other recent studies confirmed these initial findings. The first was a study by Zhang et al., who evaluated the zonal DNA content distribution in the basal versus the superficial portions of crypt cells in BE, and related dysplastic lesions, by image cytometry and analysis of high-fidelity DNA histograms. The prevalence of DNA content abnormalities increased significantly from nondysplastic BE to crypt dysplasia, low- and high-grade dysplasia, and adenocarcinoma. When different portions of the crypts were analyzed separately, the superficial crypt cells in crypt dysplasia were diploid. However, the basal crypt cells were equally abnormal to those in the basal portions of the crypts in patients with conventional, full-length crypt low-grade dysplasia, indicating that the DNA ploidy profile in basal crypt cells in crypt dysplasia and low-grade dysplasia were similar. These results provided support for the theory that dysplasia in BE begins in the basal crypt cells and then extends further up the crypts with neoplastic progression. It also provided support for the controversial theory that BE is, in and of itself, a neoplasm. This theory is based partly on the fact that BE is hyperproliferative and possesses clonal molecular aberrations, many of which occur before the onset of morphologic dysplasia. For instance, DNA content abnormalities are present in up to 30% of morphologically nondysplastic BE biopsy specimens.

Second, in a recent study by Srvistava et al., published in abstract form, the long-term outcome of 49 patients with BE who had at least 1 focus of crypt dysplasia was evaluated and compared to that of patients with conventional low- or high-grade dysplasia. In that study, a significant correlation was noted between the presence of crypt dysplasia and conventional low- or high-grade dysplasia, as in the study by Lomo et al; the former was associated with an increased risk of adenocarcinoma upon long-term follow-up. In support of this argument are the results of a study by Montgomery et al., in which patients with BE who showed deep crypt cytologic changes suggestive of dysplasia, but with surface maturation (considered indefinite for dysplasia for the purpos-
es of patient management), demonstrated a risk of malignancy similar to that of patients with conventional low-grade dysplasia.

Differentiation of crypt dysplasia from regeneration may be difficult because both of these entities show evidence of surface maturation. However, in contrast to crypt dysplasia, regenerating epithelium in BE is characterized by basal cells that show normal or slightly enlarged nuclei, without prominent nucleoli and without abnormal-appearing mitoses, loss of polarity, nuclear pleomorphism, or significant nuclear stratification. Nucleoli, when present, are not usually prominent. Furthermore, crypt regeneration is often associated with active inflammation or ulceration. Ultimately, crypt dysplasia is diagnosed by the finding of overtly dysplastic epithelial cells limited to the bases of the crypts, regardless of the status of the surface epithelium. In a recent interobserver study of BE neoplastic lesions, the degree of agreement among 6 GI pathologists was highest for BE cases with intramucosal carcinoma and cases without dysplasia, but no significant differences were observed in the degree of reproducibility in the diagnosis of crypt dysplasia ($\kappa =$...
0.44) compared to conventional low-grade (κ = 0.41) or high-grade dysplasia (κ = 0.46).

The biologic mechanisms responsible for the development and progression of dysplasia within crypts are unknown, but the theory that dysplasia begins in the bases of the crypts and progresses more luminally with time is supported by studies of stem cells and crypt cell dynamics in the GI tract. Both animal and human studies have shown that self-renewing “stem” cells reside near the crypt bases and, under appropriate stimuli, produce rapidly proliferating transit amplifying cells, which migrate upwards and lead to the production of fully differentiated and mature columnar cells. At the surface of the crypts (or villi in the small intestine), cells are lost by apoptosis. This entire process occurs in about 5 days in humans. A recently identified gene product, LGR5, was shown to be specifically expressed in cycling basal crypt columnar cells in mice and in humans and are believed to represent multipotential stem cells. In immunohistochemical studies in humans, LGR5-positive cells have been identified in the bases of crypts in the colon and in metaplastic crypts in BE. Barrett esophagus arises as a result of an acquired genetic instability and subsequent evolution of clonal populations with accumulated genetic defects. It is assumed that crypt stem cells and transit amplifying cells are most susceptible to neoplastic alteration because of their proliferative potential. It is also possible that basal crypt cells that undergo neoplastic alteration still retain some capacity for cell differentiation as they move up the crypt/villous axis, since the molecular pathways that control cell differentiation are different from those that control cell proliferation. Alternatively, neoplastic crypt cells may lose or show decreased capacity for cell migration up the crypt, until the number of cells involved by the neoplastic process reaches a critical load that results in mechanical propulsion of neoplastic cells to the surface. Clearly, further studies are needed to determine the site and mechanism of neoplastic alteration of cells in the crypts and their mechanism of spread throughout the intestinal epithelium.

**OTHER TUBAL GUT NEOPLASMS**

**Squamous Dysplasia of the Esophagus**

Squamous cell carcinoma is the most common malignant tumor of the esophagus worldwide. On the basis primarily of studies from the Far East, it is believed that this type of carcinoma develops via a chronic inflammation-based cell hyperplasia-dysplasia-carcinoma sequence. As in other portions of the GI tract, dysplasia of the esophageal squamous epithelium is characterized by both architectural and cytologic abnormalities that vary in extent and severity according to the lesion grade. Architectural abnormalities include disorganization of the epithelium, loss of cell polarity, overlapping nuclei, and irregular budding of neoplastic cells into the underlying lamina propria. Cytologic abnormalities include nuclear enlargement and hyperchromasia, pleomorphism, increased nucleus to cytoplasmic ratio, and increased mitotic activity. Squamous dysplasia is generally categorized as either low- or high-grade. Low-grade dysplasia is defined, rather arbitrarily, as the involvement with dysplastic cells of less than 50% of the thickness of the epithelium, whereas high-grade dysplasia is characterized by more than 50% involvement of the epithelium, including carcinoma in situ. Epidemiologic studies suggest that there is an increased risk of invasive squamous cell carcinoma in patients with basal cell hyperplasia (relative risk, 2.1), low-grade dysplasia (relative risk, 2.2), high-grade dysplasia (relative risk, 72.6), and carcinoma in situ (relative risk, 62.5).

Similar to other portions of the columnar-lined GI tract, mature squamous epithelium of the esophagus is generated by replication and proliferation of progenitor stem cells, which are believed to reside in the basal layer of the epithelium. Proliferation of stem cells results in the production of replicative cells (suprabasal cells), which undergo progressive levels of cell differentiation and maturation as they migrate from the basal aspect of the epithelium to the luminal surface, where apoptosis leads to discohesiveness and shedding into the lumen. By molecular and morphologic evidence, dysplasia of squamous cells begins in the basal and suprabasal zone and then progresses to involve the full thickness of the epithelium with time. In contrast to most early neoplasms in the columnar-lined tubal gut, there is evidence that neoplastic cells limited to the base of the squamous epithelium may undergo malignant transformation and invade the underlying lamina propria without first involving the full thickness of the epithelium. Morphologically, low-grade squamous dysplasia and less severe degrees of high-grade dysplasia (in which the epithelium is not replaced entirely by dysplastic cells) reveal dysplastic cells overlying mature nondysplastic cells (Figure 2). In essence, this is similar to the situation that occurs in BE (described above) in which dysplastic epithelium may reveal evidence of surface maturation in the early stages of neoplastic progression. One alternative theory is that dysplastic squamous cells do not retain their capacity for cellular differentiation and maturation, but instead develop and rapidly replace overlying mature squamous cells in a pagetoid fashion. However, this is unlikely since several studies have suggested that low-grade dysplasia may persist for long periods of time before malignant degeneration, which is far greater than the amount of time that regenerating suprabasal cells require to reach the luminal surface under normal physiologic circumstances.

There is also molecular evidence to support the theory of maturation of neoplastic epithelium in the squamous-lined esophagus. The most common molecular alterations in squamous cell carcinoma are overexpression of cell cycle regulatory proteins (cyclin D1, cyclin E) and inactivation or loss of tumor suppressor genes such as TP53, RB1, and CDKN2A (p16 gene), which occur in up to 80% of cases. Of these defects, inactivating mutations—and the resultant overexpression of p53—occur early in neoplastic progression. For instance, in some studies, p53 overexpression has been shown to occur in nondysplastic-appearing (hyperplastic) basal epithelium adjacent to squamous cell carcinoma in a high percentage of cases. Thus, in the multistep model of esophageal cancer, TP53 mutations are considered an early mutational event, possibly preceding phenotypic changes of dysplasia, once again supporting the concept of “neoplasia without dysplasia” in the esophagus. It is presumed that mutations occur in cells primarily located in the basal layer, which gives them a proliferative advantage that results in clonal expansion of mutations throughout the full thickness of the mucosa as the grade of dysplasia increases. Increasing proliferative activity related to TP53 mutations presumably...
Figure 3. Mucosal biopsy specimen of the stomach in a patient with chronic gastritis secondary to Helicobacter pylori infection. A, The mucosa is replaced by incomplete intestinal metaplasia and shows relatively mature and differentiated epithelium with small regular nuclei at the surface and in the luminal portion of the pits, whereas the bases of the pits show enlarged, hyperchromatic, and stratified nuclei with slight loss of polarity and increased mitoses. Note the absence of active inflammation in the mucosa. B, High-power view of the bases of the pits shows atypical cytologic features of the cells similar to those of conventional intestinal-type low-grade dysplasia. The nuclei are enlarged, hyperchromatic, and stratified, show focal loss of polarity and increased mitoses. There are also dystrophic goblet cells present in the base of the field (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B]).
exposes DNA more efficiently to an increasing number of epigenetic or genotoxic agents in TP53 mutant cells because of their inherent DNA instability and altered DNA repair mechanisms. Thus, dysplastic cells may begin their cycle by retaining their ability to undergo cell maturation until they have acquired a sufficient number or extent of mutations that make cell differentiation increasingly difficult or impossible to maintain.

Figure 4. Pyloric gland adenoma. A, Low-power view of a gastric pyloric gland adenoma shows a dense back-to-back arrangement of extremely low-grade pyloric-type glands with little intervening stroma. B, High-power view of the glands shows extremely low-grade cytologic features. The cells show mucinous differentiation and contain basally oriented, small, and regular nuclei with inconspicuous nucleoli, open chromatin pattern, and without stratification, loss of polarity, or increased mitoses (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]). Photographs courtesy of Elizabeth Montgomery, Johns Hopkins University Medical Center, Baltimore, Maryland.

Figure 5. Tubule neck dysplasia (signet ring cell carcinoma in situ) in a patient without underlying gastritis. A, Signet ring–like cells, composed of a central mucinous goblet and an eccentric hyperchromatic and slightly enlarged nuclei, are present within the pits and focally on the surface epithelium. Note that the surface epithelium is composed of a combination of signet ring–like cells and foveolar cells without a central goblet of mucin. B, High-power view of the superficial pit and surface epithelium shows the cytologic features of in situ signet ring cells dispersed among the residual foveolar cells (hematoxylin-eosin, original magnifications ×200 [A] and ×400 [B]).

Figure 6. Colonic mucosa in a patient with Crohn disease and adenocarcinoma (not shown). Overlying and adjacent to the adenocarcinoma is villous hypermucinous epithelium, composed of cells without cytologic atypia and with surface maturation. However, previous studies have shown a high association with carcinoma and KRAS mutations in inflammatory bowel disease (hematoxylin-eosin, original magnification ×100).

Figure 7. Mucosal biopsy specimen of a patient with chronic ulcerative colitis of more than 20 years’ duration who had multiple areas of conventional dysplasia in other portions of the colon. A, In this particular biopsy, low-grade dysplastic changes are present in the bases of the crypts, but the surface epithelium, although poorly denuded, shows evidence of maturation without cytologic features of dysplasia. Note the lack of inflammation in the lamina propria. B, High-power view of the bases of the crypts shows cytologic features of low-grade dysplasia. The cells are enlarged, hyperchromatic, and stratified and show slight loss of polarity and increased mitoses (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]).

Figure 8. Well-differentiated tubuloglandular carcinoma in a patient with chronic ulcerative colitis. In this image, very well-differentiated neoplastic glands are infiltrating through the muscularis of the colon. These glands show minimal or no cytologic atypia. This case was associated with indefinite, or at most, low-grade cytologic changes of dysplasia in the overlying surface mucosa (hematoxylin-eosin, original magnification ×200). Photograph courtesy of Noam Harpaz, The Mount Sinai Hospital, New York, New York.
Gastric Dysplasia

Many epidemiologic, histologic, and outcome studies have supported the presence of a chronic gastritis-intestinal metaplasia/atrophy-dysplasia-carcinoma sequence in the pathogenesis of intestinal-type gastric cancer, particularly as a result of chronic *Helicobacter pylori* infection. The risk of gastric cancer has been shown to be related to the presence, extent, and type of intestinal metaplasia. As with other portions of the GI tract, gastric dysplasia is a neoplastic alteration that is diagnosed on the basis of the degree of cytologic and architectural atypia of the epithelium. By conventional wisdom, it is also widely believed that gastric dysplasia must always involve the surface epithelium. However, several recent studies suggest that some forms of “atypical” intestinal metaplasia show histologic changes consistent with dysplasia, but are limited to the deep portions of the foveolar epithelium or glands (Figure 3, A and B). Histologically, because of the lack of surface involvement, these atypical foci have been termed either negative for dysplasia or indefinite for dysplasia. In a recent study, Tava et al examined 88 patients with atypical intestinal metaplasia (termed immature hyperproliferative lesions) of the stomach and assessed the histochemical appearance of the lesions, their association with non-atypical intestinal metaplasia, the presence of *H. pylori* infection, and neoplasia outcome. These lesions revealed deep glandular columnar cells that were hyperchromatic, crowded, and hyperproliferative, with decreased or completely absent goblet cells, a mild degree of nuclear atypia, and a conspicuous lack of surface involvement. However, they were associated with intestinal metaplasia and *H. pylori* infection and, most importantly, with the

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**Figure 9.** Unusual, serrated-type dysplasia in a patient with chronic ulcerative colitis who also had foci of conventional dysplasia elsewhere in the colon and had adenocarcinoma upon follow-up. A, The epithelium shows slight luminal serration and is composed of slightly enlarged hyperchromatic and stratified cells, particularly evident in the bases of the crypts, but with evidence of maturation toward the surface. B, High-power view of the surface epithelium shows small, regular, round-oval cells without significant loss of polarity or mitoses, reminiscent of regenerating epithelium. C, The bases of the crypts show higher-grade nuclei. The nuclei are more elongated, hyperchromatic, and show prominent nucleoli, with more stratification and loss of cell polarity. There are abundant lymphocytes and plasma cells in the lamina propria but only scattered neutrophils (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B and C]).

**Figure 10.** Medium-power view of a sessile serrated polyp showing architecturally distorted epithelium composed of hyperplated crypts with hypersecretion, goblet cells, and cells with microvesicular mucin. Note branching and horizontal growth of the crypts at the base of the mucosa. The basal portion of the crypts shows hyperchromatic, slightly stratified cells with increased mitoses. However, the surface epithelium shows small, mature-appearing cells, without cytologic atypia (hematoxylin-eosin, original magnification ×100).
development of neoplasia upon outcome analysis. Eighty-six percent of cases were associated with conventional full-length dysplasia or carcinoma. The authors concluded that intestinal metaplasia progresses to unequivocal dysplasia, and subsequently cancer, through an intermediate pathway of “indeterminate” lesions that show cytologic atypia limited to the glands, but without surface involvement. Not surprisingly, these cells may be derived from precursor stem cells located in the deep neck region of the foveolar epithelium, the so-called proliferative zone of the stomach. Similarly, in a cross-sectional cohort study of 50 randomly selected patients with gastric cancer examined for a wide variety of clinical and pathologic features, Agoston et al reported that dysplasia-like atypia limited to the bases of the pit epithelium, without surface involvement (“pit dysplasia”), was noted in 50% of cancer cases. This histologic finding was statistically associated with tumors that were larger in size, antral, intestinal-type, poorly differentiated, of higher pathologic stage, and infected with H. pylori. Most importantly, a topographic and statistical association was noted with conventional dysplasia, both low- and high-grade. In that study, “pit dysplasia” was situated adjacent to foci of neoplasia in 72% of cases. These studies provide evidence that, similar to BE, early dysplastic lesions in chronic gastritis may be limited to the deep gastric pits and may reveal lack of surface involvement.

Dysplasia in the stomach is categorized as intestinal, foveolar, or pyloric gland-type. Most cases of intestinal and foveolar dysplasia show full-length pit and surface epithelial involvement, without maturation. However, pyloric gland lesions correspond to an uncommon type of neoplasia that does not show conventional morphologic features of dysplasia (Figure 4, A and B). In a recent study by Chen et al, pylori gland adenomas were divided into 3 types: those without conventional histologic dysplasia and those with dysplasia, either low or high grade. In all 3 types, the nuclei of pylori gland adenomas appeared more bland, rounded, and less stratified than those seen in conventional dysplasia, closely mimicking the features of nondysplastic (reactive) epithelium. Pyloric gland adenomas were associated with autoimmune atrophic gastritis and intestinal metaplasia in the surrounding mucosa. Thus, pyloric gland adenomas represent another type of noninvasive neoplastic lesion that does not reveal conventional histologic features of dysplasia; they are believed to be “neoplasms,” partly because p53 alterations were demonstrated in these lesions.

Finally, 1 other type of neoplastic precursor lesion associated with the development of diffuse-type gastric cancer, and familial gastric cancer related to E-cadherin mutations, may also show dysplastic cells limited to the deep pits without surface involvement. In these conditions, neoplastic signet ring cells line the deep foveolar pits in a pagetoid fashion and contain deceptively bland nuclei, mimicking intestinal metaplasia (Figure 5, A and B). Some authorities have referred to this entity as “tubule neck dysplasia.” In a study by Carneiro et al, all of these lesions showed loss of E-cadherin expression at the level of the cell membrane.

Dysplasia in Inflammatory Bowel Disease

In rare instances, dysplasia associated with IBD may reveal extremely low-grade cytologic features or atypical features limited to the crypt bases, without surface involvement. For instance, rarely, neoplasia may show villi composed of elongated, predominately mucinous (“hypermucinous”) epithelium with numerous goblet cells, either with or without cytologic atypia. In cases with atypia, it is typically limited to the bases of the crypts (Figure 6). This neoplastic proliferation has been termed villous dysplasia or villous hypermucinous mucosa and has been reported in both ulcerative colitis (UC) and Crohn disease. For instance, in a study by Rubin et al, of 40 colectomy specimens from patients with UC (20 with and 20 without carcinoma), including some who also had preoperative biopsies available for review, villous changes were present in 70% of preoperative biopsies from patients with carcinoma but not in the preoperative biopsies from the patients without cancer. In that study, either no or only slight morphologic dysplasia was present in 3 of 13 patients (23%) who had cancer at colectomy. The villous neoplastic precursor lesions were usually covered by cytologically normal epithelium, whereas the bases of the crypts, in some cases, had conventional high-grade dysplasia. In another study, by Andersen et al, villous hypermucinous neoplastic precursor lesions without cytologic atypia were identified from 6 of 13 patients with UC; 61% of the lesions showed KRAS mutations, a frequency that was significantly higher than in areas of conventional low-grade dysplasia. As a result, these authors postulated the potential for a distinct pathway of carcinogenesis that progresses from a nonclassic, non-cytologically atypical form of precursor neoplasia to cancer. Similar changes were detected in patients with Crohn disease by Kilgore et al.

Although never previously reported, one of the authors of this review (R.D.O.) has noted, anecdotally, cases of conventional low- and high-grade dysplasia in which the dysplastic cells were limited to the crypt bases, showing histologic evidence of surface differentiation and maturation, in surveillance biopsy specimens of several patients who ultimately developed carcinoma upon long-term follow-up (Figure 7, A and B). The belief that some neoplastic precursor lesions in IBD may show basal crypt dysplasia, with surface maturation, is not surprising given that precursor stem cells and transient amplifying cells have been identified in the bases of the colonic crypts, as seen in BE, and these cells are presumed to be most susceptible to neoplastic alteration.

Analogous to sporadic colon cancer, carcinogenesis in IBD is driven by a succession of mutational events that preferentially involves certain genes. These events include genomic instability, aneuploidy, mutations or allelic loss of TP53, and microsatellite instability. Many of these alterations occur in morphologically nondysplastic mucosa in patients with active colitis. For instance, Chen et al showed that up to 20% of the crypt DNA in patients with UC showed mutations at a single point in time, and neither the prevalence rate nor the pattern of genomic alterations differed between morphologically dysplastic and nondysplastic crypts. These data suggest that these alterations occur early in the carcinogenic pathway in IBD, are widespread, and precede the development of morphologic dysplasia.

Other rare types of cytologically bland, morphologically nondysplastic precursor lesions in IBD include rare cases of extremely well-differentiated, so-called low-grade tubuloglandular carcinomas, which can occur in either UC or Crohn disease. In this type of neoplasm, invasive
glands show minimal cytologic atypia and bear a close histologic resemblance to overlying low-grade, or even indefinite, dysplastic crypts (Figure 8). These tumors are associated with coexpression of CK7 and CK20, and with loss of the mismatch repair protein hMLH1 in 55% of cases, implicating possible defective DNA replication error repair in the pathogenesis of these tumors.

Rarely, patients with IBD may have low-grade hyperplastic or serrated polyps that appear histologically nondysplastic, or only minimally dysplastic, and can be multiple in number (Figure 9, A through C). In a study by Srivistava et al,33 3 patients showed multiple hyperplastic/serrated polyps, many of which were cytologically nondysplastic; 2 of these 3 patients developed carcinoma. This also raises the possibility of a serrated pathway of carcinogenesis in IBD, characterized by silencing of O6-methylguanine methyltransferase (MGMT) and the presence of KRAS mutations.

**Hyperplastic/Serrated Polyps in the Colon**

There is abundant, relatively recent data to support the presence of a newly discovered pathway of colon carcinogenesis, termed the serrated neoplasia pathway, which accounts for the development of adenocarcinomas that lack chromosomal instability and loss of heterozygosity. This carcinogenic scheme implies that hyperplastic or hyperplastic-like polyps (collectively referred to as nondysplastic serrated polyps) may progress to adenocarcinoma through progressive stages of conventional dysplasia. Hyperplastic/serrated precursor lesions, which are morphologically nondysplastic, are characterized by a high rate of BRAF mutations, DNA hypermethylation, and, ultimately, microsatellite instability. These changes may lead to, or are associated with, widespread hypermethylation of the genome that affects promoter regions of repair genes such as hMLH1 and MGMT. These neoplasms are also characterized by a low rate of KRAS mutations.

From a pathologist’s point of view, it is now widely recognized that some types of hyperplastic/serrated polyps represent neoplastic precursor lesions that do not possess conventional morphologic features of dysplasia, characteristic of sporadic tubular or villous adenomas. The most common type of nondysplastic serrated polyps are “traditional” hyperplastic polyps. There is evidence to suggest that traditional hyperplastic polyps, particularly the microvesicular type, contain genetic and cell cycle regulatory defects, and there is abundant epidemiologic and morphologic evidence to suggest that these lesions may, rarely, progress to carcinoma. This is particularly true for lesions that are larger in size, atypical in architecture, and right-sided in location, lesions referred to as sessile serrated polyps (SSPs) or as sessile serrated adenomas by some authorities. Both microvesicular hyperplastic polyps and SSPs share a similar high rate of BRAF mutations, a low rate of KRAS mutations, and a moderate-to-high rate of DNA hypermethylation. However, much controversy exists as to whether microvesicular hyperplastic polyps and SSPs represent a continuous spectrum of neoplasia or whether they represent separate entities each with a distinct pathogenesis, natural history, and outcome.

The literature more strongly supports progression to malignancy for SSPs than for traditional hyperplastic polyps. Morphologically, SSPs consist of elongated, dilated, and hyperradiated crypts, and they reveal budding and lateral branching of crypts in the deeper portion of the mucosa above the muscularis mucosa (Figure 10). The cells reveal apical microvesicles, nuclei with membrane irregularity, normal or slight enlargement, and occasional mitotic figures, even in the upper portions of the crypts where proliferative cells are not normally located. However, the surface epithelium of SSPs is typically bland, consisting of small, oval nuclei without atypia, indicating evidence of cell differentiation and maturation. Most SSPs reveal a CpG island methylator phenotype, and contain BRAF mutations, but lack KRAS mutations. Some show loss of expression and methylation of MGMT. Microsatellite instability occurs typically in lesions that progress, and particularly in those that develop conventional morphologic features of dysplasia. In essence, SSPs represent the prototypical neoplastic precursor lesion that retains the capacity for cell differentiation and maturation. For a more detailed review of the pathology, molecular biology, and natural history of serrated polyps of the colon, the reader is referred to some excellent articles by Jass et al.

**SUMMARY**

There is an ever-growing list of lesions throughout the tubal gut that fulfill the most basic and classical principles of a neoplastic precursor lesion, but lack conventional morphologic evidence of dysplasia and/or maintain their capacity for cell differentiation and maturation. These include, but are not limited to, squamous dysplasia of the esophagus; dysplasia in BE, chronic gastritis, and IBD; and hyperplastic/serrated polyps of the colon. All of these entities represent early neoplastic precursor lesions, but without conventional histologic features of dysplasia. Other types of lesions may progress to carcinoma without passing through a conventional sequence of low- and high-grade dysplasia. There is an increasing body of literature that shows clonal molecular aberrations in morphologically nondysplastic epithelium in chronic inflammatory disorders, such as BE and IBD; these data support the concept that such aberrations represent the earliest manifestation of neoplasia. It is important for pathologists to be aware of these lesions, both for diagnostic and prognostic purposes, but also so that future studies can be performed on risk stratification in affected patients. Future studies may reveal that molecular defects in morphologically nondysplastic epithelium represent a more sensitive and specific biomarker of risk stratification than conventional dysplasia, which is a late morphologic alteration of carcinogenesis in the tubal gut.

**References**


