UPDATE ON PROBLEM POLYPS IN THE COLON

Robert D. Odze, M.D., F.R.C.P.C.
Chief, GI Pathology Service
Associate Professor of Pathology
Brigham & Women’s Hospital
Harvard Medical School
Boston, MA

Introduction

The majority of polyps in the colon are hyperplastic polyps, adenomas, and inflammatory polyps1 (Table 1). Pathologists usually receive material in the form of biopsies or endoscopic polypectomy specimens. The role of the pathologist is to establish a diagnosis, or at least to be able to put it into one of the general polyp categories, and to determine whether the lesion has been adequately excised. The clinical management often depends on the specifics in the pathology report. It is important to realize that a biopsy of a polypoid lesion is similar to examining the “tip of the iceberg”. Thus, it is important to know the endoscopic appearance of the polyp prior to making any final decision regarding the nature of the lesion. This lecture will not provide a detailed summary of all of the polypoid lesions of the colon, but, instead, will focus on diagnostically difficult and new and controversial areas regarding polyps in the colon. Emphasis will be placed on hyperplastic, serrated and adenomatous polyps, in both the sporadic and IBD setting.

Inflammatory Polyps

Inflammatory polyps may be isolated, associated with IBD, or with other forms of colitis, such as infectious colitis, ischemic colitis or diverticulitis2,3,4. In general, inflammatory polyps develop as a result of an exuberant mucosal regeneration and repair reaction post ulceration. Inflammatory polyps of the colon may be classified as the usual type (NOS) (“pseudopolyps”), or associated with mucosal prolapse5. This latter category includes inflammatory cap polyps6, inflammatory cloacogenic polyps7, solitary rectal ulcer syndrome (SRUS)-associated polyps5, and diverticular disease associated polyps8,9. Other rare types of inflammatory polyps include inflammatory myo-glandular polyps10 and colitis cystica polyposa11-13.

A. Inflammatory Polyps (NOS, “pseudopolyp”)

Usual type inflammatory polyps are most often associated with IBD. They represent polypoid areas of inflamed and regenerating mucosa that project above the level of the surrounding mucosa, the latter of which may be ulcerated. It may occur in patients with active, or quiescent, disease and may occur in other inflammatory disorder of the GI tract, as well, such as ischemic or infectious colitis2,3. Grossly, inflammatory polyps may be sessile or
pedunculated, but may assume almost any shape. For instance, some may consist of worm-like or long finger-like projections, often referred to as filliform. They may be single, multiple or numerous in number and my range in size from 0.5 to 10 cm. Extremely large inflammatory polyps (“giant” inflammatory polyps) can result in bleeding, obstruction, prolapse or intussusception. Endoscopically, most inflammatory polyps have a smooth, hyperemic, hypervascular appearance with, or without, surface erosion and tend to bleed when manipulated. Histologically, they are composed of a mixture of inflamed lamina propria and distorted colonic epithelium consisting of tortuous, branched, elongated and cystic crypts. Surface erosion, congestion, hemorrhage, and crypt abscesses may also be present. Some inflammatory polyps may develop markedly enlarged, spindle or epithelioid shaped, multinucleated bizarre stromal cells that mimic sarcoma, a finding that is referred to as “pseudosarcomatous” change, and most often occurs at the surface of the polyp, particularly in those that are ulcerated. These cells can be distinguished from sarcoma by the lack of atypical mitoses, their location preferentially underneath areas of ulceration within a granulation tissue reaction, and their frequent positivity for endothelial or myofibroblast phenotypic markers. Rarely, dysplasia, or even carcinoma, may develop in inflammatory polyps related to IBD. The histologic features are similar to dysplasia or carcinoma that develops in flat mucosa in IBD. However, inflammatory polyps do not carry a significantly increased risk of dysplasia above that of the surrounding mucosa and, thus, are not considered pre-neoplastic lesions. Inflammatory polyps with dysplasia should be managed similar to dysplasia in flat mucosa in IBD.

B. Prolapse-induced inflammatory polyps

Prolapse-induced inflammatory polyps develop as a result of traction, distortion and twisting of mucosa caused by peristalsis induced trauma; this leads to torsion of blood vessels and tissue damage, localized ischemia and repair in the form of lamina propria fibrosis. Depending on the anatomic location of the injury and the underlying cause, these polyps may be termed differently (see above). However, all demonstrate overlapping histologic abnormalities related to the underlying etiology. The classic histologic features of prolapse-induced inflammatory polyps include a variable degree of fibromuscular hyperplasia of the lamina propria, thickening, splaying, and vertical extension of the muscularis mucosa into the lamina propria, and crypt architectural abnormalities, such as elongation, hyperplasia, cystic dilatation, distortion and serration. Typically, a variable degree of acute and chronic inflammation, erosion, ulceration and reactive and hyperplastic epithelial changes are also present. Large polyps are often villiform and may show extension of cystically dilated crypts into the submucosa, which is a localized form of colitis cystica polyposa. This latter disorder includes any condition in which mature colonic epithelium extends through the muscularis mucosa into the submucosa or muscularis propria. It may occur as an isolated condition (e.g., SRUS syndrome) or may be diffuse, such as in IBD or as a result of radiation injury.

C. Differential Diagnosis

The clinical and endoscopic features often help distinguish the specific types of inflammatory polyps related to mucosal prolapse. For instance, inflammatory cap polyps occur predominantly in the rectosigmoid colon and have histologic features identical to that seen in mucosal prolapse injury with an overlying granulation tissue and necroinflammatory debris cap. Inflammatory cloacogenic polyps occur in the anorectal transitional zone. The SRUS syndrome occurs most typically in females, in their 30-40’s, with a history of straining upon defecation,
constipation, anorectal and abdominal pain or bleeding. Ulceration and/or polyps typically form on the anterior wall of the rectum and may be multiple in number. Diverticular disease-associated inflammatory polyps may occur at the edge of diverticular ostia, may contain marked vascular congestion, hemorrhage and hemosiderin deposition.

Colitis cystica polyposa may be differentiated from a neoplastic proliferation by the lack of desmoplasia, common association with hemorrhage, hemosiderin deposition and other features of tissue trauma, and usually contain a discrete rim of lamina propria surrounding the misplaced glands. In contrast to adenocarcinoma, misplaced crypts in colitis cystica polyposa often grow in a lobular configuration. Misplaced crypts may also show mucin depletion, pseudostratification, and/or hyperchromaticity of the nuclei. However, loss of polarity, atypical mitoses and intraluminal necrosis are not features of this disorder.

Hamartomatous Polyps

Hamartomas are defined as polyps that develop as a result of overgrowth of cells and tissues that are native to the anatomic location where they occur. In the colon, hamartomas typically incorporate both stromal and epithelial components. Hamartomas are most often solitary (Juvenile polyps), but may occur as part of a hamartomatous polyposis syndrome, such as Peutz Jeghers syndrome, Juvenile polyposis, Cowden disease or Cronkite Canada Syndrome. Hamartomatous polyposis syndromes account for less than 1% of the annual incidence of colorectal carcinoma in the United States. Isolated sporadic Juvenile polyps and isolated Peutz Jeghers polyps have essentially no malignant potential. One paper described a unique type of hamartomatous-like polyp, termed inflammatory myo-glandular polyp, which consists of hyperplastic glands with cystic dilatation and proliferation of smooth muscle of the lamina propria in a radial fashion. These polyps are usually located in the sigmoid colon and may, in fact, simply represent isolated sporadic Peutz Jeghers type polyps. Juvenile polyps may be sporadic or syndromic. Sporadic Juvenile polyps are the most common type of colon hamartoma, but they may occur in adults as well. There are several different types of Juvenile polyposis syndromes depending on the predominant location and age group of affected patients. These are categorized as infantile juvenile polyposis, juvenile polyposis coli, generalize juvenile polyposis syndrome and isolated gastric juvenile polyposis. These polyps will not be discussed here since their diagnosis is usually not problematic.

Epithelial Polyps

A. Hyperplastic and Serrated Polyps

General Comments:

The three most common types of sporadic epithelial polyps of the colon include hyperplastic polyps, serrated polyps and conventional adenomas and carcinomas. Each of these polyp categories will be discussed in more detail in the following few paragraphs with emphasis placed on new and controversial diagnostic issues.

Hyperplastic polyps are the most common type of polyps in the colon, and are often multiple. The etiology of these polyps is unclear but it is probably related to crypt fusion and defects in apoptosis in combination with hypermaturation of the upper crypt and surface epithelium. Hyperplastic polyps of the colon, recognized by their bland cytology and serrated architecture, have traditionally been considered non-neoplastic lesions with no malignant
potential. However, some “hyperplastic” polyps may grow to large sizes, show abnormal proliferation and maturation, particularly those in the right colon, and may be sessile in appearance (i.e. sessile serrated adenomas, see below)\textsuperscript{28,29}. The potential neoplastic nature of these latter lesions has recently been recognized. Thus, there is now considerable compelling evidence to implicate that this subset of “hyperplastic” polyps may progress to colorectal carcinoma at a high rate, particularly those that are large in size (>0.5 cm), contain atypical morphology and are right sided in location\textsuperscript{28,30-32}. This has led to the recognition of a serrated pathway of carcinogenesis\textsuperscript{33-35}. This carcinogenic scheme implies that hyperplastic or hyperplastic-like polyps may progress to serrated neoplastic polyps and ultimately adenocarcinoma, the latter of which often show high levels of microsatellite instability (MSI-H). Early steps in this pathway involve a decrease in the rate of cell death (apoptosis) which leads to prolonged cell life, an increase in the number of epithelial cells and a serrated appearance to the polypoid lesions\textsuperscript{36}. These lesions, for unknown reasons, have a higher susceptibility to DNA methylation, particularly in foci of DNA that are rich in cytosine-guanine bases, such as in the promoter region of many tumor suppressor genes\textsuperscript{36B}. Methylation of these areas, termed the CpG island methylator phenotype (CIMP), may lead to transcriptional silencing of the promoters of tumor suppressor genes. For instance, silencing of the hMLH-1 gene, which produces a DNA mismatch protein, may lead to high levels of microsatellite instability and MSI-H cancers. Hypermethylation is present in up to 40% of colon cancers. In approximately one-third of hypermethylated cancers, inactivation of hMLH1 has occurred which results in accumulation of DNA microsatellite repeat sequences. Hypermethylation, particularly of the BRAF gene, is a characteristic feature of early serrated and some types of “hyperplastic” polyps. Interestingly, distally located “hyperplastic” polyps do not often show methylation of hMLH-1 and are typically MSI low (MSI-L). In fact, distal serrated or hyperplastic lesions may show methylation of the MGMT gene instead. Further evidence of the serrated pathway of carcinogenesis is based on the fact that there have been many reports of adenocarcinoma associated with so called “giant” or “large” hyperplastic polyps\textsuperscript{37}. Furthermore, patients with multiple hyperplastic, or serrated, polyps (hyperplastic or serrated polyposis) are associated with a markedly increased risk of development of adenocarcinoma\textsuperscript{37-39}. A recently published large series of 90 MSI-H right sided colorectal cancers showed a high association with atypical, large, and unusually shaped “hyperplastic” polyps which, have subsequently been termed sessile serrated adenomas (see below)\textsuperscript{31}. Thus, molecular studies now provide convincing evidence for a pathway from hyperplastic polyps, or hyperplastic-like polyps, to colorectal carcinoma. In fact, there is also growing evidence to suggest that the risk of progression to cancer is determined strongly by the size, location and number of “hyperplastic” polyps rather than the specific morphologic subtypes\textsuperscript{29,40}. For instance, in general, it appears that left sided “hyperplastic” polyps still contain little or no malignant potential in contrast to large right-sided polyps which have a high rate of progression to carcinoma\textsuperscript{28,41}.

Pathologic Features of “Hyperplastic” polyps:

In a recent study by Torlakovic et al, small left-sided “hyperplastic” polyps were classified into three general types based on their morphologic growth pattern and lack of proliferative or maturation abnormalities\textsuperscript{29}. These include the vesicular, goblet cell, and mucin poor type. All of these “hyperplastic” polyps are normally less than 0.5 cm in size and show crypt and/or surface epithelial serration. The vesicular type is the most common and correlates to the lesion generally considered by most pathologists to represent a typical “hyperplastic”
polyp. It is characterized by the presence of abundant mucin and a paucity of goblet cells, compared to normal mucosa. Vesicular hyperplastic polyps have a large proliferative compartment, which occupies most of the basal half of the crypts. Nuclear atypia is variable, but some degree is present in most cases. Some cases also show thickening and extension of the muscularis into the lamina propria. The overall architecture of these polyps may be slightly distorted and, in fact, may show a mild degree of crypt dilatation. Some authorities believe that the vesicular type of hyperplastic polyp is an early, or variant, form of sessile serrated adenoma, as discussed below. This is based on the fact that both of these types of polyps show frequent BRAF mutations and DNA methylation abnormalities. Goblet cell rich hyperplastic polyps are the most under-diagnosed type. These are polyps that are rich in goblet cells but without vesicular mucin. These polyps are also normally sessile in appearance, but demonstrate a less prominent degree of serration, which is often limited to the surface and/or upper third of the crypts. Nuclear atypia, stratification, and mitoses are generally not seen in these types of hyperplastic polyps. However, slight nuclear enlargement may occur in a small proportion. Essentially, these polyps show elongated crypts with an increased number of goblet cells, and are usually smaller in size than the vesicular type. Almost all are located in the left colon similar to the vesicular type. K-ras mutation are common, but these polyps show only rare evidence of DNA methylation.

The mucin poor type of hyperplastic polyp is the least common, and differs from the others by showing a micropapillary architecture and a high concentration of neuroendocrine cells, more prominent nuclear atypia and a marked decrease, or complete absence, of mucin and goblet cells. They are also sessile in appearance but contain small cells with less cytoplasm. Overall, these polyps demonstrate a striking “regenerative” appearance. The lack of mucin, the presence of hyperchromatic nuclei and hyperplasia of neuroendocrine cells are the main features of these polyps. Some show increased inflammation in the lamina propria as well. The molecular features of this subtype of hyperplastic polyps are poorly understood.

Pathologic Features of Serrated Neoplastic Polyps:

In contrast to the predominantly left sided “hyperplastic” colon polyps, right sided “serrated” polyps are often larger in size (>0.5 cm), sessile in appearance and contain significant architectural, proliferative and maturation abnormalities. Unfortunately, there is much debate, and controversy, regarding the diagnostic features, natural history and risk of malignancy of this family of serrated polyps. Some of the terms used to describe these lesions include “giant hyperplastic polyp”, large hyperplastic polyp, “hyperplastic/adenomatous polyp”, “mixed epithelial polyp”, “sessile serrated polyp” and “sessile serrated adenoma”, “hyperplastic polyp with dysmaturation”, “atypical hyperplastic polyp”, and “hyperplastic polyp with abnormal (or increased) proliferation”. In general, there are three types of serrated neoplasms in this category (Table 2). The first, and most controversial, is a lesion referred to as sessile serrated polyp by some, or sessile serrated adenoma by others (my preferred term). There is abundant data to suggest that these lesions progress to colorectal carcinoma through a serrated pathway of carcinogenesis and lead to MSI-H colorectal carcinomas. BRAF mutations are common in these polyps. Morphologically, sessile serrated adenomas show distinctive features, characterized by crypt dilatation, crypt irregularity (horizontally shaped glands and prominent lower crypt serration), mitoses in the upper levels of the crypts, vesicular nuclei in the upper crypts, exaggerated serration in the upper crypts, reduced amount of lamina propria between crypts, hypermucinous
epithelium and, occasionally, an inverted growth pattern. These are sessile tubular lesions which are mucin rich and contain rounded vesicular nuclei with prominent nucleoli. Dystrophic goblet cells, and an irregular distribution of goblet cells, are also characteristic features. Other features include lack of a thickened basement membrane as well. Not uncommonly, foci of serrated, or conventional, “adenomatous” change may be mixed within these polyps, in which case the term “mixed hyperplastic/adenomatous polyp” has been utilized by some. In contrast, some authors (including myself) believe that “mixed” polyps are, in fact, sessile serrated adenomas with foci of more conventional morphologic evidence of dysplasia. Some contain carcinoma as well and provide direct morphologic evidence of a serrated carcinogenic pathway.

Finally, typical serrated adenomas are characterized by a prominent serrated architectural growth pattern, but these lesions also show phenotypic evidence of “dysplasia”. These polyps are normally pedunculated, may occasionally be rather large and filliform in contour, and show definite evidence of “dysplasia” characterized by the presence of nuclear atypia and pseudstratification at the surface of the polyp. Micropapillation of the surface epithelium with eosinophilic “pink” cytoplasm are also characteristic features. These lesions show increased DNA methylation abnormalities and BRAF mutations, but in contrast to sessile serrated adenomas, show non-mucinous cytoplasm and a low N/C ratio. They may occur on either side of the colon. Interestingly, the proliferation pattern of these lesions is more similar to a typical hyperplastic polyp than a conventional tubular adenoma. The proliferative compartment is often limited to the bases of the crypts. In contrast to conventional tubular adenomas, APC and beta-catenin mutations are rare. These lesions have been linked to the development of microsatellite unstable colorectal cancers similar to sessile serrated adenomas. Finally, some authors believe that sessile serrated adenomas and traditional serrated adenomas represent two extremes of the same entity and suggest classifying these lesions under the general heading of “serrated neoplastic polyps”.

Table 3 outlines some of the key features of common “hyperplastic” and serrated polyps of the colon in comparison to conventional tubular adenomas.

B. Conventional Adenomas: Update on Current diagnostic Issues

Conventional adenomas may be tubular, tubulovillous or villous and may be either flat, sessile or pedunculated in appearance. There is emerging, and somewhat, controversial data to suggest that patients with advanced adenomas (i.e. those that are either greater than 1 cm in size, have >25% villous component or contain high-grade dysplasia) have a greater propensity to develop future adenomas and/or carcinomas and, thus, may need to be surveilled at a higher rate. However, this is controversial because of the problem with interpretation and reproducibility of the histologic features of these lesions. The most important reporting issue, aside from the diagnosis, is the status of the polyp margins. Thus, at this point it is not entirely necessary to report the presence or absence of high-grade dysplasia particularly if clinicians are apt to overreact to this diagnosis. Similarly, intramucosal adenocarcinoma has no more clinical significance (i.e. risk of metastasis) than high-grade dysplasia and, as such, may not need to be reported as well. However, if reported, it should always be accompanied with a statement regarding the absence of invasive cancer, the status of the resection margins, and the overall adequacy of resection and need for further therapy (which is usually none). In contrast, adenomas that contain invasive adenocarcinoma (defined by the presence of cancer beyond the muscularis mucosa) may require further surgical resection if invasive cancer is present in less than 1-2 mm from the cauterized margin of the specimen, is poorly differentiated, or shows
lymphovascular invasion\textsuperscript{56-60}. In fact, any sessile polyp with invasive cancer should be considered for further surgical resection. The risk of metastasis in patients with an adenoma with any of the above “unfavorable” histologic features is approximately 10-20%.

On occasion, it may be difficult to differentiate benign misplaced epithelium (“pseudoinvasion”) in an adenoma from invasive adenocarcinoma\textsuperscript{61-64}. Features that favor benign misplaced epithelium include a rounded, or lobular, appearance of the glands, the presence of a discrete rim of lamina propria surrounding the glands, marked hemorrhage, hemosiderin deposition, and congestion, absence of desmoplasia, and the presence of pools of mucin which are rounded, smooth and do not contain floating dysplastic cells. Misplaced epithelium often shows a connection to the surface of the polyp upon deeper sectioning, and usually contains a similar, or even lower, degree of dysplasia compared to the intramucosal portion of the polyp. In contrast, invasive adenocarcinoma usually shows an increased degree of cytologic atypia, more architectural complexity of the glands, including branching, jagged borders, single cells, and small groups of cells, and is often, but not always, associated with a desmoplastic reaction. Hemorrhage and hemosiderin may be present in carcinomas as well. Mucin pools, when present, are often irregular in shape and may contain highly dysplastic epithelium within the pools of mucin. In diagnostically difficult cases, increased staining of the submucosal epithelium for matrix metalloproteinase 1 (MMP-1) and/or p53, combined with decreased staining of the submucosal epithelium for membranous E-cadherin and decreased or absent collagen deposition surrounding the submucosal glands, may be helpful in establishing a diagnosis of adenocarcinoma\textsuperscript{64}. For instance, in one study by Yantiss and co-workers, adenomas with invasive adenocarcinoma showed increased MMP-1 staining of the stroma surrounding the submucosal epithelium, and increased p53 staining within the submucosal epithelium, in 91% and 61% of cases respectively\textsuperscript{64}. Cases with carcinoma also showed decreased, or discontinuous, E-cadherin and collagen staining in 65% and 95% of cases, respectively.

**IBD associated Polyps**

The most common epithelial polyps in IBD include inflammatory polyps (see above), hyperplastic polyps, adenomas or adenoma-like polypoid areas of dysplasia that develop as a result of the underlying inflammatory condition. Rarely, polypoid areas of carcinoma may develop as well. Also rarely, mesenchymal polyps, such as inflammatory fibroid polyps and lymphoid polyps, both benign and malignant, may occur in association with IBD, but these will not be discussed here.

A. Hyperplastic polyps

Hyperplastic polyps may occur in patients with IBD and are usually morphologically similar to those that occur in non-IBD patients\textsuperscript{65}. They may occur in inflamed or normal appearing mucosa. In a study by our group, the molecular characteristics of 39 hyperplastic polyps from 26 ulcerative colitis (UC) patients were compared to 39 sporadic hyperplastic polyps from patients without UC\textsuperscript{65}. Most polyps (92%) were located within an area of established colitis, and in the left colon (82%). Polyps ranged in size from 0.1-1.4 cm in diameter (average: 4.3 mm). Forty-seven percent of UC-associated hyperplastic polyps showed a molecular abnormality, such as LOH of APC (21%), 3p (40%), p53 (27%), or p16 (20%). However, the frequency of molecular abnormalities was similar to sporadic hyperplastic polyps, which suggested that UC-associated hyperplastic polyps are biologically similar to the sporadic
type. Nevertheless, the finding of molecular abnormalities in these lesions supports the theory that these lesions may have neoplastic potential which is probably unrelated to the underlying IBD. Interestingly, non-polypoid flat hyperplasia-like mucosal changes has also recently been described in Crohn’s disease by Kilgore et al\(^66\). In a morphological and p53 immunohistochemical study of 30 cases of Crohn’s-related adenocarcinoma and 38 age and sex matched cases of Crohn’s disease without adenocarcinoma, hyperplastic mucosal changes were present in 33% of the former and 10% of the latter. These changes were characterized by a “diffuse expanse of flat mucosa with an architecture resembling that seen in colorectal hyperplastic polyps and composed of cells with cytologically bland basal nuclei and apical cytoplasmic mucin distention”. These features were noted both adjacent to and distant from adenocarcinoma. Fifty percent of cases showed p53 immunoreactivity. The authors of that study suggested that this may represent a distinct type of dysplastic change, but this is yet to be confirmed. A similar type of “villous mucinous mucosa” has recently been described in long-standing UC by Anderson et al in 1999\(^67\). These investigators showed a high frequency of K-ras mutations in this type of epithelium (61%), which was more frequent than low-grade dysplasia. However, it is unclear if the type of epithelium evaluated in the study by Anderson et al is the same as the one evaluated by Kilgore et al.

The natural history of hyperplastic polyps in IBD is unknown, and the treatment of these lesions is similar to patients without IBD. Clinically, hyperplastic polyps may be difficult to distinguish from small elevated polypoid areas of dysplasia and, thus, are often excised for diagnosis.

B. Dysplastic (“adenomatous”) Polyps

General comments and classification:

Elevated or raised areas of dysplastic epithelium occurs, not uncommonly, in patients with IBD\(^12,20,68\). By convention, raised dysplastic areas have been referred to as a dysplasia associated lesion or mass (DALM)\(^20\). However, there are, in fact, several different subtypes of DALM’s in IBD. These subtypes are broadly separated into adenoma-like and non-adenoma like based primarily on their gross endoscopic appearance, and are managed quite differently. Examples of non-adenoma like lesions are large, sessile, irregular masses, strictures or ill-defined nodules with a broad base. A biopsy finding of dysplasia, either low or high-grade, in a non-adenoma like DALM is usually an indication for colectomy because of the high probability of an associated adenocarcinoma. In fact, many studies have shown a carcinoma prevalence rate from 30-80% in patients with lesions of this kind\(^20,68\). More commonly, isolated, well-circumscribed, sessile or pedunculated adenoma-like polypoid dysplastic lesions develop in patients with IBD. In this instance, the clinical differential diagnosis includes an adenoma-like DALM in UC, a lesion that is pathogenetically linked to the underlying inflammatory disorder, versus a sporadic adenoma, a lesion that occurs coincidentally in a patient with underlying IBD, but is unrelated to it from an etiologic point of view. It has always been assumed that this distinction is important because the former type of lesion has been, until recently, considered an indication for colectomy in medically fit patients, due to a high rate of progression to adenocarcinoma, whereas the latter is normally treated by a polypectomy, similar to a sporadic adenoma in a patient without IBD. Thus, a common diagnostic dilemma for both clinicians and pathologists is how to differentiate these lesions. Fortunately, recent data, primarily based on the results of two follow-up studies, suggests that IBD patients with an adenoma-like DALM, regardless of whether it is determined to represent a sporadic or an IBD related lesion, may be
treated adequately by polypectomy and continued surveillance if there is no evidence of flat dysplasia elsewhere in the patient. This is discussed further below. Nevertheless, there are a variety of features that can be used to help distinguish these lesions, which are outlined in the next section.

Pathologic features and differential diagnosis:

Non-adenoma like and adenoma-like DALM’s may look identical histologically. Therefore, distinction between these two types of lesions is based solely on their gross endoscopic appearance and will not be discussed further. Adenoma-like lesions that occur proximal to histologic areas of colitis (i.e. right sided lesion in a patient with left sided UC) can easily be diagnosed as a sporadic adenoma because it is well known that dysplasia related to IBD develops only in areas involved by the inflammatory process. However, adenoma-like lesions that occur within areas of colitis are more difficult to distinguish from true polypoid dysplastic lesions related to the underlying colitis. IBD-associated lesions generally occur in younger patients (usually less than 60 years of age), with pancolitis for at least 10 years duration. These polyps are located more commonly in the left colon and are often associated with areas of flat dysplasia either near or distant from the polyp. Histologically, IBD-related lesions usually show an increase in the amount of lamina propria and crypt inflammation, and may even show crypt abscess’s involving dysplastic epithelium. In a previous study by our group, a mixture of benign dysplastic inflamed crypts at the surface of the polyp was found more commonly (60% of cases) in IBD related lesions in contrast to sporadic adenomas (16%) in addition, flat dysplasia is often detected at the base of the polyp stalk, and in the mucosa surrounding the polyp. Thus, stalk dysplasia should alert the pathologist that the polyp is likely to be an IBD-associated lesion, rather than a sporadic adenoma, and should prompt a search for dysplasia elsewhere in the colon.

Features such as polyp size, architectural type, and degree of dysplasia, as well as nuclear cytologic features, are not helpful in distinguishing these two groups of lesions. Interestingly, one recent study by Rubio et al suggested that the majority of “adenomatous growths” juxtaposing IBD-associated carcinomas have a villous or serrated morphologic growth pattern, but the significance of this finding is unclear.

By immunohistochemistry, IBD-associated adenoma-like DALM’s have a higher degree of p53, and a lower degree of nuclear beta-catenin, staining in contrast to sporadic adenomas. Although several other studies have evaluated immunohistochemical findings in these two groups of lesions, none have shown to be particularly useful in this differential diagnosis. For instance, the expression of Glut-1, or hMLH1 and hMSH2, show a similar degree and type of staining in DALM’s versus sporadic adenomas.

Molecular features:

There are well known differences in the type, prevalence and timing of certain molecular events in the pathogenesis of IBD (particularly UC)-associated neoplasia compared to sporadic colon carcinogenesis. For instance, UC associated neoplasms demonstrate infrequent and late mutations in the APC and beta-catenin genes, but show frequent early abnormalities in the 3p, p53, p27, and p16 genes in comparison to sporadic adenomas. Based on this information, several investigators have evaluated and compared the molecular findings in DALM’s, some of which included pathogenetically distinct groups of adenoma-like lesions, to sporadic adenomas in an effort to help distinguish these two types of lesions. For instance, Fogt et al showed that LOH for p16 (9p), 17p (p53) and 3p were statistically more common in adenoma-like
polypoid dysplasia compared to sporadic adenomas. LOH of p16, 17p and 3p were present in 35%, 16% and 50% in the former compared to 0%, 10% and 0% of the latter, respectively. A study by our group, in 2000, evaluated LOH of 3p, APC and P16 by PCR analysis in 21 UC patients with an adenoma-like DALM, and compared the results to 8 UC patients with a non-adenoma like DALM, and 23 non-UC patients with a sporadic adenoma. Interestingly, adenoma-like DALM’s in UC had a statistically similar molecular profile to sporadic adenomas. For instance, LOH of 3p, APC and p16 were noted in 25%, 30%, and 5% of UC-related adenoma-like DALM’s compared to 5%, 33%, and 4% of non-UC related sporadic adenomas. Furthermore, lesions that occurred either within or outside areas of chronic colitis had a similar molecular profile. However, in contrast, non-adenoma like DALM’s showed a significantly higher frequency of LOH of 3p and p16 (50% and 56%, respectively) indicating that, perhaps, a different pathogenetic molecular sequence of events occurs in adenoma-like versus non-adenoma like DALM’s in UC. Thus, although subtle molecular differences may exist between IBD and non-IBD related lesions, at this point, distinguishing groups of DALM’s by molecular analysis remains an investigational tool.

Recently, Selaru et al evaluated the ability of artificial neural networks (ANNs), based on complementary DNA (cDNA) microarray technology, to discriminate between IBD and non-IBD related cancers. Use of this technology correctly diagnosed 12 blinded samples (3 IBD cancers and 9 sporadic cancers) in a test set indicating that this methodology may have great potential to discriminate among different types of dysplastic lesions in the future. Unfortunately, this study did not compare adenoma-like lesions in IBD to sporadic adenomas.

Natural history and Treatment:

There is recent strong evidence to suggest that adenoma-like DALMS, regardless of their particular etiology (i.e. whether they represent an IBD-related or a sporadic lesion) may be treated conservatively with polypectomy and continued endoscopic surveillance, instead of colectomy. In a study by our group of 24 UC patients all of whom had a polypectomy followed by surveillance for an adenoma-like DALM, 58% of patients developed further adenoma-like lesions upon 3.5 years of follow-up, but only 1 patient developed an isolated focus of low-grade dysplasia and none developed carcinoma. These results were strikingly similar to a control group of non-UC patients with a sporadic adenoma who had a statistically similar frequency of recurrent polyp formation when treated in a same manner. In a recently published long term follow-up study by our group, the same cohort of patients noted above (in ref.69) were followed for a longer period of time (average: 8 years)81. Although, overall, 62% developed further adenoma-like lesions, which, once again, was similar to the non-UC control group, no other patients developed flat dysplasia and only one patient (4%) developed adenocarcinoma 7.5 years after his/her initial polypectomy. Strikingly similar results were found by Rubin et al in a follow-up study of dysplastic polyps in 48 IBD patients with a mean of 4.1 years of follow-up70. In their study, none of the patients developed dysplasia or carcinoma in flat mucosa upon surgical resection or follow-up colonoscopy. Based primarily on the results of these two studies, a preliminary management scheme for patients with adenoma-like and non-adenoma like DALM’s in UC has been recommended (see Figure 1 for details). However, it is important to remember that the treatment plan outlined in Figure 1 depends heavily on the endoscopic appearance of the lesion in question, and is based on the premise that there is no evidence of flat dysplasia in other areas of the patients colon by colonoscopic biopsy analysis. Regardless of the
presence of an adenoma-like dysplastic lesion, any IBD patient who has one or more areas of flat dysplasia should be considered a candidate for colectomy.
References

Table 1
LARGE INTESTINE POLYPS
[Generic]

**Epithelial Non-Neoplastic**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tr>
<td>Hyperplastic</td>
<td>Vesicular, goblet cell, mucin poor</td>
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<tr>
<td>Inflammatory</td>
<td>Inflammatory [pseudo] polyp</td>
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<tr>
<td></td>
<td>Isolated, IBD-related</td>
</tr>
<tr>
<td></td>
<td>Mucosal prolapse polyp</td>
</tr>
<tr>
<td></td>
<td>Inflammatory Cap polyp</td>
</tr>
<tr>
<td></td>
<td>Cloacogenic polyp</td>
</tr>
<tr>
<td></td>
<td>Diverticular disease-associated polyp</td>
</tr>
<tr>
<td></td>
<td>Colitis cystica polyposa/Profun da</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>Juvenile [sporadic, syndromic]</td>
</tr>
<tr>
<td></td>
<td>Peutz-Jeghers [sporadic, syndromic]</td>
</tr>
<tr>
<td></td>
<td>Cronkhite-Canada syndrome</td>
</tr>
<tr>
<td></td>
<td>Cowden’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Other (inflammatory myoglandular polyp)</td>
</tr>
<tr>
<td>Heterotopia</td>
<td>Gastric, salivary, other</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Pneumatosis</td>
</tr>
<tr>
<td></td>
<td>Endometriosis</td>
</tr>
<tr>
<td></td>
<td>Appendix intussusception/Inverted stump</td>
</tr>
<tr>
<td></td>
<td>Mucosal bumps/tags/excrescences</td>
</tr>
<tr>
<td></td>
<td>Dermoid cyst</td>
</tr>
</tbody>
</table>

**Epithelial Neoplastic**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>Conventional/flat/sessile serrated/serrated/mixed</td>
</tr>
<tr>
<td></td>
<td>Adenoma with carcinoma</td>
</tr>
<tr>
<td></td>
<td>Polypoid dysplasia in IBD</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Polypoid carcinoma</td>
</tr>
<tr>
<td></td>
<td>Carcinoid</td>
</tr>
<tr>
<td></td>
<td>Metastasis [breast, melanoma]</td>
</tr>
</tbody>
</table>

**Non-Epithelial**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamina Propria Infiltrates</td>
<td>Pneumatosis, xanthoma endometriosis</td>
</tr>
<tr>
<td></td>
<td>Muciphages</td>
</tr>
<tr>
<td>Lymphoid</td>
<td>Hyperplasia/neoplasia</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>Neurofibroma [sporadic, syndromic]</td>
</tr>
<tr>
<td></td>
<td>Ganglioneuroma [sporadic, syndromic]</td>
</tr>
<tr>
<td></td>
<td>Leiomyoma/GIST</td>
</tr>
<tr>
<td></td>
<td>Hemangioma/AV malformation</td>
</tr>
<tr>
<td></td>
<td>Lipoma/lipohyperplasia</td>
</tr>
<tr>
<td></td>
<td>Inflammatory fibroid polyps</td>
</tr>
<tr>
<td></td>
<td>Teratoma</td>
</tr>
</tbody>
</table>
### Table 2
**Serrated Polyps of the Colon**

1. “Hyperplastic” - Goblet cell  
   - Vesicular  
   - Mucin depleted

2. “Serrated” - Sessile serrated polyp (adenoma)  
   - Serrated adenoma  
   - Mixed polyp
Table 3
Features of Serrated Polyps and Conventional Tubular Adenomas

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hyperplastic Polyp</th>
<th>Sessile Serrated Adenoma</th>
<th>Serrated Adenoma</th>
<th>Tubular Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;0.5 cm</td>
<td>&gt;0.5 cm</td>
<td>&gt;0.5 cm</td>
<td>any size</td>
</tr>
<tr>
<td>Location</td>
<td>? left</td>
<td>? right</td>
<td>right or left</td>
<td>right or left</td>
</tr>
<tr>
<td>Rate of Progression</td>
<td>+/-</td>
<td>++</td>
<td>+ (right or left)</td>
<td>+ (right or left)</td>
</tr>
<tr>
<td>DNA Methylation</td>
<td>-</td>
<td>?</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>-</td>
<td>?</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>APC/B catenin mut</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Kras mutations</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>MGMT Methylation</td>
<td>-</td>
<td>? distal</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>MUC2, 5AC, 6</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Basal Crypt prolif</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Luminal Crypt prolif</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Mucin rich</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sessile</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Pedunculated</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Villous</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>N/C ratio</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Dystrophic goblet cells</td>
<td>-</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Round vesicular</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Nuclei/nucleoli</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surface maturation</td>
<td>+</td>
<td>delayed</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 1

Treatment of DALM’s in Ulcerative Colitis

DALM

Adenoma-like

- Polypectomy
- regular surveillance

Outside colitis
- Polypectomy
- Confirm absence of flat dysplasia
- ? increased surveillance

Inside colitis

Non Adenoma-like

Colectomy