

**Dysplasia can be a pain in the gut**  
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**Introduction**

Over the past 20 years or so, we have been bombarded with dysplasia: biopsies looking for dysplasia from patients with ulcerative colitis, Barrett's esophagus, atrophic gastritis; and thousands and thousands of adenomas. We have read and heard myriad discussions about definitions, clinical implications, lack of interobserver agreement, histologic features. Clearly the diagnosis of dysplasia in the gastrointestinal tract is an area of major concern.

What makes the diagnosis of dysplasia such an area of concern? Perhaps it is because most examples of dysplasia in the setting of Barrett's esophagus or ulcerative colitis have no helpful endoscopic features, so that the diagnosis depends solely on histology. Perhaps it is because the implications for these diagnoses are significant, including follow-up endoscopic examinations that are expensive and unpleasant. Perhaps it is because most pathologists' experience in this area is limited and nearly devoid of follow up correlation to tell them how they are doing. All of these factors likely contribute to anxiety over diagnosing dysplasia in these settings. However, the most likely cause of angst is the fact that the features of neoplasia may be only subtly different from those of regeneration, and the distinction maddeningly difficult. An attractive solution would be to define precancerous epithelium by its molecular changes, but this is not yet practical. At present, we must still do the best we can with morphology.

**Definitions and terminology:**

The term "dysplasia" generically means an abnormality in growth. In adults, "dysplasia" generally refers to epithelial alterations that are steps in the transition from normal to malignancy. In 1983 Riddell and a group of gastrointestinal pathologists published the paper that established the term "dysplasia" to describe premalignant lesions in ulcerative colitis (15). In this paper dysplasia is defined as "an unequivocal neoplastic epithelial proliferation." Thus, the ability to diagnose dysplasia is the ability to distinguish what is definitely neoplastic from what is not, certainly not an easy task. Some pathologists seem not to understand the fact that the diagnosis of "dysplasia" is synonymous with the diagnosis of neoplasia. Thus, they may use terms such as "atypia" for lesions that are truly dysplastic, while others are likely to use the same "atypia" to diagnose reactive or regenerative epithelium, creating confusion among the clinicians who read their reports.

The Riddell paper also established the nomenclature for GI dysplasias—low grade and high grade. It is expected that all pathologists will comply with this two tier system for diagnosing gastrointestinal dysplasias. Many pathologists have persisted in using the now-outdated three-tier system, once used for uterine cervical biopsies, grading dysplasias as mild, moderate, or severe, instead of low and high-grade. This three-grade system for dysplasia causes difficulty for the gastroenterologist in deciding management when the term "moderate dysplasia" is used, since the management recommendations do not include

that term. Furthermore, some pathologists are not aware that “carcinoma in situ” and “intramucosal carcinoma” are diagnoses that have been omitted from most classification schemes and, as a result, they have no specific management implications.

The Riddell paper was based on a study involving several exchanges of microscopic slides from chronic colitis cases, mainly ulcerative colitis, among eleven specialized gastrointestinal pathologists. They recognized that there were some epithelia with histologic features that were not clearly dysplastic, yet they also were not clearly regenerative. These were designated as “indefinite for dysplasia.” Initially, the indefinite category was divided into 3 subcategories based on the participants’ histologic suspicions. Most gastrointestinal pathologists now have a single category of indefinite for dysplasia which includes all epithelia that they cannot confidently classify as either regenerative or dysplastic.

### **Criteria for low-grade and high-grade dysplasia:**

The histologic features of dysplasia are the classic cytologic and architectural changes of malignancy that are taught in introductory pathology classes in medical school and relied upon throughout surgical pathology and cytopathology. Dysplasias are often taught as specific entities with clear-cut histologic and cytologic criteria that separate low-grade from high-grade. The histologic features are generally described as follows:

- Cytologic:
  - Nuclear enlargement, hyperchromasia, and pleomorphism
  - Increased numbers of mitoses, especially near or on the surface
  - Loss of cytoplasmic maturation, including decrease or loss of mucin
- Architectural
  - Nuclear crowding and stratification, loss of polarity
  - Complex arrangements and crowding of tubules
  - Abnormal surface contours—often villiform rather than flat

Then, the distinction between low-grade, high-grade and indefinite are often listed as follows:

- Low grade:
  - Mild, if any architectural abnormalities
  - A combination of nuclear stratification, enlargement, hyperchromasia, and pleomorphism, that extends onto the surface, but with preservation of nuclear polarity
- High-grade:
  - Architectural distortion is present and may be marked
  - Nuclear abnormalities are more pronounced than in low grade dysplasia
  - Loss of nuclear polarity
- Indefinite for dysplasia. Criteria not definable—published criteria include
  - marked nuclear atypia in deep mucosa, with surface maturation, or nuclear atypia that “mostly matures”
  - Biopsies with disturbing cytologic/architectural changes, with significant inflammation or lack of evaluable surface

Most pathologists realize that there is no specific histologic point that separates low-grade from high-grade dysplasia, making this cut-off highly subjective. In addition, although the terminology is the same, and published histologic features are similar, dysplasias occurring in different settings, such as in colonic adenomas, ulcerative colitis, Barrett's esophagus and atrophic gastritis, have different appearances, and perhaps different thresholds for separating low- from high-grade dysplasia. Thus, despite the fact that there is an accepted terminology and a set of histologic criteria, the task of diagnosing dysplasia is anything but straightforward.

### **Clinical implications of the diagnoses**

Adding to the anxiety of pathologists dealing with these biopsies is awareness of the implications of their diagnoses. The diagnoses of both low-grade dysplasia and indefinite for dysplasia in ulcerative colitis and Barrett's mucosa mean more stringent surveillance with more frequent endoscopies and more fastidious biopsy sampling. Thus, the category of indefinite for dysplasia should not be indiscriminately used for biopsies that are most likely regenerative rather than neoplastic. Certainly, the diagnosis of high-grade dysplasia in any setting has significant management implications, often immediate resection. It is not surprising that pathologists who have limited experience in this difficult and important area are increasingly seeking consultation from specialized gastrointestinal pathologists. It is also not surprising that one recommendation for dealing with a biopsy diagnosed as high-grade dysplasia is to ask for verification from a consultant.

### **The Problem Areas**

There are two principle areas of difficulty in diagnosing and reporting gastrointestinal dysplasias, and these relate to two important management thresholds. The first is in distinguishing mucosa with regenerative epithelial changes from something that deserves to be called either indefinite or low grade. The second is deciding when mucosa with high-grade dysplasia also harbors carcinoma.

#### **Is it regenerative or low-grade dysplasia?**

The most daunting challenge that pathologists face in evaluating biopsies from patients with Barrett's or ulcerative colitis is the diagnosis of low-grade dysplasia in the setting of chronic epithelial injury. It is challenging because the features used to diagnose low-grade dysplasia are also features commonly present in regenerative epithelium, and regenerative epithelium is a regular component of such mucosae. Both dysplasia and regenerative epithelium have cytologic features that include nuclear enlargement, hyperchromasia, stratification, and increased numbers of mitoses. In fact, in a single high power microscopic field, the two may be indistinguishable. For the most part, it is the *distribution* of these changes that serve to distinguish regenerative from low-grade dysplastic epithelium. Regenerative changes tend to be most marked in the normal proliferative zone of the mucosa—that is, deep to the surface—with maturation toward the surface. In contrast, dysplastic epithelium, being neoplastic, doesn't follow such rules and is often most evident at or near the surface. But these are not always easy patterns to appreciate, especially in small and randomly oriented biopsies.

Some examples of regeneration that may resemble low grade dysplasia:

- The basal regeneration that is common in Barrett's mucosa can look exactly like low-grade dysplasia, but it is accompanied by gradual loss of atypical features with maturation toward the surface. Thus, many experienced GI pathologists find it virtually impossible to diagnose low-grade dysplasia in Barrett's epithelium unless there is surface epithelial involvement.
- In reactive or chemical gastropathy, an intense neck and pit proliferation in response to surface epithelial injury may be confused with dysplasia. In this condition, the necks and pits are elongated and lined by an epithelium that is commonly more cuboidal than columnar, and has enlarged, often hyperchromatic nuclei, and mitoses in cells close to the surface. Because the normal proliferative zone of the gastric mucosa is the neck region, and because this region is close to the surface, this neck and pit expansion and proliferation mimics dysplasia.
- Finally, in any colitis, especially in the active phases, the epithelium proliferates in response to the injury, resulting in crypts lined by cells with enlarged, hyperchromatic nuclei and frequent mitoses. This regenerative epithelium may even stratify, so that it truly looks dysplastic. It is this epithelium that has led experienced pathologists to recognize that the diagnosis of low-grade colitic dysplasia in the face of active inflammation may be impossible. This resemblance between neoplastic and non-neoplastic proliferative epithelia is not limited to inflammations. In hyperplastic colonic polyps, proliferation of epithelium in the basal crypts may look exactly like low-grade dysplasia.

It is important for pathologists and the clinicians with whom they deal to recognize that all low-grade dysplasias do not look alike. All have epithelium that is neoplastic, but some have pronounced cytologic changes with few architectural abnormalities, while in others the nuclei are quite abnormal, but are only slightly stratified. In yet others, the biopsy captures dysplastic-looking epithelium that underlies a normal surface. Because of this heterogeneity, and because of the overlap of features with regenerative epithelium, it is at this low end of the dysplasia spectrum that most of the diagnostic difficulties exist, even among the most experienced pathologists. (25-32)

#### When does Dysplastic Mucosa also Contain Carcinoma?

There are two issues related to diagnosing carcinoma in the setting of dysplasia. The first is the use of the term "carcinoma in situ", and the other relates to the diagnosis of invasive carcinoma. In the Riddell, et al paper in which the definition of dysplasia appears, that definition also states that high-grade dysplasia includes something previously referred to as "carcinoma in situ." (15) Thus, the diagnosis of "carcinoma in situ" is not to be used, and any epithelial changes that formerly led to that diagnosis in ulcerative colitis are to be called "high-grade dysplasia."

The term "carcinoma", then, refers to invasive carcinoma. The point at which this term is appropriate differs based on the site within the gut, because of the differences in distribution of lymphatics. We assume that carcinomas of the GI tract, with rare exceptions, have no metastatic potential unless they have access to lymphatics. Thus, carcinoma is diagnosed when the neoplastic cells invade tissue in which lymphatics are present. In the esophagus, stomach, and small intestine, lymphatics are present in the lamina propria. In

contrast, the colonic lamina propria has virtually no lymphatics; they only begin to appear in the superficial submucosa and muscularis mucosae. Therefore, in the esophagus, stomach and small bowel, anything that invades the lamina propria is a carcinoma with metastatic potential, whereas in the colon and rectum, only invasion of the superficial submucosa implies metastatic potential. As a result, invasion only of lamina propria in the colorectum can be considered to be clinically the same as high-grade dysplasia, and most GI pathologists have adopted this approach. There are gut pathologists who still make the diagnosis of “intramucosal adenocarcinoma”, but usually add a comment that this carcinoma will not metastasize.

How does one identify invasive carcinoma in an endoscopic biopsy? Submucosal invasion is generally readily identified by the desmoplasia that carcinomas throughout the gut commonly stimulate. This desmoplasia is the fibrotic and sometimes inflamed stroma that surrounds neoplastic tubules, and only seems to occur when the invasion has reached the submucosa; it almost never occurs when the invasion is confined to the lamina propria. Thus, the finding of desmoplasia is marvelous evidence that invasive carcinoma has occurred, and it is especially useful for the colon and rectum where carcinoma is not diagnosed until the invasion has reached the submucosa. In contrast, in the esophagus and stomach, invasion of the lamina propria satisfies the definition of carcinoma. It is in these sites where we have the greatest difficulty recognizing the subtlest signs of lamina propria invasion. Even the most experienced pathologists have trouble identifying the first evidence of invasion of the lamina propria in a biopsy. There are no set criteria for making this decision. In general, since we cannot rely on desmoplasia, we hope to find small clusters of neoplastic cells or single cells in the lamina propria, separated from the adjacent dysplastic tubules, but this is not terribly reproducible. Another criterion used is architectural complexity more striking than expected in even very high grade dysplasia, forming confluent cribriform arrangements of cells—again, not a reproducible criterion. Other features that raise suspicion for invasive carcinoma include the presence necrotic debris within dysplastic tubules and ulceration of the dysplastic mucosa, since dysplasias without cancer rarely undergo necrosis and do not ulcerate. These latter features are especially helpful in biopsies of dysplastic Barrett’s mucosa. (33) Very often, the diagnosis of incipient invasion is a matter of gestalt and is based on the experience of the observer and his or her visual and probably emotional, response to the microscopic appearance of the biopsy.

### **The Reproducibility Problem**

It has been proven in several studies that even the most experienced gastrointestinal pathologists who deal with these types of biopsies have difficulty agreeing on which epithelia are low-grade dysplasia or indefinite for dysplasia. They also have difficulty agreeing on when carcinoma is present in mucosae with high grade dysplasia, particularly in Barrett’s biopsies. In contrast, they are much more likely to agree on what is non-dysplastic and what is high-grade dysplasia. Such studies indicate that equally experienced pathologists are likely to include different epithelial changes in the categories of indefinite for dysplasia or low-grade dysplasia; thus, these diagnoses are not reproducible among pathologists. A recently published study of reproducibility in the diagnosis of epithelial

changes in Barrett's mucosa by 12 GI pathologists found that reproducibility was good if all categories that did not require intervention (negative, indefinite and low-grade dysplasia) were compared with the categories that required intervention (high-grade dysplasia and carcinoma). (29) However, the reproducibility among the group for individual categories was not nearly as good. It was best for carcinoma, slightly less for high-grade dysplasia and negative, considerably less for low-grade dysplasia and much less for the indefinite category. This is much the same as the result of the study of chronic colitis that led to the Riddell et al paper. (15) Haggitt acknowledged that in Barrett's mucosa the distinction between indefinite for dysplasia and low grade dysplasia was often impossible, and since the management implication for both diagnoses was the same, he suggested that there be a single category combining the two diagnoses for more effective endoscopic and biopsy surveillance. (30)

### **What should pathologists do?**

The ability to make these diagnoses with comfort and confidence requires not only frequent exposure to these problem biopsies, but clinical correlation and follow up. Detailed and consistent communication between endoscopist and pathologist is essential, so that pathologists learn of the clinical circumstances in which the biopsies were taken, the actions instituted based on their diagnoses, and, perhaps most critically, the resultant patient outcomes

What can pathologists do to assure that we are giving the most accurate diagnosis possible in surveillance biopsies of the gastrointestinal tract? First, we must comply with the accepted two-tier system of nomenclature, using the terms "low grade dysplasia" and "high grade dysplasia", rather than "mild, moderate, and severe dysplasia." The term "carcinoma in situ" has no place in the lexicon. The terms "atypia" and "intramucosal carcinoma" may communicate different messages than intended, so it may be advisable to avoid their use, as well. Classifying a biopsy as "indefinite for dysplasia" is appropriate in some cases, but we should resist overuse of the category, and be aware that such a diagnosis may have the same management implication as a diagnosis of low-grade dysplasia.

Pathologists will need to familiarize themselves, as much as possible, with the spectrum of appearances that comprise the low grade and high-grade dysplasias. For pathologists who see small numbers of such cases, this is easier said than done. Review of cases among members of a pathology group or department may expand the experience of each member and promote consistency within the group. However, as with all groups that tried in the past, one cannot expect uniform agreement, especially among the more difficult cases—those in which the differential is between regenerative changes and low-grade dysplasia. In selected cases it may be appropriate to seek expert consultation; examples might include those cases in which one is unsure of a diagnosis that will have significant consequences, such as a diagnosis of high grade dysplasia in a biopsy from a patient with Barrett's esophagus.

In an ideal world pathologists and gastroenterologists would establish excellent lines of communication about all kinds of cases. We know, of course, that this does not always happen. We pathologists may need to seek out follow up information to assess the accuracy of our diagnoses, not only for surveillance biopsies, but for inflammatory diseases

too. In the end, surveillance biopsies from patients with chronic colitis, Barrett's esophagus, or atrophic gastritis will remain challenging, frustrating, and frequently anxiety-producing cases. On the other hand, these are the cases in which the gastroenterologists, and, therefore patients, rely heavily upon our diagnoses to decide on management, perhaps more than for any other types of gastrointestinal biopsies, and so it is with these cases that we have one of our best opportunities to serve patients.

## **References**

Parts of the above text are abridged and rearranged components of a review article written by McKenna and Appelman (McKenna BJ, Appelman HA. Dysplasia can be a pain in the gut. *Pathology*. 2002 Dec;34(6):518-28). Rather than delete and re-number the references, all of the references from that paper are listed below.

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## **Update on Neuroendocrine Tumors of the GI Tract**

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Neuroendocrine tumors develop throughout the gastrointestinal tract from the esophagus to the anus, but they are decidedly unusual in the esophagus and anus. These tumors include a spectrum of lesions that encompasses everything from endocrine cell hyperplasia through carcinoid tumors to small cell carcinomas or neuroendocrine carcinomas. The term carcinoid tumor encompasses a wide spectrum of different neoplasms that originate from various neuroendocrine cells. These tumors are referred to as carcinoid tumors or they may be referred to by the name of the cell population constituting them or by the hormones that they produce. Similar neoplasms in the pancreas are usually referred to as islet cell tumors.

Gastrointestinal neuroendocrine tumors arise in the setting of two genetic susceptibility syndromes: multiple endocrine neoplasia type-1 and neurofibromatosis type-1. Patients with MEN-1 have a mutation or deletion in the tumor suppressor gene MEN-1 that localizes to 11-13 and encodes a nuclear protein menin. ECL carcinoids constitute an integral component of the MEN-1 syndrome and gastric carcinoids arise in 13-30% of patients with familial MEN-1 and Zollinger Ellison Syndrome (ZES). Patients with neurofibromatosis type 1 typically develop a number of periampullary neoplasms, including somatostatinomas and gangliocytic paragangliomas.

In some cases carcinoid tumors arise on a background of endocrine cell hyperplasia of a similar cell type. This suggests that a relationship exists between the endocrine cell hyperplasia and subsequent development of a carcinoid tumor. Examples of this phenomenon include the ECL Type 1 and Type 2 carcinoid tumors arising on a background of ECL cell hyperplasia, duodenal gastrinomas arising on a background of G cell hyperplasia and somatostatinomas arising in a area of somatostatin cell hyperplasia.

### **CARCINOID TUMORS**

#### **General Features**

Generally the clinical features of carcinoid tumors are vague or absent unless the tumor is large enough to create a mass effect or it secretes bioactive mediators that create specific syndromes, such as the carcinoid syndrome or ZES. Patients with esophageal tumors may seek care because of dysphagia, weight loss, reflux esophagitis and chest pain. Most gastric endocrine cell tumors arise in the setting of hypergastrinemia causing the patient to present with peptic ulcer disease or chronic gastritis. More distally located gastric tumors may cause gastric outland obstruction. Most duodenal endocrine tumors become symptomatic by producing mass lesions that cause bleeding and intestinal obstruction or that block the common bile duct or pancreatic duct, causing obstructive jaundice or pancreatitis respectively. Weight loss, diarrhea, lymphadenopathy or the carcinoid syndrome may also occur. Many symptomatic patients with distal small intestinal tumors

have a long history of intermittent crampy abdominal pain suggestive of episodic intestinal obstruction. As the symptoms worsen, with progressive intestinal obstruction, abdominal distention and vomiting develop. Approximately 5% of patients develop signs of intestinal infarction secondary to intussusception, volvulus or vascular disease.

The carcinoid syndrome develops in fewer than 10% of patients with small intestinal ECL carcinoids, usually in patients with hepatic metastasis.

Most appendiceal endocrine tumors are incidental findings in appendectomy specimens. Tumors that arise proximally may obstruct the lumen, producing appendicitis. Patients with colonic carcinoid tumors tend to seek care late in life with anorexia, weight loss, weakness, abdominal pain or liver metastasis. Rectal carcinoids typically manifest with constipation or pain or bleeding, usually due to trauma associated with the passage of solid feces over the tumor. However, it is important to note that approximately 50% of all patients with rectal carcinoids remain asymptomatic and the lesions are often detected as incidental findings during screening endoscopies.

Grossly, carcinoid tumors tend to be firm, submucosal nodules that usually measure <2 cm in diameter, developing at the mucosal/submucosal junction. The overlying mucosa usually remains intact or it may become slightly eroded. The tumors range from barely palpable, tan-yellow or gray-grown thickenings to nodules that measure >3.5 cm. These tumors grow slowly and extend into the underlying submucosa and overlying mucosa. As they grow, they may infiltrate locally beyond the submucosa into the muscularis propria, eventually reaching the external surface of the gut. As the tumors become more deeply invasive, fibrosis develops and can cause angulation, kinking, or distortion of the bowel wall, eventually resulting in obstruction. Blood vessels may be caught in the fibrosing process and then secondarily compressed, leading to ischemia.

### **Histological Features**

Gastrointestinal carcinoid tumors can be divided into five histological patterns:

1. Solid, nodular and insular chords;
2. Trabecular or ribbons with frequent anastomosing patterns;
3. Tubules and glands or rosette-like patterns;
4. Poorly differentiated or atypical patterns;
5. Mixed tumors.

The classical carcinoid tumor is one that arises in the mid-gut from serotonin-producing Kulchitsky cells.

Most **esophageal carcinoid** tumors contain anastomosing ribbons, solid nest trabecular and acinar or rosettes, although mixed patterns with more typical solid nests may be seen. In patients with **gastric ECL** type tumors, multifocal gastric ECL cell micronests and multifocal carcinoid tumors develop in the atrophic and metaplastic gastric body. Some patients have coexisting adenocarcinomas and multiple carcinoid tumors.

ECL carcinoids are divided into Type 1, Type 2 and Type 3. The Type 1 carcinoid is characterized by the presence of multiple small fundic tumors limited to the mucosa and submucosa associated with ECL cell hyperplasia arising on a background of autoimmune chronic atrophic gastritis. Type 2 ECL cell carcinoids are associated with MEN-1. Type 3 ECL carcinoids are sporadic lesions having no association with autoimmune chronic atrophic gastritis, MEN-1 or the ZES. There is no association with adjacent ECL cell hyperplasia. In patients with ECL Type 1 tumors, there is a background of endocrine cell hyperplasia.

The individual stages of hyperplasia are distinguished as simple, linear, micronodular and adenomatoid. All of these exhibit intact basement membranes. As each micronodule enlarges, the basement membrane breaks down and cytological atypia and increased nuclear cytoplasmic ratios develop. These lesions are dysplastic and show morphologic variations as enlarging micronodules, fusing micronodules, microinvasive lesions or nodules with a newly formed stroma. The latter occur when the nodules acquire a lobular or trabecular pattern. Lesions initially remain completely intramucosal. Both Type 1 and Type 2 ECL carcinoids consist of small, microlobular trabecular aggregates formed by regularly distributed cells arranged in a mosaic pattern with regular monomorphic nuclei, non prominent nucleoli and abundant eosinophilic cytoplasm. Mitosis and lymphatic invasion are usually absent. More advanced lesions can invade the vascular or lymphatic channels, leading to nodal or distant metastases.

**Sporadic ECL carcinoids** are solid cellular aggregates with large trabecular and cellular crowding. There is an irregular distribution of round, spindle shaped and polyhedral cells. The nuclei tend to be large vesicular and eosinophilic with irregular chromatin clumps and mitotic activity can be brisk, sometimes with atypical mitoses. These tumors have a mitotic rate of 9-10 per high-power field with a high KI67 labeling index and are frequently positive for p53. They also frequently associate with lymphatic and vascular invasion, in comparison with the well-differentiated proximal ECL carcinoid tumors.

G-cell hyperplasia with increased numbers of G-cells, numerous uniformly distributed in the lower and middle third of the antral glands affects patients with achlorhydria. Longstanding diffuse antral G-cell hyperplasia may progress to numerous small micronodular G-cell clusters and can eventually give rise to G-cell carcinoids (gastrinomas).

A number of carcinoid tumors, many of which are **gastrinomas**, develop in the proximal small intestine. Gastrinomas cannot be differentiated from other functional non-functional carcinoid tumors based solely on their histology. Immunohistochemical staining is required to make this diagnosis. These tumors tend to consist of small, uniform appearing cells, typically arranged in ribbons and trabecular, with vascular pseudorosettes. Most gastrinomas also produce other polypeptides in addition to the gastrin.

**Somatostatinomas** demonstrate mixed architectural patterns with architectural patterns with areas of insular, trabecular, glandular or acinar differentiation similar to those seen

in other endocrine tumors. A feature that distinguishes them from other gastrointestinal carcinoid tumors is the presence of psammoma bodies and a striking glandular appearance that makes them mimic carcinomas. However, in contrast to most carcinomas, somatostatin producing carcinoid tumors consist of uniform cells with few mitoses.

**Gangliocytic paragangliomas** are distinctive neoplasms that contain a mixture of spindle cells, epithelial cells and ganglion cells. The spindle cells often are a major component and are of unknown origin. They form compact fascicles that may envelop the nerves and axons and are positive for S100. The epithelial cells are larger with eosinophilic cytoplasm and contain uniform ovoid nuclei. The cells are arranged in ribbons, solid nests or in pseudo glandular structures. Ganglion cells are scattered singly or aggregated into clusters. Because these lesions typically arise at the ampulla ovata, the various components may mingle with the smooth muscle fibers in pancreatic ducts in this region.

**Mid-gut EC cell** serotonin-producing carcinoids consist of characteristic rounded nests of closely packed tumor cells, often with peripheral palisading. In another pattern, the solid nests associate with rosette-like or glandular structures. These are often called mixed insular or glandular type and may have a more favorable prognosis than the more nested carcinoid tumors. Most of the carcinoid tumors have a indistinct cytoplasm, indistinct cell borders and a little or no cellular pleomorphism or mitotic activity. Most mid-gut carcinoids are multi hormonal. When these tumors invade the muscularis propria, they insinuate themselves between the muscle fibers, spreading the muscle fibers apart rather than destroying them. A prominent desmoplastic response may lead to thickening of the bowel wall and fibrosis that extends into the mesentery. Concentric elastic vascular sclerosis frequently affects these large mesenteric vessels and these proliferations can obliterate the vascular lumens, leading to ischemia. The elastosis and fibrosis are not confined to the vessels, but may also surround tumor cell nests, resulting in extensive matting of involved tissues and lymph nodes, sometimes producing fibrous adhesions.

Classical **appendiceal carcinoids** resemble their ileal counterparts. Approximately two-thirds of cases extend to the peritoneal surface. As is the case in all carcinoid tumors, retraction artifact of fixed tissues often creates the false impression of lymphatic invasion. However, true lymphatic invasion occurs as demonstrated by finding lymphatic endothelial cells lining spaces surrounding tumor cells. Perineural invasion also occurs. Appendiceal tumors are unique in that they contain S100 positive sustentacular cells surrounding the tumor cell nests. This suggests the tumors arise from subepithelial neuroendocrine complexes rather than from intraepithelial endocrine cells.

One variant is the so-called tubular carcinoid, which consists of small obvious tubules, but not containing inspissated mucin. The nuclei are central, round or oval and have well-defined nuclear membranes. These tumors are often positive for chromogranin, glucagon, serotonin and IGA. They can easily be misinterpreted as metastatic adenocarcinoma.

Another tumor that arises in the appendix is the adenocarcinoid tumor. It is discussed later.

The histological features of large **intestinal EC carcinoid** tumors resemble small intestinal or appendiceal carcinoid tumors. However, these hindgut lesions exhibit moderate atypia and a high mitotic rate. Therefore they tend to behave more aggressively than the average mid-gut carcinoid tumor. The use of chromogranin stains to establish the diagnosis of a carcinoid tumor in the colon and rectum is often disappointing, since these results are frequently negative. We use synaptophysin staining regularly to demonstrate endocrine cell lesions in the GI tract.

### **Prognosis and treatment**

Carcinoid tumors are potentially malignant and identifying those that behave aggressively can be quite difficult, since the presence of local invasion in these slow-growing tumors does not have the same prognostic implication that it does in adenocarcinomas. The histological features alone usually do not allow one to predict malignancy. The distinction between a benign and malignant tumor traditionally relies on the presence or absence of metastases. However, an elevated mitotic rate often associates with a worse prognosis. When a tumor invades beyond the mucosa or metastatic spread is present, the lesion is considered to be potentially aggressive. If the lesion remains confined to the mucosa or submucosa that shows vascular invasion, or is larger than 1 cm, it is considered to be of **uncertain malignant potential**. Treatment usually consists of radical surgical excision of the tumor. Exceptions are gastric Type 1 and Type 2 lesions and rectal carcinoids that are managed by local excision. In general, the five-year survival is excellent for appendiceal carcinoids (86%) and rectal carcinoids where small intestinal, gastric and colonic carcinoids have five-year survival rates of 21-55%, 6-49% and 42%, respectively.

In the stomach, if the tumors are larger than 1 cm or more than 3 lesions are present, local excision of the fundic lesions and antrectomy are recommended. Antrectomy removes the sources of the hypergastrinemia that drives the tumor growth. In Type 2 ECL cell carcinoids clinical prognosis is usually determined by the presence of pancreatic or duodenal gastrinomas rather than by the ECL carcinoids. Nevertheless, some aggressive ECL tumors can be fatal. Type 3 ECL carcinoids measuring >1 cm usually require surgical resection even if they are well differentiated.

Approximately 25% of duodenal carcinoid tumors metastasize. Features associated with metastasis include extension to the muscularis propria; a maximum diameter of >2 cm; and the presence of mitotic figures. Gastrinomas, somatostatinomas and EC cell tumors that invade beyond the submucosa or those that develop lymph node or distant metastases behave aggressively. The liver is the most common metastatic site, followed by the regional lymph nodes and bones with patients with somatostatinoma. The high incidence of malignancy in somatostatinomas parallels that seen in glucagonomas and gastrinomas.

Gastrinomas that develop in the setting of ZES behave more aggressively than nonfunctional gastrinomas in are much more likely to develop metastases and be deeply infiltrative. Pancreatic gastrinomas behave more aggressively than duodenal gastrinomas. The rate of metastases of duodenal gastrinomas is 5% versus 52% in patients with pancreatic primary tumors. The ten-year survival rate of patients with duodenal gastrinomas is 59% compared with 9% for those with pancreatic gastrinomas. Gangliocytic paragangliomas usually behave in a benign manner, although occasionally they metastasize.

Jejunioileal carcinoids are potentially aggressive if they deeply invade the bowel wall or if there are metastases. By these criteria, up to 90% of jejunioileal carcinoids can be considered to be aggressive. Up to 35% of small intestinal carcinoid tumors metastasize. The metastases first involve the mesenteric lymph nodes and then the liver. Jejunioileal carcinoids have a 21% mortality rate, compared with 6% for gastric, 3% for rectal and 4% for duodenal carcinoids. The overall five- and ten-year survival rates for patients with jejunioileal endocrine tumors are 60% and 43% respectively. Patients without liver metastases have 5 and 10-year survival rates of 72% and 60% respectively, compared with 35% and 15% for those with liver metastases.

Appendiceal and colonic carcinoid tumors can be treated by local excision if they are found at an early stage (2 cm or less in maximum diameter). Although appendiceal carcinoid tumors often extend to the peritoneal surface, they do not behave aggressively as judged by the infrequent occurrence of lymph node or distant metastases. Tumors that are >2 cm in maximum diameter or invade the mesoappendix will have metastases or aggressive lesions. If the tumors arise at the base of the appendix and involve the resection margins, or the cecum, the prognosis is more unfavorable and requires partial resection of the cecum. The frequency of metastases ranges from 1.4 to 27% and distant metastases may occur. The five-year survival of patients with appendiceal carcinoid tumors is 94% for those with localized disease, 85% for regional disease and 34% for distant metastatic disease. In contrast, goblet cell carcinoids behave more aggressively than the usual carcinoids that are not as malignant as adenocarcinomas and tubular carcinoids are clinically benign.

Colonic EC cell carcinoids are often malignant with local spread occurring in up to 44% of patients and distant metastases in 38%. The five-year survival rate is 25-42% and the ten-year survival rate is 10%. Large colonic carcinoid tumors should be treated aggressively with standard colonic resection. These tumors metastasize to lymph nodes, liver, mesentery peritoneum, pancreas, ureters, ovaries, omentum and sometimes, other organs.

Rectal carcinoids are malignant in approximately 14% of cases. Features used to diagnose a malignant tumor include tumors measuring >2 cm in greatest diameter, invasion of the muscularis propria, atypical histological features and more than 2 mitoses to 10 high-power field, as well as the presence of aneuploidy.

The principal treatment for rectal carcinoid tumors is surgery. Tumors measuring <2 cm in diameter are quite suitable for local resection, whereas radical operations are required for larger lesions. If the tumor displays atypical histological patterns, a radical operation should be considered, even if the tumor measures <2 cm. Total removal with clear margins is essential to limit local recurrence in these tumors measuring <2 cm.

## ADENOCARCINOID

Adenocarcinoid tumors contain multiple proliferating epithelial cell types, including mucinous cells, endocrine cells and Paneth cells. Both poorly formed mucin vacuoles and endocrine granules can be present in the same cell. In a minority of lesions, the endocrine cell component is so prominent that the tumor resembles a conventional carcinoid tumor. In other tumors an inconspicuous endocrine component is detectable only after the use of special stains. In this situation, the tumor histologically resembles a signet ring cell carcinoma. Mucin or CEA stains highlight the goblet cells. Mucin also highlights the extracellular mucinous pools. Immunohistochemically, the endocrine cell component is positive for chromogranin A, synaptophysin, serotonin, glucagon, somatostatin, and/or pancreatic polypeptide. The goblet cells are immunoreactive for CEA. The mucosa is typically spared except in its lower portion where the tumor contacts the crypt bases. Mitotic figures are infrequent and there is virtually no cellular atypia. These tumors tend to infiltrate all layers of the intestinal wall to the serosa in the manner resembling typical carcinoid tumors.

## SMALL CELL CARCINOMAS

Small cell carcinomas are rare gastrointestinal tumors that are much more prevalent in Japan than in the United States. This is generally a tumor of older adults aged 38-74 with a mean age of 64-66 years and a predilection for development in men.

Patients with small cell carcinomas tend to present with crampy abdominal pain, malaise, weight loss, fever, diarrhea and rectal bleeding. In most patients the symptom duration is short, being only several weeks in duration. At the time of surgery, almost all of the patients have metastases to the regional lymph nodes and liver. The patients may also have symptoms secondary to the presence of a mass lesion. These tumors behave aggressively and often present with paraneoplastic syndromes that manifest as inappropriate antidiuretic hormone, hypercalcemia or watery diarrhea.

The gross features of small cell carcinomas are variable and nonspecific. Nothing distinguishes them from ordinary adenocarcinomas. They arise in the gut from the esophagus to the rectum. The tumors tend to be deeply infiltrative. Metastases affect the lymph nodes, liver, peritoneum and lungs.

Histologically, small cell carcinomas in all gastrointestinal sites resemble small cell carcinomas of the lung. This highly malignant epithelial neoplasm consists of cells that by ordinary histological examination appear undifferentiated. The use of special techniques allows one to show the features in neuroendocrine differentiation. Squamous

or glandular differentiation may also be present. The tumor contains sheets of densely packed dark, small, oval, spindle or fusiform shaped anaplastic cells with a dark, hyperchromatic nuclei and dispersed stippled chromatin. The nuclei are approximately twice the diameter of mature lymphocytes. Focal necrosis and high mitotic rates are common. The cell size may also be intermediate or large. These patterns recapitulate the small, intermediate and large cell variance of pulmonary small cell carcinomas. The tumors may also contain large mononucleated and multinucleated tumor cells with angulated, intensely hyperchromatic nuclei. Neuroendocrine-like trabecular rosettes may also be seen. The mitotic rate is high, ranging from 10 to 90 mitoses per ten high-power field. Vascular invasion is seen in the majority of cases. Cytokeratin stains may show punctate perinuclear cytoplasmic reactivity. Immunostaining with antibodies to chromogranin are often disappointing, but synaptophysin staining is strongly positive.

The overall survival is usually <2 years following the diagnosis because approximately 75% of affected patients with metastatic disease at the time of diagnosis. These aggressive tumors have a propensity for invasion and early metastasis to the regional lymph nodes. Even after aggressive treatment, patients die between two and twelve months after diagnosis. There is a significant difference in survival between patients with limited stage disease (defined as tumor-confined to the bowel wall) and those with more extensive disease.

#### OTHER TYPES OF NEUROENDOCRINE TUMORS

**Large cell endocrine carcinoma** is a malignant neoplasm consisting of large cells with an organoid nesting trabecular rosette-like and palisading pattern that suggests endocrine differentiation. The endocrine differentiation can be confirmed by immunohistochemical or ultrastructural examination. In contrast to small cell carcinomas, the cytoplasm is much more abundant, the nuclei are more vesicular and nucleoli are present. These lesions are rare.

**Mixed exocrine/endocrine tumors** are those tumors in which neoplastic endocrine cells constitute >30% of the entire tumor cell population. These lesions generally are classified as adenocarcinomas with focal neuroendocrine differentiation rather than as neuroendocrine tumors.

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## **PRE-INVASIVE DUCTAL NEOPLASIA OF THE PANCREAS**

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The most important developments in pancreatic tumor pathology in the past few years have taken place in the area of preinvasive ductal neoplasia. In the ensuing text, an overview of these neoplasia is provided.

### **Pancreatic Intraepithelial Neoplasia (PanIN)**

It has been speculated for more than half a century that the development of invasive ductal carcinoma from normal pancreatic ducts is preceded by an intraductal neoplastic transformation in the ducts. These intraductal proliferative changes have been referred to by various names including hyperplasia, atypical hyperplasia, dysplasia among others.

In 1999, a group of pathologists were brought together by the NCI in Park City, Utah, in a think-tank meeting, to discuss precancerous ductal lesions. At this meeting, pancreatic intraepithelial neoplasm (abbreviated as PanIN) was adopted as the name for these lesions, and these lesions were proposed to be divided into four grades. The criteria were published in *Am J Surg Pathol* 25(5): 579-86, 2001<sup>1</sup>.

#### *PanIN- Criteria and grading<sup>1</sup>*

Those intraductal lesions composed of tall columnar cells without any atypia or papilla formation (previously called mucinous hypertrophy) were included into the neoplastic category as PanIN-1A/ mucinous duct lesion, because they often harbor some of the earlier molecular alterations attributed to carcinogenesis. Those that have minimal/no atypia but show early mucosal foldings are graded as 1B. Lesions with substantial pseudostratification of the cells and some degree of cytologic atypia are graded as 2. When there is irregular papillary architecture, with tufting, cytologic atypia, necrosis, mitoses and loss of polarity of cells, it is regarded as PanIN-3 (CIS).

PanINs show molecular alterations associated with neoplastic transformation<sup>10</sup>. In fact, this was the main reason why mucinous duct lesions, which were previously termed as mucinous hypertrophy/metaplasia were included in the PanIN spectrum. There is a progressive accumulation of molecular alterations from PanIN1- to invasive carcinoma. Some alterations such as k-ras mutation are early events, whereas others such as p53 loss take place later in the spectrum.

Early PanINs are common incidental findings. The frequency of PanINs in different diagnostic groups (normal/non-neoplastic pancreata, secondary tumors, CP-chronic pancreatitis, and DA-ductal adenocarcinoma) in the Wayne State University database was documented in a recent publication by Andea et al, (*Mod Pathol*,

16(10), 996-1006, 2003)<sup>11</sup>. In that study, PanINs were identified even in normal pancreata (20%) but were significantly more common in patients with ductal adenocarcinoma (80%). However, higher grade PanINs, especially PanIN-3, were seldom seen in pancreata without invasive ductal adenocarcinoma, and most of the PanINs that were seen in pancreata without invasive ductal carcinoma were PanIN-1.

### **Association of PanINs with carcinoma**

There is evidence (some circumstantial) that support the association of PanINs with invasive carcinoma. As in other exocrine organs such as breast and prostate, it is expected that the precursor of invasive ductal carcinoma lie within the ducts. There are morphologic, molecular and genetic similarities between PanINs and invasive carcinomas. PanIN-3 is more commonly seen with invasive cancer. There are some patients with PanIN-3 who developed invasive carcinoma during follow up.

### **Reporting of PanINs in surgical pathology**

It should be understood and conveyed to the clinicians that, the word neoplasm has been applied to PanINs to reflect the clonal nature of these lesions and that they express cancer associated genes. That is not to say that they require clinical treatment. In fact, PanINs 1 and 2 are common incidental findings<sup>11</sup> and generally not reported. PanIN 3, on the other hand, is strongly suspected to be a significant process (that may require therapy); however, there is not enough evidence to prove this point yet.

### **Mass Forming Pre-Invasive Neoplasia**

In addition to the PanINs, which are microscopic, incidental forms of dysplasia, there is another group of *pre-invasive* neoplasia that typically forms clinically detectable masses<sup>12</sup>. In contrast with the microscopic/incidental nature of PanINs, these mass-forming preinvasive neoplasia are characterized by either large papillary tumors that are non-invasive or cystic masses. Intraductal papillary mucinous neoplasms, intraductal oncocytic papillary mucinous neoplasms and mucinous cystic neoplasms are the tumor types that can be placed in this category of mass-forming pre-invasive neoplasia.

### **Intraductal papillary mucinous neoplasms (IPMN)<sup>13-16</sup>**

The most important category of mass-forming preinvasive neoplasia is intraductal papillary mucinous neoplasms (IPMNs). IPMN as an entity was first recognized by Ohashi et al. in their report of four cases of mucin-producing tumor of the pancreas.

In the 80's and early 90's, these tumors were reported under various names that can be placed into three broad categories: 1. Because of the exuberant papilla formation in some cases, the terms *papillary/villous adenoma/neoplasm/carcinoma* have been used in some series. Some authors have referred to IPMNs as mucin producing tumors, because the neoplastic cells are mucinous and secrete abundant mucin into the lumen of the cystically dilated ducts. Because these tumors are

*intraductal* and communicate with the main ducts, the mucin produced exudes from the ampulla of Vater, a characteristic endoscopic finding that has led to the name “*mucin producing tumor*”. In some examples of IPMNs, the ductal dilatation is very prominent, leading to multilocular cyst formation, resembling mucinous cystic neoplasms, hence the name *ductectatic variant of mucinous cystic tumor, or mucinous duct ectasia*.

There is a spectrum of cyst and papilla formation in IPMNs. In some cases, the pancreatic duct becomes tortuous and shows irregular dilatation. In other examples of IPMNs the ducts are filled with tan friable papillary nodules, with no significant “cyst” formation.

There is a spectrum of cytoarchitectural atypia in IPMNs ranging from adenoma to CIS. Foci with simple columnar cells, abundant apical mucin and well-polarized nuclei without any cytologic or architectural atypia are regarded as adenoma. Those that have substantial disorganization, loss of polarity, nuclear enlargement and pleomorphism are classified as CIS. There is a spectrum of changes in between that is regarded as borderline.

#### Different patterns of papillae in IPMNs

There are different patterns of papillae in IPMNs. Most look like villous adenomas of the colon, with pseudostratified columnar cells. We refer to this as the intestinal pattern, which typically expresses intestinal differentiation markers MUC2 and CDX2. In some, papillae are more complex and lined by cuboidal cells reminiscent of biliary papillomatosis, thus we refer to as pancreatobiliary. Other papillae resemble gastric foveolar epithelium.

IPMNs are associated with invasive carcinoma in 30% of the cases. Two types of invasive carcinoma are seen in IPMNs. The tubular type is morphologically identical to conventional ductal adenocarcinoma, and the colloid type is characterized by mucin lakes that contain scanty, detached carcinoma cells. The 5-yr survival rate of resected conventional ductal adenocarcinoma is less than <10%; whereas, that of colloid carcinoma (with or without IPMN) is >55%<sup>4</sup>.

MUC1 and MUC2 expression profiles of tubular and colloid carcinomas are the mirror image of each other<sup>12</sup>. The vast majority of tubular carcinomas expresses MUC1 and lack MUC2; however, all colloid carcinomas are positive for MUC2 and negative for MUC1.

Emerging evidence<sup>12</sup> suggests that there is a dichotomy in pancreatic ductal carcinogenesis: MUC1 is the marker of the pancreatobiliary pathway (PanINs and pancreatobiliary pattern of IPMNs) that leads to conventional ductal adenocarcinoma, whereas MUC2/CDX2 is of the intestinal pathway which is associated with the colloid type of invasive carcinoma and indolent behavior.

#### **Clinical significance and prognosis of IPMNs**

The factors that make IPMNs a clinically significant category are the following. IPMNs form relatively large tumors (mean size= 4.5 cm) in the pancreas, and produce various symptoms and signs including functional compromise of the organ. Of note, a third of the patients with IPMNs have other malignancies (in other organs). It is not known whether this is coincidental since these patients are older (mean age=68) or

whether IPMNs are a part of senescence-related propensity for tumorigenesis. More importantly, in >30% of the cases, IPMNs are associated with an invasive component. Although the “overall” 5-yr survival of IPMNs is 70% (incomparably better than that of ordinary ductal adenocarcinoma which is <10%), this statistic includes all adenomas, CIS and invasive carcinomas. In general, those with adenoma have very good prognosis, but those with invasive carcinoma may have an aggressive clinical course.

Some histologically non-malignant examples of IPMNs (without any in-situ or invasive carcinoma) followed an aggressive clinical course<sup>16</sup>. This has led to the speculation that the IPMNs are unpredictable. Other potential reasons for this discordance include multifocal nature of these tumors and focality of carcinoma, which can be missed both surgically and grossly. In addition, some cases of IPMNs were associated with invasive carcinoma elsewhere in the organ, away from the IPMN, suggesting that IPMNs may also be markers of invasive carcinoma in addition to precursors.

Another peculiar observation about IPMNs is that even tubular-type invasive carcinomas arising from IPMNs may at times follow a more protracted clinical course<sup>16</sup>. Two reasons may explain this. One is that IPMN leads to the early diagnosis of invasive carcinoma, at a stage that is relatively more curable. And two, invasive tubular carcinomas arising from IPMNs may be biologically different despite the fact that they are morphologically indistinguishable from conventional ductal (tubular) carcinomas.

Clinically, IPMNs are also classified as “branch” vs “main” duct types. This classification is mostly based on the imaging findings of the tumors. It is, however, important to recognize the relevance of this classification, because in most institutions, branch-duct type IPMNs are managed conservatively (sometimes even “wait” and “watch” approach) as long as they are small (<3cm) and don’t show any mural nodules. These branch duct IPMNs often prove histologically to be adenomas with gastric/foveolar pattern and lack papilla formation. Although this classification is mostly for pre-operative evaluation of IPMNs, and is often no longer meaningful once the tumor is resected and evaluated pathologically, it is nevertheless important for pathologists to make a note of the extent of main duct involvement, which would serve as a feedback to the clinicians.

### **Intraductal oncocytic papillary neoplasms<sup>2</sup>**

Intraductal oncocytic papillary neoplasm is another group that can be considered under the heading of mass forming pre-invasive neoplasia of the pancreas. As are IPMNs, intraductal oncocytic papillary neoplasms are intraductal tumors that lead to cystic dilatation of the ducts. Arborizing papilla formation is characteristic of intraductal oncocytic papillary neoplasms, although the complexity may vary from case to case or from area to area in a given case. In addition to the complexity of the papillae, intraepithelial lumen formation is also typical. Most characteristic finding, however, is the oncocytic nature of the cells.

Electron microscopy of intraductal oncocytic papillary neoplasms reveals the abundance of mitochondria. It has not been yet been determined whether these tumors should be regarded as a separate category or as a variant of IPMNs. Preliminary evidence suggests that their molecular characteristics are different than that of IPMNs. It is possible that, as in other organs such as the kidney where oncocytomas are biologically very different than histologically similar tumors, whatever is leading these cells to accumulate mitochondria may also give different biologic properties to these neoplasms.

### **Mucinous cystic neoplasms (MCNs)** <sup>17-20</sup>

The third category of mass forming preinvasive neoplasia is mucinous cystic neoplasms. Macroscopically, mucinous cystic neoplasms are characterized by a multilocular thick-walled cyst in the tail of the pancreas, adjacent to the spleen. In some cases, the cyst also contain papillary nodules. MCNs may sometimes get infected, develop purulent contents and may mimic pseudocysts. They are typically seen in perimenopausal females (mean age= 50 and >90% are females. The vast majority occurs in the tail of the pancreas. The cysts do not communicate with the ductal system and are therefore regarded as de-novo cysts. Presence of a distinctive ovarian-like stroma has become almost a requirement for the diagnosis of these tumors. It is pathognomonic for mucinous cystic neoplasms; present in most cases but not seen in other tumor types. Interestingly, it commonly expresses progesterone receptors. Rarely, even luteal-type cells may be seen in this ovarian-type stroma. We suspect that the ovarian stroma seen in MCNs may be a recapitulation of the periductal fetal mesenchyme which similarly condenses around the ducts of pancreas and liver in the developing fetuses <sup>21</sup>. As in IPMNs, there is a spectrum of cytoarchitectural atypia in MCNs, ranging from adenoma to CIS. Many times, an abrupt transition from one to the other may be seen, as in this example.

The grading and sub-classification of MCNs into adenoma, borderline and carcinoma have been an ongoing debate, which was resolved in the past few years. The groups from the AFIP, first in 1979 <sup>19</sup> and later in 1999 <sup>18</sup> have maintained that the grading of MCNs is not possible, and that these tumors are all low-grade malignancies, i.e mucinous cystadenocarcinoma, regardless of the degree of atypia or presence of invasion. In other words, in their experience, even the cases without any atypia could behave aggressively, and those with overt malignant features could follow an indolent course.

In 1999, however, groups from Johns Hopkins <sup>20</sup> and Europe (a multiinstitutional study) <sup>17</sup> contested this impression. They documented that grading accurately predicts the clinical outcome, and that adenomas behave in a benign fashion in most instances. In our opinion, this discrepancy is related to sampling phenomenon. Carcinoma can be very focal in these tumors and may easily be missed unless the tumor is sampled extensively and examined thoroughly. This may explain why the AFIP experience, which is mostly based on consultation material, has failed to identify the relevance of grade. It is also our personal experience that the grade accurately predicts the

outcome in most cases. Adenomas are invariably benign. However, we have seen MCNs with prominent papillary in-situ carcinomas that behaved in an aggressive fashion, despite the lack of any identifiable invasive carcinoma. Therefore, we ask for caution in cases with CIS.

**Summary of common findings in mass-forming pre-invasive neoplasia (IPMN, IOPN and MCN):**

IPMNs, IOPNs and MCNs share several characteristics. They are all *ductal* tumors. In the case of IPMNs and IOPNs it seems that the native ducts are involved by the process, whereas in MCNs, the process presumably forms de-novo cysts. In all, mucinous cells proliferate within these ductal units and secrete *mucin* to the lumen, which leads to *cystic* dilatation of these units, and in the case of IPMN (because the tumor is growing in the ductal system, and is usually located in the head of the organ) exudes from the ampulla of Vater. MCNs, on the other hand, may become infected, possibly because they do not communicate with the ducts and their contents are not drained. In all of these entities, proliferating mucinous cells may form *papillary* structures, and often the degree of cytologic atypia parallels the degree of proliferation. Presumably with accumulating genetic alterations, the proliferation acquires the capacity to *invade* and disseminate.

**Summary of differential diagnosis of mass-forming pre-invasive neoplasia (IPMN, IOPN and MCN):**

MCNs are seen almost exclusively in perimenopausal females (mean age, 50; >90% are females). They occur in the tail of the pancreas and do not communicate with the ductal system. Ovarian-type stroma is pathognomonic. IPMNs are seen predominantly in elderly patients and in the head of the pancreas. Mucin extrusion from ampulla of Vater is pathognomonic. They are intraductal tumors. IOPNs are characterized by their complex/arborizing papillae, intraepithelial luminae and oncocytic cells.

**Conclusion:**

Pre-invasive ductal neoplasia of the pancreas is an important category both clinically, in laboratory medicine as well as for cancer researchers. Our understanding of these tumors is still evolving. It is possible that these tumors will be instrumental in solving the puzzles of pancreatic carcinogenesis and bring us closer to the ultimate goal of preventing and curing these tumors.

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## Colonic Mimics of Inflammatory Bowel Diseases

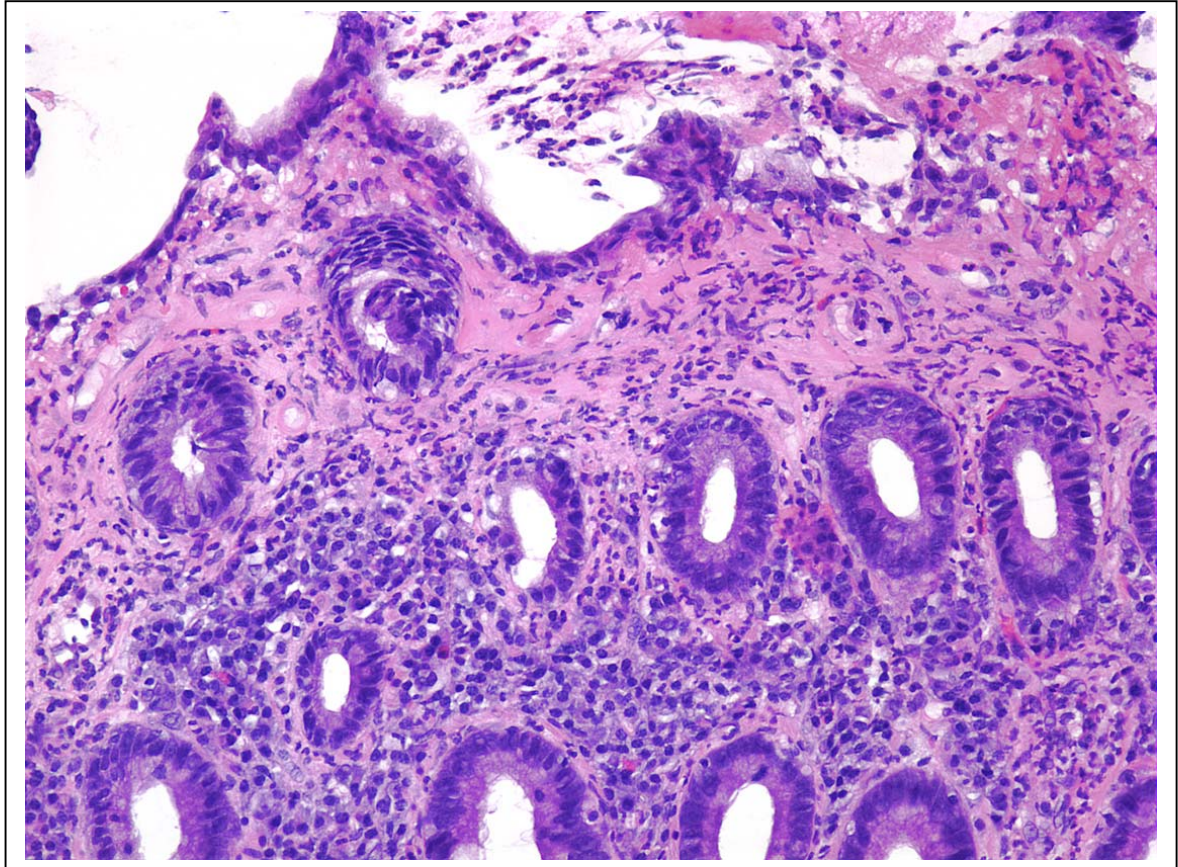
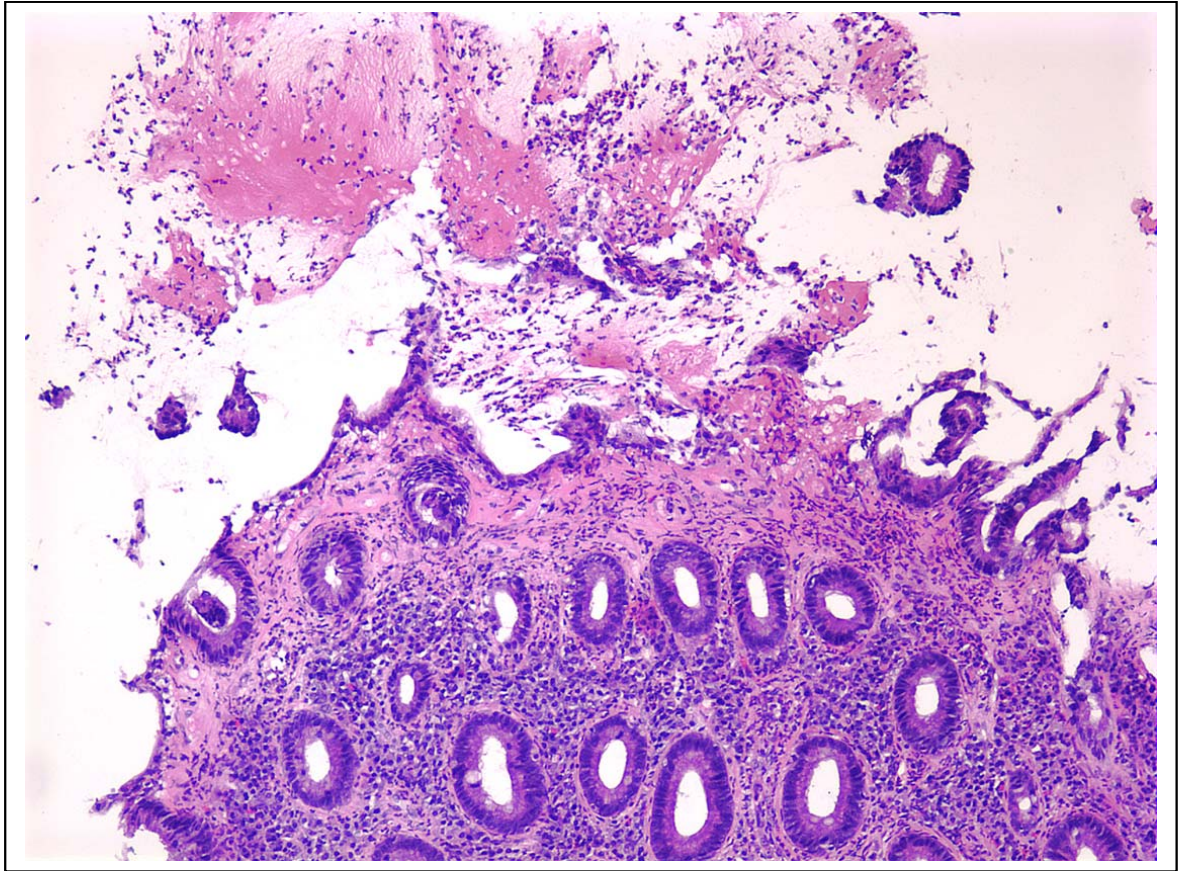
**Susan C. Abraham, M.D**

**Case Illustration: Collagenous colitis, a potential mimic of ulcerative colitis and infectious colitis**

**This 69-year-old woman complained of having up to 20 watery bowel movements per day, associated with urgency, fecal incontinence, and significant (35 pounds) weight loss. She also complained of crampy abdominal pain and had noticed some blood (both dark and bright red) in her stools, occurring about twice a week.**

**Colonoscopy was performed and showed mild edema on the right side. The transverse and left colon showed more significant edema, areas of friability, and tenacious yellowish “mucus” throughout the entire left side. There were no ulcerations.**

Stool cultures were negative. Stool toxin assay for *C. difficile* was positive.



Pseudomembranous collagenous colitis (associated with *C. difficile*)

Pathologic features of lymphocytic colitis and collagenous colitis:

The term "microscopic colitis" is frequently used by gastroenterologists to describe patients who have chronic watery diarrhea, normal or near-normal endoscopic findings, and a spectrum of histologic abnormalities that includes increased numbers of intraepithelial lymphocytes. We do not use the term "microscopic colitis" as a pathologic diagnosis. Instead, these cases are categorized as either lymphocytic colitis or collagenous colitis.

Both lymphocytic colitis and collagenous colitis share several common histologic abnormalities:

- 1) Chief among these is an increased number of lymphocytes in the colonic epithelium. The normal colonic epithelium contains only approximately 5 lymphocytes per 100 epithelial cells. In both lymphocytic and collagenous colitis, this number is increased (definitionally, *increased* is considered to be >15-20 lymphocytes per 100 epithelial cells). These are CD3+, predominantly CD8+ T-cells. They are most noticeable, and are typically counted in, the surface epithelium; however, in most cases the lymphocytosis can also be appreciated in the cryptal epithelium. One important caveat in assessing the number of intraepithelial lymphocytes is not to count over a lymphoid follicle.
- 2) In both lymphocytic and collagenous colitis, there is increased cellularity of the lamina propria which is due to increased lymphoplasmacytic inflammation in the superficial lamina propria.
- 3) Typically, the surface epithelium is "injured" -- that is, flattened and disorganized-appearing.

How do lymphocytic and collagenous colitis differ histologically? In lymphocytic colitis, the basement membrane and subepithelial collagen layer are normal. In collagenous colitis, the basement membrane itself is normal, but the subepithelial collagen layer is thickened and abnormal. Normally, this layer is only 5-6 microns; in collagenous colitis it is usually >12-15 microns. This increase is due to deposition of mature type I and type III collagen. However, we do not use the absolute thickness as the sole diagnostic feature for collagenous colitis. This is because: 1) In tangentially embedded biopsies, the collagen layer can appear thicker than it actually is. 2) Swelling of the true basement membrane, as not infrequently occurs in biopsies from the distal colon, will show a thick layer beneath the surface epithelium; however, this thickened layer is basement membrane material rather than subepithelial collagen, and it differs from true subepithelial collagen thickening in that it is very sharply demarcated from the underlying lamina propria. 3) In early or patchy collagenous colitis, the absolute thickness of the subepithelial collagen layer may not exceed 12-15 microns, but it will show other more diagnostically important abnormalities. These consist of irregularity of the basal aspect so that the collagen seems to "drip down" into the lamina propria, and abnormal incorporation of capillaries and inflammatory cells into the collagen.

What is the proper biopsy technique to diagnose lymphocytic or collagenous colitis?

This issue arises when a patient presents with watery diarrhea symptoms and the clinician performs a limited colonoscopy with only rectosigmoid biopsies. If these biopsies are “normal,” the possibility of collagenous colitis has not been ruled out and pancolonoscopy with multiple biopsies may be needed. In a series from the Mayo Clinic, Carpenter *et al* reviewed biopsies throughout the GI tract in 14 patients with collagenous colitis. They found that rectosigmoid biopsies are often normal in collagenous colitis and therefore underestimate that diagnosis. In 40% of their patients, proctosigmoidoscopic examinations alone would have missed the diagnosis of collagenous colitis. Tanaka *et al* examined the utility of left sided biopsies in collagenous colitis. They first examined the colonic geographic distribution of collagenous colitis in order to assess the utility of flexible sigmoidoscopy. They found that rectal biopsies showed no increase in collagen layer in 73% of patients with documented collagenous colitis. In approximately one-third of cases in which rectal biopsies showed no increased collagen layer, there was as well a lack of increased chronic inflammation. On the other hand, flexible sigmoidoscopy with multiple left sided biopsies did show at least increased chronic inflammation in 70% of cases. Thus, a patient presenting with watery diarrhea due to collagenous colitis is very likely to have a rectosigmoid biopsy showing normal crypt architecture with increased chronic inflammation. Pancolonoscopy with multiple right sided biopsies should then prove diagnostic. Additionally, Tanaka *et al* found the collagen layer to be patchy and not continuous; thus, multiple biopsies may be needed to detect this change. We have also observed a trend toward decreasing numbers of intraepithelial lymphocytes in distal colorectal biopsies in patients with lymphocytic colitis, but this is usually not as pronounced as in collagenous colitis.

What are the differences between lymphocytic colitis and collagenous colitis? Both lymphocytic and collagenous colitis have virtually indistinguishable clinical presentations. The typical patient is a middle-aged to older female who has had prolonged, watery diarrhea. Stool cultures are usually negative. The watery stools do not dramatically decrease with fasting and are not bloody; thus, patients are classified as having a secretory diarrhea. The collagen layer itself is not thought to play a prominent mechanistic role in the diarrhea; the severity of diarrhea has been shown to be proportional to the degree of chronic inflammation and not the thickness of the collagen layer. The diarrhea is secretory and electrophysiologic studies have shown active anion secretion (chloride) with sodium following passively (Rask-Madsen *et al*, 1983). The role prostaglandins play is unclear. Patients may present with vague abdominal pain and a weight loss of 10-15 lbs. Prior to the description of lymphocytic and collagenous colitis, these patients were frequently classified as having a psychosomatic illness or irritable bowel syndrome.

It is not clear whether lymphocytic and collagenous colitis are manifestations of a single disease or whether they are distinct but overlapping syndromes. In a 1999 article in *Gut*, Baert *et al* reviewed 96 patients with collagenous colitis and 80 patients with lymphocytic colitis. The average age at diagnosis was ~64 years for both groups. Patients with collagenous colitis were much more likely to be women (M:F ratio of 27:73) whereas there was a more even sex distribution in lymphocytic colitis (M:F ratio of 45:55). Patients with collagenous colitis were more likely to be

active smokers (25% vs. 14%). The overall prognosis of disease was good in both groups, although patients with lymphocytic colitis tended to have somewhat milder symptoms and were slightly more likely to report resolution or significant improvement in their symptoms (84%) than were patients with collagenous colitis (74%). They concluded, as have others, that lymphocytic and collagenous colitis are similar but not identical diseases.

Associations/etiologies for lymphocytic and collagenous colitis:

- **Drugs/medications, including NSAIDs, ticlopidine, lansoprazole, flutamide, and herbal preparations.** Wang *et al* found that 20/40 (50%) of patients with lymphocytic colitis were using NSAIDs at the time of their colonic biopsies. In a 1997 review, Goff *et al* found that 22/31 (71%) of patients with collagenous colitis were using NSAIDs regularly at the time of diagnosis, and in 3 patients resolution of symptoms occurred with discontinuation of the NSAIDs. Yagi *et al* (2001) demonstrated clinical and histologic resolution of collagenous colitis in a 77-year-old woman. Riddell *et al* (1992) showed that long-term NSAID use was significantly more common in patients with collagenous colitis (19 of 31 patients) than in a matched control group of patients with irritable bowel syndrome or diverticular disease (only 4 of 31 controls), and that in 3 patients the diarrhea improved after withdrawal of NSAIDs. In the study of 176 patients cited above by Baert *et al*, the authors identified cases of lymphocytic or collagenous colitis that were temporally related to ticlopidine (6 cases), flutamide (4 patients), and herbal medications (2 patients), all of which resolved without other therapy on discontinuation of the drugs.
- **Celiac disease.** Lymphocytic colitis is a frequent finding in patients with celiac disease, with estimates ranging from 11% to 31% of celiac patients. In Wang's study of lymphocytic colitis/colonic lymphocytosis patients, 16 patients had small bowel biopsies for review and celiac sprue-like changes were seen in 3/16 (19%). Matteoni *et al* (*J Clin Gastroenterol* 2001) identified celiac-like changes in small bowel biopsies from 4 of 27 patients with lymphocytic colitis (15%), but not in any of the patients with collagenous colitis (0 of 19, 0%). Gillett and Freman (*Can J Gastroenterol* 2000) studied the prevalence of celiac disease in patients with lymphocytic and collagenous colitis using IgA anti-endomysial antibody titers and IgA against tissue transglutaminase (tTG). They found that 4 of 15 (27%) patients with lymphocytic colitis had either new (1 patient) or previously diagnosed (3 patients) celiac disease, whereas none of 8 (0%) patients with collagenous colitis had serologic evidence of celiac disease. However, isolated reports of patients with both collagenous colitis and celiac disease do exist (e.g., O'Mahony *et al* 1990, Hamilton *et al* 1986, Breen *et al* 1987).
- **Crohn's disease.** Goldstein and Gyorfi (*Am J Surg Pathol* 1999) described 5 patients with Crohn's disease whose colonic biopsies showed changes resembling either lymphocytic colitis (4 patients) or collagenous colitis (1 patient). However, in 4 of 5 cases these changes were focal only, and in 3 cases separate biopsies from either the terminal ileum or elsewhere in the

colon showed more typical changes of Crohn's disease. We therefore believe that it is a rare event that cases appearing histologically typical for lymphocytic or collagenous colitis later prove to have Crohn's disease. This distinction is important because patients with lymphocytic colitis and collagenous colitis are not at increased risk for epithelial dysplasia or adenocarcinoma and do not require routine colonoscopic surveillance, whereas patients with Crohn's disease or ulcerative colitis do.

“Pseudomembranous collagenous colitis”:

Recently, Yuan *et al* (*Am J Surg Pathol* 2003) reported 10 patients with collagenous colitis and pseudomembranes. In addition to pseudomembrane formation, there was mild neutrophilic cryptitis seen in 42% of the biopsies. In contrast to most patients with collagenous colitis, the endoscopic appearance of the colon was abnormal in 7 cases and included ulcers (5 cases), erythema (2 cases), and inflammation (1 case); in fact, 6 patients were endoscopically suspicious for Crohn's disease or ulcerative colitis. An etiology for the pseudomembrane formation was identified in only one of their 10 cases, a patient with *C. difficile* colitis. However, stool cultures for pathogenic organisms were performed in only 4 cases, *C. difficile* toxin assay in only 6 cases, and evaluation for *E. coli* O157:H7 in only 3 cases. None of the 10 patients had evidence for ischemia. Overall, the clinical outcome of the 10 patients in that study did not differ from typical collagenous colitis without pseudomembranes.

This study indicates that, although perhaps infrequently, *C. difficile* colitis can co-exist with collagenous colitis and it is important to recognize both processes histologically. Other cases reports support the occasional association between the two diseases. For example, Khan *et al* (*Dig Dis Sci* 2000) described an 89-year-old woman with collagenous colitis who had three episodes of pseudomembranous colitis related to *C. difficile* infection; each episode resolved with a course of vancomycin.

Cryptitis and crypt abscesses in collagenous colitis

Ayata *et al* (*Am J Surg Pathol* 2002) reported active inflammation to be a relatively common finding in collagenous colitis, present in 24 of 79 cases (30%) in their series. Four patients (5%) had crypt abscesses, and 2 (2.5%) had surface ulcers. One of the patients with active inflammation in that study was positive for *Salmonella* on stool culture. Cryptitis also correlated significantly with recent antibiotic use, but unfortunately none of the patients in that study had stool toxin assays performed to evaluate for *C. difficile*.

In a study reported in abstract form (*Mod Pathol* 2000), we reviewed the pathology reports from 266 cases of collagenous colitis at The Johns Hopkins Hospital between 1989 and 1999. 37 of 266 (14%) had severe active inflammation (mucosal erosion/ulcer or crypt abscesses), 91 of 266 (34%) had low-grade active inflammation (mild cryptitis or surface intraepithelial neutrophils), and 138 of 266 (52%) had inactive collagenous colitis. In a subset of patients, the endoscopic findings and clinicopathologic features were reviewed. Patients with severely active collagenous colitis were more likely to have abnormal endoscopic findings (14 of 16,

88%) than patients with low-grade active (8 of 27, 30%) or inactive (3 of 27, 11%) collagenous colitis. They were also more likely to have heme + stool (6 of 13, 46%). A superimposed etiology for the active inflammation was found in 4 of 17 patients with severely active collagenous colitis (including 1 patient with *Aeromonas* infection, 1 with *C. difficile* infection, 1 with colonic ischemia, and 1 with NSAID-induced colonic ulcer) and in 4 of 17 patients with low-grade active collagenous colitis (3 with recently treated *C. difficile* colitis and 1 with recently treated *C. jejuni*), but in none of 15 patients with inactive collagenous colitis.

Unless there is significant crypt architectural distortion or basal plasmacytosis to suggest ulcerative colitis, we diagnose such cases as collagenous colitis with a note indicating that the degree of active inflammation could reflect a superimposed infectious colitis or other inflammatory etiology, so that appropriate clinical work-up is initiated.

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