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TABLE OF CONTENTS

1. COMMON COLORECTAL ADENOMAS AND MALIGNANT POLYPS	2
2. COLORECTAL ADENOCARCINOMA including the serrated pathway to carcinoma	9
3. GASTROINTESTINAL POLYPOSIS SYNDROMES and other large bowel polyps	31
4. GASTROINTESTINAL STROMAL TUMORS IN A GLEEVEC WORLD	43
5. NEUROENDOCRINE PROLIFERATIONS OF THE GUT	52
6. EPITHELIAL TUMORS OF THE VERMIFORM APPENDIX	57
7. GASTROESOPHAGEAL REFLUX AND EOSINOPHILIC ESOPHAGITIS	66
8. BARRETT'S ESOPHAGUS	74

COMMON COLORECTAL ADENOMAS AND MALIGNANT POLYPS

An adenoma, defined as a benign neoplasm composed of epithelial cells exhibiting cytological dysplasia, is considered the precursor lesion of the vast majority of colorectal carcinomas (1-3). Dysplasia is characterized by decreased intraepithelial mucin, epithelial nuclear enlargement with hyperchromasia, nuclear stratification and an increased number of mitoses figures. Large bowel adenomas are highly prevalent in Western societies, and their frequency markedly increases after age 40, reaching a peak at age 70. Adenomas are usually asymptomatic but large ones may bleed.

Adenomas usually produce a raised endoscopically or grossly detectable abnormality, usually a protrusion or polyp which can often be further subclassified as sessile or pedunculated. Some adenomas appear flat; some may even cause mucosal depressions. Adenomas occur singly or can be multiple. Multiple (≥ 10) adenomas may indicate a genetic syndrome such as familial adenomatous polyposis, attenuated familial adenomatous polyposis, or MUTYH-associated polyposis syndrome (2). Most adenomas are small, measuring < 10 mm.

Adenomas should be classified histologically based upon the pattern of growth as tubular, villous or tubulovillous (1,2,4). Adenomas in which simple tubules make up more than 75% - 80% of the area are classified as tubular. Adenomas with greater than 75% - 80% of their area showing a villiform configuration are called villous adenomas; all others should be reported as tubulovillous adenomas (1,2).

Once discovered, adenomas are characteristically removed by endoscopy or surgery because they are an important precursor lesion to colorectal carcinoma. Therefore, it is not surprising that occasionally a resected polyp thought to be a benign adenoma may contain an area of carcinoma.

Nomenclature - Overview

The various nomenclatures applied to colorectal adenomas, dysplasia, and malignant polyps can be confusing. Unfortunately, there are no unified accepted guidelines (2,4-7). Most surgical pathologists still use variations of the 1989 WHO terminology (6). In this system, the terms dysplasia, adenocarcinoma in situ, intramucosal adenocarcinoma and invasive adenocarcinoma are accepted. Each has a precise meaning when applied to colorectal polyps, and appropriate patient care requires that the endoscopist, surgeon and surgical pathologist understand the significance of each of these terms.

All adenomas demonstrate at least low-grade epithelial dysplasia. Without dysplasia, an adenoma can not be recognized and distinguished from normal colonic mucosa. Low-grade dysplasia is characterized by a slight decrease in the amount of intracellular mucin, mild nuclear enlargement with hyperchromasia, some nuclear stratification, and an increased number of mitoses figures. Increasing degrees of dysplasia (low-grade to high-grade) show progressive loss of intracellular mucin, progressive increase in nuclear size with stratification and a loss of nuclear polarity. Adenocarcinoma in situ describes the next step in the dysplasia-carcinoma sequence. Here, the atypical glands assume a complex cribriform or back-to-back gland configuration, but the basement membrane remains intact. Some experts consider adenocarcinoma in situ as part of the spectrum of high-grade glandular dysplasia and report both under the same term (7). When carcinoma cells infiltrate into the lamina propria and/or muscularis mucosae only, terms such as high-grade glandular dysplasia and adenocarcinoma in situ are technically no longer applicable because both require an intact basement membrane. Therefore, the term intramucosal adenocarcinoma is more accurate (1,2,6). Finally, when carcinoma cells have invaded the submucosa (or beyond) the lesion is labeled invasive adenocarcinoma. Invasion is invariably associated with an infiltrative pattern to neoplastic glands associated with tumor desmoplasia. This tumor desmoplasia is extremely helpful in recognizing invasion (of at least the submucosa), especially in small biopsy specimens.

The nomenclature controversy principally centers on the observation that in the colon and rectum, infiltrating carcinoma cells do not become clinically significant (i.e., able to metastasize) until they have invaded the submucosa (1,7-9). Only polyps containing invasive adenocarcinoma require a decision for additional treatment on the part of the clinician. Adenoma, adenocarcinoma in situ and even intramucosal adenocarcinoma lack metastatic capability and are considered adequately treated by polypectomy alone (1,2,4,6,9). As a result, some pathologists advocate modification of the nomenclature to account for clinical behavior and promulgate use of the term high-grade glandular dysplasia to encompass high-grade dysplasia, adenocarcinoma in situ and even intramucosal adenocarcinoma (2,5). Although the 1989 WHO guidelines accepted and defined two (low-grade, high-grade) or three (mild, moderate, severe) grades of dysplasia, adenocarcinoma in situ and intramucosal adenocarcinoma, the authors recommended a similar behavior-based modification for intramucosal carcinoma stating "... intramucosal adenocarcinoma of the colon has not been shown to metastasize, and for this reason 'carcinoma in situ' is more appropriate." (6)

The 2000 version of the WHO classification added little clarification and introduced new and even more confusing terms (10). The authors state that the defining feature of colorectal adenocarcinoma is invasion through the muscularis mucosae into the submucosa. However, once defined, worrisome lesions not fulfilling this criterion become difficult to describe. For example, the 2000 WHO defines adenocarcinoma in situ and intramucosal adenocarcinoma as lesions with morphologic characteristics of "adenocarcinoma" confined to the epithelium or that "invade" the lamina propria alone and lack invasion through the muscularis mucosae. The WHO goes on to state that these lesions have virtually no risk of metastasis. According to the WHO, the term "... high-grade intraepithelial neoplasia is more appropriate than adenocarcinoma in situ and ... intramucosal neoplasia is more appropriate than intramucosal adenocarcinoma". In the 2000 version, the WHO believes that use of these terms will help avoid overtreatment (10).

The problems with this classification are many. The inaccurate use of the term "invasion" to describe lesions that are not by definition invasive carcinoma is confusing. The lesser lesion of high-grade intraepithelial neoplasia sounds worse than the term used to describe intramucosal adenocarcinoma (intramucosal neoplasia). Furthermore, all adenomas, strictly speaking, are intraepithelial neoplasia.

An effort to achieve consensus (largely between Eastern [Japanese] and Western pathologists) (11-14) resulted in the Vienna classification of gastrointestinal neoplasia (14), presented in Table 1.

TABLE 1
Vienna Classification of Gastrointestinal Neoplasia

<u>Category</u>	<u>Definition</u>
1	Negative for neoplasia/dysplasia
2	Indefinite for neoplasia/dysplasia
3	Non-invasive low-grade neoplasia (low-grade adenoma/dysplasia)
4	Non-invasive high-grade neoplasia <ul style="list-style-type: none"> - High-grade adenoma/dysplasia - Non-invasive carcinoma (CIS) - Suspicious for invasive carcinoma
5	Invasive neoplasia <ul style="list-style-type: none"> - Intramucosal carcinoma - Submucosal carcinoma or beyond

Problems with the Vienna system include: a) inaccurate use of the word invasion, b) category 4 “non-invasive” high-grade neoplasia including potentially dangerous lesions (e.g., suspicious for invasive adenocarcinoma) and c) Category 5 “invasive neoplasms” including intramucosal adenocarcinoma which is widely accepted to be clinically benign in the colon and rectum. It is unlikely that this numerical system without clinical correlation will ever gain widespread acceptance.

Nomenclature - A Pragmatic View

As modified from the 1989 WHO classification, low-grade dysplasia, high-grade dysplasia, adenocarcinoma in situ, and intramucosal adenocarcinoma exist and can be recognized by pathologists (1,6). In 2010, the WHO has returned to a similar nomenclature (2). This nomenclature remains attractive because it can be applied throughout the gastrointestinal tract. If one chooses to diagnose high-grade dysplasia, adenocarcinoma in situ, and intramucosal adenocarcinoma in colorectal biopsy specimens, specific mention in the report that these lesions lack metastatic potential is helpful to clinicians.

Since infiltrating carcinoma cells in a colorectal polyp do not become clinically significant (i.e., able to metastasize) until they have invaded the submucosa (1,8-10,15-42), only a polyp containing invasive adenocarcinoma (invasion of at least the submucosa) should be considered malignant. Only invasive adenocarcinoma requires a decision regarding additional treatment. Therefore, the presence or absence of invasive adenocarcinoma should be specifically mentioned in the pathology report. To comply with the American College of Gastroenterology, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American Cancer Society guidelines (4,26,43), a villous component (villous or tubulovillous adenoma) and high-grade dysplasia should be reported because these require more frequent surveillance. Carcinoma in situ and intramucosal adenocarcinoma can be reported parenthetically as high-grade dysplasia. Most mistakes that pathologists make in reporting colorectal adenomas, dysplasia, and malignant polyps occur in three major categories: 1) the pathology report is not clear (nonspecific or noncommittal terms are used, or the presence or absence of invasive adenocarcinoma is not clearly stated); 2) mispositioned glands (pseudocarcinomatous invasion) are misinterpreted as invasive adenocarcinoma; 3) the margin of excision is either not identified or not commented upon.

Malignant Polyps - Differential Diagnosis

A common problem concerns differentiating invasive carcinoma complicating a colorectal adenoma from pseudocarcinomatous invasion (pseudoinvasion). Pseudoinvasion describes a situation in which neoplastic glands of the adenoma are mispositioned, presumably by trauma, into or beneath the muscularis mucosae (1,44-52). Pseudoinvasion is relatively common, having been reported in 3% to 10% of resected colorectal polyps (44,46,47). Distinguishing this epithelial misplacement from invasive adenocarcinoma can be difficult. Some reported series of “malignant polyps” have included and even illustrated polyps with pseudoinvasion as examples of invasive adenocarcinoma associated with adenoma (45). Histological features favoring pseudoinvasion include: lack of an infiltrative pattern, lack of tumor desmoplasia, presence of lamina propria around mispositioned glands, lack of increased atypia in mispositioned epithelium as compared to the surface epithelium of the adenoma, and the presence of hemorrhage and/or hemosiderin deposits in nearby connective tissue.

Occasionally, the misplaced glands of pseudoinvasion can become cystic, can rupture and can be associated with dissection of mucus into the connective tissues of the polyp. Here the distinction between mucinous adenocarcinoma and misplaced glands can be extremely difficult (44-53). Table 2 illustrates histological features that can aid in this differential. Remember that examination of additional sections can help in difficult cases because almost all mucinous adenocarcinomas contain at least small foci of typical nonmucinous-type adenocarcinoma.

TABLE 2
DIFFERENTIAL FEATURES BETWEEN DISSECTING MUCUS OF
PSEUDOCARCINOMATOUS INVASION & INVASIVE MUCINOUS ADENOCARCINOMA

<u>Feature</u>	<u>Pseudoinvasion</u>	<u>Invasive Mucinous Adenocarcinoma</u>
Shape of mucous pools	Rounded	Irregular, infiltrating
Location of epithelium	Periphery of pool	Floating in pool
Configuration of epithelium	Single often discontinuous layer, basal polarity of nuclei	Cellular piling up, complex glandular proliferation, gland in gland configuration
Cytologic features	Dysplasia similar to surface adenoma	Atypia pronounced
Tumor desmoplasia	Absent	Usually present
Hemorrhage and hemosiderin deposition	Usually present	Usually absent
Supporting lamina propria	Sometimes present	Absent

Malignant Polyps – Patient Management

A rational decision concerning management of a patient with an endoscopically removed malignant colorectal polyp (one containing invasive adenocarcinoma) requires weighing the chances of finding residual or metastatic cancer with a follow-up surgical excision (whom do I help?) against the risk of surgical mortality and morbidity (whom do I hurt?). Some have advocated surgical resection for all patients (54). Currently, however, almost all surgeons and gastroenterologists embrace a more conservative approach using a number of gross and/or histological features as “indications” for follow-up colectomy (1,52). These include sessile growth (9,15), residual villous adenoma, a short stalk (less than 3 mm) (16), stalk invasion (17), level 4 invasion (9,15), lymphatic or vascular permeation (38), lack of a residual adjacent adenoma (so-called polypoid carcinoma), poor differentiation (18,19,36,37) and invasive carcinoma at or near a margin of resection (18,19,36).

I and others (18,19,23,36) believe that two features identify patients likely to avoid an adverse outcome defined as residual or metastatic adenocarcinoma in a subsequent colectomy specimen or during clinical follow-up. Patients with “favorable histology” (well or moderately differentiated adenocarcinoma with a 2 mm tumor-free margin of resection in the polypectomy specimen) experienced no adverse outcome and are considered as adequately treated by polypectomy alone. Similar, though not identical, therapeutic recommendations have been adopted by the American College of Gastroenterology (ACG) (21,22). These guidelines consider colonoscopic polypectomy definitive treatment for a patient with a malignant polyp if the following criteria are fulfilled: 1) the polyp is considered completely excised at endoscopy, 2) the specimen is properly processed by the pathology laboratory, 3) the cancer is not poorly differentiated, 4) there is no histologic evidence of vascular or lymphatic involvement, and 5) the resection margin is not involved by carcinoma.

Lymphatic and/or venous invasion, proposed as an indication for follow-up colectomy, remains controversial (9,16,20,28,29,33,38,54). Only a few malignant polyps with these features have been reported and almost all have had positive margins, contained poorly differentiated invasive carcinoma or both. We think that lymphatic/venous invasion is not a reliable criterion because the distinction from retraction artifact is frequently difficult. Cooper et al. encountered significant interobserver variation in assessing this feature (38). Furthermore, no guidelines exist that establish the extent to which a pathologist must go to diagnose lymphatic/venous invasion (e.g., number of sections or use of immunostains). Although patients can be stratified into high-risk and low-risk groups based on margin status and grade of invasive adenocarcinoma (36), lymphatic/venous invasion is used by the ACG (22), and, in deference to these guidelines, the presence or absence of angiolymphatic invasion should be reported.

As a guide for therapy, the major studies of endoscopic polypectomy for malignant polyps (15-42) have shown that the chance of finding residual or metastatic cancer in a subsequent colon resection specimen or during follow-up in the “favorable histology” group is less than 1%. Weighing this against the published operative mortality rates for colectomy, that range between 2% to 8% (32-34), it seems that subsequent major surgery should be avoided in the “favorable histology” subgroup (19,36).

If a decision for subsequent colorectal resection is made, a cancer operation is recommended rather than a more limited procedure because cancer was the indication for surgery. Residual carcinoma in a follow-up resection specimen can be expected in only 10% of cases. These cases of residual or metastatic carcinoma that are discovered within this subset of pT1 lesions are overrepresented by cases containing poorly differentiated carcinoma.

Common Adenomas and Malignant Polyps - Specimen Handling and Reporting

Evaluation of the resection line is critical to proper patient management; therefore, correct handling of the polypectomy specimen is of utmost importance (18,19,24,36). The entire polyp should be immediately placed into fixative. Following adequate fixation, polyps with a stalk should be trimmed on either side of the stalk as illustrated in Fig. 1. The section of the polyp with stalk and margin can be embedded in a block, maintaining the correct anatomic relationship. The remainder of the polyp should be submitted in separate blocks. For polyps without stalks (sessile growths or those in which the stalk has retracted), look for the effects of cautery on the gross specimen. This will appear as a lighter-colored area or defect on the external surface of the polyp. Carefully trim on either side of this defect (Fig. 2) and place this tissue in a block. Again the remaining tissue should be submitted in separate blocks. Routine examination of a minimum of three step-sections stained with hematoxylin and eosin from each block is recommended.

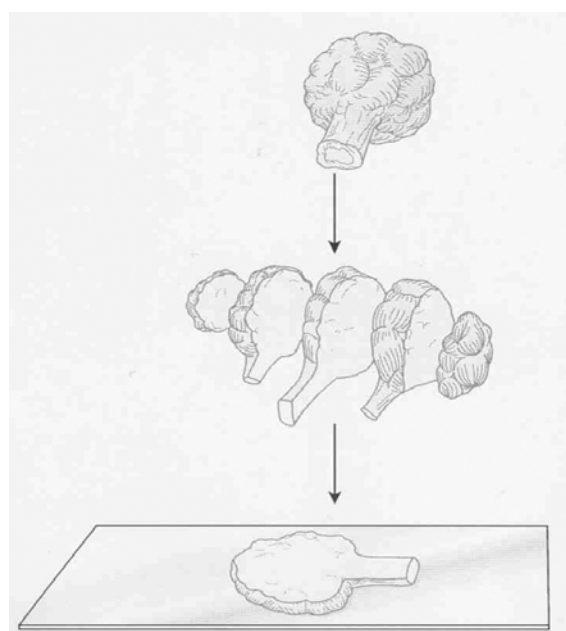


Fig. 1

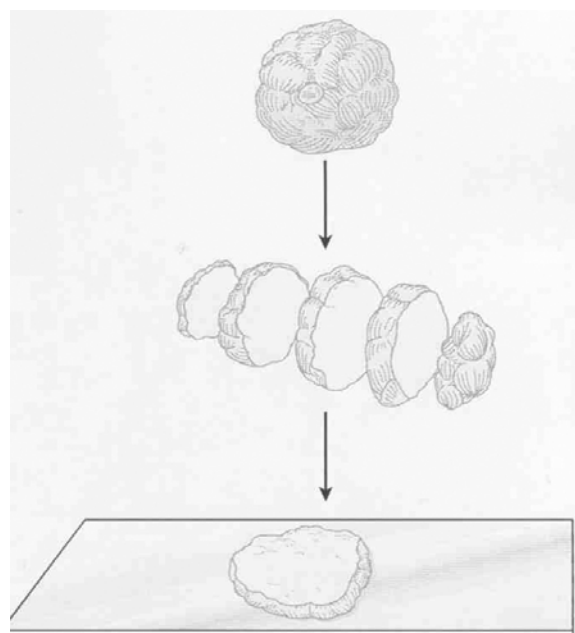


Fig. 2

In the pathology report, the presence or absence of invasive carcinoma must clearly be stated. With malignant polyps, the grade of carcinoma must be noted, the resection line must be identified and assessed and the status of that resection line must be clearly stated in the pathology report. A distance measurement of carcinoma free margin should be included in the report. In deference to the ACG, the presence or absence of angiolymphatic invasion should be investigated and reported (22).

The treating physician must individualize the decision for follow up colorectal excision by weighing the patient's wishes against the estimated cancer recurrence risk and the predicted operative morbidity and mortality (34). Advances in laparoscopic resection of the colon and rectum could drastically reduce the morbidity and mortality of operative resection which now constitutes the major contraindication for surgery. These new surgical techniques may require reassessment of the current management recommendations for malignant colorectal polyps (55).

COLORECTAL ADENOCARCINOMA

Genetic Considerations, Microsatellite Instability and Lynch Syndrome

Over 150,000 new cases of colorectal carcinoma occur in the United States each year accounting for approximately 52,000 deaths annually. The peak incidence occurs between ages 60 and 79; fewer than 20% of cancers occur in patients less than 50 years of age. Risk factors for carcinoma include diets rich in animal fat, sedentary lifestyle, and coexisting inflammatory bowel disease (2,55a).

There may be at least five separate but overlapping molecular pathways to colorectal cancer (3). Approximately 80% of colorectal carcinomas occur sporadically, whereas 20% appear to have an inherited genetic basis (1,56). This latter group includes the 3% of cases related to Lynch syndrome (Hereditary Nonpolyposis Colorectal Cancer [HNPCC] Syndrome) and the 1% associated with familial adenomatous polyposis (FAP) and its variants. The other 16% show strong familial clustering but a specific genetic cause has yet to be found.

Colorectal carcinoma can also be viewed another way. About 85% of colorectal cancers are thought to originate through the chromosomal instability pathway. These tumors typically demonstrate DNA aneuploidy, have abnormalities of chromosomes 5, 17, and 18, and contain mutational changes in the APC gene, K-ras proto-oncogene, DCC tumor suppressor gene and p53 tumor suppressor gene (57). Familial adenomatous polyposis colorectal carcinomas arise via this pathway. Approximately 15% of colorectal carcinoma appears to arise in the so-called “mutator phenotype”. These cancers tend to be DNA diploid and are associated with microsatellite instability. The Lynch syndrome cancers are associated with the “mutator phenotype”.

DNA integrity is essential for normal cell function. DNA insults can occur due to the direct effects of chemicals or radiation and are usually corrected through the excision repair system. DNA replication errors are of two types; 1) simple mispairing of nucleotides, the most common type, and 2) “slipping” errors, in which genes may contain too many or too few copies of repeat short DNA nucleotide sequences known as “microsatellites”. Normally, these errors are recognized, the cell cycle arrested and the mismatched segment corrected. For those errors not immediately corrected by DNA polymerase, the mismatch repair (MMR) system acts as a back-up for additional proofreading of DNA. Failure to repair mismatches allows the error (mutation) to persist and to become the template for subsequent DNA replication (58). The known mismatch repair genes and their relative frequency in Lynch syndrome are presented in Table 3.

TABLE 3

MISMATCH REPAIR GENES AND FREQUENCIES IN LYNCH SYNDROME

GENE	FREQUENCY	LOCATION
<i>hMLH1</i>	49%	3p21
<i>hMSH2</i>	45%	2p15
<i>hPMS2</i>	4%	7p22
<i>hPMS1</i>	1%	2p32
<i>hMSH6</i>	1%	2p15
<i>hMSH3</i>	0%	5q11-13

Microsatellite instability (MSI) is best viewed as an epiphenomenon found in colorectal tumor DNA but not in non-neoplastic tissues. It indicates that extensive mutation exists in the non-encoding repetitive DNA sequences that are particularly prone to replication error, the microsatellites. The majority of MSI is linked to somatic inactivation of *hMLH1* through hypermethylation inactivation of the promotor region, but it can also be detected in persons with germline mismatch repair gene mutations, the definition of Lynch syndrome (58). MSI is detected in 15% of colorectal cancers overall and is present in over 95% of the cancers found in patients with Lynch syndrome.

Lynch syndrome patients, because they have a germline mutation of a mismatch repair gene, are at increased lifetime risk for colorectal (up to 80%) and other cancers (56,59). These cancers develop at significantly younger ages (e.g., average age for colorectal carcinoma = 44 years) (59). Other Lynch syndrome related tumors include cancers of the endometrium, ovary, stomach, biliary tract, urinary tract, kidney, central nervous system, small bowel, and skin (59).

Lynch syndrome patients and families can sometimes be identified by taking a careful patient and family medical history, can be suggested from the pathologic findings of excised tumors, and can be detected by direct evaluation of the mismatch repair system. Pathologic features of colorectal cancer that suggest MSI/Lynch syndrome include right-sided location, synchronous or metachronous large bowel cancers, large bulky polypoid tumors with circumscribed pushing margins, tumors showing prominent lymphoid infiltrate, cancers of poor differentiation (medullary or undifferentiated carcinoma) or mucinous and signet ring cell histology (1,2,56,60).

The diagnosis of Lynch syndrome is evolving. Originally, the Amsterdam criteria were used to clinically identify HNPCC including the Lynch syndrome patients (61). The original Amsterdam criteria include: a) three or more relatives with a colorectal cancer with at least one a first-degree relative; b) colorectal carcinoma in two generations; and c) one or more colorectal carcinomas occurring in a person less than 50 years of age. In order to increase the sensitivity, the Amsterdam criteria were modified (Amsterdam II criteria) to include: a) three or more relatives with any Lynch syndrome related carcinoma; b) colorectal carcinoma in two generations; and c) and one or more Lynch syndrome related carcinomas in a person younger than 50 years of age (62). There are many problems with detecting Lynch syndrome based upon the Amsterdam criteria alone. Patient histories are less useful now than in the past because of smaller family sizes. Excision of colorectal adenomas interrupts the adenoma-carcinoma sequence. Patients in whom the family history is unknown or incomplete limit the utility of these criteria. Physician history taking is often not thorough. More importantly, depending upon the cohort, up to 33% of persons having a germline mutation of a mismatch repair gene are Amsterdam criteria negative and only 60% of Amsterdam criteria positive kindred have a detectable mutation (62-69). These Amsterdam positive/gene mutation negative kindred are often referred to as familial colorectal cancer syndrome type X. A subset of this group has been shown to have germline mutations in *EPCAM* which allows for incomplete methylation inactivation of *hMSH2* (70).

Special testing (MSI testing by polymerase chain reaction [PCR] or immunohistochemical stains) now augments the clinical criteria. Controversy over the use of MSI analysis has led to the development of the Bethesda guidelines for testing colorectal tumors for microsatellite instability. The latest iteration, the *revised Bethesda guidelines* (65) requires that just one of the following criteria be met: colorectal cancer before age 50, synchronous or metachronous colorectal or other Lynch-related tumor regardless of age, colorectal cancer with MSI-high pathology in a patient less than 60, person with colorectal cancer and a first-degree relative with colorectal carcinoma or other Lynch-related tumor (cancer less than 50), colorectal cancer with two or more relatives with colorectal or other Lynch-related tumor regardless of age.

The American Gastroenterological Association (AGA) position states that genetic testing should be performed on families meeting Amsterdam criteria, on any affected person meeting the modified Bethesda guidelines, and on any first-degree relative of those with known mutations of mismatch repair genes (56). They suggest that following pre-test genetic counseling and written informed consent, immunohistochemistry for MMR gene products and/or MSI testing by PCR be performed on tumor tissue. The international guidelines for evaluation of MSI by PCR recommend use of consensus markers; BAT25, BAT26, D5S346, D2S123, D17S250. If two or more markers are abnormal, the carcinoma is considered MSI-High (MSI-H). If one marker is abnormal, the tumor is classified as MSI-Low (MSI-L). If no markers are abnormal, the cancer is referred to as MSI-Stable (MSS). Laboratories using more than 5 loci modify this classification with $\geq 30\%$ - 40% abnormal defined as MSI-H, $< 30\%$ - 40% as MSI-L and none abnormal as MSS. Immunohistochemistry can be used to detect MSI. Almost all MSI-H cancers can be identified if the antibody panel includes MLH1, MSH2, PMS2 and MSH6 (Fig. 13,14) (66,69). Immunohistochemistry and MSI analysis by PCR each have advantages and limitations. PCR requires a molecular laboratory and usually requires normal tissue for comparison. Immunohistochemistry is more widely available but can be limited by poor tissue fixation or poor technique rendering interpretation difficult. Immunohistochemistry may be superior because the findings can direct gene sequencing and MSI is not always seen in Lynch syndrome kindred with MSH6 germline mutation (59). Patients with MSI-H cancer should undergo additional genetic testing including gene sequencing. MSS and MSI-L tumors require no further testing (56). Additional genetic evaluation may be considered if the clinical history is compelling.

The clinical significance of identifying Lynch syndrome is that affected individuals and at risk persons are identified and can be screened and treated with correct surgery. Subtotal colectomy is usually recommended to treat Lynch related colon cancer because of the high likelihood of synchronous/metachronous cancers. Partial colectomy with colonoscopy every 1-2 years is a reasonable alternative (59). Furthermore, clinicians can institute proper screening such as colonoscopy at a young age, (beginning at age 25 or 5 years younger than the youngest cancer in the family), periodic endometrial sampling (every 1-2 years starting at age 25), pelvic ultrasound, CA125 serum testing and urine cytology or molecular testing for urinary tract carcinoma. Many experts screen all resected colorectal cancers for MSI initially by PCR, immunohistochemistry, or both. Immunohistochemistry is a useful alternative and some prefer this as the initial test because an abnormality in protein expression correlates almost invariably with MSI-H by PCR. In cases showing normal MMR proteins or equivocal staining by immunohistochemistry, MSI testing by PCR should be done in clinically suspicious cases to exclude a germline mutation that can yield an antigenic protein that is biologically inactive.

MSI testing in sporadic colorectal carcinoma is a subject of considerable contemporary interest and debate. Much like their Lynch syndrome counterparts, sporadic MSI-H carcinomas have a predilection for the right colon, mucinous histology and a prominent lymphoid infiltrate (71). There are strong arguments for routine testing for MSI in all resected colorectal carcinoma including the lower mortality rate independent of tumor stage (69,72). Sporadic MSI-H cancer can also be associated with an increased rate of metachronous tumors with subsequent clinical implications for cancer surgery, surveillance and follow-up. MSI status may also have implications for chemotherapy. There is improved survival in MSS and MSI-L stage II and stage III cancers treated with fluorouracil-based regimens (2,73,74) and improved survival with MSI-H using irinotecan (2,75). Finally, routine MSI testing could increase the detection of Lynch syndrome because 44% of probands were over age 50 and up to 22% of patients in Lynch syndrome did not fulfill Amsterdam or Bethesda guidelines (69).

Colorectal Hyperplastic Polyps and Hyperplastic (Serrated) Polyposis Syndrome

Hyperplastic polyps are the most common benign polyp of the large intestine (1,76). These polyps are usually small (less than 5 mm), sessile and are often about the same color as the surrounding colonic mucosa. Histologically, evenly distributed absorptive and goblet cells line crypts that are elongate and dilated. Inhibition of normal apoptosis is thought to be the underlying mechanism for polyp formation, and, because there are more epithelial cells per unit area than normal, the cells must pseudostratify, imparting a serrated or micropapillary appearance. Characteristically, the basement membrane under the surface epithelium is thickened and hyalinized. Regenerative epithelial changes, mitoses figures and active inflammation can be quite prominent at the crypt bases. This regenerative area can occasionally cause diagnostic confusion with dysplasia and carcinoma, especially in a variant referred to as inverted hyperplastic polyp (77,78). In this inverted variety, the regenerative epithelium of the crypt base is misplaced into or beneath the muscularis mucosae. Most examples of inverted hyperplastic polyp are now probably best classified as a sessile serrated polyp (see below) and are easily recognized if one is cognizant of its existence and also notes the overall architectural and cytologic similarity to hyperplastic polyp/sessile serrated polyp. The entity is distinguished from invasive adenocarcinoma by the lack of infiltration and tumor desmoplasia.

The differential diagnosis between hyperplastic polyp and tubular adenoma can be difficult, especially in a diminutive polyp that has been treated by hot biopsy (so-called “Thermal Polyp”). Useful features in the differential are found in Table 4.

TABLE 4

HYPERPLASTIC POLYP VS. TUBULAR ADENOMA

<u>Feature</u>	<u>Hyperplastic Polyp</u>	<u>Tubular Adenoma</u>
Regenerative Zone	Basal	Surface
Dysplasia	No	Yes
Apoptosis	Usually No	Yes
Hyalinized basement membrane	Yes	No

In a “tight call”, as long as an adenoma diagnosis is not going to result in a surgical resection (e.g., right colonic adenoma incompletely excised), I err on the side of adenoma to insure that the patient will receive more frequent surveillance. Mixtures of hyperplastic polyp, sessile serrated polyp and adenoma occur (2,79,80). Mixed polyps and serrated adenomas are considered in more detail below.

Hyperplastic (Serrated) Polyposis Syndrome

Rare examples of patients with colons carpeted by hyperplastic-like polyps (so-called hyperplastic polyposis) have been described. The WHO defines hyperplastic (serrated) polyposis as individuals with: a) 5 or more serrated polyps proximal to the sigmoid colon of which 2 are ≥ 1 cm, b) any number of serrated polyps proximal to the sigmoid colon if the person has a first degree relative with serrated polyposis and c) more than 20 serrated polyps of any size distributed throughout the large bowel (2). The form with 20 or more small hyperplastic polyps without sessile serrated polyp morphology (see below) has been called type 2 and probably does not predispose to adenocarcinoma (81). The type 1 associated with large (> 1 cm) polyps with sessile serrated polyp morphology is associated with MSI-H cancers in which there is methylation-induced loss of expression of *hMLH1* (81,82). Indeed, hyperplastic polyposis may be a marker for the so-called “mutator phenotype”. Some patients with MUTYH-associated polyposis also fulfill criteria for serrated polyposis; therefore, some have suggested the existence of a third type of serrated polyposis syndrome for this subset that has serrated polyposis and (usually > 25) adenomas (82a). Colectomy specimens typically show a spectrum of serrated polyps with typical hyperplastic polyps, traditionally defined serrated adenomas (see below) and unusual hyperplastic polyps (sessile serrated polyps – see below). Serrated polyposis may be a better name for this syndrome. Hyperplastic polyposis patients are prone to colorectal carcinoma with a reported prevalence of up to 50%. Once diagnosed, careful consideration should be given to the clinical follow-up and prophylactic colectomy may be indicated (83). Some cases have shown evidence of inheritance presumably caused by a genetic predisposition to hypermethylation. The type and order of methylated genes varies and may account for MSS, MSI-L and MSI-H cancers described. When several cancers in hyperplastic polyposis syndrome families are MSI-H, the distinction from Lynch syndrome can be difficult. Features that favor hyperplastic polyposis include: background serrated adenomas and sessile serrated polyps, presence of some MSS or MSI-L cancers in the kindred, older age at onset of cancer, limited numbers of affected family members, methylation of *hMLH1* and failure to detect germline mutation of mismatch repair genes.

Serrated Polyps and Colorectal Adenocarcinoma

Several lines of evidence link “hyperplastic polyps” with colorectal carcinoma. Investigators have reported individual cases and small series of carcinoma complicating “hyperplastic polyps” (84-92). The association between colorectal cancer and hyperplastic polyposis has already been noted above. There is a high rate of co-existing hyperplastic polyps but not adenomas in patients with MSI-H carcinoma (84). A large series of MSI-H colorectal carcinoma predicated by biopsy proved “hyperplastic polyps” at the same site has been reported (89).

Molecular events involved in the serrated polyp family are now recognized. Methylation-induced inactivation of mismatch repair genes occurs in both hyperplastic polyps and carcinoma. As shown in Table 5, methylation inactivation of genes and certain gene mutations (especially BRAF) appear to be involved in the serrated pathway to carcinoma (93,94). These molecular events have been verified (95-100).

“Hyperplastic polyps” associated with carcinoma have been unusually large and right-sided. They have been reported under a number of synonyms including giant hyperplastic polyp, sessile serrated adenoma, sessile serrated polyp, inverted hyperplastic polyp, and polyp with epithelial serrated proliferation.

It is becoming clear that there are several different pathological entities that have been called “hyperplastic polyps” in the past. This serrated polyp family includes conventional hyperplastic polyp, mixed hyperplastic/sessile serrated polyp/adenoma, serrated adenoma (epithelial dysplasia defined, usually pedunculated and left sided, having eosinophilic cytoplasm and showing gastric foveolar change

and often referred to as the traditionally defined serrated adenoma) and hyperplastic-like polyps with unusual features that have been referred to as sessile serrated polyps or sessile serrated adenomas (2,79,87-90). Sessile serrated polyps appear related to serrated adenomas and mixed polyps and could be the specific precursor lesion to sporadic MSI-H carcinoma. Transitions from sessile serrated polyps to areas of dysplasia and carcinoma with loss of *hMLH1* protein expression have been described (91,92). Sessile serrated polyps as the name implies are sessile, large (frequently 1 cm or more), right-sided, and often show poor endoscopic circumscription. A number of cytological and architectural abnormalities have been reported in the sessile serrated polyp, especially those that have been associated with carcinoma (86,89,91,92). The abnormal proliferation/dysmaturation features include persisting nuclear atypia with large nuclei and nucleoli high (upper third) in the crypts, high (upper third of the crypt) mitoses figures and irregular distribution of dystrophic goblet cells. Architectural abnormalities include basal crypt dilatation, horizontally oriented crypts, crypt branching, an increased epithelial:stromal ratio (>50%), inverted crypts, prominent serration, increased surface villosity/papillations and the lack of a surface basement membrane thickening typical of conventional hyperplastic polyps. Some authors suggest that a diagnosis of sessile serrated polyp requires the presence of at least four of the architectural and abnormal proliferation features mentioned above (96).

TABLE 5

METHYLATION/MUTATIONS IN SERRATED POLYP FAMILY

	<u>HP (%)</u>	<u>SSP (%)</u>	<u>Mixed (%)</u>
MINT 1	23	30	100
MINT 2	32	70	100
MINT 31	23	70	100
<i>hMLH 1</i>	0	13	70
MGMT	36	57	60
KRAS (mutation)	18	13	0
BRAF (mutation)	19	75	89

HP = hyperplastic polyp; SSP = sessile serrated polyp; Mixed = mixed polyps and serrated adenomas.

Once recognized, the sessile serrated polyp creates a patient management dilemma. Calling them “sessile serrated adenomas” may not be an appropriate default diagnosis because it can be confused by the clinician for serrated adenoma. It is unknown whether colonic resection which is typically done for incompletely excised adenomas should be recommended for sessile serrated polyps which are incompletely excised at endoscopy. Furthermore, endoscopic follow-up for serrated adenoma would typically be at three-years (if the clinician considers serrated adenoma or sessile serrated adenoma a variant villous adenoma) or in five-years. In a cohort of 91 patients with sessile serrated polyps preceding MSI-H carcinomas, 19 predated the carcinomas by less than three years (89). Sessile serrated polyps

should be treated by complete endoscopic excision if possible. Until more is known, a shorter surveillance interval (e.g., 1-2 years) seems prudent for these types of polyps that are incompletely excised or associated with additional similar endoscopically appearing polyps that have remained unsampled (87-90,90a).

Pathologic Evaluation of Colorectal Carcinoma

Clinical Features and Gross/Endoscopic Pathology

Colorectal carcinoma occurs more often in men (M:F = 3:2) with a median age of 62 (1). Most present with rectal bleeding, anemia, change in bowel habits, bowel obstruction or less often, perforation (1). Right-sided colon carcinoma is more likely to present with anemia and fatigue; whereas left-sided carcinoma is more likely to produce melena, constipation and change in bowel habits. Approximately half of all large bowel carcinomas occur in the rectum with 25% occurring in the sigmoid colon; and the rest are evenly distributed throughout the remainder of the colon (1). That said, with increased use of colonoscopy with removal of adenomas, there has been a right-sided migration of carcinomas over the last 30 years.

Carcinomas of the right colon tends to produce large exophytic tumors. Carcinomas of the left side are more likely to be stenotic and produce the so-called “napkin ring” tumor. Carcinomas anywhere can be fungating, ulcerated or necrotic masses with the most common macroscopic appearance being an ulcer with raised indurated edges. MSI-H colorectal carcinoma, whether sporadic or associated with the Lynch syndrome, tend to be right-sided, multiple, large and bulky.

Prognostic Factors

Histologic typing, grading and pathologic staging provide prognostic information and are used to guide management of patients with colorectal carcinoma. Obviously, the surgical pathologist’s skill, knowledge, and enthusiasm determine the assessment of these prognostic variables. Carcinomas should be classified and graded following the guidelines of the WHO (1,2). Staging should follow American Joint Commission on Cancer and International Union Against Cancer (TNM) guidelines (1). Reporting is facilitated by use of the College of American Pathologists (CAP) cancer protocols which are available at their website (www.cap.org).

The following features adversely affect prognosis: advanced stage, extensive local spread, lymph node involvement, aggressive histologic type, high histologic grade, extramural venous invasion and free mesothelial surface invasion (1,101-104). Although useful information is gleaned through these “classic” grading and staging exercises, the process is not without problems and controversy. There is not general agreement on staging or grading and all current schemes have shortcomings (103,105,106). Using current systems, the majority of patients fall into a moderate stage, moderate grade category where the probability of survival is roughly 50/50.

The CAP has considered and commented upon the multitude of reputed prognostic factors in a consensus statement (104). They conclude that there are factors definitively proven to be of prognostic import including: local extent of tumor (pT), regional lymph node metastases (pN), blood or lymphatic vessel invasion, and residual tumor following surgery with curative intent. Other factors that have repeatedly been shown to be of prognostic importance include tumor grade, radial margin status and residual tumor in specimens following neoadjuvant therapy (104); The CAP recommends that these additional features should also be included in pathology reports. Although customarily included in pathology reports, parameters such as tumor size and gross configuration have been well studied and are of no prognostic

significance (104). That still leaves an incredibly large group of factors that may be considered prognostic but have not yet been sufficiently studied.

Lymph Node Dissection

The single most important factor related to patient prognosis is the presence or absence of lymph node metastases. There is no doubt that searching for lymph nodes in a resection specimen is tedious. The lymph node yield per case is directly proportional to the dissector's enthusiasm and skill. As a general rule, a "standard" resection specimen for carcinoma of the sigmoid colon or rectum should contain 10-25 lymph nodes, though we all have had cases in which the dissector found far less. Minimum numbers of lymph nodes harvested is increasingly considered a measure of quality (107,108). Therefore, the routine use of clearance techniques for lymph node dissection has been debated. There are certainly advantages to clearance techniques. One is likely to find more lymph nodes in a specimen and the lymph node yield will no longer depend solely upon the dissector's ability and enthusiasm. However, the clearance process is time-consuming and it may delay reporting (109,110). Clearing is relatively expensive because of the large volumes of clearing agents used and prolonged technologists' or pathologists' time. Common clearing agents are often flammable and toxic.

Cawthorn et al (109), showed that clearance techniques increase the yield of lymph nodes per specimen when compared to routine dissection. However, the proportion of stages 1, 2 and 3 cases did not change. The number of positive lymph nodes found was similar between cleared and non-cleared groups. This finding has been confirmed (108). Clearance techniques are considered unnecessary for routine cases (104,111).

Additional controversy is added by consideration of non-traditional methods of lymph node examination such as immunohistochemistry for CEA, cytokeratins and epithelial membrane antigen, PCR testing looking for various tumor DNA or RNA and sentinel lymph node examination. The biologic significance of these non-traditional methods lacks validation (104,112-116) and "positive" nodes found by these techniques may have no effect on prognosis (117). Currently, the CAP recommends that all grossly identified lymph nodes be sectioned (without multiple levels) in a routine fashion (104,116). Pathologists should find as many lymph nodes as possible recognizing that the rules of representative sampling and probability apply (107). As a general rule, 12 negative lymph nodes usually correlate with true pN0 status (107,116,118,119). Extramural tumor nodules of any size with smooth contours are counted as replaced regional lymph nodes (116). Sentinel lymph node examination does not accurately predict either conventionally defined nodal metastasis or micrometastasis and is not considered useful in the study of patients with colorectal carcinoma (120).

Histologic Grading

Pathologists admit that grading is more art than science. Grading is subjective and prone to interobserver and intraobserver variation. One multicenter trial noted 3% well-differentiated adenocarcinomas from one institution, while another hospital reported 97% well-differentiated cases (106). Marked heterogeneity exists within a given tumor. Some observers grade "on the average" while others assign a grade corresponding to the least differentiated area. Many grading systems are used for colorectal carcinoma (1,106,121-127). All employ slightly different criteria that are poorly defined. Some use three grades; others four. Some exclude mucinous carcinoma altogether and others include it as grade IV or grade III. Criteria for mucinous carcinoma are almost never defined.

We follow the guidelines of Dukes and Bussey (127) and use a three-grade system (1). Well-differentiated adenocarcinoma (grade I), which should account for 10% - 20% of cases, shows tubular differentiation, the nuclear polarity is easily discerned, and nuclei are, in general, uniform in size.

Approximately 70% of adenocarcinomas are moderately differentiated (grade II) exhibiting a more complex and irregular tubular pattern, and the polarity of nuclei is lost or only barely discernible. The remaining poorly differentiated adenocarcinomas (grade III) consist of highly irregular glands or may show an absence of glandular architecture. Nuclear polarity is lost. When variability exists within a given tumor, the grade is determined by the worst area no matter how small. Mucinous carcinoma and signet ring cell carcinoma are considered poorly differentiated or grade III (128).

Jass et al (106) investigated grading using a Cox Regression Analysis Model in 447 resection specimens. The only grading parameters associated with prognosis were the amount of tubule configuration, the pattern of growth (expanding vs. infiltrative), and the degree of lymphocytic infiltration. When stage related parameters were added into the Cox Regression Model, only three factors emerged as significant: lymph node involvement and local spread (i.e., the components of stage), and the amount of lymphocytic infiltration in the neoplasm (i.e., a reflection of MSI status). This study provided the scientific verification of Dukes' original observation that grade was subservient to stage in prognosis (127) and re-emphasizes the need for careful specimen dissection and examination to determine the amount of local spread and lymph node status.

Histologic Type

Many believe that mucinous carcinoma and signet ring cell carcinoma are associated with significantly worse prognosis than nonmucinous adenocarcinoma. Unfortunately, the definitions of mucinous and signet ring cell carcinoma vary (1,104,129-133). Work by Sasaki et al (132) and Umpleby et al (133), verified that mucinous and signet ring cell carcinomas are associated with a worse prognosis, but they present at high stage and are associated with extensive local spread.

Sasaki et al scrutinized a large cohort of mucinous, signet ring cell and nonmucinous carcinomas using a Cox Multiple Regression Model (132). According to this study, the only significant adverse prognosis-related independent variables were the presence of lymph node metastases and the extent of local spread (i.e., the components of stage), along with an infiltrative growth pattern, and minimal lymphocytic infiltration. Both Sasaki et al and Umpleby et al concluded that mucinous carcinoma (greater than 75%-80% by volume) and signet ring cell carcinoma (greater than 50% cells with signet ring morphology) are more aggressive (132,133). These histologies were not, however, significantly associated with poor prognosis if controlled for stage.

Flow Cytometry

Flow cytometry for examination of DNA content in human tumors involves cells or isolated nuclei stained in suspension with a fluorescent dye that binds stoichiometrically with double-stranded DNA. These stained cells/nuclei are then passed one by one through an excitor light source (laser). The amount of fluorescence produced by the bound dye is detectable by a photoelectric cell and the information is stored electronically. With this technique, thousands of measurements can be made in seconds and displayed on a histogram. The position of peaks on the x-axis is proportional to the amount of DNA per cell, and the height of the peaks on the y-axis is proportional to the number of cells demonstrating a particular DNA content. Using this method, "diploid" cell populations can be distinguished from "non-diploid" (including DNA aneuploid) cell populations.

Studies of paraffin-embedded and fresh colorectal carcinoma specimens have demonstrated an inconsistent association between DNA aneuploidy and survival (128,129,134). In at least one of these studies (134), stage was retained as a strong independent variable associated with prognosis after multiple regression analysis. Others show no independent association between DNA aneuploidy and prognosis in

a large group of patients with colorectal carcinoma with stage as the only independent variable associated with prognosis (135).

DNA content analysis by flow cytometry is of no proven clinical value (104). The technology and methods lack standardization, and, in general, the results between groups are not comparable. Most published studies have employed paraffin-embedded material. This may not be optimal because DNA fragments and partial nuclei tend to stick together, leading to increased yields of “pseudo-aneuploid” histograms (128). The proportion of cases showing aneuploid peaks is lower when fresh intact cells are used. In terms of interpretation, control histograms are easy to read but tumor histograms are less clean and interpretations are subject to interobserver variation. In a cohort of 165 patients with colorectal carcinoma prospectively studied, results of flow cytometric analysis showed no correlation between DNA aneuploidy and any standard staging or grading parameter and had no independent association with prognosis (128,136). The CAP believes that DNA analysis has not been adequately studied for determination of prognostic value and the data are insufficient to recommend a specific technological method (104).

Various proliferation markers have been studied in colorectal carcinoma. For example, a cohort of 122 patients with colorectal carcinoma were studied utilizing an antibody that recognizes Ki-67, a nuclear antigen expressed in all phases of the cell cycle except G₀ (103). There was no correlation between Ki-67 scores and stage, grade, or prognosis. Stage, growth pattern, and lymphocytic infiltration were the only factors independently associated with prognosis. The CAP believes that there are insufficient data to recommend inclusion of proliferation indices in pathology reports for prognostic information (104).

Early Non-Polypoid Colorectal Carcinoma

Early invasive colorectal carcinoma (pT1-invasive carcinoma limited to the submucosa) warrants special mention given the advent of endoscopic techniques allowing gastroenterologists/surgeons to locally resect some carcinomas either at surgery or via the endoscope (e.g., endoscopic mucosal resection [EMR]). Given that lymph node status is the strongest prognostic factor in colorectal carcinoma, the question asked, particularly by surgeons, is whether local excision or EMR is enough or definitive surgical resection should be performed for pT1 lesions. The issue is further complicated by the low rate of lymph node metastases in pT1 colorectal carcinoma, estimated at 3%-17% (127,137-140). This dilemma has prompted evaluation of histologic parameters and molecular markers that correlate with positive lymph node status in excised pT1 colorectal carcinoma.

Features that consistently correlate with positive lymph node status in pT1 colorectal carcinoma include angiolymphatic invasion, poor differentiation, tumor budding and SM3 invasion (invasion of the deepest 1/3 of the submucosa) (139-143). Although various immunostains and molecular markers have not been significantly associated with lymph node status (139), gene expression profiling could improve the prediction of patients likely to have positive lymph nodes and improve outcomes (144).

Treatment-Related Ancillary Testing

Cetuximab is a chimeric monoclonal antibody which binds to epidermal growth factor receptor (EGFr). It has clinically significant activity when given alone or in combination with irinotecan in patients with advanced irinotecan-refractory colorectal carcinoma (145-147). Approximately 85% of colorectal cancers express EGFr by immunohistochemistry but that expression does not correlate with gene amplification (148). Immunohistochemistry for EGFr is sometimes used as a selection criterion for cetuximab (149). The threshold for positive staining has been extraordinarily low (1+ staining in $\geq 1\%$ of cancer cells) and neither the proportion of positive tumor cells nor the intensity of staining correlated with clinical response. Some patients who tested negative for EGFr responded to cetuximab and many positive

patients did not. Consequently, the National Comprehensive Cancer Network guidelines for colorectal cancer management recommend against using EGFR expression by immunohistochemistry to select patients for cetuximab (141,150). KRAS with reflex testing for NRAS and BRAF (all downstream of EGFR) should be performed in situations in which cetuximab therapy is contemplated. Cetuximab has shown significantly improved survival in patients with wild type KRAS whereas mutated KRAS cancers showed no change in survival versus supportive care above (150a).

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF) which is critical in the regulation of angiogenesis. This monoclonal antibody added to fluorouracil-based chemotherapy regimens resulted in significant improvement in patients with advanced colorectal carcinoma (151,152). VEGF is expressed in approximately 50% of colorectal carcinomas (152). Neither microvessel density determination which is prone to significant methodological variation (153) nor VEGF determinations by immunohistochemistry were considered a selection criterion.

Before 2000, fluorouracil, a thymidylate synthase inhibitor, was the only effective treatment for advanced colorectal cancer and because leucovorin (folinic acid) enhances the effect by stabilizing the bond between fluorouracil and thymidylate synthase, both agents are often given together (147,154,155). Other cytotoxic drugs, including irinotecan (an inhibitor of topoisomerase I) and oxaliplatin (distorts DNA by cross linking into adducts) are now approved for treatment for advanced colorectal carcinoma (147,154,155).

Irinotecan has efficacy as a first-line treatment for advanced colorectal cancer but lacks efficacy as adjunct therapy. Irinotecan is hydrolyzed into an active metabolite (SN-38) by hepatic carboxyl esterase. SN-38 is converted into an inactive form by uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A1). In patients with polymorphisms of UGT1A1, the toxicities of irinotecan (diarrhea, nausea, vomiting, myelosuppression, alopecia) are more severe. Although results indicate that UGT1A1*28 polymorphisms have some relevance to toxicity, especially hematologic toxicity with the first cycle of chemotherapy (156), determination of the polymorphism seems to have marginal clinical implications. The observed toxicities can be managed clinically, other UGT1A enzymes may play a role as well (157) and data do not support dose reduction based on a molecular test.

Cisplatin and its analogues (oxaliplatin) are particularly toxic and molecular markers to identify patients likely to respond have been investigated. Oxaliplatin adducts are repaired by the nucleotide excision repair complex. ERCC1 (excision repair cross-complementation group 1) is 1 of 16 genes that encode proteins of this complex (158). Polymorphisms that reduce levels of ERCC1 correlate with clinical sensitivity to oxaliplatin (158,159) and could be used for patient selection.

Histologic Variants of Colorectal Carcinoma

Medullary (Undifferentiated) Carcinoma

The medullary variant of colorectal carcinoma occurs predominantly in women and usually occurs in the cecum and ascending colon (1,2). Histologically, it is composed of uniform polygonal cells arranged in a nesting or trabecular pattern with minimal gland formation. Immunohistochemistry is often employed to rule out neuroendocrine carcinoma or melanoma. Other characteristic features of medullary carcinoma include a prominent lymphoid component which can either be peritumoral, often described as Crohn's disease-like or intratumoral with tumor infiltrating lymphocytes (> 5 per high-magnification field) (160). Medullary carcinoma is seen with increased frequency in MSI-H colorectal carcinoma whether sporadic or in association with the Lynch syndrome.

Adenosquamous and Squamous Carcinoma

Adenosquamous carcinoma, defined by having both malignant glandular and squamous components, occurs rarely as a primary carcinoma in the colon and rectum (1,2). The possibility of a metastasis must always be considered. Adjacent adenoma can help to confirm a primary tumor. Adenosquamous carcinoma has been described in patients with ulcerative colitis, familial adenomatous polyposis, schistosomiasis and endometriosis. Occasionally, squamous differentiation can be found in adenomas. Pure squamous colorectal carcinoma outside of the anal canal is extremely rare. The possibility of a metastasis must be ruled out. Squamous carcinoma has been reported in fistula, in association with radiation and in patients with inflammatory bowel disease, tuberculosis and schistosomiasis (1,2,161).

Microglandular Goblet Cell Adenocarcinoma (So-Called Goblet Cell Carcinoid)

Occasional case reports of microglandular goblet cell adenocarcinoma (goblet cell carcinoid) identical to that seen in the vermiform appendix have been described in the large bowel. These tumors are composed of trabeculae and nests of well differentiated adenocarcinoma cells showing differentiation towards goblet cells. Scattered or no endocrine differentiation is characteristically seen by immunohistochemistry for chromogranin and synaptophysin. Although cytologically bland, these are often aggressive carcinomas in the colon and rectum (1).

Carcinosarcoma

Carcinosarcoma is often referred to as spindle cell carcinoma or metaplastic carcinoma and can occur rarely in the large bowel. Frequently, a high-grade squamous or glandular component is detected. The mesenchymal component can be undifferentiated or can show striated or smooth muscle differentiation or areas of cartilage or bone. These tumors are associated with a poor prognosis (1,2,162,163).

Giant Cell Carcinoma and Choriocarcinoma

Giant cell carcinoma and choriocarcinoma can occur purely or as focal components of an otherwise typical high-grade adenocarcinoma or carcinosarcoma. In choriocarcinoma, the giant cells express beta human chorionic gonadotropin (HCG). Carcinomas with giant cells that fail to stain for beta HCG are referred to as giant cell carcinomas (1,164,165).

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GASTROINTESTINAL POLYPOSIS SYNDROMES AND OTHER LARGE BOWEL POLYPS

Familial Adenomatous Polyposis and Variants

Familial adenomatous polyposis (FAP) is inherited as an autosomal dominant trait (1,2). HJR Bussey recognized that 100 or more colorectal adenomas (recognized grossly) phenotypically identified patients with FAP and distinguished them from patients with multiple adenomas in whom inheritance was not seen (3,4). In typical FAP, hundreds to thousands of adenomas develop within the colon. The adenomas begin to appear in the second or third decades of life and are surprisingly asymptomatic considering their usually large numbers. Symptomatic patients present with signs and symptoms of increased bowel motility and the passage of blood and/or mucus, which often heralds the onset of carcinoma. The average age of patients with colon cancer and FAP is 39 years (5). Two-thirds of these so-called proband cases present with carcinoma and nearly one-half of them will have more than one carcinoma in the colon. This high risk of invasive cancer in symptomatic patients forms the basis for polyposis registries and the extensive screening of asymptomatic kindred at risk for FAP.

Screening recommendations have evolved with increased genetic information. Genetic testing should be considered for FAP, attenuated FAP, and mutY homologue (MYH) associated polyposis when 10 or more colorectal adenomas have been found in a patient at one examination or over time (2,4). Screening of first degree relatives of affected individuals should begin at age 10 (6). In the absence of genetic testing, endoscopic screening is still useful to detect FAP. All affected patients have adenomas within the range of a flexible sigmoidoscope. It is therefore recommended that screening sigmoidoscopy begin at age fourteen with reexamination every two years. The diagnosis of FAP must be confirmed with biopsy because lymphoid polyposis and hyperplastic polyposis can mimic FAP grossly and endoscopically (6a). Once a diagnosis of FAP has been established, prophylactic proctocolectomy is recommended. Most investigators recommend sigmoidoscopy for mutation negative kindred at age 12 just in case the genetic test is erroneous. Thyroid examination for associated thyroid lesions (usually papillary carcinoma with cribriform pattern [7]) and serum alpha-fetoprotein determination (to screen for hepatoblastoma) are recommended.

Regular upper endoscopy should also be done. Gastric and duodenal polyps develop in 30%-90% of FAP patients (8). The gastric lesions are usually fundic gland polyposis whereas the duodenal polyps are usually adenomas. The fundic gland polyps can develop a peculiar surface epithelial atypia called foveolar “dysplasia” (9) but progression to carcinoma is extremely rare. The incidence of duodenal adenomas in FAP increases with increasing age. There is a propensity for these to develop in the periampullary region. Adenomas anywhere in the GI tract can proceed through the dysplasia-carcinoma sequence. The relative risk of duodenal/periampullary carcinoma in FAP patients is approximately 125 times to 350 times that seen in the general population and duodenal/periampullary carcinoma has become the major cause of morbidity and mortality in FAP patients in the post prophylactic colectomy era (10).

The gene responsible for familial adenomatous polyposis (APC gene) has been localized to the long arm of chromosome 5 (5q21-q22) and has been cloned (11-15). Some APC gene mutation negative cases may be caused by mutation of MYH (2,16) (see below). Mutation in most FAP patients creates a stop codon resulting in a truncated protein product. The APC gene is a tumor-suppressor gene and the APC protein is part of the Wnt-signaling pathway (5,17) involved in cell growth control. When APC is mutated, β -catenin accumulates, altering expression of a number of genes affecting proliferation, differentiation, migration and apoptosis (2,18).

Most patients are now diagnosed by DNA sequencing and additional testing to detect large-segment rearrangements. This approach has largely replaced the assay to detect the truncated APC protein (PTT) (2,6,18).

Over 700 disease-causing APC mutations have been reported (18). Localization of gene mutations within the APC gene locus correlates with phenotype. For example, germline mutations between codon 1250-1464 are associated with very large numbers of colonic adenomas, whereas, mutations elsewhere, especially near the 5' end or the 3' end of APC and an area of exon 9, yield lesser numbers of colonic adenomas (see Attenuated Familial Adenomatous Polyposis-below) (2,6,18-20).

In Gardner's variant, in addition to colonic adenomas and upper GI polyps, patients can exhibit extraintestinal manifestations such as osteomas, epidermal inclusion cysts and other benign skin tumors, desmoid tumors of the abdomen/abdominal wall, fibrosis of mesentery, dental abnormalities, carcinoma of the periampullary region/duodenum and carcinoma of the thyroid. Patients with Gardner's syndrome have APC gene mutations; however, no particular APC mutation distinguishes FAP from Gardner's variant. Even within a "Gardner's family", Gardner's stigmata can be variably expressed and can skip generations (15). Therefore, some unknown disease-modifying factors are required for phenotypic expression of the extra-intestinal manifestations.

Turcot's syndrome has been the subject of some controversy. In many investigators' zeal to publish, the phenotypic spectrum has been unduly broad with colonic manifestations ranging from a single adenoma to a virtual carpeting of the colonic mucosa with polyps. Furthermore, the brain tumors have comprised almost every histologic type. Molecular studies done on fourteen Turcot's syndrome families have clarified the situation (21). Turcot's syndrome families with germline mutations of the APC gene have a typical FAP colonic phenotype and develop medulloblastomas. Other patients originally thought to have Turcot's syndrome have mutations in the DNA mismatch repair genes that are characteristic of Lynch syndrome. The brain tumors in this group have varied with many reported as glioblastoma multiforme.

Mutations of the APC gene near the 5' end and 3' end and in a particular region of exon 9 result in fewer adenomas (fewer than 100, average of 30), a tendency for the adenomas to be macroscopically flat, and a propensity for these adenomas to cluster in the right colon (5). Originally reported as hereditary flat adenoma syndrome, this form is now more accurately referred to as attenuated FAP (6,20). Like typical FAP, these patients can develop fundic gland polyposis, duodenal adenomas and periampullary carcinoma. The risk of colorectal carcinoma is increased in these patients albeit to a lesser degree than in the other form of FAP and the cancers tend to occur later in life (average age 49 years).

Recently, inherited variants of a base-excision repair gene MYH have been associated with colorectal polyposis with an autosomal recessive mode of inheritance (2,16,22,23). Some cases phenotypically resemble FAP or attenuated FAP and are referred to as "MYH polyposis" or MUTYH-associated polyposis (MAP) (2,16). Of those patients with a phenotype typical of FAP or suspected AFAP in whom an APC mutation is not found, 10-20% will have mutation of the MYH gene (2,5). Approximately 80% of affected persons have one of two specific MYH mutations (Y165C and/or G382D). If one is found, then sequencing is done to find the mutation on the other allele because MAP is biallelic (2,5). These patients should be treated and followed similarly to FAP patients.

Juvenile Polyps and Juvenile Polyposis Syndrome

Juvenile polyps can occur in a sporadic form or can be part of juvenile polyposis syndrome (1,2). In the sporadic form, juvenile polyps have their peak prevalence in children between ages 1 and 7. There is some evidence that juvenile polyps once formed can regress; they can certainly be seen in adults. Sporadic juvenile polyps typically occur singly but patients can have up to 5 usually located in the rectum. Juvenile polyps typically range in size up to 2 centimeters, and can be associated with overt prolapse (24). Since these polyps are often attached by a small pedicle, they are prone to auto-amputation. Histologically, typical juvenile polyps consist of a hamartomatous overgrowth of the lamina propria accompanied by elongation and cystic dilatation of colonic crypts lined by non-dysplastic colonic

epithelium (1,2,5). Osseous and cartilaginous stromal metaplasia can occur. The inflammatory component of juvenile polyps can be quite prominent with neutrophils and lymphoid follicles within the lamina propria. Frequently, the distinction between juvenile polyps and inflammatory polyps of primary inflammatory bowel disease cannot be made on histology alone and requires clinical correlation. Non-syndromatic juvenile polyps appear to have no malignant potential (25).

Juvenile polyposis syndrome can be familial or non-familial and usually becomes clinically apparent within the first decade of life with painless rectal bleeding, prolapse, iron deficiency anemia or by passing an auto-amputated polyp (4). A patient is considered to have juvenile polyposis syndrome if they have 6 or more juvenile polyps in the colon and rectum, have juvenile polyps throughout the GI tract, or have any number of juvenile polyps in association with a positive family history (2,24,26). In the non-familial forms of juvenile polyposis syndrome (approximately 30% of the total), patients frequently have associated abnormalities, such as cardiac defects, hydrocephalus, gut malrotation, undescended testes, and skull abnormalities (4). The familial forms usually lack these extraintestinal manifestations. Inheritance has varied although almost all are considered autosomal dominant with variable penetrance (4). Familial forms of juvenile polyposis syndrome appear to be associated with an increased risk of colorectal carcinoma (26); prophylactic colectomy may be prudent in juvenile polyposis syndrome. There may also be increased risk of gastric, small intestinal and pancreatic carcinoma (27). Juvenile polyposis syndrome coexisting with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) is rarely reported (27).

The number of polyps in juvenile polyposis syndrome typically ranges from a few dozen to several hundred. Phenotypically, juvenile polyposis syndrome appears to occur in three varieties: a) polyps limited to the colon; b) polyps limited to the stomach; and, c) polyps throughout the entire gastrointestinal tract (28-30). The mucosal polyps found in the context of juvenile polyposis syndromes are often unusual histologically. In addition to typical juvenile polyps (described above), one can find juvenile polyps with atypical features in which there is much more epithelium than lamina propria. In addition, mixture polyps (juvenile polyps with areas of adenoma/dysplasia) are quite frequent (4,26). A family showing an autosomal dominant inheritance of atypical juvenile polyps, adenomas, hyperplastic polyps and polyps showing a mixture of all three types (Hereditary Mixed Polyposis Syndrome) (31) may be variant of juvenile polyposis (27,32).

Two genes have been identified to cause familial juvenile polyposis syndrome, MADH4 (Mothers Against Decapentaplegic Homolog 4) [a.k.a. SMAD-4 (18q21.1) and DPC-4]) seen in about 15% of patients and BMPR1A (Bone Morphogenetic Protein Receptor Type 1A) (10q22.3) (27,33-35) seen in 25% of cases. One should consider genetic testing for juvenile polyposis syndrome when 3 or more juvenile polyps have occurred in one individual, or if juvenile polyps are found outside of the colon (5). MADH4 and BMPR1A are both components of the signaling pathway for TGF-beta and the bone morphogenetic proteins. Patients with MADH4 gene mutation are more likely to have gastric juvenile polyposis (27,36,37). Juvenile polyps can be found in patients with other hamartomatous syndromes of the colon, such as intestinal ganglioneuromatosis/ganglioneurofibromatosis (38-40), although some of these are now best classified as "PTEN syndrome" (see below).

Patients can sometimes be managed with endoscopy and polypectomy (q1-3 years), however, colectomy must be considered for patients with large numbers of polyps, polyps with dysplasia or patients with complications (e.g., bleeding, obstruction). Screening colonoscopy every three years should commence with symptoms or in the early teenage years in an asymptomatic patient (5,41). Upper endoscopy is also recommended in patients with juvenile polyposis syndrome. Esophagogastroduodenoscopy and small bowel examination (every 2 years) should begin at age 15 (5,41).

Ruvalcaba-Myhre-Smith Syndrome (a.k.a. Bannayan-Zonana Syndrome, Riley-Ruvalcaba Syndrome, Bannayan-Ruvalcaba-Riley Syndrome)

The Ruvalcaba-Myhre-Smith syndrome consists of macrocephaly, mental deficiency, unusual craniofacial appearance, pseudopapilledema, pigmented macules on the penis and hamartomatous polyps in the gastrointestinal tract. The syndrome appears to be passed on in an autosomal dominant pattern (42). The gastrointestinal polyps have been indistinguishable from juvenile polyps and in rare instances, intestinal ganglioneuromatosis has also been described. The syndrome has been linked to mutations or deletions in the PTEN gene (10q23.3) (29,33,43) and with Cowden's syndrome and can be considered as one of the PTEN polyposis syndromes (27).

Peutz-Jeghers Syndrome

Peutz-Jeghers polyps can be found throughout the gastrointestinal tract, either sporadically or as part of the Peutz-Jeghers syndrome (1,2,44,45). The polyp itself is characterized by fairly normal epithelium and lamina propria lining an abnormal arborizing network of smooth muscle that represents hamartomatous overgrowth of the muscularis mucosae (1,2,44,46). Peutz-Jeghers syndrome, usually inherited as an autosomal dominant trait, is the combination of skin hyperpigmentation and Peutz-Jeghers polyps in the gastrointestinal tract. Some consider the diagnosis of Peutz-Jeghers syndrome as definitive if the patient has a Peutz-Jeghers polyp and at least two of the following criteria: 1) family history, 2) hyperpigmentation of the skin, 3) small bowel polyposis (27,45). The WHO recommends the following diagnostic criteria: 1) three or more histologically confirmed Peutz-Jeghers polyps; or, 2) any number of polyps with a family history; or, 3) prominent mucocutaneous pigmentation with a family history; or, 4) any number of polyps in a patient with mucocutaneous pigmentation (2). The pigmentation consists of clusters of brown/black freckles about lips, buccal mucosa, perianal and genital region. Pigmented areas can occasionally be seen on the fingers and toes. The spots appear in the first year of life and tend to fade toward middle age. The polyps usually number only in the dozens and can be found throughout the gastrointestinal tract. There is a propensity for these polyps to form in the small intestine where they often cause intussusception. There are rare kindreds in which Peutz-Jeghers polyps have been limited to the large bowel. Cases of complicating gastrointestinal carcinoma have been reported (47,48). Approximately 5% of females with Peutz-Jeghers syndrome have a peculiar ovarian tumor, sex cord tumor with annular tubules (SCTAT) (49). The rate of detection may go up if the ovaries are carefully examined (49,50) and some tumors may be associated with sexual precocity (51). Males with Peutz-Jeghers syndrome occasionally have unilateral or bilateral Sertoli cell tumors of the testes (52,53). Adenoma malignum and pancreaticobiliary tract carcinomas are reported to occur at increased rates (54).

The gene for Peutz-Jeghers syndrome has been linked to the STK 11 (serine/threonine-protein kinase 11, a.k.a. LKB1) gene on chromosome 19p13.3 (55-58) and can be demonstrated in 70% of cases (27). This is a tumor-suppressor gene involved in transduction of intracellular growth signals (5). It has been suggested that genetic testing be considered for Peutz-Jeghers syndrome when any Peutz-Jeghers polyps or typical perioral pigmentation are found (5).

Meta-analysis of cancer risk in an evaluation of patients with known mutations of STK11 gene have shown increased lifetime risk for cancer of the esophagus, stomach, small bowel, colon, pancreas and breast (45,59). Putting this into perspective, the risk for breast cancer in Peutz-Jeghers syndrome is similar to the risk seen in individuals with germline mutations of BRCA1 and BRCA2 and Peutz-Jeghers syndrome is the strongest known risk factor for pancreatic carcinoma except for hereditary pancreatitis (45).

Screening at-risk individuals (first degree relatives of a Peutz-Jeghers syndrome patient) should begin at birth with an annual history and physical exam looking specifically for melanotic spots, precocious

puberty, and testicular tumors. Asymptomatic at-risk individuals without stigmata by age 8 should be tested for STK 11/LKB1 gene mutations. If mutation is not found in the family, small intestinal contrast radiography every 2 years until age 25 is recommended. Others suggest that upper and lower endoscopy with small bowel series should be done at ages 12, 18 and 24 (45).

Esophagogastroduodenoscopy, upper GI series with small bowel follow through are recommended in Peutz-Jeghers patients commencing at age 8 and repeated every two years thereafter (45,60). Colonoscopy, every 3 years, is recommended starting with symptoms or by age 18 years if symptoms have not occurred (5,45). Testicular examination, pelvic examination by age 20, mammographic exam by age 25 and endoscopic ultrasound of the pancreas by age 25-30 have been recommended (45,60). Annual transvaginal ultrasound and serum CA-125 are also recommended commencing at age 25 (45).

Intestinal Ganglioneuromatosis

Intestinal ganglioneuromatosis is defined as a proliferation of ganglion cells, neurites, and supporting cells that can affect any layer of the gastrointestinal wall (42). These proliferations often present as mucosal polyps in the colon. Although these lesions most often occur as an isolated phenomenon, the importance of intestinal polypoid ganglioneuromatosis is in recognizing the other settings in which it can occur such as von Recklinghausen's disease (NF-1 gene mutation), MEN type 2b (RET gene mutation), Cowden's syndrome (PTEN mutation), Ruvalcaba-Myhre-Smith syndrome (PTEN mutation) and tuberous sclerosis (TSC1 [9q34] or TSC2 [16p13] mutation) (61-65). Intestinal ganglioneuromatosis can coexist with juvenile polyps although these patients may be better classified at PTEN polyposis (38-40).

Cowden's Syndrome

Cowden's syndrome describes an autosomal dominant multiple hamartoma syndrome in which patients have multiple orocutaneous hamartomas (e.g., facial trichilemmomas, mucosal papillomas, acral keratosis, subcutaneous lipomas), fibrocystic disease of the breast, an increased risk of breast carcinoma, thyroid abnormalities and hamartomatous polyps in the stomach, small intestine and colon (2). Polyps of the gastrointestinal tract, when described, have often demonstrated an abnormal proliferation of the smooth muscle in the lamina propria and have generally resembled the polypoid variant of solitary rectal ulcer syndrome (66). Some juvenile polyp-like proliferations have been described (27). Intestinal ganglioneuromatosis has also been reported (64). Other associated abnormalities include macrocephaly, high arched palate, hypoplastic mandible and maxilla, microstomia, supernumerary nipples, pectus excavatum, hemangiomas, ovarian cysts and uterine leiomyomas (27,65). The gene (PTEN [phosphatase and tensin homolog]) for Cowden's disease has been mapped to chromosome 10 (10q22-23) (34,67,68). Cowden's syndrome and Ruvalcaba-Myhre-Smith syndrome are sometimes referred to as the PTEN-polyposis syndromes. Genetic testing is suggested when features of this syndrome are present (5). EGD and small bowel examination every 2 years beginning at age 15 is recommended (5).

Cronkhite-Canada Syndrome

Cronkhite-Canada syndrome is an acquired non-familial syndrome characterized by intestinal polyposis, dystrophic changes of the fingernails, alopecia and cutaneous hyperpigmentation (69,70). Patients first present with diarrhea, abdominal pain and anorexia that progresses to weight loss and protein losing enteropathy. Many patients complain of loss of taste (hypogeusia) and loss of smell. As a rule, the ectodermal changes occur weeks to months after the other symptoms. The nail dystrophy consists of thinning, splitting and separation from the nail bed (onycholysis). Onychomadesis (complete loss of the nail) can also occur. The hair loss is rapid and may be seen in the scalp, eyebrow, face, axilla or pubic region. The cutaneous hyperpigmentation ranges from small macules to confluent areas of

hyperpigmentation and can be 10 cm or more. Histologically, the pigmented macules are due to increased melanin in the basal layer.

Cronkhite-Canada polyps are found throughout the gastrointestinal tract but are most commonly seen in the stomach and large bowel. Grossly, they are sessile; a few are pedunculated. The polyps tend to occur on a background of diffuse mucosal thickening. Histologically, the polyps themselves are identical to juvenile polyps. However, the mucosa between polyps is abnormal showing edema, congestion and inflammation (chronic inflammation often with prominent eosinophils) of the lamina propria coupled with glandular ectasia. Carcinomas of the colon and stomach have been rarely described in Cronkhite-Canada syndrome patients. The malabsorption in this syndrome is usually progressive and with no specific therapy available, the prognosis is generally poor. Death results from anemia, septic shock, bleeding or post-operative complications. Treatment consists of supportive therapy, antibiotics, corticosteroids and surgery. Within the stomach, Cronkhite-Canada syndrome closely mimics Menetrier's disease. Menetrier's disease, however, is confined to the stomach and has no associated ectodermal changes.

Other Large Bowel Polyps

Mucosal Heterotopia

Heterotopic gastric, pancreatic, sebaceous and salivary gland tissue have been described in the colon and rectum. These ectopic tissues can be found throughout the gastrointestinal tract but are most often seen in the rectum where they can cause a plaque, polyp or mass (71-73).

Inflammatory Fibroid Polyp

Inflammatory fibroid polyp is most commonly found in the stomach but it can be encountered throughout the gastrointestinal tract including the colon and rectum (1,2,74-76). Symptoms include abdominal pain and bleeding. The polyp is usually solitary. It can be sessile or pedunculated and typically shows a pale solid tan cut surface.

Microscopically one sees a loose myxoid fibrous tissue background containing regularly distributed blood vessels, some of which show hyaline change in their walls. The fibrous tissue can layer in a whorl-like fashion around these vessels in an onion-skin pattern. Most lesions are rich in inflammatory cells including plasma cells and eosinophils. Scattered macrophages and Touton-type giant cells can also be seen. The stroma in most lesions is positive for CD34 but negative for CD117. The mucosa overlying these typically submucosal tumors can be ulcerated, presumably by trauma and show areas of inflamed granulation tissue. The ulcerated surface can contain bizarre stromal cells which have also been seen in a variety of inflammatory polyps with chronic ulceration (e.g., inflammatory bowel disease, trauma/prolapse and radiation injury). Even though many inflammatory fibroid polyps show somatic mutations of PDGFRA, the inflammatory fibroid polyp is benign and typically does not recur (6a,77).

Malakoplakia

Malakoplakia, an abnormal immune response to gram-negative bacteria can cause a tumor or polyp in any site of the gastrointestinal tract including the large bowel. Histologically, it is characterized by xanthogranulomatous inflammation accompanied by the pathognomonic Michaelis-Gutman body (1). The partially digested bacteria accumulate in macrophages and lead to deposition of calcium and iron on the residual bacterial glycolipids (78). There may be an association between colorectal malakoplakia and colorectal neoplasia (78).

Endometriosis

Defined as the presence of endometrial glands and/or stroma usually with hemorrhage and hemosiderin deposits in an extrauterine location, endometriosis tends to affect sites closest to the female genital tract such as the sigmoid colon and rectum (1). Symptoms include episodic abdominal pain. Hematochezia can occur with mucosal involvement. Endometriosis usually involves the serosa and muscularis externa and can cause smooth muscle proliferation and stricture. Mucosal and submucosal involvement can cause mucosal polyps (79). Endometriosis must be distinguished from müllerian adenocarcinoma and endometrial stromal sarcoma. The glandular component can be confused with colitis cystica profunda and adenocarcinoma. Immunohistochemistry for CD10, which highlights endometrial stromal cells, can be helpful in the differential diagnosis as can recognition of ciliated epithelial cells. Differential cytokeratin immunostaining can also help because endometriosis is commonly positive for CK7 whereas colorectal epithelium usually expresses CK20. Examples of malignant transformation (mostly endometrioid carcinoma and clear cell carcinoma) in endometriosis has been reported (79).

Oleogranuloma

Injection of materials containing lipid bases into the lower rectum and anus can cause a mass or polyp which is referred to as an oleogranuloma. The lesion is composed of lipid containing cysts surrounded by a foreign body giant cell reaction (1).

Benign Fibroblastic Polyp/Colorectal Perineurioma

Benign fibroblastic polyps and perineurioma have been described in the colon and rectum where they may represent the same or a similar lesion (80-82). These mucosal polyps are usually solitary but can be multiple and have been reported throughout the gastrointestinal tract but most commonly in the colon and rectum. Histologically, these polyps contain proliferations of small tightly packed spindle cells within the lamina propria that often orient themselves parallel to the muscularis mucosae. This lesion frequently co-exists with hyperplastic polyp-like epithelial proliferations and indeed the polyp could represent a trauma related change seen in the otherwise typical hyperplastic polyp or sessile serrated polyp. The spindle cells are negative for immunoreactive S100 protein and other neuromarkers; expression of immunoreactive epithelial membrane antigen by immunohistochemistry has been described.

Elastosis and Elastofibromatous Change

Areas of increased elastin fibers in the submucosa and muscularis mucosae are referred to as elastosis or elastofibromatous change and can cause polyps in the colon and rectum. Histologically, the elastosis appears as finely granular or fibrillar amphophilic material usually with a fibrous component and is often centered around prominent blood vessels. The change could also be a manifestation of mucosal trauma/prolapse. Elastosis can be confused with amyloid deposits but congo red stains have been negative (83).

Mucosal Neuroma/Schwann Cell Hamartoma

Benign spindle cell proliferations that express immunoreactive S100 protein can present as mucosal polyps in the colon and rectum and are usually termed mucosal neuromas (1) or Schwann cell hamartomas (6a). Care must be taken not to overlook ganglion cells which would indicate a ganglioneuroma. These lesions can be seen with neurofibromatosis but most have occurred sporadically and are unassociated with syndromes (84).

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DIFFERENTIAL DIAGNOSIS OF GASTROINTESTINAL STROMAL TUMORS (GISTs) IN A GLEEVEC WORLD

Introduction

Historically, spindle cell neoplasms of the gastrointestinal (GI) tract were classified as smooth muscle tumors (i.e., leiomyoma, leiomyosarcoma, or leiomyoblastoma) (1-3), despite ultrastructural and immunohistochemical studies that rarely confirmed smooth muscle differentiation and some studies that actually concluded that a minority of these tumors were neural in origin or differentiation (1). In 1983, the term “stromal tumor” was introduced by Mazur and Clark (4). The observation that GISTs express the tyrosine kinase, c-KIT (CD117) and CD34 (which decorates many of the KIT receptors) provided an important clue to the possible cell of origin or differentiation (5, 6). The interstitial cells of Cajal (ICC) are dendritic-like cells that are widely distributed throughout the muscularis externa of the GI tract. These cells play an important role in the coordinated contraction of the muscularis externa and have been shown to express both CD117 and CD34. The hypothesis that GISTs are related to ICC is now widely accepted (5-8). The link to ICC, which are related to both smooth muscle and nerve, helps to explain the historical observations that hypothesized a relationship between GISTs and both smooth muscle and nerve. The expression of KIT is caused by activating KIT gene mutations primarily in exons 11 (65%), 9 (20%), 13 (<5%) and 17 (<5%) (8-10).

Gleevec (a.k.a. Imatinib Mesylate, STI571, Glivec)

Gleevec, an inhibitor of a specific protein tyrosine kinase, targets platelet-derived growth factor (PDGF) receptor (9, 11, 12). Gleevec inhibits the BCR-ABL fusion product arising from the Philadelphia chromosome of chronic myelogenous leukemia and c-Kit (CD117) of GISTs. The effectiveness of Gleevec in treating CML and metastatic GIST and its relative lack of side effects led to FDA approval in 2002. Gleevec reduces the size of metastatic deposits in GISTs with post-treatment tumors histologically showing marked decrease in cellularity, hemorrhage and myxoid degeneration (13-15). Side effects are typically minimal (e.g., periorbital edema, nausea, diarrhea, myalgia, fatigue, rash). The most serious side effect, gastrointestinal or intra-abdominal hemorrhage, occurs in only 5% of patients and is associated with very large tumors (15). The site of c-Kit mutation seems to have prognostic significance. 85% of patients with exon 11 mutations have at least a partial response to Gleevec, whereas 50% of those with exon 9 mutation, and only a few with exon 13 or 17 mutations respond (10). With longer follow-up, most patients eventually develop resistance to Gleevec characterized clinically by tumor expansion, focal nodular re-growth, or development of new metastatic deposits (16). Genetically, patients with Gleevec resistance develop many different secondary mutations in KIT or PDGFRA while others apparently amplify KIT by other methods (8). Sunitinib is the standard drug given for Gleevec resistant GIST (16a). If disease progresses, hsp 90 inhibitors and other tyrosine kinase inhibitors (sorafenib and nilotinib) may have some activity. Histological changes that correspond to resistance have been described including a change from spindle-cell morphology to epithelioid and pseudopapillary growth, loss of immunoreactivity to CD117 and CD34, and increased reactivity to desmin (16).

Diagnosis and Prognosis of GIST

The diagnosis of GIST must be entertained for all mesenchymal tumors involving the muscularis externa of the gastrointestinal tract and should also be considered in all spindle cell neoplasms involving other abdominal sites. Use of an immunohistochemical panel including CD117, CD34, smooth muscle actin, desmin, cytokeratin, S100 protein and melan-A can be useful in classifying such tumors. Protein kinase C theta is also specifically and strongly expressed in GISTs (8). More than 96% of GISTs have a gain in function mutation of c-Kit that can be demonstrated by KIT immunohistochemistry and controversy remains as to whether GIST can ever be diagnosed in the absence of KIT (5, 7, 17, 18). Medeiros and

colleagues appear to have proved that KIT-negative GISTs exist (19). KIT gene and PDGFRA mutation analysis may be helpful in this setting (tumor with GIST morphology and negative c-Kit immunoreactivity) because approximately 60% harbor a mutation but do not overexpress the protein (19). Some KIT negative “GIST” do respond to Gleevec (8). Heinrich et al and Hirota et al have described PDGFRA mutations in GISTs containing wild type KIT (19-21). PDGFRA mutations have been observed in approximately two-thirds of the KIT-negative GISTs (19-21) principally in exons 12,14, and 18 (8). Some of these KIT-negative GISTs respond to Gleevec; therefore, patients should not be denied Gleevec based solely on a negative CD117 immunostain (19).

Familial GISTs with germline KIT mutations have been described and there is an association between neurofibromatosis type I and GISTs. Although the latter show typical positive staining for CD117 and CD34, these tumors only rarely contain KIT or PDGFRA mutations (22,23). This immunohistochemical and genetic profile may also be true for GISTs occurring as part of the Carney triad (GISTs, pulmonary chondromas and extra-adrenal paragangliomas), typically occurring in young woman (24). GISTs associated with familial syndromes and NF-1 are typically small bowel, multifocal, show skeinoid fibers and occur in a background of ICC hyperplasia (8).

In the past, I tried with varying degrees of success to predict behavior in GISTs based on such features as size, mitoses counts, subjective assessments of cellularity and the consideration of other morphological features such as infiltration of the mucosa, loss of the perinuclear vacuole, necrosis, nuclear atypia, epithelioid differentiation (in small bowel tumors), and loss of organoid arrangement (in small bowel tumors) (25-31). My experience was that a few tumors were obviously malignant, based on concurrent metastasis, large size and high mitotic counts. Some I considered benign (low cellularity gastric tumors < 5 cm with mitoses counts of less than 5 per 50 high magnification field or low cellularity; non-epithelioid small bowel tumors < 2 cm. with less than 5 mitoses per 50 high magnification fields with preserved organoid arrangement). Most tumors seemed to be of indeterminate biologic behavior.

Criteria for distinguishing benign from malignant GISTs have been described, analyzed and debated for years. Factors such as mucosal invasion, tumor necrosis and high cellularity were statistically associated with malignant behavior but were criticized as subjective and not reproducible. Others have looked at cell proliferation markers such as Ki-67, MIB-1, PCNA, DNA cell cycle abnormalities, and assessment of nucleolar organizing region; however, none of these have been proven useful (1). Size and the number of mitoses figures has been fairly consistent in almost all papers (1). In general terms, I have embraced the consensus approach to the classification of GISTs (see Table 1) which has also been embraced with modifications by the College of American Pathologists (31a). This classification system appears to have prognostic significance (see Table 2). Many believe that high-risk GISTs should be given Gleevec adjunctively (32, 33, 34).

TABLE 1
PROPOSED APPROACH FOR DEFINING RISK OF
AGGRESSIVE BEHAVIOR IN GISTs (1)

RELATIVE RISK	SIZE	MITOTIC COUNT
Very low risk	< 2 cm	< 5/50 HMF
Low risk	2-5 cm	< 5/50 HMF
Intermediate risk	< 5 cm	6-10/50 HMF
	5-10 cm	< 5/50 HMF
High risk	> 5 cm	> 5/50 HMF
	> 10 cm	Any mitotic count
	Any size	> 10/50 HMF

TABLE 2
GASTROINTESTINAL STROMAL TUMORS
PROGNOSIS BY RISK GROUP

RISK GROUP	ADVERSE OUTCOME		
	Gastric***	SI**	Colon*
Very low	0%	0%	0%
Low	1.8%	4.3%	0%
Intermediate	7.3%	24.6%	0%
High	45.9%	77.2%	75%

*18 pts; FU 5.5 years. Hassan I et al. *Dis Colon Rectum* 49:609, 2006

**603 pts; FU 15.5 years. Miettinen M et al. *Am J Surg Pathol* 30:477, 2006

***1068 pts; FU 15 years. Miettinen M, et al. *Am J Surg Pathol* 29:52, 2005

Differential Diagnosis

Fibromatosis (Desmoid Tumor)

Fibromatosis typically occurs in the abdominal wall, mesentery and retroperitoneal tissues and these tumors can attach to, grow into and even extend through the muscularis externa anywhere in the GI tract (35). Histologically, desmoids are composed of spatially homogeneous wavy spindled or stellate cells without atypia arranged around evenly spaced, usually prominent blood vessels, and often show a collagenous (keloid-like) background. These tumors may have rare mitoses figures but nuclear pleomorphism is generally absent. Infiltration of the spindle cells at the tumor-mesentery interface favors fibromatosis over GIST (36). Surprisingly, immunohistochemistry may not necessarily resolve the diagnostic dilemma because CD117 can be positive in fibromatosis although the positivity varies with the antibody and technique used (36-39). Many do not use antigen retrieval with KIT immunohistochemistry because of this reason (8). Immunopositivity with beta-catenin protein favors a diagnosis of fibromatosis (40). Interestingly, clinical trials of STI-571 (Gleevec, Glivec) in the treatment of fibromatosis are underway with some favorable results (41).

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor encompasses a number of unusual lesions that show a proliferation of spindle cells admixed with chronic inflammatory cells (42,43). Some of these lesions are clearly benign inflammatory conditions but others have been shown to be clonal and on rare occasions have behaved in a malignant fashion (inflammatory fibrosarcomas). Histologically, inflammatory myofibroblastic tumors are composed of elongate spindle cells and inflammatory cells. Immunostains for desmin and actin are typically positive in inflammatory myofibroblastic tumors whereas CD117 and CD34 are reported as negative.

Smooth Muscle Tumors

True smooth muscle tumors can occur in the gastrointestinal tract with most arising in the muscularis mucosae (leiomyomas) (44), some rarely in the duodenum (leiomyoma and sarcomas) (45) or muscularis externa (usually leiomyosarcomas) of the esophagus, colon, rectum and anus (46-48). The lesions typically stain positively for desmin and smooth muscle actin and negative for CD117 and CD34. Once recognized as a true smooth muscle tumor, classification can be a challenge because of the paucity of cases with follow-up. Small tumors without atypia that are mitotically inactive can be classified as leiomyomas (49). Tumors with mitosis and mild atypia are best regarded as atypical smooth muscle tumors of uncertain malignant potential (49). When atypia and mitotic activity are present, the tumor is best considered a leiomyosarcoma (49).

Schwannomas

Schwannomas of the GI tract are rare and have been most often described in the stomach (50). A peripheral cuff of lymphoid aggregates, nuclear palisading and hyalinized blood vessels can be useful in suggesting the diagnosis (50, 50a). Schwannomas stain for S100 protein and are CD117 negative. CD34 immunoreactivity can be variable.

Solitary Fibrous Tumor (Submesothelial Fibroma)

Solitary fibrous tumor can occur anywhere in the peritoneal cavity and can adhere to the bowel. They are typically highly cellular spindle cell proliferations with depositions of collagen that usually have very few

mitoses figures. These tumors are CD34 positive and can easily be confused with GISTs. Solitary fibrous tumors are negative for CD117 (42, 51).

Glomus Tumor

Approximately 100 cases of gastrointestinal glomus tumor have been described, almost all occurring in the stomach. These tumors typically show solid arrangements of tumor cells around mildly dilated blood vessels. These tumor cells have sharply defined cellular membranes, centrally located round uniform nuclei with delicate chromatin, and inconspicuous nucleoli. Mitoses figures are rare. Since ultrastructural analysis had shown a relationship of glomus tumors to smooth muscle, it is not surprising that the tumor cells show positive immunoreactivity to smooth muscle actin. Focal CD34 reactivity has also been described. Gastrointestinal glomus tumors have been consistently negative for CD117, desmin and S100 protein (52).

Osteoclast-Rich Tumor Resembling Clear Cell Sarcoma

Rare examples of an osteoclast-rich tumor of the GI tract with features resembling clear cell sarcoma of soft parts that can mimic GISTs have been reported (53,54). These highly malignant tumors are cKit negative, strongly positive for S100 protein and stain variably for cytokeratin and other melanoma markers (HMB45, Melan-A).

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NEUROENDOCRINE PROLIFERATIONS OF THE GUT – BIOLOGICAL DIFFERENCES THAT MAKE A DIFFERENCE: SPORADIC CARCINOID VERSUS CARCINOIDOSIS OF THE STOMACH AND TUBULAR VERSUS INSULAR VERSUS GOBLET CELL CARCINOID OF THE APPENDIX

Neuroendocrine Proliferations of the Stomach

Approximately five percent of all gastrointestinal neuroendocrine tumors involve the stomach and most (up to 80%) are associated with atrophic gastritis (1,2). There are important pathologic, epidemiologic, and prognostic differences between sporadic gastric carcinoids (so-called type 3) and those associated with hypergastrinemic states such as atrophic gastritis.

Sporadic gastric carcinoids make up approximately 15% of gastric carcinoids but are responsible for almost all examples of carcinoid tumor metastatic from the stomach (1-5). The gastric primary tumors often form isolated masses. Gastric carcinoid tumors may produce 5-hydroxytryptophan, gastrin, or ACTH; however, systemic syndromes (e.g., carcinoid syndrome, Cushing syndrome) rarely occur. Histologically, sporadic gastric carcinoids typically have a foregut carcinoid tumor pattern with neoplastic cells forming ribbon-like arrangements. Trabeculae and rosette patterns occasionally occur. Immunoperoxidase stains are usually positive for the pan-neuroendocrine markers such as chromogranin and synaptophysin. Factors associated with metastasis include large size (71% of tumors > 2 cm that also have muscularis externa or vascular invasion have lymph node metastasis), and aggressive histologic features (intermediate or high-grade neuroendocrine carcinomas). Gastric carcinoids with aggressive histologic features are sometimes referred to as type 4. In the latest WHO classification, a grading system based on mitotic activity and Ki-67 staining has been adopted (3). Grade 1 tumors must have < 2 mitoses per 10 high magnification fields and ≤ 2% of Ki-67 positive nuclei; grade 2 can have 2-20 mitoses per 10 high magnification fields and > 2% to 20% Ki-67 positive nuclei. The grade 3 or high-grade neuroendocrine carcinomas are usually subclassified as small cell or large cell type and have > 20 mitoses per 10 high magnification fields and > 20% of the nuclei that are Ki-67 positive.

The carcinoids associated with atrophic gastritis (type 1) merit special consideration. Patients with atrophic gastritis manifest achlorhydria or hypochlorhydria (7-11). This absence of gastric acid leads to compensatory hypergastrinemia. The high gastrin levels have a trophic effect on gastric enterochromaffin-like (ECL) cells causing hyperplasia, dysplasia and small carcinoid tumors (microcarcinoidosis) (12-14). Hypergastrinemia-associated gastric carcinoids are also seen with the Zollinger-Ellison syndrome associated with MEN syndrome type 1 (so-called type 2), and have been seen in an extremely rare disorder caused by an intrinsic acid secretion abnormality of the parietal cells (no type assigned) (15).

Histologically, patients with “hypergastrinemic” type 1 carcinoid tumors have gastric atrophy with reduced or absent gastric glands and extensive intestinal metaplasia. Additionally, near the base of the crypts and glands round to cuboidal cells with round and regular nuclei containing coarsely granular chromatin proliferate. These cells often nest in an “endocrinoid” fashion and may infiltrate the muscularis mucosae or beyond. The appearance of these cells is typical of ECL-cell hyperplasia, endocrine cell dysplasia, microcarcinoids, and carcinoid tumors that can coexist with atrophic gastritis and hypergastrinemia.

The distinction between ECL-cell hyperplasia and carcinoid tumor is arbitrary. Some authors suggest that only ECL-cell nodules greater than 1 cm be considered carcinoid tumors (7). Another proposed histologic classification of gastric endocrine cell proliferation occurring in the setting of chronic atrophic gastritis differentiates hyperplasia, dysplasia, and neoplasia (16,17). The hyperplasias (defined as five or

more endocrine cells in a chain or cluster) encompass growths up to 150 microns in diameter. Dysplasia describes growths measuring 150 microns to 0.5 mm. Lesions greater than 0.5 mm are considered carcinoid tumors (neuroendocrine tumors) and are further subclassified as intramucosal or invasive (1,16,17).

An alternative nomenclature based on the WHO classification has been offered in the CAP protocol (1,3). *Well differentiated neuroendocrine tumor* is proposed for grade 1 tumors measuring less than 1 cm that are confined to the mucosa and/or submucosa. As a subset of this, nodules 0.5 mm to 1 cm can be referred to as *microendocrine tumors*. These well differentiated neuroendocrine tumors act in a benign fashion. Grade 1 tumors measuring 1 cm to 2 cm and confined to the mucosa/submucosa are considered as having uncertain malignant potential. Grade 1 tumors that are greater than 2 cm, those that invade the muscularis externa or beyond, and those associated with metastases are referred to as *well differentiated neuroendocrine carcinoma* and are considered a tumor of low malignant potential. *Intermediate grade and high-grade neuroendocrine carcinomas* are more aggressive with metastasis common and a poor prognosis. In practice, carcinoid tumors arising in the setting of gastric atrophy, hypergastrinemia and ECL-cell hyperplasia rarely metastasize.

Treatment of atrophic gastritis with ECL-cell hyperplasia and carcinoids remains controversial. Some have promulgated endoscopic management with removal of larger carcinoids (7). Subtotal gastrectomy has also been used. Isolated antrectomy represents the most intellectually satisfying treatment strategy because it removes the gastrin-producing cells (18-21). In the absence of the trophic factor (gastrin), reversal of the ECL-cell hyperplasia and disappearance of carcinoids have occurred. The use of long-acting SST analogues may be efficacious but require repeated injection, continued endoscopic surveillance and are associated with adverse reactions such as hypertension.

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Neuroendocrine Cell Proliferations/Neoplasms of the Vermiform Appendix

Discussion of appendiceal neuroendocrine neoplasms must begin with a description of the phenomenon referred to as fibrous obliteration/appendiceal neuroma. Fibrous obliteration occurs commonly with a prevalence of nearly 30% of resected appendices. Microscopically, fibrous tissue, chronic inflammatory cells, and neuronal and neuroendocrine cell proliferations obliterate the appendiceal lumen. The latter two can be highlighted by S100 protein and pan-endocrine immunostaining. Interestingly, “appendiceal carcinoid” often coexists with fibrous obliteration. Some believe “appendiceal carcinoid’s” excellent prognosis (versus other gut carcinoids) relates to the fact that many reported as carcinoids may in fact be exaggerated neuroendocrine cell hyperplasia seen in an otherwise typical fibrous obliteration/appendiceal neuroma. Currently, I require the following for a diagnosis of appendiceal carcinoid; 1) a collection of tumor cells demonstrating an insular or tubular growth pattern with extension of cells into or through the appendiceal muscular wall or 2) a proliferation of neuroendocrine cells producing a gross nodule or gross expansion of the appendiceal wall.

Having described minimum criteria for the diagnosis of appendiceal carcinoid, three variant types based on histologic and clinical features can be recognized: insular carcinoid, tubular carcinoid, and goblet cell carcinoid (synonyms: microglandular carcinoma, goblet cell carcinoma, crypt cell carcinoma, adenocarcinoid, composite carcinoid, mucinous carcinoid).

Insular carcinoid consists of nests or sheets of polygonal cells containing round to oval nuclei with stippled chromatin. The cytoplasmic cell borders are usually indistinct. The cytoplasm often stains eosinophilic and is sometimes granular. The neoplastic cells of tubular carcinoid arrange in small, well-organized tubules and trabeculae. Some of the tubular lumens may contain mucus and can be confused with adenocarcinoma. The neoplastic cells are cuboidal with a peripherally placed round nucleus with stippled chromatin. The neoplastic cells usually demonstrate positive immunostaining for CEA and variable staining for chromogranin. The insular and tubular carcinoids of the appendix usually measure less than 1 cm in greatest cross dimension, occur near the appendiceal tip, and generally act in a benign fashion. Right hemicolectomy is recommended for carcinoid tumors larger than 2 cm or for incompletely excised tumors.

Goblet cell carcinoid has features intermediate between insular carcinoid and well-differentiated adenocarcinoma. Goblet cell carcinoids typically infiltrate the appendiceal wall causing a grossly subtle thickening. Mucosal involvement is frequently limited to a proliferation around the base of the crypts. Goblet cell carcinoid infiltrates as small uniform nests or strands of tumor cells. Most cells resemble goblet cells with prominent intracytoplasmic mucin and a crescent-shaped nucleus located at the cell’s periphery. Neuroendocrine cells are frequently absent or in the minority and the typical immunostaining profile shows diffuse positive staining for CEA with only scattered chromogranin positive cells. It is important to recognize goblet cell carcinoid because the prognosis (5 year survival of 80%) is worse than insular and tubular carcinoids (5 year survival of 95%) but is far better than invasive adenocarcinoma (5 year survival of 50%). Right hemicolectomy is the preferred treatment for appendiceal goblet cell carcinoids that have penetrated the muscularis externa of the appendix, for incompletely resected tumors, and for those tumors having greater than 2 mitoses per 10 high magnification fields (although this may relate to coexisting adenocarcinomas-see below).

A common diagnostic pitfall involves invasive adenocarcinoma containing neuroendocrine cells or showing areas of carcinoid tumor. Many invasive adenocarcinomas of the appendix, colon and rectum contain small numbers of neuroendocrine cells. As a general rule, if any part of the tumor has an infiltrative pattern and cellular morphology typical of intestinal adenocarcinomas, they behave like adenocarcinoma and should not be diagnosed as carcinoids or adenocarcinoids simply because they contain scattered focal carcinoid-like areas of neuroendocrine cells.

Incomplete surgical excision of appendiceal neoplasms represents a major indication for right hemicolectomy. Since neoplasms of the appendix are frequently discovered incidentally during microscopic evaluation of the specimen, we recommend routine sampling of the resection margin.

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TUMORS AND TUMOR-LIKE LESIONS OF THE VERMIFORM APPENDIX (EXCLUDING CARCINOID TUMOR AND ITS VARIANTS)

Mucosal Hyperplasia/Hyperplastic Polyps

Hyperplasia of the appendiceal mucosa can occur as a localized polyp or as a diffuse process involving the appendiceal mucosa (2,5,36,44,48,50a,66). Most cases are found coincidentally in women, probably reflecting the increased frequency of incidental appendectomy in women. Most patients are older than 40 (2,5,36,44,48,66). Histologically, localized polyps closely resemble and probably are identical to the common hyperplastic polyp of the large intestine (5). There is a proliferation of columnar and goblet cells associated with elongation and dilatation of tubules with serration of the luminal outlines. Some investigators report subtle differences between appendical hyperplastic polyps and more typical colonic hyperplastic polyps such as an increase in goblet cells relative to the number of columnar cells and the lack of a thickened surface basement membrane (2). Some of these may represent sessile serrated polyps. The diffuse form of hyperplastic polyp can be difficult to differentiate from sessile serrated polyp, villous adenoma with low-grade dysplasia, and serrated adenoma. In this setting, the diagnosis of hyperplastic polyp must be based on essentially normal sized nuclei with little or no hyperchromasia and no stratification. More diffuse mucosal hyperplasias with any cytologic deviation or those in association with appendiceal luminal dilatation by mucus are best interpreted as adenomas/cystadenomas (see below).

Mucocele

Few terms in pathology have caused as much controversy as *mucocele*. If mucocele is to be used at all, it is best to limit its usage to describing a grossly dilated appendix filled with mucus (i.e., a gross descriptive term only). Mucocele cannot be used as a specific diagnostic term because its use in the literature encompasses a morphologically and pathologically diverse group of neoplastic and apparent non-neoplastic conditions. Neoplastic conditions such as mucinous cystadenoma and cystadenocarcinoma account for most (if not all) of the reported mucoceles (5,50a). Cases reported as non-neoplastic mucosal hyperplasia producing enough mucus to cause mucocele probably are in fact mucinous cystadenomas with low-grade epithelial dysplasia.

The terms “retention-cyst” and “simple mucocele” have been used to refer to an appendix with sterile outflow obstruction with resultant intraluminal mucus accumulation and luminal dilatation (1,5). Such cysts are usually small, rarely exceeding 5 to 6 mm in diameter. Obstruction of the appendiceal lumen can be caused by a variety of conditions, including fecalith, endometriosis, carcinoid tumors, or cecal tumors. The mucosa in such cases must be extensively sampled and remain histologically normal or show a flat atrophic mucosa lacking the features of hyperplasia or dysplasia. If all of these conditions are met, such “retention cysts” or “simple mucoceles” are of no clinical significance. It is probable that many cases reported as “retention cyst” or “simple mucocele” associated with appendiceal dilatation of 1 cm or more, actually represent cystadenomas in which the neoplastic epithelium was not sampled or was overlooked.

Myxoglobulinoses is a rare cause of appendiceal dilatation and is characterized by intraluminal mucin and pearl-like globules which occasionally calcify (19). Histologically, the globules consist of faintly eosinophilic laminations of mucin surrounding an amorphous granular and/or mucinous core. Myxoglobulinoses, like mucocele, is merely a descriptive term and does not imply any specific pathologic diagnosis.

Epithelial Neoplasms

Non-cystic Colonic-type Adenomas

Localized non-cystic colonic type adenomas identical to those seen elsewhere in the colon occur in the appendix but are extremely rare (2,5,24,50a). Architecturally, these adenomas may be classified as tubular, tubulovillous, or villous. Most appendiceal non-cystic adenomas are sessile, but rarely, a small stalk can be seen. The epithelium has the features of dysplastic colonic epithelium with mucin depletion, cellular crowding, nuclear elongation, stratification, nuclear hyperchromasia, pleomorphism and increased number of mitotic figures. Non-cystic adenomas of the appendix may be isolated, associated with other colonic adenomas or neoplasms, and can be seen in the setting of familial adenomatous polyposis (5).

Mucinous Cystadenoma (Villous Adenoma)

Mucinous cystadenomas of the appendix are much more common than the non-cystic colonic type adenomas (2,5,50a). The distinction between cystadenoma and adenoma is arbitrary. It is likely that non-cystic colonic type adenomas of the appendix increase in size and cause the intraluminal accumulation of mucus with resultant luminal dilatation (cystadenoma). Mucinous cystadenomas occur in patients in the second through ninth decades of life with a peak incidence in the seventh decade. Although a large number of cases are discovered coincidentally, some patients present with signs and symptoms of acute appendicitis. Others have palpable abdominal masses, usually in the presence of appendiceal rupture and extravasation of mucus into the peri-appendiceal soft tissues or abdomen (pseudomyxoma peritonei).

Cystadenomas show variable cystic lumen dilatation and are filled with usually viscid mucin. The appendiceal wall often becomes thin and fibrotic. Some appendices show gross evidence of rupture and fibrosis within the surrounding soft tissues caused by a localized reaction to extravasated mucus. Occasionally, a thickened mucosa or even villous fronds can be visualized grossly. Extrusion of mucus onto the external surface of the appendix is an important finding because it may be associated with concurrent or subsequent pseudomyxoma peritonei and is associated with a worse prognosis (5,50a).

Most cystadenomas are lined by epithelium typical of villous adenomas seen elsewhere in the intestines and are composed of histologically crowded columnar cells with basally oriented elongated hyperchromatic nuclei, sometimes with large blobs of apical mucus (2). The dysplasia, which can be extremely low-grade, is typically accentuated in the crypt bases and lessens toward the tips of the villi. The villous adenomas are usually diffuse and completely replace the mucosa (so-called “diffuse circumferential adenoma”) (2). Some appendiceal cystadenomas demonstrate a more undulating architecture or mucosa typical for “serrated adenoma” (mixed adenoma/hyperplastic polyp) although this is more likely a sessile serrated polyp admixed with serrated adenoma or more conventional adenoma (5). Others may histologically resemble ovarian mucinous tumors of low malignant potential (2). Epithelial ulceration may occur and the mucin can elicit a stromal foreign body giant cell reaction, granulation tissue, chronic inflammation, fibrosis, or calcification. Many cystadenomas can have epithelial cells that are highly dysplastic and otherwise typical adenomas/cystadenomas can be found adjacent to an invasive appendiceal adenocarcinoma, suggesting that an adenoma (dysplasia)-carcinoma sequence similar to that proposed in the colon also affects the appendix (40,49,50a,63,64,65). Like non-cystic adenomas, cystadenomas may be isolated, or associated with other colonic adenomas or carcinomas (5,66). Therefore, the discovery of an adenoma or cystadenoma of the appendix should prompt examination of the remainder of the colon.

When significant amounts of mucus accumulate in the lumen, the resultant increased intraluminal pressure may cause adenomatous epithelium to herniate through points of weakness in the muscularis

mucosae or muscularis externa, resulting in misplaced epithelium and dissecting mucus lying deep in the appendiceal wall (29,65). This herniation may be difficult to distinguish from invasive well-differentiated or mucinous adenocarcinoma. An infiltrating or dissecting pattern to neoplastic glands/mucus, and at least some desmoplastic stromal reaction are required to diagnose invasive adenocarcinoma (50a). Mucinous cystadenomas frequently show widespread thinning or absence of the muscularis mucosae associated with hyalinizing fibrosis of the submucosa. Occasionally, this fibrosis and thinning replaces even the muscularis externa. This fibrosing process can make recognition of tumor desmoplasia difficult or impossible. If infiltrating dissecting mucus pools extend to the serosal surface and the possibility of an invasive mucinous adenocarcinoma cannot be excluded, some investigators have applied the term “mucinous tumor of uncertain malignant potential” (5). Pools of mucus may also dissect into and through the appendiceal wall and spill into the peri-appendiceal soft tissues, eliciting usually a fibrotic response (localized pseudomyxoma peritonei) (28). On rare occasions, large amounts of mucus may be found extruded into the peritoneal cavity (diffuse pseudomyxoma peritonei).

Invasive Adenocarcinoma of the Appendix

Invasive adenocarcinoma of the appendix is rare and certainly less common than adenomas. They can be solid, non-cystic masses or more often present as cystic tumors (mucinous cystadenocarcinoma). Histologically, appendiceal adenocarcinomas can be classified similarly to colonic adenocarcinomas, into intestinal, mucinous, and signet ring cell types (2,5,50a). The peak age of incidence is similar to that of colonic adenocarcinoma being most often found in the fifth to seventh decade (10,42). There is a slight male predominance (5,15). About 25% of cases are discovered coincidentally. Seventy-five percent of patients are symptomatic and may present with signs and symptoms of acute appendicitis, a palpable abdominal mass, or complications of pseudomyxoma peritonei, such as intestinal obstruction.

Mucinous cystadenocarcinomas are often indistinguishable from cystadenomas on gross examination and presentation (24). If rupture of the appendix occurs, a localized or diffuse form of pseudomyxoma peritonei may also occur. The diagnosis of invasive adenocarcinoma requires an infiltrative pattern of neoplastic glands and at least some desmoplastic stromal response. Signet ring cell carcinoma, which closely resembles those found elsewhere in the gastrointestinal tract, is rare and has a particularly poor prognosis (50). Signet ring cell adenocarcinoma should be distinguished from the pure microglandular goblet cell carcinoma (goblet cell carcinoid tumor) which characteristically arises from the basal glandular portion of the mucosa, spares the luminal mucosa, infiltrates in an insular pattern without tumor desmoplasia and has a much better prognosis than signet ring cell adenocarcinoma. Many signet ring adenocarcinomas arise in association with microglandular goblet cell carcinomas.

Although controversial, most studies advocate right hemicolectomy for invasive adenocarcinoma of the appendix (3,7,24,32,42,54). Carcinoma should be staged according to the TNM Classification of the International Union Against Cancer (UICC) (23). Stage is significantly associated with patient outcome, with 5-year survival rates of 100%, 67%, 50% and 6%, for stages I, II, III, and IV, respectively (42). In difficult cases complicated by dissecting mucus, the depth of the malignant epithelial cells rather than the depth of the dissecting mucus has been suggested as the determinant of the T-category (5). If pseudomyxoma peritonei is present, many advocate the meticulous removal of mucus and peritoneal implants (“bailing out procedure”) (16,38,57). Interestingly, the presence of pseudomyxoma peritonei alone or pseudomyxoma peritonei with perforation does not seem to independently affect prognosis in appendiceal adenocarcinoma (42). Repeat laparotomy with debulking to relieve bowel obstruction and recurrent disease is thought to increase survival (3,17,38,57).

Pseudomyxoma Peritonei

The literature regarding pseudomyxoma peritonei can be confusing. Some have used the term to refer to an accumulation of gelatinous ascites in the peritoneal cavity, regardless of whether epithelium is present (18,47). Others reserve this term for diffuse peritoneal involvement by a malignant mucin-producing tumor (16,24,30,57). Adopting the former definition for this discussion, rupture of a mucinous cystadenoma or cystadenocarcinoma can lead to pseudomyxoma peritonei. We agree with those authors who believe that adenomatous epithelium can be found in peritoneal mucus from appendiceal cystadenomas (5,18,47,50a,64) and disagree with those who diagnose appendiceal cystadenocarcinoma if any epithelium (even adenomatous epithelium with low-grade dysplasia) is found in peritoneal mucus regardless of whether actual invasive carcinoma of the appendix is found (24,57). However, regardless of what the primary appendiceal lesion is considered, it is generally agreed that the finding of mucus outside the right lower quadrant and the presence of epithelium in the peritoneal mucus especially epithelium showing high-grade dysplasia portends a worse prognosis with an increased risk of recurrence and increased complications, such as bowel obstruction (5,47,57).

Patients with adenomas/cystadenomas with localized pseudomyxoma peritonei and no peritoneal mucus at all, have an excellent prognosis after simple appendectomy. Patients with diffuse peritoneal mucus do somewhat worse and the finding of epithelial cells in the extravasated mucus generally imparts a worse prognosis (regardless of whether they are considered cystadenomas or cystadenocarcinomas) (5,47). Finally, those patients with pseudomyxoma peritonei associated with frankly invasive adenocarcinoma have a grave prognosis (53). It should be noted, however, that many deaths in patients with pseudomyxoma peritonei are not due to metastatic carcinoma per se but are related to bowel obstruction and septic complications of either disease or surgery (47).

Pathologists dealing with a case of pseudomyxoma peritonei should attempt to address all potential prognostic factors within the body of their report. The appendiceal primary tumor should be classified as benign (cystadenoma) or malignant (cystadenocarcinoma) using criteria outlined above. We do not advocate the use of the term, “mucinous tumor of low malignant potential” for equivocal cases. The degree of pseudomyxoma can frequently be classified as localized or diffuse. The amount of epithelium within the extravasated mucus should be semiquantitated as absent, few or many and then, the highest degree of cellular dysplasia noted (e.g., low-grade or high-grade).

Coexisting Appendiceal and Ovarian Neoplasms

The relationship between appendiceal and ovarian mucinous tumors, especially in the setting of pseudomyxoma peritonei, remains controversial (37,52,53,67,68). Secondary spread of primary ovarian neoplasms to the appendix is relatively common, but is typically limited to the outer appendiceal wall, serosa, and subserosa, and is associated with disease in other sites (37,67). In those female patients with concurrent appendiceal and ovarian mucinous tumors, some authors believe that the lesions are independent and arise as part of a multifocal neoplastic process (55,60). Others believe that the ovarian tumors invariably represent “metastases” or implantation from a primary appendiceal mucinous neoplasm. This latter argument is supported by the increased frequency of bilateral ovarian tumors observed in the presence of the appendiceal tumor as compared with ovarian tumors alone (22,67) as well as a preponderance of right-sided ovarian tumors in those cases of ovarian and appendiceal mucinous tumors, an indication that this predilection may be the result of the proximity of the appendix to the right ovary (67). Experience with cytokeratin 7 and 20 expression, K-ras mutations and chromosomal abnormalities supports an appendiceal origin for almost all of these tumors (13,21,51,61). Other genetic and immunocytochemical analyses seem to support two separate primary lesions in only a few patients (8,20). Given the continued controversy, the recommendations outlined by Carr and Sobin seems reasonable (6). In cases of pseudomyxoma peritonei and mucinous neoplasms apparently primary in the

ovary, appendectomy should be performed in all cases. If appendectomy is not possible, the surgeon should carefully inspect the appendix at operation. The pathologist should sample a resected appendix adequately, perhaps even totally submitting the organ for histologic analysis.

Other Tumors of the Vermiform Appendix

Neurofibromas can be found anywhere in the gastrointestinal tract. Rare cases of appendiceal neurofibromas have been described, some of which have been manifestations of von Recklinghausen's disease (25,39,43). These tumors resemble neurofibromas as described elsewhere. The gastrointestinal tract is a rare site for granular cell tumors; however, in one study, 4 of 74 cases were found in the appendix (26). The tumors are composed of polygonal cells with bland nuclei and granular cytoplasm. Immunohistochemistry demonstrates strong S100 protein positivity. Granular cell tumors must be distinguished from granular cell transformation of the appendiceal smooth muscle (58). The latter can be distinguished by negative immunoreactivity to S100 protein and /or the ultrastructural demonstration of actin-like filaments. Paraganglioma, heterotopic tissues and endometriosis can also cause appendiceal tumors (9,11,14,31,62). Ganglioneuromas occur in the appendix but are extremely rare (69). Some have been associated with von Recklinghausen's disease (34). Examples of smooth muscle tumors/gastrointestinal stromal tumors (GISTs) (27,46), fibrosarcoma, liposarcoma, and malignant lymphoma (12,33,35,66) have been described in the appendix but are extremely rare.

Fibrous Obliteration (Appendiceal Neuroma)

Partial or complete obliteration of the appendiceal lumen is relatively common and has been reported in up to 35% of surgical specimens. The process typically affects the distal appendix but occasionally the entire lumen is obliterated. Histologically, the lumen is replaced by a collection of spindled cells in a loose fibromyxoid background, mixed with variable numbers of chronic inflammatory cells, fat, and collagen. Usually, there is a loss of mucosa, crypts, and lymphoid follicles.

Some studies suggest that many of these cases represent a neurogenic proliferation and have been termed "appendiceal neuromas" or "neurogenic appendiculopathy" (4,59). Most of the spindled cells are S100 protein positive and have the ultrastructural features of Schwann cells. There are also cells that stain with neuron-specific enolase and chromogranin, an indication that neuroendocrine cells may be an integral part of this proliferation (59). Intramucosal neuromas that resemble the central obliterative form may also occur and expand the lamina propria and separate the crypts (59). These neuromas are typically found incidentally in appendectomy specimens. They are likewise composed of cells that stain with S100 protein, neuron-specific enolase, and chromogranin. The pathogenesis of appendiceal neuromas remains unclear. Most investigators doubt that it is a sequela of appendicitis and many believe that the fibrous obliteration-appendiceal neuroma may be the result of hyperplasia of the neuroendocrine cells (59). Interestingly, "appendiceal carcinoids" are often reported in association with fibrous obliteration-appendiceal neuroma. Perhaps the excellent prognosis of appendiceal carcinoid (relative to other gut carcinoid tumors) is due to the fact that many reported cases may be exaggerated endocrine-cell hyperplasia, seen in otherwise typical fibrous obliteration. Strict criteria must be used to differentiate appendiceal carcinoid from fibrous obliteration/appendiceal neuroma, which include neoplastic cells with a definite insular pattern, extension of neuroendocrine cells into or through the muscularis propria, association of a neuroendocrine cell proliferation with a gross nodule or thickening of the appendiceal wall (45).

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GASTROESOPHAGEAL REFLUX AND EOSINOPHILIC ESOPHAGITIS

Gastroesophageal Reflux

Gastroesophageal reflux disease (GERD) describes a symptomatic clinical condition related to reflux of gastric and/or duodenal contents into the esophagus that usually presents with pyrosis (heartburn), acid regurgitation, and dysphagia. The term reflux esophagitis refers to a subset of patients, usually but not always having symptoms of GERD, who show endoscopic and/or histological manifestations of inflammation within squamous and/or gastric cardia type mucosa (1).

Although increasing numbers of patients are initially given a trial of proton pump inhibitors, many consider esophagoscopy (with biopsy) a prudent initial evaluation for patients with symptoms of GERD (1). It quickly excludes other conditions in the clinical differential such as gastritis, infective esophagitis, “pill esophagitis”, and peptic ulcer disease.

The endoscopic changes described with GERD are seen more often in severe cases and include erosions, ulcers, and stricture. Biopsy specimens are generally obtained to rule out infection and malignancy and to establish a diagnosis of Barrett’s esophagus. Erosive lesions are often sampled to rule out *Candida* species and herpes virus infection. Approximately one-third of patients with reflux have endoscopically normal or only slightly hyperemic esophageal mucosa; however, endoscopic biopsy specimens will show characteristic histologic changes (see below) (2). Some consider histologic evaluation of biopsy specimens the “gold standard” in the diagnosis of GERD and reflux esophagitis.

Histologic Changes – Squamous Mucosa

Well-oriented normal esophageal squamous mucosa demonstrates a basal cell layer that is usually 1-3 cells thick. These basal cells can be discerned by their smaller size and their more basophilic cytoplasm as compared to normal surface squamous cells. The cytoplasmic appearance of basal cells and their relative lack of glycogen can be highlighted with the PAS-stain. Lamina propria papillae are present, but make up only one-half of the total epithelial thickness (3,4).

Biopsy specimens from endoscopically demonstrable lesions in GERD (erosions, ulcers) show acute inflammation of the mucosa and submucosa. Exudates contain neutrophils and eosinophils often overlying an erosion or an ulcer with an inflamed granulation tissue base. Acute inflammation is fairly specific but insensitive for reflux (4,5). Many patients with clinical symptoms and with the acid abnormalities of GERD as measured by intraesophageal pH probes have endoscopically normal appearing esophagi or only show minimal esophageal changes such as hyperemia and lack neutrophils in biopsy specimens. These patients show characteristic squamous mucosal changes of reflux esophagitis consisting of hyperplasia (lamina propria papilla greater than 67% of the thickness of the squamous epithelium) and an increase in the basal cell layer (greater than 15% of the squamous epithelial thickness) (4-6). These abnormalities are often accompanied by increased numbers of intraepithelial eosinophils and lymphocytes (4-10).

Histologic Changes - Glandular Mucosa

Several investigators have suggested that the presence of gastric cardia-type mucosa in the esophagus at or near the squamocolumnar junction may be metaplastic and that inflammation of this metaplastic gastric cardia-type mucosa (so-called “carditis”) is highly correlated with reflux (11,12). Oberg and colleagues, in a study of 334 patients, convincingly linked inflammation and intestinal metaplasia of gastric cardia mucosa at the squamocolumnar junction to GERD (as documented by abnormal lower esophageal sphincter manometry and increased esophageal acid exposure measured by pH probe) and not to

Helicobacter pylori infection (11). In contrast, other investigators have concluded that this “carditis” is a manifestation of gastric *Helicobacter pylori* infection (13-15).

After critical review, coupled with my own observations, I have come to the conclusion that both schools of thought are correct. These apparent disparate viewpoints can be reconciled based on methodologic differences and inherent biases within these studies. For instance, Oberg et al. obtained biopsy specimens from the esophagus directly at the squamocolumnar junction. Furthermore, they performed fairly sophisticated tests (e.g., pH monitoring, esophageal manometry) to establish GERD (11). In contrast, Goldblum et al. obtained their biopsy specimens in the stomach 5 mm below the squamocolumnar junction and prospectively did more tests (e.g., special stains, serology) to establish a diagnosis of *Helicobacter pylori* infection. Furthermore, these authors based a diagnosis of GERD on symptoms alone. (13)

I believe that biopsy specimens from the stomach even millimeters below the squamocolumnar junction reflect disease processes of the stomach. Therefore, inflammation and intestinal metaplasia in that area are highly correlated with *Helicobacter pylori* infection. *Helicobacter pylori*-associated pangastritis can affect the gastric cardia and can also cause inflammation in the esophagus at the squamocolumnar junction. Although statistical correlation between this form of “carditis” and *Helicobacter pylori* exists, these studies also argue strongly for other causes of inflammation in gastric cardia-like mucosa at the esophagogastric/squamocolumnar junction that are not associated with *Helicobacter pylori*. For instance, over 70 percent of the “carditis” described by Spechler et al. was not associated with *Helicobacter pylori* infection (15) and approximately 12 percent of the intestinal metaplasia found at the gastric cardia by Goldblum et al. was not associated with *Helicobacter pylori* infection (13). In these studies, this non-*Helicobacter pylori* “carditis” did not necessarily correlate with symptoms of GERD because it may reflect the physiologic response of the region to low level reflux of gastric contents (a normal phenomenon) (1). However, “carditis” at the esophagogastric junction or above is also characteristic of patients with gastroesophageal reflux disease as demonstrated by symptoms, manometric and pH probe abnormalities.

Similar to “carditis”, the etiology and the significance of intestinal metaplasia at the gastroesophageal junction is the subject of considerable debate (16,17) that raises a number of interesting/important questions. Is intestinal metaplasia at the gastroesophageal junction caused by *Helicobacter pylori* or reflux? Can intestinal metaplasia in the gastric cardia at or near a “normally” located gastroesophageal junction be reliably distinguished from the specialized columnar epithelium of Barrett’s esophagus? Is intestinal metaplasia at a “normally” located gastroesophageal junction associated with an increased risk of adenocarcinoma?

Although the answers to these questions remain unknown, there is evidence that differential cytokeratin staining may be exploited in a classification system for intestinal metaplasia at the gastroesophageal junction. Ormsby and colleagues showed that superficial mucosal staining for cytokeratin 20 combined with strong cytokeratin 7 staining of both superficial epithelium and deep glands was virtually unique to specialized columnar epithelium of Barrett’s esophagus (18,19). These observations have also been verified by others (20,21). Differential staining for cytokeratins 7 and 20 may also help distinguish gastric carcinoma from adenocarcinoma arising in Barrett’s esophagus (22,23).

Differential Diagnosis

Infectious Esophagitis

Herpetic esophagitis typically occurs in immunosuppressed (e.g., AIDS, chemotherapy, bone marrow transplant) patients (24). Endoscopically, ulcers occur and are typically described as shallow and

“punched out” with adjacent normal-appearing squamous mucosa. Biopsy specimens demonstrate an ulcer base that is relatively bland in terms of acute inflammation but may have prominent aggregates of larger mononuclear cells (24). The diagnostic epithelial changes are found in the adjacent squamous mucosa with giant cell formation, ground-glass nuclei, and eosinophilic intranuclear (Cowdry type A) inclusions (25,26). Occasional multinucleated epithelial giant cells without viral inclusions can be seen as part of regeneration in esophagitis and should not be confused with herpetic infection (27).

Inclusions of cytomegalovirus (CMV) can be seen in the base of some esophageal ulcers. The role CMV plays as a primary etiologic agent can be difficult to prove. CMV inclusions typically effect mesenchymal cells such as fibroblasts, smooth muscle, and endothelial cells, and usually spare the epithelium (28,29).

Candida species esophagitis usually presents endoscopically as brownish-white plaques with exudate that has been described as “cheesy.” *Candida* esophagitis often occurs in patients with other debilitating illnesses, such as immunosuppression, diabetes mellitus, and long-term antibiotic therapy. The diagnosis of *Candida* esophagitis requires the identification of budding yeast and pseudohyphae, usually within the inflammatory exudate. Their identification is certainly enhanced by using special stains for fungi. I recommend routine use of an Alcian blue/PAS combination stain with a hematoxylin counterstain because it is a useful fungal stain, it highlights the basal cell layer, it vividly decorates signet ring cell adenocarcinoma making it easier to identify and can be used to verify the specialized columnar epithelium of Barrett’s esophagus.

Allergic (Eosinophilic) Esophagitis in Children and Adults

Symptomatic and histologic reflux esophagitis can certainly occur in children (30). One should, however, be wary of diagnosing reflux esophagitis in the presence of large numbers of eosinophils because many of these cases could represent “allergic (eosinophilic) esophagitis”, a condition related to eosinophilic gastroenteritis (31-33). Children with allergic esophagitis usually present with dysphagia or “food-catching”, and often have an “allergic history”. Endoscopic erosions or ulcers are seldom seen but many patients exhibit esophageal furrows or rings (34). Esophageal pH probe studies have shown normal or borderline acid levels in these children and the symptoms of allergic esophagitis will typically not respond to acid suppression therapy. Walsh and colleagues have found that the most useful histologic criteria to differentiate allergic esophagitis from reflux esophagitis are: large numbers of intraepithelial eosinophils, intramucosal eosinophilic aggregates, and superficial eosinophils (31).

Once thought to be only a pediatric disease, it is now clear that eosinophilic esophagitis is not uncommon in adults (35-39) in which the disease may have been “unmasked” because of the change in medical management of reflux (antihistamines vs. PPIs) (40). In adults, eosinophilic esophagitis more often affects men who often present with dysphagia for solid foods and have a number of endoscopic correlates including uniform small caliber esophagus, single or multiple rings (corrugation), proximal esophageal stenosis or small whitish vesicles (35-37). A single esophageal ring must be distinguished from the mucosal or Schatzki’s ring which is very common (6% - 14% of patients) in the distal esophagus. This ring can be congenital or acquired through reflux and is usually asymptomatic. Patients with eosinophilic esophagitis often have a history of asthma or atopy. Adults and children are treated similarly with elemental diets, corticosteroids, mast cell stabilizers and swallowed fluticasone (38,39).

Consensus recommendations sponsored by the AGA and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition have suggested the following diagnostic guidelines: a) symptoms of esophageal dysfunction, b) ≥ 15 eosinophils per one high magnification field, c) lack of response to PPIs, d) normal esophageal pH and exclusion of other diseases associated with eosinophilia

(41). The definitional exclusion of reflux is controversial because there is probably no reason why both conditions could not coexist.

“Pill Esophagitis”

Esophageal injury can occur with prolonged direct mucosal contact with medicinal tablets or capsules, even in therapeutic doses (42-46). Symptomatic “pill esophagitis” has been associated with odynophagia (pain on swallowing) or a feeling of a “lump in the throat”. Lesions have been associated with various drugs including antibiotics, alendronate, potassium chloride, ferrous sulfate, quinine and nonsteroidal anti-inflammatory drugs. Patients frequently give a history of taking pills “on the run” with little or no water (44). Endoscopic erosions and ulcers are found in more proximal locations of the esophagus (versus GERD), often in areas of external esophageal compression such as near the arch of the aorta or near the left atrial appendage especially in patients with cardiomegaly. The histology of “pill esophagitis” is nonspecific but tends to show endothelial proliferation sometimes with vascular thrombosis.

A dramatic endoscopic lesion referred to as esophagitis dissecans superficialis or “sloughing esophagitis” has on occasion been associated with medication such as bisphosphonates for osteoporosis (47,48). Endoscopists often note whitish strips of peeling esophageal mucosa. Some patients have even vomited tubular casts made up of degenerating squamous mucosa. Histologically, there is intraepithelial splitting with the luminal layer showing bland necrosis of squamous epithelium with little or no inflammation, occasionally with bacterial colonization. Similar histology can be seen with strictures in which the superficial necrosis might represent trauma/pressure damage and indeed cases of sloughing esophagitis have been described following particularly traumatic esophagoscopy and in esophageal motility disturbances (47). Other associations with sloughing esophagitis have included bullous skin conditions, cigarette smoking and immune deficiency.

“Lymphocytic Esophagitis”

Increased intraepithelial lymphocytes within esophageal squamous mucosa is best thought of as non-specific and can certainly be part of reflux (49). Prominent lymphocytosis should, however, bring up a number of additional differential diagnostic considerations. For instance, this histology can be seen in young patients and has been apparently associated with pediatric Crohn’s disease. Many with increased lymphocytes within squamous mucosa have an allergic history in which the esophageal histology may be a manifestation of an allergic contact mucositis. Intraepithelial lymphocytosis is also seen in achalasia, pseudoachalasia (achalasia-like clinical syndrome associated with cancer), Candida esophagitis and interface mucositis (e.g., lichen planus and lichenoid drug eruption) (50). Lichen planus can involve the esophagus and demonstrates a band-like lymphoid infiltrate in the superficial lamina propria with intraepithelial degenerating squamous cells, so called Civatte bodies. Papules and plaques are often seen in the skin and the mouth and can be helpful in establishing the diagnosis. Esophageal involvement with lichen planus can lead to stricture formation.

Squamous Dysplasia/Squamous Carcinoma

Regenerative epithelial changes of reflux esophagitis can be quite alarming and may mimic squamous dysplasia or carcinoma (50). In most pathology practices in the United States, esophageal squamous cell carcinoma is becoming quite rare and atypical squamous changes near the esophagogastric junction are much more likely to represent regenerative changes of reflux esophagitis. Histologic features that favor regeneration over squamous carcinoma include: uniform nuclear enlargement with hyperchromasia that maintains a relatively low nuclear to cytoplasmic size ratio, nuclei that are evenly distributed, smooth external nuclear membranes, nuclei that contain one or several chromocenters but have similar size and staining characteristics and look very similar, one to another. In my experience, squamous

dysplasia/squamous carcinoma is often accompanied by a curious simplification of the epithelium (versus the papillomatosis more characteristically seen in reflux esophagitis) or a major alternation in mucosal architecture with an invasive pattern and tumor desmoplasia. The cytologic abnormalities must be quite severe before I call something squamous carcinoma. Squamous dysplasia/carcinoma typically shows irregular nuclear crowding with overlap, variable nuclear hyperchromasia, irregular nuclear contours, atypical mitoses, high nuclear to cytoplasmic size ratio, single cell necrosis, and a tendency toward paradoxical maturation (i.e., individual cell keratinization and squamous pearl formation).

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BARRETT'S ESOPHAGUS

Barrett's esophagus, the eponym given to columnar epithelium-lined esophagus, is acquired through chronic gastroesophageal reflux (1). Barrett's esophagus is associated with an increased risk of esophageal adenocarcinoma. Therefore, for purposes of cancer surveillance, the American College of Gastroenterology (ACG) defines Barrett's esophagus as an endoscopic change in esophageal epithelium of any length that contains intestinal metaplasia and recommends that patients with longstanding reflux symptoms have endoscopic examination to detect Barrett's esophagus. Once Barrett's esophagus is discovered, such patients should undergo endoscopic surveillance (2-4).

The Clinical Diagnosis of Barrett's Esophagus

Endoscopy has become the mainstay in the diagnosis of Barrett's esophagus (2-5). In general, the color (orange-red) and appearance (velvety) of Barrett's esophagus as seen through the endoscope is similar to that of normal gastric mucosa. Barrett's esophagus can appear as circumferential or tongue-like extensions of orange-red mucosa into the tubular esophagus (5,6). Occasionally, Barrett's can present as an island of orange-red mucosa entirely surrounded by the more pale pink to gray-white squamous epithelium of the normal esophagus. Some endoscopists augment endoscopic visualization with the use of vital stains such as methylene blue (7,8). Since other conditions such as a hiatal hernia, especially one occurring in the setting of severe gastroesophageal reflux, can sometimes mimic Barrett's esophagus endoscopically, the endoscopist's impression of Barrett's esophagus must be confirmed histologically (2-4).

The Histologic Diagnosis of Barrett's Esophagus

Specialized columnar epithelium (intestinal metaplasia) is a distinctive epithelial type that is virtually unique to and considered diagnostic for Barrett's esophagus (2-4). Specialized columnar epithelium can occur in a flat or villous configuration and consists of goblet cells and columnar cells. The goblet cells contain mucin that stains positively both with periodic acid-Schiff and with Alcian blue at pH 2.5. The columnar cells between goblet cells most often resemble gastric foveolar epithelium or rarely intestinal absorptive cells (5).

Barrett's esophagus is now defined by the ACG as a change of esophageal epithelium of any length, recognized at endoscopy, that is proved by biopsy to contain intestinal metaplasia (2-4). My current practice is to confirm intestinal metaplasia by using an Alcian blue/PAS combination stain with a hematoxylin counterstain. Prior ACG practice guidelines encourage use of at least an Alcian blue stain citing that its use decreases the change of missing goblet cells or of misinterpreting cells with prominent cytoplasmic vacuoles as goblet cells (3).

Cancer Risk and Surveillance

Patients with Barrett's esophagus are at increased risk for esophageal adenocarcinoma (1-5,9). Therefore, it is prudent to place all patients with Barrett's esophagus into a cancer surveillance program (2-4). The marker currently used for cancer surveillance programs is identification of epithelial dysplasia in a biopsy specimen.

Dysplasia, the presumed precancerous epithelial lesion, has been regularly recognized in esophageal specimens adjacent to and distant from Barrett's-associated adenocarcinomas (1,9). Circumstantial evidence suggests that dysplasia may not only be a marker for carcinoma, but may itself be the early carcinomatous change that can progress to invasive carcinoma (9). Dysplasia is recognized histologically and criteria for identifying these changes in ulcerative colitis are applied in studying Barrett's esophagus.

A reaffirmation of criteria with numerous illustrations has been published (10). Under this three-tiered system, biopsy findings are classified as negative for dysplasia, positive for dysplasia, or indefinite for dysplasia. Biopsy specimens interpreted as positive for dysplasia are further subdivided as low-grade or high-grade based upon the degree of cytologic change present.

The histologic grade of dysplasia has clinical significance (2-4,11,12). Infiltrating carcinoma is rare (0-3%) in patients with Barrett's esophagus initially negative for dysplasia. In contrast, 60% of patients with initial HGD have developed or already have infiltrating carcinoma (12-14). The results are intermediate for LGD and indefinite for dysplasia (10-28% for each) (11,13,15,16). One study stands out in stark contrast by observing a much lower cancer progression rate in HGD (16%) (17). This study has been criticized for its possible pathology "overreads" because 70% of their patients had at least LGD, in contrast to most other studies in which the prevalence of LGD is only about 5% (13).

During surveillance endoscopy, four quadrant biopsy specimens at 1-2 cm intervals are obtained throughout the entire length of the Barrett's epithelium (2,3,13). Patients negative for dysplasia can safely continue regular surveillance (q 1-2 years). The ACG suggests that after 2 negative surveillance endoscopies, that the interval can be increased to 3 years (3,4). Investigators recommend shorter term follow-up for "indefinite" and "low-grade" dysplasia. The ACG suggests 1 year (4) although I prefer their former recommendation of every 6 months (2). Management of high-grade dysplasia remains controversial. Some recommend continued surveillance for some patients (2-4) whereas others recommend intervention. Many opt for esophagectomy for the surgically fit candidate if life expectancy clearly exceeds 10 years and the surgical expertise is available (13). Other modalities (mucosal ablation, photodynamic therapy, EMR, cryospray) may be preferred to resection (4). Since the operative mortality and morbidity of esophagectomy is high, many think it prudent to confirm a diagnosis of high-grade dysplasia with an expert pathologist before moving on to esophagectomy (3). The ACG recommends that any grade of dysplasia be confirmed by an expert (4).

The ACG states that dysplasia is the best current indicator of the risk of cancer in Barrett's esophagus (2-4). The ACG also concludes that no biomarkers or panel of biomarkers are currently ready for routine use (4).

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