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Introduction, disclaimer and references

This lecture outline was developed as a guide to a slide presentation now encompassing about 1100 35mm slides dealing with the gross and microscopic features of colorectal pathology. It started as a simple outline intended for Fellows in Colon and Rectal Surgery in preparation for the American Board of Colon and Rectal Surgery Examination, a subspecialty surgical board that includes a section on pathology. Initially, the lecture covered the following topics in colorectal pathology: carcinoma, inflammatory bowel disease (IBD) and colitis, epithelial polyps and other polypoid lesions and anal pathology. Subsequently, additional sections on the appendix, small bowel, and HIV-AIDS colorectal lesions were added by request, always with emphasis on adult surgical disease. I only touch on some of the conditions causing malabsorption and some pediatric diseases of the colorectum. However, I do cover many of the colitides because of the differential diagnostic difficulties with IBD and because many colorectal surgeon are performing colonoscopy and want to be aware of these entities. Thus, this once simple lecture outline has grown to the point, where I was urged to share it not only with colorectal surgeons trainees, but also with pathologists. It is for these reasons that I now consider the lecture syllabus of more general interest and appropriate for wider distribution. It is available at http://www.neosoft.com/~uthman/. Unfortunately, at present, the photomicrographs are not available in electronic format.

The information presented here is not comprehensive and is intended purely as an educational resource for anyone interested in the subject of gastrointestinal tract (GIT) pathology. This outline is not intended as advice for patients in need of medical care. Any visitor to this outline in need of work up or treatment for colorectal disorders should see his/her own physician. In addition, this outline is a work in progress that I intend to update periodically, but at any point in time is not current and comprehensive in all areas. I can be reached at 713 527-5285 and gerry@houston.rr.com.

Besides the references as noted in the text and the recommended texts below, I have had the privilege to attend various CME conferences, such as the USCAP short courses and ASCP workshops, local lectures, etc. from which I acknowledge great influence and many pearls. Some such material has no doubt crept into this outline, but it is now difficult for me to remember all the exact sources. Therefore, I acknowledge the good fortune to have attended workshops/lectures given by the following eminent GI pathologists: Rodger Haggitt, Harvey Goldman, Henry D. Appleman, Robert E. Petras, John R. Goldblum, Robert Pascal, Harry S. Cooper, Klaus Lewin among others. Many of the insights herein are really theirs.
General textbooks and atlases dealing with pathology of the colorectum and gastrointestinal tract

Chandrasoma P: Gastrointestinal pathology, Stamford, Conn., Appleton and Lange, 1999


Book chapters


Petras RE: Nonneoplastic intestinal diseases; Cooper HS: Intestinal neoplasms; Antonioli DA, Appleman HD: Anus and perianal area In Sternberg SS editor Diagnostic surgical pathology, third edition, Lippincot Williams and Wilkins, Philadelphia, 1999
Rosai J: The Gastrointestinal tract In Rosai, J editor, Ackerman’s surgical pathology, 8th edition, Mosby, St. Louis, 1995


Wolber RA, Scudamore CH: The Gastrointestinal tract, In Banks PM, Kraybill WG editor Pathology for the surgeon, Saunders, 1996
I. Colonic Anatomy and Histology

A. Gross

The various regions of the colon are the cecum, ascending or right colon, hepatic flexure, transverse colon, splenic flexure, descending or left colon, sigmoid, rectum and anal canal.

B. Histology

Normal Components of the Colonic Mucosa

<table>
<thead>
<tr>
<th>Epithelium</th>
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<tbody>
<tr>
<td>Goblet mucous cells</td>
</tr>
<tr>
<td>Absorptive cells</td>
</tr>
<tr>
<td>Microfold (membranous) (M) cells</td>
</tr>
<tr>
<td>Paneth cell</td>
</tr>
<tr>
<td>Endocrine cells (enterochromaffin cells)</td>
</tr>
<tr>
<td>Undifferentiated columnar crypt cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lamina propria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes and plasma cells</td>
</tr>
<tr>
<td>Lymphoid nodules</td>
</tr>
<tr>
<td>Macrophages and eosinophils</td>
</tr>
<tr>
<td>Vessels and ganglia</td>
</tr>
<tr>
<td>No lymphatics, no neutrophils</td>
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<table>
<thead>
<tr>
<th>Muscularis mucosae</th>
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<tbody>
<tr>
<td>Smooth muscle layer</td>
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</table>

1. Mucosa

Surface epithelium: A single cell layer of columnar epithelium covers the surface and lines the crypts. The two main cell types are the absorptive and goblet cells. Endocrine, Paneth, and regenerative cells are present in the crypts. The normal colonic luminal surface is straight. The colonic tubules are normally tightly packed, evenly spaced, parallel, non-branching, and all the tubules closely approximate or even touch the muscularis mucosae forming “test tubes in a rack.” The surface layer has fewer mucous cells than the crypts and the surface cells are predominately short, columnar and are involved in water and salt absorption. The regenerative zone is the lower third of the crypt. Paneth cells are limited to the cecum and first portion of the ascending colon. When they are seen outside of this area, “Paneth cell metaplasia,” their presence signifies chronic inflammation, especially inflammatory bowel disease. Paneth cells occur in the base of the crypts. Their most notable feature is the presence of large eosinophilic granules in their apical cytoplasm. These granules are the largest in the GIT. Their precise function is unknown, but newly discovered Paneth cell products are called cryptdins and appear to be secreted antimicrobial agents. The

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epithelium rests on a basement membrane and a subepithelial collagen table. The pericrypt fibroblast sheath migrates from the regenerative zone to the surface in tandem with the epithelium.\(^3\)

The lower few centimeters of rectum has shortened and more widely spaced crypts, a greater amount of lymphoid tissue, and a thicker muscularis mucosae. All of these features may be seen in chronic inflammatory bowel diseases; thus, it is recommended that biopsies of the lower rectum be avoided in making this diagnosis.

Lymphoid-glandular complexes are solitary lymphoid follicles located in the mucosa that are randomly scattered throughout the colon. The lymphoid follicles often protrude through the muscularis mucosae into the submucosa. They are a component of the mucosa associated lymphoid tissue (MALT). The overlying epithelium includes specialized microfold (membranous) enterocytes (M cells) which are best visualized with the electron microscope.

The lamina propria is the connective tissue beneath the surface epithelium (note: the submucosa is not immediately beneath the mucosal lining). The lamina propria is the investing stroma and it extends from the subepithelial basement membrane to the muscularis mucosae. Normally present is a modest infiltrate of plasma cells, lymphocytes, macrophages and eosinophils, but neutrophils are rarely present. Eosinophils are variable in number and show regional variation, but sheets of eosinophils are considered abnormal. Most of the diffuse lymphocytes are T-cell with only scattered B-cells and with B-cell lymphoid follicles. Plasma cells tend to be concentrated superficially, beneath the surface epithelium. Lymphatics are not present in the upper lamina propria, and occur only in the lower third of the mucosa and below (around the muscularis mucosae).

The muscularis mucosae is a thin regular layer of smooth muscle that normally measures approximately 5 cells in thickness and separates the mucosa (epithelium and lamina propria) from the deeper submucosa. Some smooth muscle from this layer may extend upwards into the lamina propria and may become more numerous whenever there is traction on the mucosa as for example in mucosal prolapse.\(^4\)

2. Submucosa

The submucosa is loose connective tissue containing blood vessels and nerves (the submucosal plexus of Meisner), but generally devoid of inflammation.

3. Muscularis propria externa

The thick muscularis propria contains two layers, the inner circular layer and outer longitudinal layer. The later forms three thickened bands, the teniae coli. The myenteric plexus (Auerbach) with ganglion cells is situated between the two layers. There are also a surprisingly large number of cells of neural origin within the muscular layers. These cells have escaped recognition until recently. They are the interstitial cells of Cajal, the pacemaker cells. They are probably the origin of most gastrointestinal stromal tumors.

Hirschsprung disease is a congenital disorder that results from the absence of ganglion cells in the plexuses of Meisner and Auerbach. This is associated with hypertrophy of nerve trunks.

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4. Serosa and subserosa

The serosa of the colon in incomplete with portions of the colon situated in the retroperitonum. It is a layer of mesothelium and immediate adjacent fibroelastic tissue. The subserosa is the layer of connective tissue between the serosa and the muscularis propria.

C. Melanosis (lipofuscin) coli

Traditionally, melanosis is related to chronic use of anthroquinone purgatives such as senna, cascara sagrada, rhubarb, aloe and danthron. Melanosis results from increased apoptosis in the colonic mucosa induced by the ingestion of these laxatives.\(^6\)\(^7\) It is also seen in chronic inflammatory conditions due to accumulation of lysosomal breakdown products. The right side of colon including the appendix is most affected; lymphoid follicles and polyps are spared. The generic term “melanosis” (Greek: melas, “black”; osis, “condition”) describes conditions in which there is an abnormal gray-black or brown-black pigmentation of an organ or part. The term should not be taken to imply that the pigment is melanin, only that is black. In fact, despite its name, the pigment is lipofuscin/ceroid and it is present in lysosomes.\(^8\)

D. Electrocautery artifact

Commonly, electrocautery produces nuclear pyknosis, elongation and “streaming” in the direction of the current, sometimes making it difficult or impossible to differentiate between normal and neoplastic (adenomatous) epithelium.\(^9\)

E. Enema /laxative effect

Enemas using polyethylene glycol produce no histologic changes; however, bisacodyl enemas can cause mucin depletion, sloughing of superficial epithelial cells and a sparse infiltrate of Europhiles. One can also see edema of the lamina propria resulting in separation of the crypts and scattered foci of fresh hemorrhage. Soapsuds enema can cause a low grade acute colitis that can last for several months. These effects of preparation can be confused with disease.

F. Ileocecal valve

Two to three cm. of ileum protrudes into the large intestine and is associated with a muscular sphincter. The ileal mucosa blends imperceptibly and gradually with the mucosa of the large bowel. Abundant fat is normal in the submucosa here (but not elsewhere), and it is diffusely distributed and proportional to the adipose content in the rest of the abdomen.

\(^6\)Histopathol 1997;30:160-4
\(^7\)Am J Pathol 1988;113:465-76
\(^8\)Histopathol 1994;25:197-207
G. Reactive patterns of the large bowel mucosa

In only a minority of cases is the cause of the mucosal damage seen on a colorectal biopsy specimen evident. Most often, the changes are nonspecific and may be produced by a number of different pathogenic agents. These changes can be divided into patterns according to the severity, activity, or chronicity of the epithelial damage and the type of inflammatory response that it evokes.

1. Mild reactive pattern

Increased chronic inflammatory cells (especially plasma cells, eosinophils and to a lesser extent lymphocytes and histiocytes) are present in the lamina propria without epithelial damage or architectural disturbance. This pattern must be interpreted with caution. A diagnosis of “chronic colitis” is not warranted.

2. Acute reactive pattern

There is recent epithelial damage in the absence of architectural disturbance of the crypts with an acute inflammatory response (neutrophils, edema, congestion). There also may be ulceration and pseudo membranes. The acute reactive pattern is seen in acute self-limiting colitis and with specific infections such as bacillary dysentery and salmonella colitis, but it may possibly also occur in the initial phase of IBD.

3. Chronic reactive pattern

There is disturbed mucosal architecture and an increase in round cells such as plasma cells and lymphocytes. These changes are indicative of a chronic inflammatory process associated with recurrent episodes of epithelial damage and regeneration. There is often crypt distortion and irregularity. The crypt bases are frequently clearly separated from the muscularis mucosae by a layer of lamina propria expanded by chronic inflammatory cells or fibrosis. The recurrent epithelial damage leads to the development of epithelial metaplasia by appearance of Paneth cells in the basal part of the crypts. The lamina propria shows an increase in chronic inflammatory cells especially plasma cells and eosinophils. Lymphoid aggregates at the mucosal base can also be pronounced. IBD accounts for most biopsies showing the chronic reactive pattern, CUC more often than CD. Some chronic infections such as amebic dysentery can produce a similar appearance, but such infections are rare in Western societies.

4. Hyperplastic pattern

This is an under recognized pattern also termed transitional mucosa. There is elongation of the crypts and goblet cells are prominent and enlarged. Typically, found immediately adjacent to and invasive carcinoma, but also next to colostomies and SRUS. Whether this is a premalignant condition or simply the effect of mechanical factors such as abnormal traction and prolapse is not entirely clear.

5. Traumatic pattern

This is related to the hyperplastic pattern, possibly as the final phase. There is expansion of the lamina propria by proliferation of connective tissue and smooth muscle fibers. The latter clearly

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10Lee FD, Anderson NH, Toner PG Non-neoplastic diseases of the small and large intestine In Silverberg SG Principles and Practice of Surgical and Cytopathology, third edition, 1997, p1738-45
taking origin from the muscularis mucosae. The deeper parts of the crypts sometimes appear disrupted and displaced among the tangled muscle fiber of the underlying muscularis mucosae and may undergo cystic dilation. Some forms of colitis cystica profunda are thought to arise in this way. The surface epithelium may show regenerative changes sometimes with erosion and even pseudomenbrane formation. Mucosal prolapse is the major associated etiology.

6. Ischemic pattern

In the acute phase, there is damage to the surface epithelium with edema, capillary dilation and hemorrhage without chronic inflammation. The crypts often appear compressed and atrophic (“withered”) and the superficial lamina propria may be unusually pink and homogenous in appearance (“hyalinized”). Overt necrosis and ulceration may supervene starting at the epithelial surface. Fibrin thrombi in the superficial capillaries are a useful diagnostic feature. In mild cases, complete recovery is possible. In full thickness necrosis, repair results in granulation tissue and scar covered by a single layer of flattened epithelium. With regeneration of crypts architectural disturbance similar to the chronic reactive pattern is seen, but there is often more extensive interruption and fibrosis of the muscularis mucosae and hemosiderin laden macrophages.
II. Colorectal Adenocarcinoma

A. Diagnostic terms and definitions

**Intraepithelial neoplasia:** a lesion characterized by morphological changes that include altered architecture and abnormalities in cytology and differentiation. It results from clonal alterations in genes and carries a predisposition for progression to invasion and metastasis.

**High-grade intraepithelial neoplasia:** A mucosal change with cytologic and architectural features of malignancy, but without evidence of invasion into the stroma. It includes lesions termed severe dysplasia and carcinoma in situ.

**Polyp:** A generic term for any excrescence or growth protruding above a mucous membrane. Polyps can be pedunculated or sessile, and are readily seen by examination or conventional endoscopy.

**Adenoma:** A circumscribed benign lesion composed of tubular and/or villous structures showing intraepithelial neoplasia. The neoplastic epithelial cells are immature and typically have enlarged, hyperbasophilic and stratified nuclei.

**Tubular adenoma:** An adenoma in which branching tubules surrounded by lamina propria comprise at least 80% of the tumor.

**Villous adenoma:** An adenoma in which leaf-like or finger-like processes of lamina propria covered by dysplastic epithelium comprise at least 80% of the tumor.

**Tubulovillous adenoma:** An adenoma composed of both tubular and villous structures, each comprising more than 20% of the tumor.

**Serrated adenoma:** An adenoma composed of saw-toothed glands.

**Intraepithelial neoplasia (dysplasia) associated with chronic inflammatory diseases:** A neoplastic epithelial proliferation occurring in a patient with a chronic inflammatory bowel disease, but with macroscopic and microscopic features that distinguish it from an adenoma, e.g. patchy distribution of dysplasia and poor circumscription.

**Peutz-Jeghers polyp:** A hamartomatous polyp composed of branching bands of smooth muscle covered by normal-appearing or hyperplastic glandular mucosa indigenous to the site.

**Juvenile polyp:** A hamartomatous polyp with a spherical head composed of tubules and cysts, lined by normal epithelium, embedded in an excess of lamina propria. In juvenile polyposis, the polyps are often multilobated with a papillary configuration and a higher ratio of glands to lamina propria.

**Adenocarcinoma:** A malignant epithelial tumor with glandular differentiation.

**Mucinous adenocarcinoma:** An adenocarcinoma containing extracellular mucin comprising more than 50% of the tumor. Note that ‘mucin producing’ is not synonymous with mucinous in this context.

**Signet-ring cell carcinoma:** An adenocarcinoma in which the predominant component (more than 50%) is composed of isolated malignant cell containing intracytoplasmic mucin.

**Squamous cell (epidermoid) carcinoma:** A malignant epithelial tumor with squamous cell differentiation.

**Adenosquamous carcinoma:** A malignant epithelial tumor with significant components of both glandular and squamous differentiation.

**Small cell carcinoma** similar in morphology, immunophenotype and behavior to small cell carcinoma of the lung.

**Medullary carcinoma:** A malignant epithelial tumor in which the cells form solid sheets and have abundant eosinophilic cytoplasm and large, vesicular nuclei with prominent nucleoli. An intraepithelial infiltrate of lymphocytes is characteristic.

**Undifferentiated carcinoma:** A malignant epithelial tumor with no glandular structures or other features to indicated definite differentiation.

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**Carcinoid:** A well differentiated neoplasm of the diffuse endocrine system.

**Microsatellite:** Repetitive stretches of short sequences of DNA used as genetic markers to track inheritance in families.

**Microsatellite instability:** “a change of any length due to either insertion or deletion of repeating units, in a microsatellite within a tumor when compared to normal tissue. It has been recommended that a panel of five microsatellites should be used as a reference standard (BAT25, BAT26, D5S346, D2S123, D17S250) for carcinomas of the large intestine. If two or more of these markers show MSI, the lesion is classified as high-frequency microsatellite instability (MSI-H); if only one marker show MSI, it is classified as low-frequency microsatellite instability (MSI-L); if no marker show MSI it is classified as microsatellite stable (MSS).”

B. WHO histological classification of tumors of the colon and rectum

<table>
<thead>
<tr>
<th>Epithelial tumors</th>
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<tbody>
<tr>
<td>Adenoma</td>
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<tr>
<td>Tubular</td>
</tr>
<tr>
<td>Villous</td>
</tr>
<tr>
<td>Tubulovillous</td>
</tr>
<tr>
<td>Serrated</td>
</tr>
<tr>
<td>Intraepithelial neoplasia (dysplasia) associated with chronic inflammatory diseases</td>
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<tr>
<td>Low-grade glandular intraepithelial neoplasia</td>
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<tr>
<td>High-grade glandular intraepithelial neoplasia</td>
</tr>
<tr>
<td>Carcinoma</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
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<tr>
<td>Signet-ring cell carcinoma</td>
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<tr>
<td>Small cell carcinoma</td>
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<tr>
<td>Squamous cell carcinoma</td>
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<tr>
<td>Adenosquamous carcinoma</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
</tr>
<tr>
<td>Carcinoid (well differentiated endocrine neoplasm)</td>
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<tr>
<td>EC-cell, serotonin-producing neoplasm</td>
</tr>
<tr>
<td>L-cell, glucagon-like peptide and PP/PYY producing tumor</td>
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<tr>
<td>Mixed carcinoid-adenocarcinoma</td>
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<tr>
<td>Others</td>
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<table>
<thead>
<tr>
<th>Non-Epithelial tumors</th>
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<tbody>
<tr>
<td>Lipoma</td>
</tr>
<tr>
<td>Leiomyoma</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Malignant melanoma</td>
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<td>Others</td>
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### Malignant lymphomas

- Marginal zone B-cell lymphoma of MALT Type
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Burkitt lymphoma
- Burkitt-like / atypical Burkitt-lymphoma

### Secondary tumors

#### Polyps

- Hyperplastic (metaplastic)
- Peutz-Jeghers
- Juvenile

1. **Mucinous (colloid) carcinoma**

   This neoplasm produces abundant extra cellular mucin pools with carcinoma cells surrounding and floating within the pools. 50% or more of the tumor mass must be mucinous to qualify as mucinous carcinoma. A tumor is said to have a mucinous component when it is 25-50% mucinous. With these criteria, 5-15% of colonic tumors are mucinous and 5% have a mucinous component. Grossly these tumors are gelatinous and sticky. Most appear to arise from adenomas. They are most often located in the right colon and rectum. K-ras and microsatellite instability are more frequent and p53 mutation less frequent than in conventional colonic adenocarcinoma. Mucinous carcinomas are often of advanced stage and less resectable. The prognostic significance of mucinous carcinoma is controversial. Familial occurrence has been described. Many high-frequency micro-satellite instability carcinomas are of this type.

2. **Signet-ring cell carcinoma**

   This carcinoma diffusely invades as single cells rather than cohesive glands. It gets it name from a large cytoplasmic mucin vacuole that pushes the nucleus to the cell periphery thus resembling a finger ring bearing a signet (seal). It comprises about 1-4% of primary colorectal carcinomas. It may be either a diffusely infiltrating (linitis plastic-like) tumor or an exophytic tumor. Patients with signet ring cell carcinoma of the colon and rectum have a worse prognosis compared with matched controls with the same stage of disease (mean survival of 45 months versus 78 months)\(^\text{14}\). One must always r/o metastatic signet ring cell carcinoma to the colon from the stomach, breast or bladder.

3. **Small cell carcinoma**

   This carcinoma resembles small cell (oat cell) carcinoma of the lung and is highly aggressive with ~70% having liver metastasis at the time of diagnosis. About half are associated with or arise from an adenoma or colorectal carcinoma of usual type. They are composed of small or intermediate sized cells with minimal cytoplasm and dark staining fusiform nuclei with dispersed chromatin and inconspicuous nucleoli. They have a high mitotic rate and prominent necrosis. Neurosecretory granules are present on electron microscopic examination. These tumors show positive reaction for cytokeratins, epithelial membrane antigen, neuron-specific enolase and neurofilaments by immunohistochemical techniques. Grossly they may be polypoid, fungating or constrictive. These

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\(^{14}\) *Dis Colon Rectum* 1999;42:1176-80
tumors, even when small are often associated with widespread metastasis and most patients die within a year of diagnosis.

4. Squamous cell carcinoma
Pure squamous cell carcinoma of the large bowel is very rare.

5. Adenosquamous carcinoma

Adenosquamous carcinoma of colorectum is a rare tumor, constituting 0.06% of all colorectal carcinomas. These tumors show features of both squamous and adenocarcinoma, either in separate areas within the tumor or admixed. For a lesion to be so classified, there should be more than just occasional foci a squamous differentiation. The overall adjusted 5-year survival rate was 31%. Patients with stages B2 through D (Astler-Coller) have significantly poorer survival rates than do patients with conventional adenocarcinoma. Locally aggressive and metastatic disease at diagnosis appears to account for the poor prognosis.\textsuperscript{15}

6. Medullary carcinoma

This rare variant is characterized by sheets of malignant cells with vesicular (pale) nuclei, prominent nucleoli and abundant pink cytoplasm exhibiting prominent infiltration by intraepithelial lymphocytes. It is strongly associated with a high degree of microsatellite instability (MSI-H) indicative of loss of normal DNA repair gene function. These tumors have a favorable prognosis compared with microsatellite stable tumors. Medullary carcinoma may occur either sporadically or in association with the hereditary nonpolyposis colon cancer syndrome. This tumor type is characterized by uniform polygonal tumor cells that exhibit solid growth in nested, organoid or trabecular patterns and that only focally produce small amounts of mucin. In addition, medullary carcinomas are typically infiltrated by lymphocytes (tumor-infiltrating lymphocytes) and have no immunohistochemical evidence of neuroendocrine differentiation.

7. Undifferentiated carcinoma

These neoplasms lack evidence of differentiation beyond that of the epithelial tumor and have variable histology. Despite their undifferentiated appearances, these tumors are genetically distinct and typically associated with MSI-H.

8. Other rare large bowel carcinomas

Unusual histological types of colonic and rectal carcinomas include spindle cell carcinoma, choriocarcinoma, clear cell carcinoma, pleomorphic giant cell carcinoma, and endometrioid and serous carcinomas arising in colonic endometriosis.

7. Secondary carcinoma

Gastric carcinoma of signet ring type can metastasize to the colon and can be mistaken for a primary colon carcinoma. Colon carcinoma can metastasize to the small bowel and cause annular narrowing. Melanoma and carcinoma of the breast and lung are the most common tumors to spread to the GIT. These lesions are usually submucosal and small with an intact covering mucosa.

\textsuperscript{15} Dis Colon Rectum 1999;42:258-663
C. Tumor Configuration

Configurations include exophytic (fungating), endophytic (ulcerative), and diffusely infiltrative (linitis plastica), or annular, but overlap among these types is common. Exophytic is divided into pedunculated and sessile. Gross configuration has no independent influence on prognosis, with the possible exception of the uncommon linitis plastica type, which has an unfavorable prognosis. Its association with adverse outcome is probably related to the underlying histologic type of tumor (signet-ring carcinoma) rather than the macroscopic configuration itself. In some studies, a pushing border rather than infiltrative border has been shown to be an independent marker of favorable prognosis.

D. WHO Histological grade of conventional colorectal adenocarcinoma

Histologically, most tumors are well to moderately differentiated and composed of irregularly shaped glands lined by tall columnar to cuboidal epithelium. A stromal host fibroblastic reaction is characteristic (desmoplasia). There is often “dirty” necrosis in the center of the malignant glands and partial gland formation. Below is the WHO grading scheme that is based on the percentage of gland forming versus non gland forming components. Grading should be based on the least differentiated component not including the leading front of invasion. Other methods of grading are used and grading of colorectal carcinomas is not yet standardized. Recently a more reproducible 2-tiered grading scheme has been advocated as follows: low grade > 50% gland formation and high grade < 50% gland formation.

Grade X Grade cannot be assessed  
Grade 1 Well differentiated (>95% of tumor composed of glands)  
Grade 2 Moderately differentiated (50-95% of tumor composed of glands)  
Grade 3 Poorly differentiated (5-49% of tumor composed of glands)  
Grade 4 Undifferentiated (<5% of tumor composed of glands)

High grade tumors (grade 3 and 4) have been shown by multivariate analyses to have adverse prognostic significance that is independent of tumor stage. By convention, mucinous adenocarcinoma and signet ring carcinoma are considered poorly differentiated, grade 3. Paradoxically MSI-H tumors are often poorly differentiated (mucinous and signet ring types) or undifferentiated (medullary carcinoma), but with improved stage-specific survival. More studies are needed to clarify the relationship of grade, molecular subtype and prognosis.

Surgical resection remains the most effective therapy and the best estimation of prognosis is related to the pathologic findings on the recession specimen. The anatomic extent of disease is by far the most important prognostic factor in colorectal cancer. The TNM staging system of AJCC/UICC is recommended.

E. Prognostic Factors in Colorectal Cancer, College of American Pathologists Consensus Statement 1999, Categorized by Level of Scientific Validation

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16 Arch Pathol Lab Med 2000; 124:1016-1024  
17 Arch Pathol Lab Med 1997; 121:1247-54  
18 Arch Pathol Lab Med 2000; 124:1016-1024  
19 Arch Pathol Lab Med 2000; 124:979
I. Well supported: pathologic TNM stage, blood or lymphatic vessel invasion, residual tumor following surgery with curative intent especially as it relates to positive surgical margins and preoperative elevation of CEA

II. A. Extensively studied biologically and/or clinically and repeatedly shown to have prognostic value, but remains to be validated: tumor grade, radial margin status (for resection specimens with nonperitonealized surfaces), and residual tumor in the resection specimen following neoadjuvant therapy

   B. Factors shown to be promising: histologic type, histologic features associated with microsatellite instability (MSI) (i.e., host lymphoid response to tumor and medullary or mucinous histologic type), high degree of MSI, loss of heterozygosity at 18q (DCC gene allelic loss), and tumor border configuration (infiltrating vs. pushing border)

III. Factors not yet sufficiently studied to determine their prognostic value: DNA content, all other molecular markers except loss of heterozygosity 18q/DCC and MSI-H, perineural invasion, microvessel density. Tumor cell-associated proteins or carbohydrates, peritumoral fibrosis, peritumoral inflammatory response, focal neuroendocrine differentiation, nuclear organizing regions and proliferation indices

IV. Factors well studied and shown to have no prognostic significance: tumor size and gross tumor configuration
III. Adenomas and Polyps

A. Adenomas (adenomatous polyp)

An adenoma is a benign neoplasm of colonic epithelium with architectural and cytological dysplasia (intraepithelial neoplasia). The diagnosis of an adenoma depends on the presence of dysplasia. (N.B. the definition of a polyp is any abnormal elevation on the mucosal surface, not necessarily epithelial.) Subtypes of adenomas include elevated, flat and depressed. Size is more important than villosity in terms of frequency of adenocarcinoma in an adenoma. The distinction of villous structures from elongated separated tubules is problematical. Villous architecture is defined arbitrarily by the length of the glands exceeding twice the thickness of the normal colorectal mucosa.21

Tubular (>75% tubular)
Tubulovillous adenoma (>25% villous)
Villous adenoma (>75% villous)

Terminology of a pedunculated adenoma:

- **Head** is lined by adenomatous (dysplastic) epithelium
- **Neck** is the junction between the head and the stalk
- **Stalk** is lined by normal colonic epithelium

B. Familial adenomatous polyposis (FAP) and attenuated FAP

FAP is autosomal dominant, with APC (adenomatous polyposis coli) gene mutation (5q21) and characterized by the presence of at least 100 adenomas in the large bowel, but beware of the attenuated FAP phenotype (later age of onset, and sometimes only segmental distribution of adenomas). Chemoprevention, desmoid tumors and congenital hypertrophy of retinal pigment epithelium.22

In the attenuated FAP phenotype the mutation is in the initial exons of the large FAP gene and this results in fewer adenomas, mostly located in the proximal colon and upper GI lesions particularly fundic gland polyps. The polyps are often flat rather than polypoid, and previously AFAP was termed hereditary flat adenoma syndrome.23 This phenotype is easily confused with HNPCC.

Polyposis Syndromes24

<table>
<thead>
<tr>
<th>Familial Adenomatous Polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardner Syndrome (a FAP variant)</td>
</tr>
<tr>
<td>Turcot Syndrome (a FAP variant)</td>
</tr>
<tr>
<td>Attenuated FAP (a FAP variant)</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
</tr>
</tbody>
</table>

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21. Hamilton SR, Aaltonen LA Tumous of the digestive system, p113
22. Cancer 1996;78:2499-10
24. Cooper HS Benign epithelial polyps of the intestines In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
Juvenile Polyposis
Peutz-Jegher Syndrome
Cowden syndrome
Hyperplastic polyposis

C. Hereditary nonpolyposis colorectal cancer (HNPCC)\textsuperscript{25 26 27}

HNPCC is characterized by early onset of colon carcinoma, proximal colon involvement, absence of adenomatosis (i.e. absence of hundreds of adenomas) with germline DNA mismatch repair gene mutation (hMSH2 or hMLH1). HNPCC cannot be differentiated from sporadic colon cancer based on physical or endoscopic features. A careful family history is the main element of diagnosis. The Amsterdam Criteria are restrictive especially for small families and the extra colonic malignancies are not given any weight and have been updated:

Revised diagnostic criteria for HNPCC (Amsterdam criteria II)\textsuperscript{28}

<table>
<thead>
<tr>
<th>There should be at least three relatives with an HNPCC-associated cancer: colorectal cancer or cancer of the endometrium, small bowel, ureter or renal pelvis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>One patient should be a first degree relative of the other two</td>
</tr>
<tr>
<td>At least two successive generations should be affected.</td>
</tr>
<tr>
<td>At least one tumor should be diagnosed before age 50</td>
</tr>
<tr>
<td>Familial adenomatous polyposis should be excluded in the colorectal cancer case(s) if any.</td>
</tr>
<tr>
<td>Tumors should be verified by histopathological exam.</td>
</tr>
</tbody>
</table>

D. Serrated adenoma and mixed hyperplastic/adenomatous polyp or dysplasia in hyperplastic polyp

Compared to hyperplastic polyps, serrated adenomas will have: dilatation of the crypt that is most pronounced at the base, presence of horizontally oriented crypts (just above the muscularis mucosae), large areas without endocrine cells, nuclear atypia including basally oriented oval or round nuclei that are enlarged with prominent nucleoli, focal mucous overproduction (resembling mucinous cystadenoma of the appendix), proliferation zone frequently moved from the base of the crypt to middle or upper part of the crypt with presence of numerous goblet cells in base of crypt, frequent or focal eosinophilia of cytoplasm.\textsuperscript{29}

E. The dysplasia (adenoma)/carcinoma sequence vs. de novo carcinoma (vis-à-vis the flat adenoma)

The study of human colon cancer has become a paradigm of cancer molecular biology:\textsuperscript{30} Multiple genetic changes occur during progression from a polyp to a carcinoma.\textsuperscript{31} The aberrant crypt focus (ACF) is the earliest morphological precursor of epithelial neoplasia. Examinations of dissected sheets of mucosa stained with methylene blue or examinations of the mucosa with a magnifying endoscope reveal crypts with enlarged caliber and thickened epithelium with reduced mucin.

\textsuperscript{25}Advances in Anatomic Pathol 1996;3:343-9
\textsuperscript{26}Cancer 1996;78:1149-67
\textsuperscript{27}JAMA 1997;278:1278-81
\textsuperscript{28}Hamilton SR, Aaltonen LA Tumous of the digestive system, p127
\textsuperscript{29}Gastroenterology 1996; 110:748-55
\textsuperscript{30}Advances in Anatomic Pathol 1966;3:343-50
\textsuperscript{31}N Engl J Med 1988;319:525-532
Microscopically two main types of ACFs are those with features of hyperplastic polyps and high frequency of ras mutations and dysplastic ACFs (micro-adenomas) with APC mutations.32

F. Adenoma with carcinoma33

“Malignant polyps” represent about 3% of polypectomies. The 10% rule of thumb: Of 1000 random polyps -> 900 hyperplastic polyps and 100 adenomas; of the 100 adenomas -> 10 big adenomas (>1.5 cm.); of these 10 big adenoma -> 1 invasive carcinoma in a polyp.34

The morphological steps in neoplastic progression of an adenoma are: low grade dysplasia (by definition all adenomas have at least low grade dysplasia). Next, an adenoma with high grade dysplasia/ “adenocarcinoma in situ” (true stratification with complex cribriform configuration, but the basement membrane remains intact), then -> adenoma with intramucosal carcinoma (invasion of the lamina propria only, lacking desmoplasia) -> adenoma with invasive carcinoma (when the carcinoma cells have invaded the submucosa and beyond it is invariably associated with desmoplasia) -> metastatic carcinoma.

Low grade dysplasia is characterized by a slight decrease in the amount of intracellular mucin, mild nuclear enlargement with hyperchromasia and increased mitotic rate. With increasing degrees of dysplasia, there is progressive loss of intracellular mucin, progressive nuclear enlargement with stratification and loss of nuclear polarity.

Invasive carcinoma cells in a polyp become clinically significant (i.e. able to metastasize) only when they have invaded the submucosa, therefore only a polyp containing invasive adenocarcinoma should be considered a malignant colorectal polyp.

Endoscopic polypectomy is considered adequate therapy in malignant colorectal polyps with favorable histology. This is defined as complete excision, plus cancer not close (<2 mm) to margin and not grade 3.

Indications for possible definitive follow-up resection of endoscopically removed malignant polyp (the first two are the most useful):

- Unresectable, positive resection margin or carcinoma close to margin (less than 1-2 mm.)
- Poorly differentiated (grade 3) carcinoma
- Grade 3 carcinoma includes poorly differentiated carcinoma of the intestinal type (sheets of non gland forming carcinoma), signet ring cell carcinoma, and mucinous carcinoma. For mucinous and signet ring types, greater than 50% of the invasive component must be made up that particular histology.
- Lymphatic or venous vessel involvement (usually seen in grade III carcinomas)
- Sessile configuration (probably not useful)

Other considerations in the therapy of a polyp with invasive adenocarcinoma include: appropriate specimen processing; not using the “C” word (cancer) unless there is invasion through muscularis mucosa; operative morbidity/mortality; the recently introduced laparoscopic segmental resection with its lower complications; life expectancy; patient preference; economics; the expected negative resection (about 90% follow-up resections will contain no carcinoma) and its legal implications (remember cautery necrosis is extensive); the high sensitivity and specificity of a negative (absence of the above indications for follow-up resection), but the low sensitivity and specificity of a positive.

32 Hamilton SR,
33Human Pathol 1998;29:15-26
34 Pascal R, Colorectal adenoma, dysplasia and cancer, intellectual thinking and plain talking, presentation at Houston Society of Clinical Pathologists, 10/25/95
G. Adenoma with pseudoinvasion (misplaced epithelium/entrapped glands)

A condition possibly the result of torsion or other trauma, the mucosa of a polyp has been misplaced into the submucosa, mimicking invasive carcinoma. This pseudoinvasion is relatively common, and is reported in about 3 to 10% of adenomatous polyps; the male to female ratio is 3:1. It is usually found in the sigmoid and in polyps with well defined stalks. It is characterized by deep glands, but a non–invasive pattern. The glands lack desmoplasia and are surrounded by lamina propria, and often have stromal hemorrhage and hemosiderin. (The desmoplasia of invasive carcinoma is defined as a cellular fibroblastic tissue, typically amphophilic, related to invading carcinoma, and contrasting with the native stroma.)

Differential Diagnosis of Carcinoma vs. Misplaced Epithelium

<table>
<thead>
<tr>
<th>Feature</th>
<th>Misplaced Epithelium</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamina propria around glands</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Desmoplasia around glands</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hemosiderin &amp; dense fibrosis</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Mucous lakes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Occasionally the misplaced glands can become cystic and can be associated with gland rupture and dissection of mucus into the connective tissue of the polyp. This can make the distinction between invasive mucinous adenocarcinoma and the misplaced glands of pseudocarcinomatous invasion extremely difficult.

Differential Features Between Dissecting Mucus of Pseudoinvasion and Invasive Mucinous Adenocarcinoma

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

H. Hyperplastic polyp

The definition of a hyperplastic polyp is a “mucosal excrescence characterized by elongated, serrated crypts lined by proliferative epithelium in the bases with infolded epithelial tufts and
enlarged goblet cells in the upper crypts and on the luminal surfaces, imparting a saw-tooth outline."\textsuperscript{35}

The hyperplastic polyp is the most common polyp of the large bowel. More than 90% are less than 5 mm in diameter, and almost always < 1.0 cm; larger “hyperplastic” polyps are often serrated adenomas. Hyperplastic polyps are small sessile mucosal elevations that are slightly paler than the background mucosa and are non-pigmented in melanosis coli. Microscopically they have characteristic serrated upper crypts lined by mature cells. The nuclei tend to be ovoid and basally placed. The collagen table is thickened. (Note: the collagen table is not thickened in an adenomatous polyp.) Traditionally considered as non neoplastic, recent evidence suggests that hyperplastic polyps are neoplastic, but they have a different molecular pathogenesis (ras mutations are common) than the adenoma-adenocarcinoma sequence (APC/beta-catenin pathway).

Life used to be simple: hyperplastic polyps were considered to show no relationship to the future development of carcinoma in contrast to the adenomas, the immediate precursor to colorectal cancer.\textsuperscript{36} \textsuperscript{37} This dogma is being reevaluated now that we know that a high frequency of ras mutations and p53 over expression is present in hyperplastic polyps, markers thought to be associated with neoplasia. Do hyperplastic polyps sometimes evolve into adenomas? Are hyperplastic polyps neoplastic? Can adenomas be ranked according to their biologic aggressiveness and in order as follows: serrated adenoma, tubular adenoma, tubulovillous adenoma, villous adenoma, and depressed adenoma?

Inverted variants hyperplastic polyps have been described and may have an invasive appearance.\textsuperscript{38}

I. Peutz–Jeghers polyp (hamartoma)\textsuperscript{39}

Diagnostic criteria for Peutz-Jeghers syndrome (PJS) are recommended as follows: (1) three or more histologically confirmed PJ polyps, or (2) any number of PJ polyps with a family history of PJS, or (3) characteristic, prominent, mucocutaneous pigmentation with a family history of PJS, or (4) any number of PJ polyps and characteristic, prominent, mucocutaneous pigmentation.

P-J polyps are rare in the colon and somewhat more common in small bowel. They have an diagnostically useful central arborizing core of smooth muscle (muscularis mucosae) that show tree-like branching forming broad bands of smooth muscle covered by cytologically normal mucosa.

J. Juvenile polyp (retention) and juvenile polyposis\textsuperscript{40}

Juvenile polyps are considered hamartomatous. They usually present as rectal bleeding. About 75% are found in the rectum. As the name implies, they are most common between 1-7 years of age, but can be seen in adults. Most are single, spherical or multilobated masses usually no larger than a few centimeters in diameter that may be pedunculated and smooth–surfaced. They may ulcerate and undergo torsion and autoamputation. Cystically dilated spaces with mucinous content are often grossly evident. Microscopically, they show cystically dilated crypts, and an excess of lamina propria. Focally the epithelium may have a serrated hyperplastic appearance. Foci of dysplasia may be found in juvenile polyps, generally in the larger lobulated or villous-appearing polyps and in older individuals. Carcinoma developing within a solitary juvenile polyp, while extremely rare, has been reported. Unlike Peutz-Jeghers polyps, smooth muscle is not a component of juvenile polyps.

\textsuperscript{35} Hamilton SR et al p 112
\textsuperscript{36} Am J Surg Pathol 1999;23:1001-3
\textsuperscript{37} Am J Surg Pathol 1999;23:1158-60
\textsuperscript{38}Am J Surg Pathol 1985;9:265
\textsuperscript{39} Hamilton SR et al p 73-76
\textsuperscript{40}Owen DA, Kelly JK:Atlas of gastrointestinal pathology, Philadelphia, 1994, Saunders, p170
Most juvenile polyps are solitary or few in number and are not part of the juvenile polyposis syndrome. Juvenile polyposis has been defined as the presence of (1) more than five juvenile polyps in the colorectum; (2) juvenile polyps throughout the GIT; and/or (3) any number of juvenile polyps with a family history of juvenile polyposis. Most patients with juvenile polyposis have between 50 and a few 100 polyps. These may be limited to colorectum or may be present throughout the GIT. The mode of inheritance is autosomal dominant and Jacoby et al have identified a juvenile polyposis suppressor locus at 10q22. When first described by McCall in 1964, juvenile polyps were not considered premalignant lesions. However, it is now known that as many as a quarter of juvenile polyposis syndrome patients may develop GIT carcinoma at a mean age in the fourth decade. Most of these are colorectal adenocarcinomas.

K. Lymphoid polyps

Most common in females and in the rectum. They are aggregates of mucosa associated lymphoid tissue with germinal centers (focal nodular lymphoid hyperplasia of the rectum).

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IV. Other Lesions of the Colon

A. Lipoma

Lipomas are benign proliferations of mature fatty tissue that arise in the submucosa. Most lipomas are asymptomatic, occur in adults, and are seen throughout the colon with a slight preference for the cecum. They are usually sessile, smooth surfaced, yellow nodules covered by intact mucosa. The cut surface is yellow with a yielding consistency. In cases with intussusception, hemorrhage, necrosis, cyst formation and ulceration may occur.

B. Lipohyperplasia of Ileocecal valve

This is a common normal variant, but it can be mistaken for a lesion endoscopically, radiographically and grossly. It may occasionally be associated with clinical symptoms (RLQ pain). It correlates to some extents with right ventricular and pancreatic fatty infiltration and with greater body weight.

C. Pseudolipomatosis

Pseudolipomatosis is a misnomer. It is insufflation artifact (pneumatosis) due to iatrogenic gas insufflated during colonoscopy. The air is inadvertently forced from the lumen into the tissue during endoscopy. Histologically it appears as numerous tiny bubbly empty cystic spaces within the lamina propria, which resemble fat. There is no foreign body giant cell reaction, in contrast to that seen in pneumatosis coli.

D. Gastrointestinal stromal tumors

Gastrointestinal stromal tumor (GIST) is now the preferred term for mesenchymal tumors specific for the GIT (60% in the stomach, 30% small intestine, 10% elsewhere). GISTs include most tumors previously designated as leiomyoma, cellular leiomyoma, leiomyoblastoma, and leiomyosarcoma. However, in the esophagus leiomyoma is the most common mesenchymal tumor. GISTs are composed of spindle (70%) or epithelioid (30%) cells and 10-30% are malignant showing intra-abdominal spread or liver metastases. They are immunohistochemically positive for c-kit (CD117), CD34, and sometimes for actin but are usually negative for desmin and S100-protein. The malignant GISTs especially show activation mutations in the c-kit gene. GISTs and gastrointestinal autonomic nerve tumors (GANT) overlap. The cell of origin is not fully understood, but resemble the interstitial cell of Cajal. Expression of some smooth muscle markers and occurrence outside of the GIT (omentum and mesentery) suggest origin from multipotential cells that can differentiate into Cajal and smooth muscle cells.

For routine diagnosis, specialized techniques such as electron microscopy are not critical since the clinical behavior is governed by the light microscopic appearances, not the histogenesis.

GISTs occur predominantly in persons over 40 years of age with an equal sex incidence. Histologically they may show a spindle cell or epithelioid pattern. Immunohistochemically most

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43 Am J Clin Pathol 1990;93:440
44 Am J Clin Pathol 1985;84:575
45 Human Pathol 1999;30:1213-20
46 Am J Surg Pathol 1999;23:1109-18
GISTs are positive for CD34 and c-kit (CK117). The latter is quite specific for GISTs among mesenchymal tumors. Genetically GISTs commonly show DNA losses in the long arm of Chromosome 14, and c-kit gene mutations occur at least in some cases. Evaluation of malignancy in GISTs is based on mitotic count, tumor size and extra-intestinal spread. Tumors with mitotic counts higher than 5/10 high power fields or larger than 10 cm have a significant risk for recurrence, metastasis and are considered histologically malignant. However, some tumors with mitotic activity of less that 1/10HPF may metastasize indicating some uncertainty in malignant potential of GISTs especially those larger that 5 cm. GISTs are very rare in the colon. They do occur in the esophagus and rectum. Most esophageal and rectal GISTs are clinically and histologically malignant tumors and are mostly of spindle cell type.

Tumor size >5 cm and >2 mitotic figures per 10 high power fields (HPF) is most consistently associated with poor clinical outcome for GI stromal tumors. Tumors with both of these features have the highest risk of aggressive clinical behavior, while tumors with neither feature would have the lowest risk. Tumors with only one of the two high-risk findings should have an intermediate risk of local recurrence or metastasis. Thus, the simple application of tumor size and mitotic rate enable one to assign a relative risk of aggressive clinical behavior to an individual GI stromal tumor. Admittedly, there persist small, mitotically inactive tumors that will metastasize. It is important to remember this and to realize that histology gives a probability of future behavior, not a guarantee.

Recently it has become apparent the GISTs exhibit marked site specificity. For example gastric and esophageal stromal tumors are unique and different from each other and from small and large bowel stromal tumors.

With regards to the small and large bowel GIST: The small bowel contains about 25% of GIST. It is the origin of spindle stromal tumors with organoid vascular patterns and “skeinoid fibers” (masses of modified collagen resembling skeins of yarn on EM). Such tumors are not found elsewhere in the GIT except on rare occasions in the proximal colon and the mesentery. The skeinoid fibers are seen in benign stromal tumors or in benign areas of a sarcoma. Small bowel sarcomas tend to be highly cellular and composed of uniform small spindle cell.

The colon excluding the rectosigmoid is an unusual site for GIST, so unusual that minimal data has been published. The colon may be the only gut site in which truly pleomorphic sarcomas arise albeit rarely.

The rectum and to a lesser extent the sigmoid contain two characteristic neoplasms. One is a small nodule of expansion of the muscularis mucosae, the leiomyomatous polyp. This is a fully differentiated benign smooth muscle neoplasm of the muscularis mucosae, which is cured by local excision. The second is a deep intramural highly cellular spindle cell tumor that superficially resembles the benign spindle cell lesion in the stomach but is likely to be malignant.

Morphologic Criteria of Malignancy

<table>
<thead>
<tr>
<th>Size &gt; 5 cm in diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltration of adjacent structure</td>
</tr>
</tbody>
</table>

48 Appelman HD: Mesenchymal tumors of the gastrointestinal tract In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
Presence of tumor necrosis
Increased nuclear: cytoplasmic ratio
Mitotic rates of >1-5 per 10 HPF
Infiltration of overlying mucosa by the tumor

Assessing Risk of Aggressive Clinical Behavior in Gastrointestinal Stromal Tumors, one approach

<table>
<thead>
<tr>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Size ≥ 5 cm and mitotic rate ≥ 2/10 HPF</td>
</tr>
<tr>
<td>b. Size ≥ 5 cm or mitotic rate ≥ 2/10 HPF; PCNA index &gt;10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Size ≤ 5 cm and mitotic rate ≤ 2/10 HPF</td>
</tr>
<tr>
<td>b. Size ≥ 5 cm or mitotic rate ≥ 2/10 HPF; PCNA index ≤10%</td>
</tr>
</tbody>
</table>

HPF = high power fields; PCNA = proliferating cell nuclear antigen

The recently characterized gastrointestinal autonomic nerve tumors (GANT) overlap with GISTs and are defined based on ultrastructural characteristics. Most are c-kit positive, but only limited data is available. Grossly GANTs are well demarcated but unencapsulated, often heterogeneous with hemorrhage, necrosis or cystic areas. Microscopically, the neoplastic cells are spindled or epithelioid and adopt a diffuse, storiform, palisading or interlacing fascicular pattern often with a rich vascular network. No distinctive light microscopic features are present making the identification dependent on ultrastructural examination. Several recent studies have shown the GANT constitute a much higher proportion of GISTs than previously anticipated (29% to 46%).

E. Rectal gastric heterotopia

The term heterotopia refers to the finding of normal tissues at foreign sites. This is a rare lesion presenting as a polyp or plaque-like lesion, which can be asymptomatic or can bleed. Histologically there is gastric mucosa of the fundal type with or without inflammation, ulceration and infection with Helicobacter pylori. Endoscopic or surgical excision is the treatment of choice, although the lesion also responds to histamine 2 receptor blockers.

F. Ganglioneuroma

1. Solitary polypoid ganglioneuromas

Focal ganglioneuroma is often an incidental colonoscopic finding unassociated with an underlying condition. Most are small, sessile, or pedunculated polyps and measure less than 2 cm. Microscopically they expand the lamina propria and submucosa and consist of nerve fibers and variable numbers of mature ganglion cells. They are not associated with NF1 or MEN IIb.
2. Intestinal ganglioneuromatosis

This lesion is common in MEN IIb and often provides the earliest clue that the patient has the syndrome. Other prominent features include constipation and diarrhea, generalized colonic diverticulosis, megacolon and disturbance of esophageal motility. There is band-like and nodular enlargement of both the submucosal and myenteric plexus with an increase in all nerve elements, including ganglion cells, their processes and accompanying Schwann cells.

G. Neurofibromatosis

Neurofibromatosis type 1 can affect the viscera in a variety of ways, the so-called “visceral neurofibromatosis.”

The spectrum of NF1-associated GI lesions includes ganglioneuromatosis, neurofibromas of both localized and plexiform type, GIST’s, and various neuroendocrine neoplasms. Ganglioneuromatosis, focal and localized or diffuse results in a Hirschsprung-like picture in children and in pseudo-obstruction or megacolon in adults.57

H. Solitary rectal ulcer syndrome (SRUS)58

A misnomer, mucosal prolapse syndrome is now the preferred designation. It can be single or multiple (10-15% of cases) and ulcerated (early and by endoscopy only about half the patients with SRUS have an actual ulcer) or polypoid; anterior or anterolateral wall; motor disturbance. Histology variable, but with fibromuscular hyperplasia or obliteration of lamina propria often with depleted mononuclear cells; also elongated, branched and dilated crypts, imparting a villiform appearance. The tops of the villiform projections may be ulcerated and covered with a pseudomembrane. The hyperplastic and serrated crypts may resemble a hyperplastic polyp. Crypts can be misplaced into the submucosa, a condition known as colitis (proctitis) cystica profunda.

Summary of histology of SRUS: 59

- Erosion/ulceration of the surface epithelium with adherent exudate (pseudomembrane)
- Obliteration of upper lamina propria with granulation tissue and lower lamina propria by fibroblasts and smooth muscle
- Epithelial hyperplasia, which can lead to an erroneous diagnosis of adenoma or carcinoma
- Displacement of glands into the submucosa in a minority of cases
- Hyalinization of submucosal vessels (in resection specimens)

Variants:
- Localized colitis cystic profunda
- Inflammatory cloacogenic polyp
- Prolapsed hemorrhoids

57Ibid 389-393
59Haggitt RC, presentation at San Antonio Society of Pathologists 52nd Annual Seminar, 12/95
I. Carcinoids

Carcinoids are rare in the colon, but not uncommon in the rectum and sigmoid. These hindgut carcinoids constitute about 25% of all GIT neuroendocrine tumors. They are the third most common group of GI carcinoids (after jejunoileal and appendiceal carcinoids). Rectosigmoid carcinoids are usually small submucosal tumors composed of well differentiated glands or ribbons of columnar cells. Approximately 80% of rectal carcinoids are less than 1.0 cm in diameter and are discovered incidentally as dome-shaped lesions covered by intact mucosa. Only a minority resembles classic carcinoids of the appendix. Most rectal carcinoids arise from the undifferentiated epithelium of the crypts. Colonic carcinoids, on the other hand, tend to be large invasive and metastatic tumors at the time of diagnosis. The prognosis of colorectal carcinoid tumors is related to their size. Tumors under 1 cm are benign, whereas tumors over 2 cm are likely to be malignant. Invasion of the muscularis propria is the only consistent reliable criterion of malignancy. GI carcinoid tumors are traditionally classified as foregut, midgut, and hindgut tumors. This has some merit, but is limited by the heterogeneity of each of these embryologically based subdivisions. This is illustrated by the differences between the clinicopathological features of gastric and duodenal carcinoids in the foregut or the jejunoileal and appendiceal carcinoids in the midgut. Thus carcinoids tumors of the GI tract are best classified by specific topographic regions, for example appendiceal, jejunoileal and rectal.

Traditional Classification of Endocrine Neoplasia of the GIT

<table>
<thead>
<tr>
<th>Carcinoid tumors</th>
<th>Foregut</th>
<th>Midgut</th>
<th>Hindgut</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroendocrine carcinomas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo–exocrine tumors</td>
<td>Composite</td>
<td>Amphiocrine</td>
<td></td>
</tr>
</tbody>
</table>

Classification of Digestive Carcinoid Tumors

<table>
<thead>
<tr>
<th>Localization</th>
<th>FOREGUT</th>
<th>MIDGUT</th>
<th>HINDGUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus, stomach, duodenum</td>
<td>Jejunum, ileum, appendix, ascending colon</td>
<td>Transverse, descending, sigmoid colon and rectum</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Silver Affinity</th>
<th>Argentaffinity</th>
<th>Argyrophilia</th>
<th>Secretion products</th>
<th>Functional expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ (–)</td>
<td>– (+)</td>
<td>+</td>
<td>Serotonin, substance P, tachykinins</td>
<td>Typical carcinoid syndrome and several others</td>
</tr>
<tr>
<td>– (+)</td>
<td>+</td>
<td>– (+)</td>
<td>Glucagon, somatostatin, other</td>
<td>Atypical carcinoid syndrome</td>
</tr>
<tr>
<td>Generally silent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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60 Cancer 1997;79:1294-8
61 Cancer 1997;79:1086-93
62 Pathol Annual 1995;229–46
J. Endometriosis

Endometriosis is an abnormal growth of benign endometrial glands and stroma outside the uterine cavity. The sigmoid and rectum are most common sites of bowel involvement. Most intestinal involvement is confined to the serosa or subserosa and is asymptomatic. Only about 1–2.5% of patients with endometriosis require bowel resection for symptomatic disease. Intestinal sites of involvement in descending order of involvement are the rectum and sigmoid, the appendix, the terminal ileum, the cecum, and other parts of the large and small bowel including Meckel diverticulum. The rectosigmoid is usually involved by a solitary lesion, several cm in length, whereas ileal involvement is usually multifocal. Grossly the bowel is indurated and often angulated by an ill-defined mass, usually noncircumferential. The serosa may be puckered and covered by adhesions. Sectioning reveals a firm, gray–white solid, mural mass, the bulk of which represents markedly thickened muscularis propria. The later often has a radiating fan–like appearance. The overlying mucosa is often intact. Endoscopic biopsies are usually of no diagnostic value, but endometriosis can mimic malignancy and rarely CD on biopsy due to various inflammatory and ulcerative changes of the overlying mucosa.63

K. Diverticular disease64

Diverticula are protrusions of the mucosa through the muscle coat. A triad of findings underlies diverticular disease: thickened muscularis propria of the sigmoid colon; the diverticulum itself penetrating through the muscle, composed of mucosa and muscularis mucosae; and the redundancy of the surface mucosal folds. Muscle changes antedate the development of diverticula and include thickening and shortening of the teniae coli producing a deformity called myochosis (there is attributed to excess elastin within the teniae) thickening and corrugation of the circular muscle coat, narrowing of the lumen, and sacculations of the mucosa that do not protrude through the muscle coat. Uncomplicated diverticula form two rows that protrude into the pericolic fat between the mesenteric and antimesenteric teniae. A third row of small diverticula is sometimes seen. The lumen may be virtually obliterated by the combination of muscle coat contraction and redundant mucosal folds. The folds are accentuated and drawn closer together and may show polypoid projections, congestion, hemosiderin deposition, and histologic features of mucosal prolapse; the so called polypoid prolapsing mucosal folds in diverticular disease.65

Diverticulitis results from inflammation and subsequent perforation of a colonic diverticulum. It occurs in 10–25% of patients with diverticulosis and is the most common complication. The mechanism is thought to be the result of fecalith formations with secondary abrasion of the mucosal lining. This results in either a microperforation with localized peridiverticulitis or macroperforation with either a free perforation or a pericolonic abscess. Although colovesicle or colovaginal fistula can occur in diverticular disease, other fistula combinations must raise the suspicion of CD, because both diseases can and do coexist.

63Hum Pathol 1994;25:1030–4
1. Left sided (sigmoid) colonic diverticular disease
Common, older age, multiple, false (contains only the mucosa and submucosa), acquired and increase with age.

2. Right sided colonic diverticular disease
Uncommon in Western countries but more common in Japan and Asia, younger age, single, true (all layer of the colonic wall) and congenital. May have false diverticula in the right colon usually associated with left-sided diverticulosis. Acquired right-sided diverticulosis in the absence of generalized diverticulosis is very rare and may be related to appendectomy.

L. Pneumatosis coli

Multiple gas filled cysts are present in the wall without evidence of infection probably due to raised intraluminal pressure and mucosal defects including COPD, emphysema, diverticulitis, appendicitis, cholelithiasis, peptic ulcers, trauma, CD, or complication of GIT surgery. Commonly seen on CT scan and may be asymptomatic if it involves the bowel proximal to the terminal ileum. Gas cysts of chronic pneumatosis are lined by macrophages including foreign body giant cells.

Insufflation of gas at endoscopy may force gas into the mucosa giving a microscopic appearance that is called pseudolipomatosis (insufflation pneumatosis). It resembles fat in the lamina propria.

M. Angiodysplasia (vascular ectasia of the right colon)

This condition is a common cause of recurrent acute colonic bleeding in patients over 60 years and is composed of acquired vascular dilatations of degenerative type. Most collapse after resection and are difficult or impossible to find. They are usually less the 5 mm in diameter. Microscopically they are small collections of dilated thin walled blood vessels in the mucosa and submucosa. There is no evidence of a vascular proliferation (i.e. a hemangioma) They may be diagnosed endoscopically and treated by cauterization.

N. Diffuse and localized cavernous hemangiomas of the rectosigmoid

Isolated intestinal vascular abnormalities: a classification

<table>
<thead>
<tr>
<th>Vascular ectasia of right colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioma</td>
</tr>
<tr>
<td>Capillary hemangioma</td>
</tr>
<tr>
<td>Cavernous hemangioma</td>
</tr>
<tr>
<td>Localized</td>
</tr>
<tr>
<td>Diffuse</td>
</tr>
<tr>
<td>Arteriovenous hemangioma</td>
</tr>
<tr>
<td>Phlebectasia</td>
</tr>
</tbody>
</table>

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67 Hum Pathol 1992;23:37–40
68 Pis Colon Rectum 1988; 31:797-805
69 Petras RE: Nonneoplastic intestinal diseases In Sternberg, SS editor, Diagnostic surgical pathology, third edition
O. Amyloidosis

Rectal mucosal biopsy can establish the diagnosis in about 80-85% of cases if an aspiration type specimen is obtained to ensure that a large portion of submucosa is obtained. The amyloid is seen mainly in submucosal arteries as a hyaline amorphous eosinophilic material that stains with Congo red and shows green birefringence.

P. Malakoplakia

Malakoplakia is an unusual inflammatory response to a bacterial infection, which is characterized by collections of macrophages that may have a foamy appearance. A distinctive round cytoplasmic laminated body, the Michaelis-Gutmann body, is present in some histiocytes. It contains iron and calcium. Bacteria are present in the histiocytes. Malakoplakia occurs most often in the bladder and kidney, but can occur in the colon, usually associated with other pathology such as a carcinoma or diverticulitis. A key factor in this disease is an acquired defect in monocyte bactericidal activity.

Q. Lymphoma\textsuperscript{70 71}

A primary gastrointestinal lymphoma is defined as a lymphoma presenting with the main bulk of disease in the GIT, with or without contiguous lymph node involvement. The GIT is the site of origin of about 50% of extranodal lymphomas. The relative frequency of primary GIT lymphoma is stomach > small intestine > colon and rectum.

Controversy exists as to whether the spectrum of lymphomas found in the gut can be adequately accommodated within the conventional classification of nodal lymphomas or whether a site specific classification of GI lymphomas is needed.\textsuperscript{72} In contrast to nodal lymphomas, many lymphomas of the GIT are derived from mucosa associated lymphoid tissue (MALT) that they resemble histologically. In further contrast to nodal lymphomas, many lymphomas of the GIT tend to be localized at the time of diagnosis and may be effectively treated with local therapy. There is a unique etiologic association of gastric B cell lymphoma of MALT type and Helicobacter pylori infection of the stomach and between gluten enteropathy and primary T cell lymphomas of the GIT. In addition, nodal type lymphomas (e.g. Burkitt, mantle cell and follicle center lymphomas) may also present in the GIT.

Classification of Primary Gastrointestinal Lymphoma\textsuperscript{73}

<table>
<thead>
<tr>
<th>B-CELL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa associated lymphoid tissue (MALT)-type</td>
</tr>
<tr>
<td>Low grade *</td>
</tr>
<tr>
<td>High grade with or without a low grade component *</td>
</tr>
<tr>
<td>Immunoproliferative small intestinal disease (IPSID)</td>
</tr>
<tr>
<td>Low grade</td>
</tr>
<tr>
<td>High grade with or without a low grade component</td>
</tr>
<tr>
<td>Mantle cell (lymphomatous polyposis)</td>
</tr>
</tbody>
</table>

\textsuperscript{70}Seminars in Diagnostic Patholo 1996;13:260-296
\textsuperscript{71}Isaacson PG:Lymphoproliferative disorders of the gastrointestinal tract In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
\textsuperscript{72}Compton C, Sobin LH: Reporting on Cancer Specimens Protocols and Case Summaries, College of American Pathologists Cancer Committee, Gastrointestinal Lymphoma, 1998
\textsuperscript{73}Isaacson PG:Lymphoproliferative disorders of the gastrointestinal tract In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
Burkitt and Burkitt-like lymphoma
Other types of low or high grade lymphoma corresponding to lymph node equivalents
Immunodeficiency related
  Post-transplant
  Acquired (AIDS)
  Congenital

**T-CELL**
Enteropathy associated T-cell lymphoma
Other types unassociated with enteropathy

* Equivalent entity: extranodal marginal zone B cell lymphoma (low grade B cell lymphoma of MALT). The term MALT lymphoma (“MALToma”) should be restricted to histologically low grade B cell lymphoma of MALT type. High grade B cell lymphoma of the GIT should be referred to as diffuse B large cell lymphoma (with or without a residual low grade component).

Some Basic Facts about Primary GIT Lymphomas

The GIT is the most common site for occurrence of primary extranodal lymphomas, accounting for 24% to 37% of cases.
Almost all primary gastrointestinal lymphomas are of non-Hodgkin type; primary Hodgkin lymphoma is a rarity.
Most non-Hodgkin lymphomas are of B lineage; diffuse B-cell lymphoma is the most common type.
The stomach is the most common site of involvement, followed by the small intestines. Some, but not all, studies report the small intestine to be the most common primary site for GIT lymphomas in the Middle East.
The prognosis becomes worse with increasing distal location of the lymphoma along the GIT, i.e. worst for rectal lymphoma.
Pseudolymphoma is practically nonexistent; most cases diagnosed as such in the past represent low-grade B-cell lymphoma, and some cases represent exuberant lymphoid reaction around peptic ulcers.
The lymphomas that occur in immunocompromised hosts (including patients with AIDS and post transplant lymphoproliferative disease) are commonly extranodal, and the GIT is one of the most common sites of involvement. Such tumors are commonly multiple.

Most Common Lymphoma Types in Various Segments of the Alimentary Tract

<table>
<thead>
<tr>
<th>Segment</th>
<th>Lymphoma Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>Very rare</td>
</tr>
<tr>
<td>Stomach</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Low-grade B-cell lymphoma of MALT</td>
</tr>
<tr>
<td>Small bowel</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Immunoproliferative small intestinal disease (Mediterranean and Middle East)</td>
</tr>
<tr>
<td>Large bowel</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
</tbody>
</table>
Diffuse B large cell lymphoma
This is the most common GIT lymphoma with approximately 60-70% of cases. Most are diffuse (not follicular or nodular). The vast majority of large cell lymphomas are of B cell type, which is not surprising given that the GIT is a major B-cell lymphoid organ. Some show evidence of transformation of a low grade MALT lymphoma. HIV related lymphomas are most often diffuse aggressive B-cell type lymphomas and classified as large cell, immunoblastic or Burkitt like.

Burkitt Lymphoma
Both endemic and sporadic Burkitt lymphoma, but particularly the latter may present in the GIT. Typically, Burkitt lymphoma occurs as an ileocecal mass in children and presents with obstruction or intussusception. It is identical in all ways to the more common extraintestinal Burkitt lymphoma. Histologically, the lymphoma cell grow in sheets, and are composed of small non cleaved cell with a very high mitotic rate and with interspersed macrophages resulting in a “starry sky” appearance.

Mucosa associated lymphoid tissue lymphoma (MALT lymphoma)
MALT lymphomas have a good prognosis and usually manifest as localized sessile or ulcerated lesions. The lymphoma cells recapitulate the histology of mucosa associated lymphoid tissue (MALT), the Peyer patches. The lymphoepithelial lesion is characterized by invasion of individual glands by lymphoma cells with distortion of gland architecture, destruction of epithelium, and eosinophilic degeneration of gland epithelium. The number of lymphoepithelial lesions varies. They are highly characteristic but not pathognomonic of MALT lymphoma. The most common MALT lymphoma of the stomach is associated with acquired MALT secondary to Helicobacter pylori infection. Gastric MALT lymphoma cells show T-cell mediated strain specific responses to H. pylori. Eradication of H. pylori leads to regression of gastric MALT lymphoma and amazingly also colonic and MALT lymphomas at other sites. Most intestinal B cell lymphomas are of MALT type. The majority arises in the small intestine. Most occur in the elderly and present with obstruction or melena. In colorectal cases, there may be a history of IBD. The majority present with single lesions and any part of the intestine may be involved. Mesenteric lymph nodes are commonly involved, but extra-abdominal spread is unusual at presentation. High grade lymphomas are much more common in the intestine than the stomach and in some a low grade MALT component is present. The high and low grade intestinal MALT lymphomas resemble their gastric counterparts. Histologically, the typical neoplastic cells have small to medium sized nuclei with round to slightly irregular nuclear outlines. The chromatin is condensed and nucleoli are indistinct. A characteristic feature is the presence of moderate to abundant pale to clear cytoplasm. Cell borders are often prominent.

Immunoproliferative small intestinal disease is a subtype of MALT lymphoma, which occurs almost exclusively in the Middle East. It is a disease of young adults and usually presents with severe malabsorption. The histology is similar to low grade gastric MALT except that plasma cell differentiation is more prominent. These plasma cell synthesize large amounts of alpha heavy chain without light chain, which can be detected in the serum, hence the alternative name alpha heavy chain disease. IPSID remains localize to the small intestine for prolonged periods and the patients usually die from severe malabsorption. In its early stages, it may respond to broad spectrum antibiotics that presumably remove a bacterial antigen from the lumen. This unidentified agent, like H. pylori in gastric MALT lymphoma is presumably stimulating growth of the tumor cells.

Mantle cell lymphoma (lymphomatous polyposis)\textsuperscript{74}
This is an unusual form of lymphoma manifested by innumerable polyps affecting long segments of the GIT. Ileocecal masses are common. Nodules of lymphoma are located in the mucosa and submucosa and are composed of small lymphocytes with variably irregular nuclei growing around

\textsuperscript{74}Cancer 1994;74:3042-50
naked germinal centers. In some cases colonization of these germinal center results in a remarkably follicular growth pattern. Lymphoepithelial lesions may be seen. Mesenteric lymph nodes are usually involved. This lymphoma is morphologically, immunophenotypically and molecularly identical to node-based mantle cell lymphoma. LP with mantle cell histology has a poor prognosis with rapid extra intestinal dissemination and a median survival of 3-4 years. Rarely other subtypes of lymphoma can also present as multiple polypoid masses for example MALT lymphoma and follicular lymphoma can cause polyposis. In small endoscopic biopsies, it can be difficult or impossible to differentiated mantle cell lymphoma from MALT lymphoma since the cytological features may be similar and lymphoepithelial lesions can be seen in both. Immunohistochemical detection of IGD, CD5 and cyclin-D1 expression in mantle cell lymphoma, but not MALT lymphoma is the best way of differentiating between the two.

R. Granular cell tumor

A rare neoplasm composed of sheets of large plump cells with eosinophilic granular cytoplasm. The granules are lysosomes on electron microscopy and stain for S100 protein. These neoplasms are of neural (Schwann cell) origin. They occur in the lamina propria or submucosa of the bowel, and perianal area near the anal verge, but are more common in the tongue, soft tissue and other sites.
V. Idiopathic Inflammatory Bowel Disease

Primary Colonic Inflammatory Bowel Disease: Pathologic Classification

<table>
<thead>
<tr>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Indeterminate colitis, probably UC</td>
</tr>
<tr>
<td>Indeterminate colitis, probably CD</td>
</tr>
</tbody>
</table>

A. Indications for mucosal biopsy in inflammatory bowel disease

1. Detect or exclude other specific lesions
2. Identify or confirm the presence of colitis
3. Distinguish acute and chronic colitis
4. Differentiation of UC from CD
5. Determination of disease activity and distribution
6. Detection of dysplasia and carcinoma

It is important that the endoscopist provide a clinical history with the biopsy specimen.

B. Ulcerative colitis may have variable extent: ulcerative proctitis, left-sided colitis, extensive colitis, pancolitis and variable activity (in remission or active)

Major histologic features of chronic colitis (e.g. IBD) as opposed to ASLC (see VI):

- Crypt atrophy and budding
- Villiform surface
- Paneth cell metaplasia
- Marked increase of mononuclear inflammatory cells and eosinophils in lamina propria
- Basal lymphoid aggregates

4. Diagnostic features of UC:

- Absence of known cause
- Rectum always involved
- Colonic disease in the majority of cases; when present, it is always diffuse and there are no skip areas
- Appendix may be affected and may be discontinuous, but there is no involvement of other parts of the gut
- Inflammation and ulceration are usually limited to the mucosa and submucosa; involvement of deeper parts of bowel wall is seen in one-third of surgical resections and in toxic megacolon

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75 Goldman H: Ulcerative colitis and Crohn's disease In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
77 Crohn's and Colitis Foundation of America (http://www.ccfa.org/)
78 Petras RE: Nonneoplastic intestinal diseases In Diagnostic surgical pathology, Sternberg SS
79 Goldman H: Ulcerative colitis and crohn's disease In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
80 Goldman H: Ulcerative colitis and crohn's disease In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
81 Goldman H: Ulcerative colitis and crohn's disease In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
82 Modern Pathol 1994;7:322-25
• Absence of discrete inflammatory sinus tracts, fissures, and fistulas; must distinguish from multiple “cracks” in the wall that may be seen in cases with toxic megacolon
• Absence of well-formed, sarcoid-type granulomas; must distinguish from granulomas due ruptured crypts or foreign bodies

“The definitive diagnosis of UC requires all of the following: diffuse disease limited to the large intestine, involvement of the rectum, more proximal colonic disease occurring in continuity with an involved rectum (i.e. no gross or histological skip lesions), no deep fissural ulcers, no mural sinus tracts, no transmural lymphoid aggregates, and no granulomas.”

C. CD of the colon

Originally described in the small bowel, CD is known to involve the large bowel in about 40% of all cases, with or without a concomitant ileal component. There may be two or more subtypes (fistulizing and stenotic). Recently, a frameshift mutation in Nod2 (Chromosome 16) was found in CD. Nod2 encodes a protein that helps the innate immune system recognize bacterial outer membrane lipopolysaccharides. Nod2 is found primarily in monocyte. The inability of these monocytes to recognize bacteria may lead to an exaggerated inflammatory response by the adaptive immune system.

Grossly there is segmental distribution and preference for the right colon; other significant gross findings include stricture formation, fissuring, a cobblestone appearance of the mucosa, transmural involvement and fat wrapping. The microscopic appearance is similar in the large and small bowel. In biopsies the most useful criteria for diagnosis of CD are: apthous ulcers and focal involvement; disproportionate submucosal inflammation is rare. Microscopic skip areas may be present in multiple mucosal biopsies from the same area or even in a single biopsy with normal mucosa adjacent to an area of fully developed colitis. Biopsy of the terminal ileum is useful because in about 50% of cases of CD, the ileum is involved. A normal rectal biopsy in a case of definite IBD strongly favors CD over UC. It must be remembered that the ability to diagnose CD by endoscopic biopsy has significant limitations because the mucosa lacks many of the diagnostic features of CD namely transmural inflammation, submucosal edema, lymphoid hyperplasia, deep fissuring ulcers, sinus tracts or fibrosis.

1. Diagnostic features of CD

• Absence of known etiology
• Common involvement of the distal small intestine and/or colon; disease tends to have a focal or segmental distribution, and the rectum is often spared
• May affect all other parts of the gut, including the oral cavity, esophagus, stomach, proximal small intestine, appendix, and anal region
• Characterized by ulceration and inflammation extending deep into the bowel wall and by early fibrous stricture formation
• Presence of discrete inflammatory sinus tracts, fissures, or fistulas, in two-thirds of cases; must distinguish from multiple “cracks” in wall that may be seen in cases with toxic megacolon
• Presence of well-formed, sarcoid-type granulomas in one-half of cases; must distinguish from granulomas due to ruptured crypts or foreign bodies

“The definitive diagnosis of CD requires histologic verification with the demonstration of transmural lymphoid aggregates in an area not deeply ulcerated or the presence of non-necrotizing

83 Petras, RE Lecture notes
84 www.ccfa.org
85 Goldman H: Ulcerative colitis and Crohn's disease In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
granulomas. In cases in which the gross and clinical features suggest CD (e.g. skip lesions, linear ulcers, cobblestoning, fat wrapping, terminal ileal inflammation), we advocate extensive histologic sampling to find the definitive histologic features of CD.\textsuperscript{86}

2. Histologic features of CD \textsuperscript{87}

- Focal (segmental) ulceration
- Proliferation of lymphoid nodules
- Dilatation of submucosal lymphatics
- Submucosal fibrosis
- Neuronal hyperplasia
- Hypertrophy of muscularis propria
- Serosal inflammation
- Inflammatory sinus tracts that extend into or through the muscularis propria
- Sarcoid–type granulomas

3. But beware of potential diagnostic traps such as apparent skip areas or rectal sparing in CUC:

- 5-ASA enemas: 36\% will have normal biopsies including normalization of: mixed inflammation, crypt architectural abnormalities, basal lymphoid aggregates, basal plasmacytosis (defined as an increased number of plasma cells in the lower one fifth of the mucosa), Paneth cell metaplasia and villiform surface\textsuperscript{88}
- steroid enemas can also normalize the mucosa
- ulcerative proctitis with a more proximal biopsy of normal mucosa
- acute fulminating ulcerative colitis

4. Frozen section of resection margins in CD is problematic

If the gross exam suggests involvement (erosion or ulceration), a frozen section can be performed to confirm involvement of the margin. Granulomas at a resection margin do not indicate active disease.

\textsuperscript{86} Petras, RE Lecture notes
\textsuperscript{87} Goldman H: Ulcerative colitis and crohn's disease In Pathology of the gastrointestinal tract, second edition, Ming C, Goldman H
\textsuperscript{88} Am J Surg Pathol 1993;17:869–75
D. CD vs. UC

Distinguishing Gross Features of CD and UC 89

<table>
<thead>
<tr>
<th>Feature</th>
<th>Crohn Enteritis</th>
<th>Crohn Colitis</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serositis</td>
<td>Yes</td>
<td>Yes</td>
<td>No, except in fulminant colitis</td>
</tr>
<tr>
<td>Thick bowel wall</td>
<td>Yes</td>
<td>Yes</td>
<td>No, except when complicated by carcinoma</td>
</tr>
<tr>
<td>Stricture</td>
<td>Often</td>
<td>Sometimes</td>
<td>No, except when complicated by carcinoma</td>
</tr>
<tr>
<td>Mucosal edema</td>
<td>Yes</td>
<td>Yes</td>
<td>Usually no</td>
</tr>
<tr>
<td>Discrete mucosal ulcers</td>
<td>Yes</td>
<td>Yes</td>
<td>Usually no, except in fulminant colitis</td>
</tr>
<tr>
<td>Fat wrapping</td>
<td>Often present</td>
<td>Often present</td>
<td>Usually no</td>
</tr>
<tr>
<td>Fistula</td>
<td>Common</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>Distribution</td>
<td>Focal</td>
<td>Usually focal</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Rectal involvement</td>
<td>No</td>
<td>Sometimes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inflammatory polyps</td>
<td>Rare</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
</tbody>
</table>

Distinguishing Histologic Features of CD and UC 90

<table>
<thead>
<tr>
<th>Feature</th>
<th>Crohn Enteritis</th>
<th>Crohn Colitis</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomas</td>
<td>Common</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>Fissuring ulcer *</td>
<td>Common</td>
<td>Common</td>
<td>No, except in fulminant colitis</td>
</tr>
<tr>
<td>Transmural inflammation</td>
<td>Yes</td>
<td>Yes</td>
<td>No, except in fulminant colitis</td>
</tr>
<tr>
<td>Submucosal edema</td>
<td>Yes</td>
<td>Yes</td>
<td>Usually no</td>
</tr>
<tr>
<td>Submucosal inflammation</td>
<td>Yes</td>
<td>Yes</td>
<td>Usually no</td>
</tr>
<tr>
<td>Neuronal hyperplasia</td>
<td>Yes</td>
<td>Sometimes</td>
<td>Usually no</td>
</tr>
<tr>
<td>Thickening of muscularis mucosae</td>
<td>Yes, patchy</td>
<td>Yes, patchy</td>
<td>Yes, diffuse</td>
</tr>
<tr>
<td>Pyloric gland hyperplasia</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Mucosal inflammation and architectural distortion</td>
<td>Focal</td>
<td>Usually focal</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Paneth–cell metaplasia</td>
<td>No</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
</tbody>
</table>

* Fissuring ulcers are lined by granulation tissue rather than neutrophils and extend into the deep submucosa, muscularis propria or beyond

E. Apthous ulcer indicates focal disease

Apthous ulcers are also seen in Yersinia and Campylobacter jejuni infection, but not UC.

89 Petras RE: Nonneoplastic intestinal diseases, In Sternberg SS, editor, Diagnostic surgical pathology
90 Petras RE: Nonneoplastic intestinal diseases, In Sternberg SS, editor, Diagnostic surgical pathology, third edition
F. The possible diagnostic value of pANCA (perinuclear antineutrophil cytoplasmic antibody) and ASCA (anti-Saccharomyces cerevisaeae antibodies) in inflammatory bowel disease. \(^{91,92}\)

G. Crohn disease of the colon (CDC) vs. diverticular disease of the colon (DDC)

But note the newly described: diverticular disease-associated chronic colitis: \(^{93}\) a chronic segmental sigmoid colitis displaying morphological features traditionally reserved for IBD, but confined to the diverticular segment.

<table>
<thead>
<tr>
<th>CD Versus Diverticular Disease of the Colon (^{94})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feature</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Intrinsic colitis</td>
</tr>
<tr>
<td>Lining of mural sinus tracts</td>
</tr>
<tr>
<td>Granulomas</td>
</tr>
</tbody>
</table>

H. Indeterminate colitis (~5%-10% of IBD)

Most common scenarios:
1. Gross and histology indicate UC, but granulomas are found
2. Involved areas suggest UC, but distribution is patchy and lacks major diagnostic criteria of CD (transmural inflammation, granulomas, fissuring ulcers)
3. The fulminant colitis/toxic megacolon problem. In fulminant colitis both fissuring ulcers and transmural lymphoid aggregates—normally major criteria of CD—may be seen in otherwise typical UC; that is two of the three major histologic diagnostic criteria of CD are no longer valid in the fulminant colitis situation.

Today with the pouch procedures, the diagnosis of CD is more grave than ever because CD is an absolute contraindication for the pouch. “There is nothing quite like a pouch to bring out the CD.” \(^{95}\) If a case is ambiguous, it is best to diagnose it as indeterminate colitis. This allows the clinician to review the endoscopic, radiological, clinical and intraoperative findings before making a final decision on offering a pouch procedure.

I. Dysplasia in UC \(^{96}\)

Risk factors: extent (pancolitis), and duration (>8–10 years), but not activity. The definition of dysplasia is the unequivocal, but non–invasive neoplastic alteration of the colonic epithelium. Only two grades are recognized: low grade and high grade. Dysplasia is identified based on a combination of microscopic features including:

\(^{91}\) Am J Gastroenterol 2001:730
\(^{92}\) Inflamm Bowel Dis 2001:192
\(^{93}\) Am J Surg Pathol 1996;20:94-102
\(^{94}\) Goldman H: Ulcerative colitis and Crohn's disease In Pathology of the gastrointestinal tract, second edition, Ming SC, Goldman H
\(^{95}\) Petras RE, guest lecture in Practical Reviews in Pathol 1996:21 No. 2
\(^{96}\) Cancer 1996;78:2261-3
• Architectural alteration exceeding that resulting from repair in chronic colitis, often resembling the glandular arrangement of adenomas.
• Cytological abnormalities, principally cellular and nuclear pleomorphism, nuclear hyperchromatism, loss of nuclear polarity, and marked stratification of nuclei.\textsuperscript{97}

High grade dysplasia (encompassing “carcinoma in situ”) has true stratification and/or cribriform glands.

1. Grading dysplasia in UC

The problem of regeneration (regeneration mimics dysplasia but tends to have widely spaced nuclei, vesicular chromatin and prominent nucleoli) and reproducibility. Expect some variation in grading results between pathologists. Areas of controversy are low grade dysplasia, indefinite probably positive, indefinite unknown. Aneuploidy is more widespread than dysplasia, but still experimental. Confirmation of dysplasia is desirable before colectomy. Confirmation can take one or more forms, depending on circumstances:

• Demonstration that dysplasia is present in multiple biopsies
• Verification on rebiopsy
• Concurrence with other pathologists about findings

<table>
<thead>
<tr>
<th>Classification of Dysplasia</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for dysplasia</td>
<td></td>
</tr>
<tr>
<td>Indefinite for dysplasia</td>
<td></td>
</tr>
<tr>
<td>Probably negative</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Probably positive</td>
<td></td>
</tr>
<tr>
<td>Positive for dysplasia</td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td></td>
</tr>
</tbody>
</table>

The Inflammatory Bowel Disease Dysplasia Morphology Study Group subdivides indefinite for dysplasia into three groups. This subcategorization is cumbersome, subjective and not reproducible.

Management recommendation based on surveillance biopsy

<table>
<thead>
<tr>
<th>Biopsy interpretation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for dysplasia</td>
<td>Continue regular follow-up</td>
</tr>
<tr>
<td>Indefinite for dysplasia</td>
<td>Short term follow-up</td>
</tr>
<tr>
<td>Positive; low grade dysplasia</td>
<td>Short term follow-up; consider colectomy if associated with suspicious gross lesion *</td>
</tr>
<tr>
<td>Positive; high grade dysplasia</td>
<td>Consider colectomy *</td>
</tr>
</tbody>
</table>

* Dysplasia must be confirmed

\textsuperscript{97}Hum Pathol 1993;14:931–966
\textsuperscript{98}Lewin KJ, Riddell RH, Weinstein WM: Gastrointestinal pathology and its clinical implications p937-44
2. Problems with detection of dysplasia:
   - Sampling error
   - Distinction from reactive or regenerative changes
   - Observer variation
   - Lack of knowledge concerning the natural history of dysplasia

### Dysplasia versus repair: comparison of histological features

<table>
<thead>
<tr>
<th></th>
<th>Dysplasia</th>
<th>Repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear enlargement</td>
<td>+ to +++</td>
<td>+</td>
</tr>
<tr>
<td>Nuclear hyperchromatism</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>+ to +++</td>
<td>0 to +</td>
</tr>
<tr>
<td>Irregular nuclear contour</td>
<td>+ to +++</td>
<td>0 to +</td>
</tr>
<tr>
<td>Chromocenters/ nucleoli</td>
<td>0 to +</td>
<td>++ to +++</td>
</tr>
<tr>
<td>Nuclear stratification</td>
<td>0 to +++</td>
<td>+</td>
</tr>
<tr>
<td>Loss of nuclear polarity</td>
<td>0 to ++</td>
<td>0</td>
</tr>
<tr>
<td>Increased mitoses</td>
<td>+ to +++</td>
<td>++</td>
</tr>
<tr>
<td>Inflammatory milieu</td>
<td>+ to ++</td>
<td>++</td>
</tr>
<tr>
<td>Decreased intracellular mucin</td>
<td>+ to +++</td>
<td>++</td>
</tr>
<tr>
<td>High nuclear to cytoplasmic ratio</td>
<td>++ to +++</td>
<td>0 to +</td>
</tr>
<tr>
<td>Cytoplasmic eosinophilia</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Distortion of mucosal architecture</td>
<td>0 to +++</td>
<td>+ to ++</td>
</tr>
<tr>
<td>Villous configuration</td>
<td>0 to +++</td>
<td>0</td>
</tr>
</tbody>
</table>

0 None; + mild; ++ moderate; +++ severe.

3. DNA content analysis

Recent attempts have been made to try to find specific markers of precancer in UC including mucin staining, lectin binding studies, CEA immunocytochemistry as well as molecular studies including DNA aneuploidy, and p53 mutations. Although some of these studies are promising, they are preliminary and not ready for routine practice.

4. Sporadic adenoma vs. polypoid dysplasia-the dysplasia-associated lesion or mass (DALM)

Dysplasia in IBD is categorized as either flat or associated with a raised lesion or mass (DALM). When a DALM consists of isolated discrete nodules or polyps it is difficult to distinguish from sporadic adenomas. The distinction between IBD associated polypoid dysplastic lesions and sporadic adenomas is important because the former occur as a result of IBD and their presence is an indication for colectomy, whereas the treatment of sporadic adenomas even with high grade dysplasia is simple polypectomy. The distinction can be very difficult or impossible, however a DALM must be in an area of colitis (e.g. an adenoma in the right colon in a patient with ulcerative proctitis is not a DALM). DALM may be in the form of polypoid, elevated, nodular or villous formations, ulcers or strictures. In a recent study, IBD-associated polypoid dysplasia, as compared to

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sporadic adenomas, had a statistically significant higher proportion of polyps with tubulovillous or villous architecture, an admixture of normal and dysplastic epithelium at the surface of the polyps and increased lamina propria mononuclear inflammation (see Table below). It is not known if DALM can be pedunculated. One should biopsy around the base of a pedunculated adenoma in IBD. If these biopsies show a dysplasia, this suggests that the lesion is not a sporadic adenoma.

An adenoma in a colitic can be treated by local excision alone only if all the following criteria are met: the patient is in an adenoma age group (older than 40), the polyp is pedunculated, excision is complete, the patient is endoscopically easy to survey (e.g. without inflammatory polyposis) and the mucosa of the stalk and mucosa away from the “adenoma” lack dysplasia. This type of patient should receive careful short term follow-up.

Recently molecular differences have been described between sporadic adenoma and DALM, but these approaches remain to be tested clinically.

Summary of distinguishing clinical, endoscopic, and pathologic features between patients with probable sporadic adenoma and IBD polypoid dysplasia (IPD)\textsuperscript{101}

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>SPORADIC ADENOMA</th>
<th>IPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age</td>
<td>Older (median 63.5 yrs)</td>
<td>Younger (median 48 yrs)</td>
</tr>
<tr>
<td>Disease Activity</td>
<td>Inactive (50%)</td>
<td>Active (85%)</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>Shorter (median 5 yrs)</td>
<td>Longer (median 11 yrs)</td>
</tr>
<tr>
<td>Increased lamina propria inflam., mononuclear</td>
<td>Uncommon (16%)</td>
<td>Common (60%)</td>
</tr>
<tr>
<td>Increased LP inflam., polys</td>
<td>Less Common (36%)</td>
<td>Common (60%)</td>
</tr>
<tr>
<td>Tubulovillous/Villous architecture</td>
<td>Absent</td>
<td>Occasional (20%)</td>
</tr>
<tr>
<td>Admixture of normal and dysplastic crypts at polyp surface</td>
<td>Uncommon (16%)</td>
<td>Common (60%)</td>
</tr>
</tbody>
</table>

Summary of Pathomorphologic Criteria for the Distinction Between Adenomas and Dysplastic Lesions in Patients With Ulcerative Colitis According to Schneider and Stolte\textsuperscript{102}

<table>
<thead>
<tr>
<th>PATHOMORPHOLOGIC CRITERIA</th>
<th>ADENOMA</th>
<th>DYSPLASIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroscopic appearance</td>
<td>Circumscribed polyp</td>
<td>Ill-defined, variable</td>
</tr>
<tr>
<td>Gland Configuration and arrangement</td>
<td>Regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Gland Size</td>
<td>Equal</td>
<td>Unequal</td>
</tr>
<tr>
<td>Mucin vacuoles Configuration and size</td>
<td>Regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Mucin vacuoles Distribution</td>
<td>Often near luminal surface</td>
<td>Irregular</td>
</tr>
<tr>
<td>Dystrophic goblet cells</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

\textsuperscript{101}Am J Surg Pathol 1998;22:275-84
\textsuperscript{102}Schneider A, Stolte M: Gastroenterol 1993;31:653-56
### Nuclei
- Stratified, same level
- Stratified, various levels

### Stroma
- Sparse
- Variable, some broad stromal bridges

### Proliferative zone
- Luminal zone
- Frequently basal zone

### Separation from surrounding mucosa
- Sharp
- Gradual transition

### Surrounding mucosa
- Mild architectural distortion
- Architectural distortion more severe

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J. Carcinomas in UC are characterized by:\(^{103}\)

- Occur about 10 years earlier than non colitic carcinomas
- Especially high incidence in UC with sclerosing cholangitis
- Greater tendency to be located proximal to the recto–sigmoid and in the right colon
- Frequent occurrence as flat lesions covering broad areas of mucosa rather than early polyp formation in patients without colitis
- Polypoid and stricture forming tumors are less common than in non–colitic cancer
- Histologically there is a greater incidence of well–differentiated and mucinous carcinomas approaching 40-50% in some series, increasing the difficulty of biopsy diagnosis
- Multiple carcinomas in 10-20% of cases
- Surveillance cancers vs. symptomatic cancers in UC are lower stage and have better 5 year survival. When matched by stage and grade colitic carcinomas have the same survival as controls without colitis.

K. Carcinoma in CD\(^{104}\)

Intraepithelial neoplasia is seen in a high proportion of CD carcinomas, either adjacent to or at a distance form the invasive carcinoma. Like UC, polypoid dysplastic lesions are diagnosed as DALM. Mucinous adenocarcinomas are seen with an increased frequency as compared to sporadic colorectal carcinomas. There is also an increased frequency of adenocarcinoma in perianal fistulas and squamous cell carcinoma of the anal mucosa. Like UC, TP53 and c-KRAS mutations are seen earlier than in sporadic colorectal adenomas-carcinomas.

L. Polypoid and pseudopolypoid manifestations of IBD\(^{105, 106}\)

These polyps follow episodes of severe inflammatory bowel disease, beginning as pseudopolyps, but with regeneration of the ulcerated mucosa, becoming inflammatory polyps. They are found in about 15% of UC in clinical series, but 60% of UC and 40% of CD in resection specimens.

1. Inflammatory polyps

Inflammatory polyps project above the level of the surrounding mucosa and are composed of mucosa and muscularis mucosa following episodes of severe IBD. They begin as pseudopolyps, mucosal islands and tags in a sea of ulceration. When mucosa regenerates across the ulcers, the islands of original mucosa protrude above the regenerated mucosa as inflammatory polyps. With time, these polyps may progressively elongate by the propulsive action of the gut. Inflammatory

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\(^{103}\)Gut 1994;35:1419-23
\(^{104}\) Hamilton et al p 114
\(^{105}\)Radiographics 1991;293-306
polyps vary considerably in size and shape. Mucosa is the major part of these polyps and it may show the features of IBD including inflammation and crypt abnormalities.

2. Pseudopolyps

Pseudopolyps (in UC) or cobblestone mucosa (in CD) results when extensive ulceration develops with only scattered islands of relatively normal mucosa remaining

3. Post inflammatory (filliform) polyps

These are finger-like projections of submucosa covered by mucosa on all sides reflecting healing of undermined mucosal and submucosal remnants and ulcers and are almost always multiple.

4. Giant and symptomatic inflammatory polyps of the colon in idiopathic inflammatory bowel disease

This an extreme variant in which large inflammatory polyps are present and are segmental and circumferential and typically involve a short segment of colon. The transverse colon is the most common location. More than 50% of cases mimic neoplasm on barium enema. They may be symptomatic independent of the IBD (pain and chronic iron-deficiency anemia due to blood loss).

VI. Non–IBD Colitis and Related Conditions

A. Acute self–limited (infectious colitis) (ASLC)

Non-relapsing colitis may be a better term than ASLC. ASLC is infectious, but in ~1/3 no organism is identified. Many of these cases of acute colitis, which eventually resolve without a definite diagnosis, are thought to represent acute reversible infections in which the organisms are not identified with routine culture such as Campylobacter and Chlamydia. ASLC is most commonly caused by Campylobacter jejuni, E. coli, Salmonella, Shigella and Yersinia enterocolitica. Microscopically ASLC shows neutrophil inflammation mainly of the lamina propria, also with acute cryptitis and crypt abscesses, preservation of crypt architecture, capillary congestion, minimal increase in mononuclear cells, superficial predominance of inflammation and the absence of plasmacytosis at the base of the mucosa. ASLC must be distinguished from acute IBD especially CD. NSAID associated colitis can also overlap ASLC histologically and therefore a clinical drug history is essential. In contrast with acute colitis, chronic colitis has crypt distortion, basal plasmacytosis and Paneth cell metaplasia.

Differential Features in Biopsy Specimens Demonstrating the Active Colitis Pattern

<table>
<thead>
<tr>
<th>Feature</th>
<th>UC</th>
<th>Resolving UC</th>
<th>Crohn Disease</th>
<th>Infectious Colitis/ASLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse change</td>
<td>Yes</td>
<td>Yes</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Focal change</td>
<td>Never</td>
<td>Sometimes</td>
<td>Usually</td>
<td>Usually</td>
</tr>
<tr>
<td>Irregular luminal surface</td>
<td>Yes</td>
<td>Yes</td>
<td>Sometimes; may be focal</td>
<td>Sometimes; may be focal</td>
</tr>
<tr>
<td>Crypt abscesses and cryptitis</td>
<td>Yes</td>
<td>Yes; focal</td>
<td>Yes; focal</td>
<td>Yes; luminal accentuation</td>
</tr>
<tr>
<td>Mucin depletion</td>
<td>Diffuse</td>
<td>Focal</td>
<td>Usually focal</td>
<td>Usually focal</td>
</tr>
<tr>
<td>Architectural abnormality</td>
<td>Diffuse</td>
<td>Usually diffuse</td>
<td>Usually focal</td>
<td>Usually focal</td>
</tr>
<tr>
<td>Basal plasmacytosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Usually absent</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Neutrophils in the lamina propria</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Usually yes</td>
</tr>
<tr>
<td>Granulomas</td>
<td>No</td>
<td>No</td>
<td>Yes, up to 28%</td>
<td>Usually no</td>
</tr>
<tr>
<td>Submucosal inflammation</td>
<td>Usually no</td>
<td>Usually no</td>
<td>Sometimes</td>
<td>Usually no</td>
</tr>
</tbody>
</table>

B. Pseudomembranous (Clostridium difficile toxin, antibiotic-associated) colitis

This is a form of colitis in which plaques of inflammatory exudate form a “pseudo”membrane on the mucosal surface. PMC can be right-sided, especially in AIDS. The classical histology is a “focal explosive mucosal lesion” characterized by the presence of a mushroom-like mass of mucus and neutrophils attached to the surface epithelium, but a spectrum of histologic changes may be present with Types I-III lesions. Clostridium difficile toxin is associated with classic PMC in only 22% of

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patients and the biopsy can vary from normal to non-specific colitis to classical PMC. Metronidazole is recommended as first line therapy for treatment of antibiotic-associated colitis. Oral vancomycin should be used when PMC does not respond to metronidazole.

C. Diversion colitis and proctitis (out of circuit rectum or bowel/bypass colitis/defunctionalized bowel)\textsuperscript{110}

This is a result of luminal starvation of short-chain fatty acids, especially butyrate. Endoscopically diversion colitis may be similar to mild UC. Histology: mucosal lymphoid hyperplasia is the principal finding; crypt architecture is normal or minimally distorted, with increased mononuclear cells in lamina propria and focal acute cryptitis, crypt abscesses, follicular hyperplasia and aphthoid ulcer over follicles. With longer duration the muscularis externa and the muscularis mucosae undergo hypertrophy and there may be submucosal fibrosis and stricture. Of all the changes, lymphoid follicular hyperplasia is the most common and prominent and is a consistent part of diversion colitis. A milder form with normal gross appearance and no neutrophils is call diversion reaction.\textsuperscript{111} Diagnosis of diversion colitis requires clinicopathological correlation.

D. Ischemic colitis: acute vs. healing

Any area of the colon can be involved although the splenic flexure is traditionally considered more susceptible. The mucosa is metabolically the most active layer and it therefore most susceptible to ischemic injury. A major problem is that no diagnostic gold standard exits for chronic low-grade ischemia exists.

Ischemic Disease of the Colon and Rectum

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low arterial blood flow</td>
</tr>
<tr>
<td>Arterial atherosclerosis, thrombi and emboli</td>
</tr>
<tr>
<td>Venous thrombi and compression</td>
</tr>
<tr>
<td>Vasculitis and trauma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal infarct</td>
</tr>
<tr>
<td>Mural infarct</td>
</tr>
<tr>
<td>Transmural infarct</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible but recurrent</td>
</tr>
<tr>
<td>Persistence and stricture</td>
</tr>
<tr>
<td>Perforation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causes of Intestinal Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Henoch-Schonlein disease</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
</tr>
</tbody>
</table>


\textsuperscript{111}Petras RE In Practical Reviews in Pathology
• Acute ischemic colitis involvement is typically patchy and ulcers may be discrete or serpiginous mimicking IBD, especially CD. Microscopically there is hemorrhage into the lamina propria with superficial epithelial necrosis usually sparing the deep portions of the crypts. Inflammation is usually mild, but there can be an inflammatory pseudomembrane, mimicking pseudomembranous colitis. Hyalinization of the lamina propria is a specific and sensitive marker for ischemia in colon biopsies with pseudomembranes.112 The histology becomes nonspecific when the ulcerations become full-thickness.

• Healing phase is often associated with fibrous stricture. Fibrosis in the lamina propria is a better marker than hemosiderin.

Most often, the vascular lesion is not found. Two examples in which the etiology was determined:

• Atheroemboli: ischemic colitis due to cholesterol emboli is only rarely diagnosed. Ischemic colitis is usually caused by non occlusive atherosclerosis of the mesenteric arteries.
• Polyarteritis nodosa with ischemic bowel and perforation.

Recently described is a transient and reversible ischemic colitis in young females associated with oral contraceptive use (and pregnancy) with abrupt onset of severe cramping abdominal pain followed by hematochezia or bloody diarrhea.113

Additional entities with an ischemic component:

• Necrotizing enterocolitis of the neonate
• Hemorrhagic necrosis of GI tract (typhilitis, neutropenic enterocolitis)
• Ureemic colitis
• Behçet disease
• Pseudomembranous colitis
• Late radiation enterocolitis
• Stercoral ulcer–ulcers associated with impacted feces with pressure necrosis usually in elderly bedridden or constipated patients.
• CMV colitis
• Staphylococcal enterocolitis
• E. coli 0157 H7

E. Collagenous colitis114 115 116

Collagenous colitis and lymphocytic colitis share common features suggesting a possible relationship. Because the endoscopic appearance of the mucosa is normal, they are collectively referred to as a “microscopic colitis” by some. Familial cases of microscopic colitis (both lymphocytic and microscopic colitis) are described and there is an association with lansoprazole and aspirin in some cases. Eighty percent (80%) of cases of collagenous colitis are middle-aged or elderly women. Symptoms are chronic watery diarrhea. The endoscopic appearance of the mucosa is normal or near normal (patchy erythema may be present typically in the left colon). The subepithelial collagen band is thickened at >10 microns in thickness, about the diameter of 2 red blood cells. The

114 Petras RE In Practical Reviews in Patholo 1993:17 No. 12
normal collagen band measures about 5 microns in thickness. This thickening is not distributed uniformly. The rectosigmoid is a “cold spot” for collagen deposition. Biopsy yield is highest from the transverse colon. A trichrome (collagen) stain and actual measurement of the thickness of this layer is recommended (Immunostains for tenascin and type IV collagen can be quite helpful also). In some cases, amyloidosis must be excluded. There are also entrapped red blood cells and capillaries in the thickened collagen layer and its inferior margin is irregular in a zigzag pattern. The lamina propria has a mild to moderated increase in chronic inflammatory cell including plasma cells. There is patchy injury to the surface epithelium characterized by increased numbers of intraepithelial lymphocytes, epithelial degeneration, and sloughing much like that seen in lymphocytic colitis. There is an association with celiac disease. CC can be ANCA+. It is essential that the pathologist is made aware of the clinical setting of normal endoscopy because for example diverticulosis can mimic collagenous colitis closely.

F. Lymphocytic (microscopic) colitis

Idiopathic entity with watery diarrhea, normal endoscopy; male/female ratio is about 1:1, may be associated with celiac disease. Histologically identical to collagenous colitis but without the thickened collagen band: increased intraepithelial lymphocytes: >10 but usually in the range of 20–25 lymphocytes per 100 colonic epithelial cells (normal is 4–5), normal architecture, damaged surface epithelium, increased plasma cells. A trichrome stain should be done to rule out collagenous colitis. Increased intraepithelial lymphocytes are seen in collagenous colitis, lymphocytic colitis, IBD, celiac disease, NSAID, infection, around normal lymphoid follicles and possibly normal colon mucosa. The differential diagnosis includes Brainerd diarrhea.119 120

Should grossly normal colonic mucosa be biopsied? Yes, in some cases, because the following entities have normal or near normal endoscopy with abnormal biopsy:121

- collagenous/lymphocytic (microscopic) colitis
- Brainerd diarrhea (petechiae, aphthous ulcers and erythema may be seen)
- MAC (Mycobacterium avium-intracellulare complex) colitis
- cryptosporidiosis
- sprochotosis
- amyloidosis
- eosinophilic gastroenteritis
- diabetes

In addition, the following pathological conditions are often overlooked unless specifically sought in each colorectal biopsy (histologically normal or near normal colonic mucosa). One must remember to search the:

- Lumen for parasites (ameba)
- Surface (spirochetes, cryptosporidium and the recently described adherent E. coli)
- Epithelium (intraepithelial lymphocytes, i.e. lymphocytic and collagenous colitis)
- Subepithelial collagen (collagenous colitis)

117Petras RE In Practical Reviews in Pathology 1993;17 No. 12
120http://www.cdc.gov/health/disease/htm
121Haggitt RC, presentation at San Antonio Society of Pathologists Annual Seminar
G. Radiation colitis122

Radiation changes can be nonspecific and difficult to distinguish from other causes of mucosal damage. In chronic radiation damage there is usually atrophy of the mucosa, reduced numbers of inflammatory cells, submucosal fibrosis and “radiation fibroblasts” (enlarged fibroblasts with large nuclei and irregular nucleoli). In addition, the mucosa may show vascular sclerosis and telangiectasia with capillaries dilated > width of a crypt. The vascular lesions of radiation telangiectasia are identical to those seen in angiodysplasia, portal hypertension and scleroderma.

H. Amebic colitis123

Amebiasis is a disease caused by a one-celled protozoan parasite Entamoeba histolytica that is transmitted by the fecal-oral route. In the US, at risk populations are immigrants from developing countries, travelers to developing countries, people who live in institutions with unsanitary conditions and male homosexuals. It can cause an acute colitis, a chronic colitis, or an asymptomatic carrier state. Not all E. histolytica are pathogenic. The classic description is discrete areas of ulceration covered by exudate, with normal intervening mucosa; however, many cases depart from this. Amebiasis may involve any part of the bowel, but it has a predilection for the cecum and ascending colon. The ameba may be invasive or only found in the surface mucus and therefore all mucus received with endoscopic biopsies should be processed. Phagocytosed erythrocytes by trophozoites are diagnostic of invasive amebiasis. Only the trophozoite is seen in tissue. They usually measure 15-25 microns in diameter. They are round or ovoid and contain an abundant cytoplasm with a distinctive vaculated appearance and relatively small, perfectly round nuclei with prominent nuclear borders and central karyosome. The transmissible cysts are passed in the stool in a multinucleate form containing up to four nuclei.

I. Balantidium coli infection124

A ciliated protozoan capable of causing colitis or appendicitis similar to amebiasis, can also be asymptomatic. The gross appearance may be similar to amebiasis with multiple ulcers showing undermined edges. It is the largest protozoan parasitizing humans with oval organisms up to 100 microns, and with a large dense macronucleus. The organisms tend to cluster and they may penetrate into the submucosa. The differential diagnosis includes Entamoeba histolytica, which is much smaller than B. coli, does not have a macronucleus and may contain ingested red blood cells. Three states of infection are recognized:

- asymptomatic carrier state
- chronic diarrhea disorder
- severe colitic form.

J. Schistosomiasis (Schistosoma japonicum and Schistosoma mansoni)125

The adult fluke lives in the mesenteric circulation; ova pass through bowel wall; reaction to ova varies from cellular to granulomatous to fibrotic, with a polypoid/ulcerative gross appearance reminiscent of CD or neoplasm. The descending and rectosigmoid colon are mainly affected. Diagnosis is based on the characteristic morphology of the eggs in the stool or on colon biopsy. Treatment with

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praziquantel is highly effective and the polyps regress rapidly. Chronic schistosomiasis may be associated with colonic carcinoma.

K. Enteroheamorrhagic Escherichia coli (EHEC)126 127

E. coli 0157:H7 (90% of cases) and several other serotypes produce large amounts of Shiga’s toxin or Shiga–like toxin (verotoxins) and cause outbreaks of hemorrhagic diarrhea with colitis. This organism is estimated to be responsible for 0.6%-2.4% of all cases of diarrhea and 15% to 36% of cases of hemorrhagic colitis. Typically, there is a several day history of abdominal pain and watery diarrhea progressing to bloody diarrhea with little or no fever, usually lasting about 1 week. Histologically there is a spectrum of findings. One set of findings includes acute ischemic injury characterized by hemorrhage and necrosis within the superficial mucosa and preservation within the deep crypts. The second set of findings depicts an ASLC-like picture with edema and neutrophils, including cryptitis, in a background of relative preserved crypt architecture. This histologic combination and the appropriate clinical history should suggest to the pathologist and clinician a need for an appropriate culture.

E. coli 0157:H7 EHEC received notoriety when 606 people became seriously ill in four northwestern states in January, 1993. The outbreak was traced to Jack–in–the–Box restaurants and contaminated undercooked hamburgers (below 60°C). Four children died with the hemolytic-uremic syndrome (HUS). Subsequently, CDC began tracking all cases, not just published reports of clusters. The CDC estimates 73,000 cases annually in the US with 2,100 hospitalizations and 61 deaths and 3-5% of HUS cases dying128. The major source is ground beef; other sources include unpasteurized milk, and juice, sprouts, lettuce, salami and contact with cattle. Waterborne transmission occurs and there has been person-to-person transmission in day-care centers. Since not all clinical labs screen for this organism, it may be necessary to specifically request stool cultures for the organism.

L. Spirochetosis (see X. Appendix)

M. Drug-associated intestinal diseases 129 130

<table>
<thead>
<tr>
<th>Pseudomembranous enterocolitis</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clindamycin and lincomycin</td>
</tr>
<tr>
<td></td>
<td>Cephalosporins</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Others</td>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Mercury-containing laxatives</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Gold</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Antiocoagulants</td>
</tr>
<tr>
<td>Arterial or Venous Thrombosis</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>with Ischemia</td>
<td>Estrogen</td>
</tr>
</tbody>
</table>

127 http://www.cdc.gov health/disease/htm
128 http://www.cdc.gov/health/disease.htm
129 Candrasoma P: Gastrointestinal pathology, Stamford, Ct 1999, Appleton and Lange, p209
130 Histopathol 1994;25:303-8
Inflammation (Colitis, Enteritis) or Ulceration

- NSAIDs
- Gold
- Potassium chloride
- Iron
- Methyldopa
- Clofazimine (granulomatous enteritis)

Melanosis Coli
- Antraquinone laxatives

Pseudo-Obstruction (myenteric plexus damage)
- Phenothiazines
- Antidepressants

NSAIDs cause nonspecific acute and chronic inflammation of the (right) colon and ileum, ulcers and diaphragm strictures. The ulcers are discrete, sometime multifocal and occur in normal mucosa (must rule out CD). Narrow circumferential ulcers produce diaphragm strictures. Ischemia seems to be the pathogenesis. The histology is nonspecific.

Other: azulfidine, gold, cocaine, enemas, suppositories. Penicillin–type antibiotic associated hemorrhagic colitis (ampicillin and amoxicillin).

Kayexalate (sodium polystyrene sulfonate) in sorbitol can induce necrosis of the GIT when administered orally or by enema in the treatment of hyperkalemia. The crystals may be seen in the ulcer debris. The necrosis may necessitate resection.

N. Obstructive colitis

This name is given to a ulcero-inflammatory lesion(s) proximal to a partial or complete obstruction from which it is separated by a variable length of normal mucosa; most commonly the obstruction is due to carcinoma or diverticular disease; predominately found in elderly females with hypertension or diabetes. Ischemia may be contributory and related to mucosal hypoperfusion in the dilated colon according to the law of Laplace. The ulcers vary from small shallow and well–defined lesions to confluent, and circumferential and are non–specific histologically. They occur in a dilated segment and may involve the small bowel (“obstructive enterocolitis”; here must rule out CD).

\(^{131}\text{Am J Surg Pathol 1997;21:60-69}\)
\(^{132}\text{Histopathol 1994;25:57-64}\)
\(^{133}\text{Am J Surg Pathol 1990;14:719-28 and Histopathol 1994;25:57-64}\)
VII. Select Non–Medical Diseases of the Small Bowel

A. Small intestine histology

B. Meckel diverticulum

Rule of 2’s: Meckel diverticulum occur in about 2%, is located about 2 feet from the cecum, averages 2 inches long, and is symptomatic in 2% of cases. Histologically lined by normal small bowel mucosa, but in about 40% ectopic gastric or pancreatic tissue is present which predisposed to ulceration or occult blood loss.

C. Jejunal diverticulosis

Multiple diverticula are present on the mesenteric border and consist of mucosa extending through the muscularis externa (pseudodiverticula: all layers of the intestine are not present). Jejunal diverticulosis may be a marker of an underlying gut motility disorder such as scleroderma, hollow visceral myopathy, and visceral neuropathy.

D. Heterotopic pancreas

This is pancreatic tissue located a distance from the pancreas. It is usually an asymptomatic submucosal nodule, most commonly located in the stomach or duodenum and consists mainly of ducts and ascini, islet tissue may also be present.

E. CD (cf. V) and endoscopic terminal ileal biopsy in IBD

F. Pouchitis

Pouchitis is a complex and evolving subject. The histology of an asymptomatic ileal pouch is normal or near normal terminal ileum. There may be a minor degree of villous shortening, and an increase in chronic inflammatory cells in the lamina propria. Goblet cells are intact and the usual lymphoid aggregates of the terminal ileum may be present. Another common finding in well functioning pouches is a mild acute inflammatory infiltrate in the superficial epithelium and small clusters in the lamina propria. This should not be diagnosed as pouchitis. The clinical syndrome of pouchitis probably represents at least five different conditions (see table).

Pouchitis Syndromes: Proposed Clinicopathologic Classification

<table>
<thead>
<tr>
<th>Antibiotic–responsive pouchitis syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic pouchitis</td>
</tr>
<tr>
<td>Proximal jejunal bacterial overgrowth</td>
</tr>
</tbody>
</table>

---

137 Petras RE In Practical Reviews in Pathol 1996;21 No. 2
138 Petras RE Nonneoplastic Intestinal diseases In Sternberg SS Diagnostic surgical pathology, third edition
Chronic and refractory pouchitis syndromes
   Short–strip pouchitis
   CD
   Chronic primary refractory pouchitis

1. Classic (usual) pouchitis

This shows marked acute inflammation, ulceration, granulation tissue and there is usually associated architectural changes like shortening of the villi, complex branching of crypts loss of the goblet cell population and obliteration of the lymphoid aggregates. These changes can be impossible to differentiate from CD, but the latter may have fistulas, granulomas, and pyloric gland metaplasia. Clinically classic pouchitis involves 16-30% of patients. They experience an increase effluent, which can be bloody or foul smelling, and they may become incontinent. Endoscopically there is erythema, edema, and friable mucosa. Classic pouchitis patients respond to metronidazole.

2. Chronic primary refractory pouchitis

This is a clinicopathologic syndrome of chronic pouch diarrhea and inflammation unresponsive to antibiotics. It occurs in patients who had a colectomy for CUC but not in those who had FAP. Biopsies may resemble CUC and if granulomas are present, CD is likely. In other cases, removal of the pouch is required and there is no evidence of CD either in the excised pouch or the original colectomy specimen. Such chronic pouchitis is most likely a form of, “recrudescent ulcerative colitis within the novel environment of the pouch.” There is also a suggestion that high levels of preoperative pANCA are associated with the development of post-operative chronic pouchitis after IPAA.

Occasional patients who have undergone total proctocolectomy and ileal pouch-anal anastomosis for CUC develop chronic pouchitis and also develop GI and systemic complications that are identical to those seen in CD. These complications include enteric stenosis, or fistulas, arthritis, iridocyclitis and pyoderma gangenosum. The development of Crohn-like GI complications in a patient with chronic pouchitis does not necessarily imply a misdiagnosis.

In short strip pouchitis, clinical symptoms may be caused by exacerbation of UC in the small retained rectal segments. Many patients with this form of pouchitis respond to topical corticosteroids.

Some believe that missed CD is much more likely to present as late pouch fistula than as refractory pouchitis.

The causes of classic pouchitis and primary refractory pouchitis are unknown, but are probably related to a combination of stasis, bacterial overgrowth, the abnormal immune response of the patients with primary IBD, and colonic type metaplasia occurring in some pouches.

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139 Petras RE Ibid
141 Gut 2001:49:671-7
G. Small bowel tumors\textsuperscript{143}

WHO histological classification of tumors of the small intestine\textsuperscript{144}

<table>
<thead>
<tr>
<th>Epithelial tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenoma</strong></td>
</tr>
<tr>
<td>Tubular</td>
</tr>
<tr>
<td>Villous</td>
</tr>
<tr>
<td>Tubulovillous</td>
</tr>
<tr>
<td>Serrated</td>
</tr>
<tr>
<td><strong>Intraepithelial neoplasia (dysplasia) associated with chronic inflammatory diseases</strong></td>
</tr>
<tr>
<td>Low-grade glandular intraepithelial neoplasia</td>
</tr>
<tr>
<td>High-grade glandular intraepithelial neoplasia</td>
</tr>
<tr>
<td><strong>Carcinoma</strong></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
</tr>
<tr>
<td>Signet-ring cell carcinoma</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
</tr>
<tr>
<td><strong>Carcinoid (well differentiated endocrine neoplasm)</strong></td>
</tr>
<tr>
<td>Gastrin cell tumor, functioning (gastrinoma) or non-functioning</td>
</tr>
<tr>
<td>Somatostatin cell tumor</td>
</tr>
<tr>
<td>EC-cell, serotonin-producing neoplasm</td>
</tr>
<tr>
<td>L-cell, glucagon-like peptide and PP/PYY producing tumor</td>
</tr>
<tr>
<td><strong>Mixed carcinoi-adenocarcinoma</strong></td>
</tr>
<tr>
<td><strong>Gangliocytic paraganglioma</strong></td>
</tr>
<tr>
<td><strong>Others</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Epithelial tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoma</td>
</tr>
<tr>
<td>Leiomyoma</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td><strong>Others</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignant lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoproliferative small intestinal disease (includes []-heavy chain disease)</td>
</tr>
<tr>
<td>Western type B-cell lymphoma of MALT</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>Burkitt-like / atypical Burkitt-lymphoma</td>
</tr>
</tbody>
</table>

\textsuperscript{143}Dig Dis 1996;14:245-257

\textsuperscript{144} Hamilton SR, Aaltonen LA: World Health Organization classification of tumors, pathology and genetics, tumours of the digestive system, IARC Press, 2000
Small bowel adenocarcinoma accounts for 2% of GI tumors and 1% of GI cancer deaths. About 55% occur in the duodenum, 18% in the jejunum, 13% in the ileum and 14% not specified.\textsuperscript{145} The overall 5-year disease specific survival is 30.5%. Malignant small intestinal tumors usually present at advanced stage with a poor prognosis. The reasons for late diagnosis include relatively hidden anatomic location and nonspecific symptomatology. The WHO classification of small intestinal carcinoma is identical to that used for the colorectum and histologic grade is also the same. Surgical resection is the most effective therapy for small intestinal carcinoma and the best estimation of prognosis is related to the anatomic extent (stage) of disease at the time of resection. Margins include the proximal a distal and radial margins of resection. For all small bowel segments, except the duodenum, the mesenteric resection margin is the only pertinent radial margin. For the duodenum, the non-peritonealized surface constitutes the pertinent radial margin.

The most common benign lesions are of the small bowel are leiomyoma, adenoma, lipoma and Brunner gland adenoma. The most common malignant tumors are adenocarcinoma, carcinoid tumor, lymphoma and leiomyosarcoma.

H. Tumors of the Ampulla of Vater

Periampullary tumors arise from the duodenum around the ampulla, from the ampulla itself, from the common bile duct, or from the main pancreatic duct. They may be adenomas, adenocarcinoma, or both. Periampullary adenomas may be troublesome in practice. They contain an invasive adenocarcinoma in up to 15% of cases, but the invasive component may not be present on superficial biopsy. Microscopically small bowel adenomas and adenocarcinomas resemble their counterparts in the colon.

I. Jejunoileal carcinoids\textsuperscript{146}

Jejunoileal carcinoids are the second most common group of carcinoids in the GIT. They often are symptomatic, probably secondary to fibrogenic factors produced by the neoplasms that cause kinking of the bowel and/or vascular sclerosis of the mesenteric vessels. They also have a propensity to be multicentric and these multiple carcinoids arise from a background of diffuse intraepithelial endocrine cell hyperplasia, whereas solitary carcinoids do not. It therefore appears valid to classify jejunoileal carcinoids into single and multiple types.

\textsuperscript{145} Cancer 1999;86:2693-706
\textsuperscript{146}Cancer 1997;79:1086-93
J. Gangliocytic paraganglioma of the duodenum

This tumor is a distinct neoplasm occurring almost exclusively in the second part of the duodenum especially in the proximity of the ampulla of Vater. They are small, pedunculated, and submucosal with frequent ulceration and bleeding. Three components are present histologically: endocrine cells with a carcinoid-like appearance; isolated ganglion cells and spindle-shaped Schwann cells. They have a benign course.
VIII. Anal Region

A. Anatomy and Histology

1. Zones in the anal canal:147

- The zone covered with uninterrupted mucosa of the colorectal type
- The zone with epithelial variants (ATZ)
- The zone covered with uninterrupted squamous epithelium
- The perianal skin with keratinized squamous epithelium and skin appendages

2. Anal transitional zone (AZT)

The zone interposed between uninterrupted colorectal mucosa above and uninterrupted squamous epithelium below, irrespective of the type of epithelium present in the zone itself.

3. The extent of the zones and their variability

In 88% the AZT starts at the dentate line (DL) and extends 3 to 20 mm. cranially; in 7% the AZT starts below the DL; in 4% the AZT starts above the DL, and in 1% the AZT is totally absent.

4. Anal glands

About 6-10 anal glands arise from the anal sinuses in the AZT. They are lined by AZT type epithelium.

B. Hemorrhoids

Internal hemorrhoids are covered by columnar and transitional zone mucosa and external hemorrhoids by nonkeratinizing squamous epithelium. Microscopic examination is necessary since gross examination can miss carcinoma in situ and even invasive carcinoma.

C. Fissures, ulcers, fistulas and perirectal abscess148

The anal glands can become inflamed because of blockage or some other mechanism resulting in stasis and infection and abscess formation in the plane of tissue between the anal sphincters. Although some perirectal abscesses heal completely after drainage, 50-80% of them cause fistulas, which drain from the involved anal gland to the skin where the abscess was drained.

Possible Causes of a Perirectal Abscess

<table>
<thead>
<tr>
<th>Cryptop glandular infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Actinomycosis</td>
</tr>
<tr>
<td>Carcinoma</td>
</tr>
</tbody>
</table>

147 Fenger C: Anal canal In Sternberg SS editor, Histology for pathologists, second edition
Lymphoma
Leukemia
Lymphogranuloma venereum
Pelvic inflammation
Trauma (e.g., operative trauma, related to enemas, or impalement)
Foreign body
Radiation

D. Anal tags, papillae and fibroepithelial polyps

E. Anal CD

Anal involvement in CD is more common than in UC with about 25% of patients with small bowel CD and 75% of Crohn colitis patients developing anal involvement during the course of their disease. In some patients, anal involvement may antedate other clinical manifestations of CD by years. The features most characteristic of anal CD are absence of pain, and presence of chronicity, induration, multiplicity and cyanotic coloration. The diagnosis of anal CD may be confirmed by the demonstration of sarcoid-like granulomatous inflammation. It is necessary to exclude anal TB with appropriate special stains, and to exclude giant cell response to fecal/foreign body debris commonly seen in fistulas. There is a possible association of anal CD and squamous/cloacogenic carcinoma of the anus.

F. Syphilis, gonorrhea, and chancroid

G. Condyloma acuminatum (HPV–6 and less often 11)

Condylomas are warty cauliflower-like growths typically arising at the anal margin. They are squamous papillomas with fibrous cores covered by thickened squamous epithelium often with koilocytic change (the intermediate and superficial cell have a clear perinuclear cytoplasm and slightly pyknotic, atypical nuclei).

H. Anal intraepithelial neoplasia

AIN is the result of HPV infection especially HPV–16 and 18. AIN may occur in flat mucosa or in condylomas. Ten percent of cases are discovered incidentally in hemorrhoidectomy specimens. AIN is not recognized grossly and is a histologic/cytologic diagnosis. It is characterized by dysplasia involving squamous epithelium with nuclear crowding, enlargement, and pleomorphism and mitotic activity above the level of the basal layer, atypical mitoses, and individual cell keratinization. Anal cytology is useful in high risk patients.

Bowenoid papulosis: multiple hyperpigmented papules on genital and perianal region which characteristically regress spontaneously but are often simply diagnosed histologically as squamous carcinoma in situ or high grade dysplasia and may therefore be over treated (HPV–16 and 18). It is considered part of AIN and vulvar intraepithelial neoplasia.

I. Keratoacanthoma of perianal skin

This is a dome-shaped lesion composed of squamous cells with a central crater filled with keratin. It typically arises from normal skin, grows rapidly for 4-6 weeks and then undergoes spontaneous

---

regression over the following 4-6 weeks, leaving a slightly depressed annular scar. It can be difficult to differentiate from a well differentiated squamous carcinoma.

J. Inflammatory cloacogenic polyp (cf. SRUS)

Grossly mimics hemorrhoids; middle age patients; rectal bleeding; presumably due to prolapse of proximal anal mucosa; histologically reminiscent of the polypoid phase of SRUS, but lined by areas of ATZ/ squamous epithelium in addition to colonic epithelium.

K. Neoplasms\textsuperscript{150, 151}

Classification of anal neoplasms can be difficult because the site of origin may not be apparent and the histogenesis is controversial. Accurate assessment of location may be complicated by several factors: resections are infrequent or follow failure of chemo/radiation therapy, and precise location of the primary tumor from biopsy specimens can be difficult or impossible. Assessment of tumor location is further complicated by controversy and confusion over the normal anatomy of the anal canal (e.g. surgical anal canal vs. anatomic anal canal). A histologic definition of the anal canal based on the lining mucosa is perhaps most logical and includes the ATZ proximally to its junction with rectal mucosa and the non-hair/sweat gland-bearing mucosa extending distally to the junction with perianal skin.

The great majority of carcinomas of the anus are variants of squamous cell carcinoma with the varied histologic patterns reflecting the diverse microscopic anatomy of the area. Many tumors, especially of the proximal anal canal, have a mixed histologic appearance including squamous, basaloid and occasional glandular elements, the latter being designated as mucoepidermoid or squamous carcinomas with mucinous microcysts in some classifications. Some systems such as the previous WHO classification designate all squamous carcinoma variants of the anal canal as cloacogenic, whereas others classify only those tumors with a predominant basaloid pattern as cloacogenic. Tumors of the more distal anal canal and especially anal margin are generally purely squamous and show fewer basaloid or glandular features.

Tumors arising within anal canal distal to the dentate line are most often keratinizing squamous carcinomas, whereas those appearing in the ATZ above the dentate line are frequently non-keratinizing subtypes of squamous carcinoma. The biology and prognosis of keratinizing and non-keratinizing tumors of the anal canal appear to be similar. The size of the tumor is the most important prognostic factor. Mobile lesions that are no more than 2 cm in diameter can be cured in about 80% of cases, whereas tumor of 5 cm or more can be cured in less than 50% of cases. The probability of nodal involvement is also directly related to the size of the tumor.\textsuperscript{152}

Risk Factors for Anal Cancer

\begin{center}
<table>
<thead>
<tr>
<th>Strong evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human papillomavirus infection (anogenital warts)</td>
</tr>
<tr>
<td>History of receptive anal intercourse</td>
</tr>
<tr>
<td>History of sexually transmitted disease</td>
</tr>
<tr>
<td>More than 10 sexual partners</td>
</tr>
</tbody>
</table>
\end{center}

\textsuperscript{150}Histopathol 1994;25:507-16
\textsuperscript{151}Rickert RR, Compton CC Reporting on Cancer Specimens Protocols and Case Summaries, College of American Pathologists Cancer Committee, Anus 1999
\textsuperscript{152}Ryan DR, Compton CC, Mayer RJ: Carcinoma of the Anal Canal. NEJM 342:792-800, March 16, 2000
### History of cervical, vulvar, or vaginal cancer

- Immunosuppression after solid-organ transplantation

### Moderately strong evidence

- Human immunodeficiency virus infection
- Long-term use of corticosteroids
- Cigarette smoking

### WHO histological classification of tumors of the anal canal\(^{153}\)

#### Epithelial tumors

- **Intraepithelial neoplasia (dysplasia)**
  - Squamous or transitional epithelium
  - Glandular
  - Paget disease

- **Carcinoma**
  - Squamous cell carcinoma
  - Adenocarcinoma
  - Mucinous adenocarcinoma
  - Small cell carcinoma
  - Undifferentiated carcinoma
  - Others

- **Malignant melanoma**

- **Non-epithelial tumors**

- **Secondary tumors**

#### Anal Margin

- **Malignant epithelial tumors**
  - Squamous cell carcinoma
  - Giant condyloma (verrucous carcinoma)
  - Basal cell carcinoma
  - Others
  - Bowens disease
  - Paget disease

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Anal Canal Zones: Epithelial Type and Neoplastic Counterparts

<table>
<thead>
<tr>
<th>Zone</th>
<th>Epithelium</th>
<th>Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Colorectal</td>
<td>Colorectal</td>
<td>As in the colon and rectum</td>
</tr>
<tr>
<td>B. AZT</td>
<td>AZT epithelium</td>
<td>Basaloid carcinoma?</td>
</tr>
<tr>
<td></td>
<td>Squamous epithelium</td>
<td>Squamous carcinoma variants</td>
</tr>
<tr>
<td></td>
<td>Colorectal epithelium</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Endocrine cells</td>
<td>Endocrine tumor</td>
</tr>
<tr>
<td></td>
<td>Melanocytes</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td></td>
<td>Anal glands</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>C. Squamous zone</td>
<td>Nonkeratinizing squamous epithelium</td>
<td>Squamous carcinoma</td>
</tr>
<tr>
<td></td>
<td>Melanocytes</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>D. Perianal skin</td>
<td>Keratinizing squamous epithelium</td>
<td>Squamous carcinoma, basal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Melanocytes</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td></td>
<td>Apocrine glands</td>
<td>Apocrine tumors</td>
</tr>
<tr>
<td></td>
<td>Skin appendages</td>
<td>As in skin</td>
</tr>
</tbody>
</table>

1. Anal Squamous Carcinoma

These tumors may arise from the ATZ or from the anal margin epithelium below the pectinate line.

a. Transitional zone squamous carcinomas

Transitional zone squamous carcinoma are 75% of all anal carcinomas, more common in women, aggressive behavior, two thirds moderately to poorly differentiated keratinizing squamous carcinoma, one third are cloacogenic (basaloid) carcinomas consisting of basal type cells with small quantities of cytoplasm growing in islands with central necrosis and pallisading at the edge. The mitotic rate is generally high and focal keratinization may be present. By in situ hybridization for HPV, 67% of anal squamous carcinomas are positive, whereas all 14 cases of anal cloacogenic carcinomas were negative. Patterns of cloacogenic carcinoma include keratinizing, non–keratinizing, basaloid, with mucous cysts, pseudo–adenoid cystic. Typically a basaloid proliferation without gradual squamous differentiation or maturation, with peripheral pallisading; cell nests may display focal abrupt central keratinization or central necrosis with cyst formation.

Distinction of Squamous and Cloacogenic Carcinomas

<table>
<thead>
<tr>
<th>Feature</th>
<th>Squamous</th>
<th>Cloacogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of tumors</td>
<td>All parts of the anal canal and skin</td>
<td>Transitional zone</td>
</tr>
<tr>
<td>Histological types</td>
<td>Squamous</td>
<td>Basaloid, transitional and squamous</td>
</tr>
<tr>
<td>Association with HPV</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

b. Anal margin squamous carcinoma

More common in men, relatively less aggressive, more common in third-world countries, usually well to moderately differentiated keratinizing squamous carcinoma

c. Verrucous carcinoma (giant condyloma of Buschke and Lowenstein)\textsuperscript{155}

Verrucous carcinoma can occur in the anal margin mucosa, but is a rare lesion. It closely resembles simple condylomas (exophytic, cauliflower-like, warty growth), but is typically larger (over 2 cm) and has invasion at the base. This invasion may not be apparent in a superficial biopsy. The invasion of the underlying tissue is characterized by broad bulbous pushing margins, rather than individual cell invasion. Verrucous carcinoma does not have significant cytological atypia (no high grade AIN). Verrucous carcinoma never metastasizes unless dedifferentiation occurs. All squamous verrucous lesions larger than 2 cm should be excised with a sufficient deep margin and classified histologically as large condyloma acuminata or verrucous squamous carcinoma based on the presence or absence of invasion at the base.

2. Adenocarcinoma

a. Anal gland carcinoma\textsuperscript{156}

HPV may be associated with anal adenocarcinoma, but not with colorectal adenocarcinomas. These tumors arise from the ducts of the anal glands, rather than from the glands themselves and are extremely rare. Three different histologic types are described: well–differentiated adenocarcinoma, mucinous carcinoma and mucoepidermoid carcinoma.

Differential Features of Perianal Mucinous Adenocarcinoma (Adenocarcinoma of anal glands and ducts) versus Rectal Adenocarcinoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Perianal Mucinous Carcinoma</th>
<th>Rectal Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Mucinous</td>
<td>Variable; mucinous uncommon</td>
</tr>
<tr>
<td>Rectal mucosa</td>
<td>Not involved</td>
<td>Mass, possibly ulcerated, may be residual adenoma at a margin</td>
</tr>
<tr>
<td>Fistula</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>Frequency</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Buttock mass</td>
<td>Possibly</td>
<td>Rare</td>
</tr>
<tr>
<td>Invasion</td>
<td>Laterally into buttock</td>
<td>Rectal wall</td>
</tr>
<tr>
<td>Discharge</td>
<td>Gelatinous</td>
<td>Bloody</td>
</tr>
<tr>
<td>Constipation</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

\textsuperscript{156}Owen DA, Kelly JK: Atlas of gastrointestinal pathology, Philadelphia, 1994, Saunders, p192
b. Paget disease

Paget disease is a form of adenocarcinoma in situ that is most commonly seen in the nipple. Extramammary Paget disease can involve the anal region, predominately the perianal skin, but can also occur in the anal canal. It consists of intraepidermal spread of adenocarcinoma as either single cells or small groups of cells. Mucin stains are often positive. Differential diagnosis includes anal melanoma. There may be coexistent invasive adenocarcinoma arising in perianal glands or rectal mucosa. Immunohistochemistry may be an especially helpful adjunct in this setting. Cytokeratin 7 is a sensitive method for detection of Paget cell within involved anal and perianal epithelium. In addition, the specific immunophenotype of Paget cells correlate with pathogenesis and outcome. CK20 positive Paget disease is likely to be associated with underlying rectal adenocarcinoma, whereas CK20 negative, gross cystic disease fluid protein (GCDFP) positive Paget disease is likely to represent primary cutaneous intraepithelial malignancy (with sweat gland differentiation).

3. Small cell carcinoma

This tumor is identical histologically and biologically to the pulmonary and colonic small cell undifferentiated carcinoma.

4. Malignant melanoma

Most anal melanomas affect adults and arise in the ATZ; 1% of all melanomas; usually present late with bleeding, pain or a mass; frequently polypoid, 80% pigmented; histologically identical to cutaneous melanoma. Distinctive findings are melanin production, nesting growth pattern, junctional changes, and appropriate immunocytochemistry including positive staining for S-100 and HMB-45. Anal melanoma has a poor prognosis.

5. Basal cell carcinoma (of perianal skin)

Basal cell carcinomas are common skin tumors of the head and neck seen on sun damaged skin of fair complected individuals. Rarely, they can occur on the perianal skin. They are composed of nests of small uniform basaloid cells with a peripheral palisade surrounded by reactive stroma.

6. Hidradenoma papilliferum of anogenital sweat glands

Characteristically a tumor of white women over 30 years of age (average age of 45 years) occurring as a solitary mobile skin-colored nodule rarely larger than 1 cm. The tumor consists of a well-circumscribed spherical epithelial lined spaces within the dermis. The spaces are lined by an inner layer of apocrine columnar epithelium with decapitation type secretion and an outer layer of less conspicuous myoepithelial cells. Papillary and tubular patterns are common.

IX. Colorectal Pathology in HIV–AIDS

Gastrointestinal tract manifestations in AIDS were second only to pulmonary manifestations in frequency with GIT symptoms occurring in 30% to 50% of North American and European and in 90% of African patients infected with HIV. The recent addition of highly active anti-retroviral therapy and chemoprophylaxis (PCP, MAC and CMV) has delayed/prevented the occurrence of GIT opportunistic infection. GIT manifestations of HIV disease include diarrhea, dysphagia and odynophagia, nausea, vomiting, weight loss, abdominal pain, anorectal disease, jaundice and hepatomegaly, GI bleeding, interactions of HIV and hepatotropic viruses, and GI tumors (KS and non-Hodgkin lymphoma).

The GI tract is also the most common portal of entry for HIV in homosexual men who acquire the retrovirus through mucosal tears in the rectum or, if the mucosa remains intact, through membranous (M) cells. These specialized epithelial cells bind macromolecules and viruses to their apical surface, transport them intact to their basal surface, and deliver them by exocytosis to the mononuclear cells of the lymphoid follicle, the main target cells of HIV. Eventually HIV–induced intestinal immunodeficiency develops largely from the reduction of mucosal CD4+ T cells. The lymphocytes in the lamina propria exhibit a reversed T4:T8 ratio similar to that of the peripheral blood and lymph nodes. Diarrhea and weight loss are the most common symptoms. In fact, the diarrhea/wasting syndrome is now included as an AIDS–defining diagnosis and is second in frequency only to Pneumocystis pneumonia. It is defined as diarrhea persisting for more than 1 month and associated with a weight loss of at least 10% of body weight. This diagnosis accounts for about 17% of newly reported cases of AIDS. The main colorectal and anal manifestations of AIDS are due to opportunistic infection and neoplasms. Multiple infections are frequently seen.

A. HIV–related proctocolitis and HIV–related enteropathy

Because HIV DNA and proteins have been identified in epithelial cells and lymphocytes within the small bowel and colon in the absence of documented intestinal infections, a primary AIDS enteropathy has been postulated. Focal crypt epithelial cell degeneration (apoptosis) is present. In the small intestine, there is mild villous atrophy. The degree of inflammation appears to correlate with the mucosal level of p24 antigen and clinical symptoms, suggesting an etiologic role of HIV. Are mild histologic abnormalities due to uncharacterized intestinal infection or HIV itself?

Idiopathic ulceration of the anorectal area similar to those seen in the esophagus occurs with increased frequency.

B. Opportunistic infections

1. Viral Infections

   a. Herpes simplex virus

   HSV most commonly involves the squamous epithelium of the esophagus (HSV type I) or anal canal (80% HSV type II). Distal colonic and gastric involvement occurs rarely. Infection with HSV

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161Koch J, Kim,LS, Friedman S: The AIDS knowledge base, Chapter 5, June 1998, HIV InSite
in the immunocompromised host is thought to represent reactivation of latent virus acquired earlier in life. Perianal herpes presents with severe anorectal pain, tenesmus, constipation, fever, difficulty in urination, inguinal lymphadenopathy, and sacral parasthesia. Vesicles or ulcers are seen in the anus and in the distal 5 cm. of the rectum. It may cause proctocolitis and severe anal ulceration, especially in patients with AIDS. Histologically there is ulceration with multinucleated squamous cells and basophilic “ground–glass” intranuclear inclusions (Cowdry B) or eosinophilic inclusions with a clear halo (Cowdry A). Immunostains are available and stain the nuclear inclusions.

b. Cytomegalovirus

Infection with CMV may involve any part of the GIT. In patients with AIDS, the colon is most frequently affected. It represents reactivation of latent virus, like herpes. Diarrhea may be watery or bloody. Endoscopically the colon can vary from normal to punctate superficial erosions to deep ulcers and granular friable masses. Severe cases may manifest as necrotizing colitis due to CMV vasculitis with ischemia. Fatal hemorrhage and toxic megacolon have been reported. The colitis is patchy and predominantly affects the cecum and right colon. The appendix can also be involved. Intestinal perforation may occur and the distal ileum, right colon and appendix are the most common sites of perforation. The most plausible mechanism for intestinal ulceration and perforation is local vasculitis and capillary thrombosis due to endothelial cell infection, in turn leading to ischemia and necrosis. The infected cells are enlarged (‘cytomegalic’) with intranuclear and cytoplasmic inclusion. Intranuclear inclusions consist of homogeneous eosinophilic masses with a clear zone separating the inclusion from the nuclear membrane (owl’s eye). Cytoplasmic inclusions are multiple, granular, and basophilic. In some cases, the classic nuclear inclusions are not present, but smudged cells are seen. CMV affects a variety of cell types, primarily endothelial cells, but also smooth muscle cells, fibroblasts, histiocytes and ganglion cells. Immunoperoxidase methods are available to demonstrate CMV antigen in doubtful cases. The differential diagnosis includes adenovirus. Note: because CMV may be seen in otherwise normal mucosa or associated with nonspecific inflammation, it has been recommended that the terminology be “cytomegalovirus-associated” gastrointestinal disease. When CMV infects the epithelium there is little or no inflammation, but when it infects the mesenchyme there is an inflammatory reaction.

c. Others

Adenovirus, EBV, HPV and other novel enteric viruses

2. Bacterial Infections

Increased incidence of common enteric pathogens:

• Salmonella typhimurium is 20 times more common in AIDS than in the general population
• Shigella found in 5% of AIDS patients with diarrhea
• Campylobacter 39 fold increase in incidence
• Clostridium difficile
• Intestinal spirochetosis: in AIDS, it is reported to be symptomatic and to cause morphologic acute colitis and to respond to metronidazole
• Bacillary angiomatosis (Bartonella spp.)
• Diarrheogenic bacterial enteritis in AIDS

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165Pathology 1989;21:235-8
167Human Pathol 1995;26:481-92
3. Mycobacterial Infections

- **GIT Tuberculosis.** Although TB is common in AIDS, GIT involvement is rare.
- **Mycobacterium avium–intracellulare complex (MAC, mycobacteriosis).** GI involvement is common and is seen in 10% of GI biopsies in AIDS patients, second only to CMV (18%). Endoscopically yellow granules or plaques may be seen in the small bowel. The organisms are frequently numerous, and within the cytoplasm of large granular histiocytes which do not form granulomas. The organisms stain with the Ziehl-Neelsen acid fast stain.

4. Fungal Infections

- **Candida (esophagus especially)**
- **Histoplasma**
- **Cryptococcus**
- **Mucormycosis (Phycomycosis)**
- **Pneumocystosis colitis** is rare, but it can cause diarrhea and resolve with antipneumocystis therapy.

5. Protozoan infections

- **Cryptosporidium.** On biopsy, the organisms can be easily seen on H&E-stained sections as rows or clusters of basophilic spherical structures 2 to 4 microns in diameter attached to the microvillous border of the epithelial cells. The anatomic distribution is important with proximal small bowel involvement correlating with mucosal injury, malabsorption, dehydration, weight loss and shortened survival versus colonic involvement.
- **Microsporidia.** Predominately small bowel, but can involve gallbladder respiratory tract, kidney and disseminate, several species, complex life cycle, difficult to see, use of special stains.
- **Isospora belli.** Common in Haitian and African patients with AIDS but is rare in USA
- **Others: Leishmaniasis of the small bowel, the colon, rectum and anus;**

C. Neoplastic processes of increased incidence in homosexual men

Malignant neoplasms of the GIT are present in about 12% of patients with AIDS, and 60% of these are KS. The incidence of KS is declining while non-Hodgkin lymphoma continues to increase. Lymphomas account for about 35% of malignant GIT neoplasms in AIDS patients. The majority is symptomatic, aggressive and likely to originate in Epstein Barr Virus (EBV)-transformed B-cells. A few cases of multicentric benign and malignant smooth muscle tumors in the GIT and other viscera have been reported in children with AIDS with an association with EBV infection.

1. Anal intraepithelial neoplasia and squamous carcinoma

There was an increased prevalence of anal cancer in homosexual males before the AIDS epidemic. Characteristic cytological changes of HPV infection as well as HPV protein, RNA and DNA are found in 70-100% of anal carcinomas. HPV associated culposcopic abnormalities are identified in 86% of asymptomatic homosexual men and dysplasia is identified on biopsy in 92% of this group. The clinical significance of anal squamous intraepithelial lesion in HIV+ and HIV– homosexual males and the likelihood of progression to invasive carcinoma is not yet clear. Recently it was found that most anal HSIL (high grade squamous intraepithelial lesions) in AIDS do not regress in

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169 Am J Clin Pathol 2000;113:64-72  
171 Mod Pathol 1996;9:966-69
recipients of HAART. The proportion of regression of low grade squamous intraepithelial lesion is also low and some case of LSIL progressed to HSIL despite HAART therapy. The combination of longer survival due to HAART, but no effect of HAART on anal SIL may portend an increase incidence of anal carcinoma in the future.

2. Kaposi sarcoma

GIT KS is often widely disseminated yet rarely leads to symptoms. Because of its submucosal location, mucosal biopsies are often negative. KS is characterized histologically by a mixture of spindle cells and endothelial lined vascular spaces. Red cell extravasation and hemosiderin pigment may be present. In early lesions, only the irregular thin vascular spaces are present. This can usually be distinguished from granulation tissue by the disorganized, angulated pattern of the vessels. More advanced lesions show a cellular spindle cell proliferation. Eosinophilic globular bodies can be helpful in diagnosis, but are thought to represent effete red blood cells. Although an unlikely cause of death, GI KS is a poor prognostic sign, with a striking decrease in length of survival at 24 months (11% vs. 88%). Recently a Herpesvirus–like DNA sequence was isolated in more than 90% of KS tissues obtained from patients with AIDS and also in classical KS. It is called human herpesvirus 8.

3. Lymphoma

Non-Hodgkin lymphoma (NHL) was the second most common neoplasm occurring in association with HIV infection (KS was more common), but more recently has increased in incidence while KS has decreased and is the most common neoplasm occurring in some AIDS risk groups, i.e. IV drug abusers and hemophiliacs. NHL occurs in all AIDS risk groups worldwide. NHLs in AIDS frequently arise in unusual anatomic sites, often extranodal. Frequently there is widespread disease, advance stage (III or IV) or bulky disease. 50% are EBV positive. Diffuse NHL of intermediate or high grade B-cell or indeterminate type is an AIDS defining illness in HIV patients according to the 1987 CDC revised criteria. Virtually all AIDS related NHLs display aggressive histology and are diffuse B cell lymphomas. About 40% are small cell undifferentiated Burkitt-like lymphoma and the remainder is large cell lymphomas and large cell immunoblastic lymphomas. Some AIDS related NHLs exhibit transitional morphologic features rendering their precise classification difficult. In the GIT these NHL usually present with symptoms (compare to KS) such as an ulcer, mass, perforation, hemorrhage or in the case of anorectal lymphoma a fistula. Rectal involvement can be subtle with discharge or nonhealing ulcerations as the only manifestation. Median survival is 5-11 months with the prognosis correlating with the extent of immunocompromise and Karnofsky performance rather that the characteristics of the lymphoma itself.

X. Vermiform Appendix

A. Anatomy, histology\textsuperscript{174} and other lesions

1. Fecalith, serosal decidual reaction

2. Fibrous obliteration/ appendiceal neuroma

These two lesions are grossly indistinguishable and are incidental findings.\textsuperscript{175} Appendiceal neuromas are common reported in 10-27\% of excised appendices. On cut surface, they are gray and glistening with obliteration of the lumen. Histologically appendiceal neuromas somewhat resemble traumatic neuromas. They have variable replacement of the appendiceal wall and luminal obliteration by a proliferation of loosely arranged, spindle shaped cell with delicate eosinophilic processes. These cells are immunoreactive for S-100 protein representing Schwann cells investing nerve fibers. There may be an associated increase of argentaffin-positive neuroendocrine cells in the lamina propria.

2. Diverticulosis

3. Acute appendicitis

Most cases are caused by obstruction (although this is debated) with secondary bacterial invasion. With continued secretion by the mucosa and distention of the lumen, the venous pressure is exceeded leading to ischemia and ultimately necrosis.\textsuperscript{176}

4. Idiopathic granulomatous appendicitis vs. CD of the appendix

Chronic appendicitis resembling CD is an uncommon enigmatic condition that presents as appendiceal disease. While most patients remain disease free, a small group will develop CD elsewhere. In one study, granulomatous appendicitis contains about 20 granulomas per tissue section in contrast to about 0.3 granulomas per tissue section in CD. Ironically, the presence of numerous granulomas is the histopathological feature distinguishing idiopathic granulomatous appendicitis from CD. However, other studies suggest that histologic features alone, including granuloma density, do not always predict the clinical outcome and follow-up is essential.\textsuperscript{177} More recently, PCR analysis for Yersinia enterocolitica and Yersinia pseudotuberculosis was positive in 10 of 40 cases. Two subsequently developed CD.\textsuperscript{178}

5. Ulcerative colitis

Appendiceal involvement as a skip lesion in UC is well documented. For example, ulcerative appendicitis may be seen in UC without involvement of the cecum. This should not be erroneously diagnosed as CD based on discontinuous disease.

\textsuperscript{174} Segal GH, Petras RE: Vermiform appendix In Sternberg SS, Histology for pathologists, second edition
\textsuperscript{175} Scheithauer BW, Woodruff JM, Erlandson RA Atlas of tumor pathology, Tumors of the peripheral nervous system 1999: 81-83
\textsuperscript{176} JAMA 1996;276:1589-94
\textsuperscript{177} Mod Pathol 1996; 10:975-81
\textsuperscript{178} Am J Surg Pathol 2001;25:508-15
B. Parasites and infections

1. Actinomycosis

Occasionally, Actinomyces israelii, a normal inhabitant of the mouth and GIT will cause chronic appendicitis or colitis, usually of the right colon and appendix. Fistulas and sinus tracts may form. Grossly “sulfur granules” can be seen. Histologically these are colonies of gram positive filamentous bacteria surrounded by neutrophils.

2. Enterobius vermicularis (pinworms)\textsuperscript{179}

Enterobius is the most common nematode in humans. The mature female lives in the cecal region including the terminal ileum, appendix and cecum and migrates to the anal canal to deposit eggs in the perianal skin. Although many people are asymptomatic, anal pruritus, disturbed sleep, and irritability are the most common symptoms. The adult female measures approximately 1.0 cm in length and up to 0.5 cm in cross section. Males worms are smaller. The adult worm is identified in the lumen of the appendix by the thick cuticle and lateral cuticular alae.

3. Ascaris lumbricoides (round worm)

Ascaris is the largest nematode of the human small intestine, with adult females measuring about 35 cm long and 0.8 cm in diameter (males are smaller). Most people are asymptomatic, but heavy worm loads can cause intestinal obstruction. Diagnosis can be made by a stool exam.

4. Spirochetosis\textsuperscript{180} \textsuperscript{181}

A condition in which colonic or appendiceal surface epithelium is colonized by spiral bacteria. It is caused by several different organisms, most often Brachyspira aalborgi, some related to nonpathogenic spirochetes normally found in pigs. There are recent reports of symptomatic disease with mucosal invasion. It may be related to oral anal contact in homosexuals. In the appendix, it is usually found incidentally. The prevalence appears to be decreasing in Western countries. Luminal antibiotics eradicate the organisms and therefore spirochetosis is rarely seen in resections.

C. Neoplasms\textsuperscript{182} \textsuperscript{183} \textsuperscript{184}

WHO histological classification of tumors of the appendix\textsuperscript{185}

\textsuperscript{179} Petras RE, Goldblum JR: The Appendix In Damjanov I, Linder J editor, Anderson's pathology 10th Edition
\textsuperscript{181} Pathology 1996; 28:283-286
\textsuperscript{182}Cancer 1995;75:757-68
\textsuperscript{183}Appleman HD: Epithelial neoplasia of the appendix, In Norris HT editor, Pathology of the solon, small intestine, and anus, Second Edition
\textsuperscript{184}Seminars in Diagnostic Pathol 1996;13:314-325
\textsuperscript{185} Hamilton SR, Aaltonen LA: World Health Organization classification of tumors, pathology and genetics, tumours of the digestive system, IARC Press, 2000
### Epithelial tumors

- Adenoma
  - Tubular
  - Villous
  - Tubulovillous
  - Serrated

- Carcinoma
  - Adenocarcinoma
  - Mucinous adenocarcinoma
  - Signet-ring cell carcinoma
  - Small cell carcinoma
  - Undifferentiated carcinoma

- Carcinoid (well differentiated endocrine neoplasm)
  - EC-cell, serotonin-producing neoplasm
  - L-cell, glucagon-like peptide and PP?PYY producing tumor
  - Others

- Tubular carcinoid
- Goblet cell carcinoid (mucinous carcinoid)
- Mixed carcinoid-adenocarcinoma
- Others

### Non-epithelial tumors

- Neuroma
- Lipoma
- Leiomyoma
- Gastrointestinal stromal tumor
- Leiomyosarcoma
- Kaposi sarcoma
- Others

### Malignant lymphoma

### Secondary tumors

### Hyperplastic (metaplastic polyp)

Neoplasms of the appendix are unusual. They share some features of colonic neoplasms, but also exhibit distinctive features. Some neoplasms are unique or almost unique to the appendix (e.g. tubular and goblet cell carcinoid).

Non-Endocrine Epithelial Neoplasms and Proliferations of the Vermiform Appendix, a Classification

- Hyperplastic mucosa or polyp
- Colonic type neoplasia
  - Localized villous, tubulovillous or tubular adenoma
### Adenocarcinoma
- Signet ring cell carcinoma

### Distinctly appendiceal neoplasia
- Mucinous cystadenoma
- Mucinous cystadenocarcinoma
- Goblet cell carcinoid

#### Diagnostic criteria for various categories of epithelial noncarcinoid tumors and tumor like lesions of the appendix

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| Simple mucocele (inflammatory or obstructive mucocele)                  | Appendix dilated by accumulated mucus  
No evidence of hyperplasia or neoplasia of the mucosa                                                                                           |
| Hyperplastic polyp                                                       | Localized sessile, or pedunculated lesion resembling colonic hyperplastic polyp  
Elongated tubules showing serrated lumens and reduction in goblet cells  
No evidence of epithelial dysplasia (categorized as “adenoma” if dysplasia is present)  
Intact muscularis mucosae                                                                                                                        |
| Adenoma (adenoma and cystadenoma)                                        | Some resemble colonic tubular adenoma (colonic-type)  
Most are of mucinous (appendiceal) type: sessile lesion, usually circumferential, frequently cystic or multicystic, composed of mucin-rich epithelium forming villous structures or an undulating lining  
It is acceptable to have acellular mucin in the wall if the muscularis mucosa is intact throughout, with no evidence of invasion  
It is acceptable to have scattered gland-like structures in the submucosa                                                                 |
| Mucinous tumor of uncertain malignant potential (UMP)                    | Dysplastic mucinous tumors that are difficult to classify as clearly benign or malignant (e.g. difficult to distinguish between “pushing” invasion versus lack of invasion and between diverticulum-like extension versus true invasion)  
Defined as well-differentiated mucinous neoplasm with epithelium pushing deeply into underlying tissues, but without clear-cut invasion or with mucin present in the wall or outside the appendix in the absence of clear-cut invasion by malignant cells, provided that there is loss of the muscularis mucosae |
| Adenocarcinoma                                                          | Defined as an epithelial neoplasm with invasive neoplastic cell beyond the muscularis mucosae  
Invasion evidenced by infiltrative invasion, single-cell invasion, unequivocal desmoplasia, or growth of viable cells outside the appendix  
Presence of small groups of epithelial cells in extra-appendiceal mucin pools does not automatically place the lesion in this category if the appendix has ruptured  
Classified as mucinous type (>50% of lesion composed of mucin) and colonic type |

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186 Advances in Anatomic Pathol 1996;3:355-61
1. Hyperplastic polyp

These are localized, sessile or pedunculated lesions resembling their colonic counterpart. The distinction from adenomas can be difficult because adenomas frequently have minimal dysplasia. In addition, mixed hyperplastic/adenomatous polyps are relatively frequent in the appendix (serrated adenoma).

2. Adenoma

Villous adenomas greatly outnumber tubular and tubulovillous adenomas. In addition, appendiceal adenomas tend to have only low grade dysplasia.

3. Villous adenoma with mucocele formation (“mucinous cystadenoma”)
   • With or without extrusion of mucus on serosa
   • With or without invasion (well differentiated adenocarcinoma, “cystadenocarcinoma”)

4. Mucocele

A gross descriptive term used to indicate mucinous distention and dilation of the appendiceal lumen, not a diagnosis. Most are neoplastic, only rarely are true simple retention mucoceles encountered. They show a dilated appendix by accumulated mucus with no evidence of hyperplasia or neoplasia of the mucosa.

   • Normal/atrophic appendiceal mucosa: excellent prognosis
   • Low grade adenomatous epithelium: moderately good prognosis
   • Goblet cell carcinoid or poorly differentiated adenocarcinoma including signet–ring variant: poor prognosis
   • Rule out metastatic mucinous ovarian carcinoma. Cases with involvement of appendix and ovaries are usually primary in the appendix rather than in the ovaries.
   • The two factors that are significantly associated with survival by multivariate analysis are the presence of mucin outside the RLQ of the abdomen and the presence of epithelial cells in the peritoneal cavity outside the appendix.187

5. Pseudomyxoma peritonei188 189

This term should be used for a macroscopic description of the clinical finding of jelly-like material on the peritoneal surfaces. The term should not be used unqualified. Like “mucocele” polyp or “ulcer”, it is not a diagnosis, but rather it is a useful clinical/ gross term. The distribution of mucus within the abdomen and the presence or absence of epithelial cells is important prognostically.

6. Adenocarcinoma

   • Large bowel type (r/o cecal primary with direct extension into appendix)
   • Signet–ring carcinoma

187 Cancer 1995;75:757-68
189 National Organization of Rare Disorders, Inc. (http://www.pcnets.com/-orphan/)
7. Carcinoid tumors of the appendix

<table>
<thead>
<tr>
<th></th>
<th>Typical Cacinoid</th>
<th>Tubular Carcinoid</th>
<th>Goblet cell Carcinoid</th>
<th>Mixed Carcinoid-Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Common</td>
<td>Very rare</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Pattern</td>
<td>Insular or trabecular</td>
<td>Tubular</td>
<td>Solid or trabecular</td>
<td>Any plus &gt;50% adenocarcinoma</td>
</tr>
<tr>
<td>Mucin</td>
<td>Negative</td>
<td>Positive in lumen</td>
<td>Positive in cells</td>
<td>Positive in cells</td>
</tr>
<tr>
<td>Extracellular mucin</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive or negative</td>
<td>Positive or negative</td>
</tr>
<tr>
<td>Gross tumor</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Positive</td>
<td>Positive</td>
<td>Focal</td>
<td>Focal</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive or negative</td>
<td>Positive or negative</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td>Positive or negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>5-year survival rate (%)</td>
<td>99</td>
<td>99</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

The appendix is the most common site of GIT carcinoids. They have a relatively good prognosis even when metastatic to local lymph nodes. The typical appendiceal carcinoid arises from subepithelial endocrine cells, is argentaffin–positive and stains for serotonin. Others may arise from the undifferentiated crypt epithelium.

9. Possible indications for right hemicolecction rather than appendectomy
- Tumor involves appendiceal resection margin
- Carcinoids >1.5-2.0 cm.
- Goblet cell carcinoid
- Poorly differentiated carcinoma
XI. Pitfalls\textsuperscript{190}

A. PITFALLS FOR THE PATHOLOGIST

1. Failure to use standard terminology when describing a histologic finding.

2. Failure to contact a clinician if there are any questions with regard to clinical, endoscopic, or surgical findings or with regard to the histological diagnosis.

3. Unwillingness to diagnose a specimen as normal.

4. Habitual diagnosis of mucosal inflammatory process as “nonspecific.”

5. Incorrect orientation of tissue section for histology.

B. FOR THE SURGEON

Endoscopic specimens

1. Inadequate endoscopic biopsies. The informational value of endoscopic biopsies is directly proportional to the amount of tissue sampled.

2. Placing endoscopic biopsies from separate sites in the same container. Always place biopsies from separate sites in separate container and clearly label with the precise site of origin (e.g. “splenic flexure” not “colon”)

3. Using the wrong fixative. Specimens are best fixed immediately in 10\% buffered formalin.

4. Sending lymphomas biopsies in fixative. It is preferable to contact the pathologist prior to or during the procedure to discuss strategy for tissue handling of a suspected lymphoma.

5. Requesting frozen section interpretation of endoscopic biopsy specimens. A frozen section diagnosis is usually less informative than the corresponding fixed, permanent section biopsy. In addition, the frozen section biopsy is sub optimal for standard histology after it has been thawed and fixed. A frozen section should be reserved for cases when an intra procedural therapeutic decision is required and when another sample can be obtained for fixation and standard histology.

6. Failing to provide the pathologist with adequate endoscopic information. The endoscopist is the gross pathologist for the GI histologist. Pathologists rely on both the gross and the microscopic appearances of lesions to make a diagnosis. All endoscopic biopsy specimens should be accompanied by a brief summary of pertinent clinical data and a description of the distribution, severity, extent, and character of endoscopic changes. Specific diagnostic questions should be asked on the requisition.

\textsuperscript{190}Wolber RA, ScudamorCH: The gastrointestinal tract, In Banks PM, Kraybill WG, Pathology for the surgeon, Philadelphia, Saunders 1996
Surgical Specimens

1. Allowing a resected viscus to languish, unopened and unfixed, in a refrigerator overnight or over the weekend. Similarly, specimens should not be dropped unopened into a container of fixative. Unfixed GI mucosa autolyses rapidly. GI resection specimens should be sent fresh, unopened to the pathology lab for immediate opening and fixation. If opened in the OR, the specimen should be cut longitudinally with scissors, along the antimesenteric border, avoiding the lesion of interest. The specimen should then be completely immersed in 10% buffered formalin. Labeling of the proximal and distal resection margins, sites of potential sidewall invasion, or areas of potential neoplastic adhesion to a contiguous organ is helpful to the pathologist and easily accomplished with sutures.

2. Ignoring what constitutes an adequate resection margin for specific malignancies. A microscopically negative mucosal resection margin is important for surgical therapy of carcinomas.

3. Failing to label separately submitted lymph nodes from a mesenteric node dissection with the site of origin. Prognostic implications of nodal involvement vary according to distance from the primary lesion and proximity to mesenteric margin.