Part 3

Case #7
History:

The patient is a 25 year old woman who had a colectomy for familial adenomatous polyposis 2 years ago.

No carcinoma was found in her colectomy specimen.

She presents now with 2 liver masses, suspected clinically to be metastases from an unrecognized colorectal adenocarcinoma, or from another unknown gastrointestinal primary site.

The patient takes oral contraceptives.
Summary:
Hepatocellular lesion
Sheet-like arrangement of cytologically bland hepatocytes
No portal tracts; scattered arteries/arterioles and veins
Small, inconspicuous nucleoli
No mitoses

All of this in a young woman, without cirrhosis, taking oral contraceptives.
So, this should be a liver cell adenoma.
On the other hand, there are prominent pseudoglandular spaces, some of them containing bile, unusual in a liver cell adenoma.

What is the appropriate classification of this liver nodule?

We are all seeing increasing numbers of liver nodules. Why?

North America has been an area of the world with a relatively low incidence of hepatocellular carcinoma, until recent years.

The age-adjusted incidence rates for HCC consecutive 3-year periods between 1976 and 2002.

The incidence is expected to increase until 2008, then stay high for 20 years.
Only HCV-related HCC Increased Between 1993 and 1998

- VA hospitals
- HCV-related HCC accounted for 50% of the increase
- Overall only a third of all cases were HCV-related

El-Serag HB, Mason AC. Arch Intern Med 2000

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Diabetes Is Associated with a Two-fold Increase in Risk of HCC

El-Serag HB, Tran T, Everhart JE, Gastroenterology 2004

The increasing incidence of hepatocellular carcinoma in the US is certainly related to increased prevalence of Hepatitis C beginning in the 1960’s and 1970’s, and likely also due to the prevalence of diabetes, obesity and steatohepatitis.

More patients undergoing surveillance for HCC

Serum AFP Ultrasound
Algorithm for investigation of mass discovered in a cirrhotic liver

Only a subset of masses will be biopsied.

Even so, we are seeing more and more challenging biopsies.

The histologic diagnosis of hepatocellular carcinoma

Hepatocellular differentiation

Malignant features

Classic hepatocellular carcinoma has cells that look like hepatocytes to a variable extent, but has cytologic and architectural abnormalities.....
Cells resemble hepatocytes, with granular eosinophilic cytoplasm, but have increased nuclear:cytoplasmic ratio.

Prominent nucleoli
Bile pigment in canaliculi

Abnormal, dilated bile canaliculi form pseudoglandular spaces
Intranuclear cytoplasmic invaginations may be prominent in some cases.

The cells of HCC are classically arranged in abnormally wide trabeculae separated by sinusoid-like spaces lined by endothelial cells.

Less commonly, the sinusoid-like vascular spaces are compressed, forming a sheet-like pattern.

Stroma is usually sparse……..
...but occasional cases have sclerotic stroma.

The histologic diagnosis of hepatocellular carcinoma

- Hepatocellular differentiation
- Malignant features

What is the differential diagnosis for a low grade hepatocellular mass lesion?

- Dysplastic nodule or macroregenerative nodule in the setting of cirrhosis (surveillance)
- Adenoma
- Focal nodular hyperplasia
- WD HCC

How do we tell these apart?
Well differentiated HCC vs. macroregenerative nodule—a common differential in the setting of a patient with cirrhosis who has a nodule detected.

Cellular features that favor HCC

- Increased N:C
- Often subtle
- Compare to normal liver to see subtle difference

Cellular features that favor HCC

- Macronucleoli
- Intranuclear cytoplasmic invaginations
- Even one mitotic figure
Architectural features that favor HCC

- Open, gaping sinusoids
- Thick trabeculae
- Unpaired arteries
- Pseudoglandular spaces

Focal nodular hyperplasia

Benign nodules in noncirrhotic liver that must be distinguished from HCC.

Liver cell adenoma

Focal Nodular Hyperplasia

- Benign lesion most common in young women
- Related to altered vasculature—a vascular abnormality
- Not caused by, but may be stimulated to grow by oral contraceptives
- Central, radiating scar
Focal Nodular Hyperplasia

- Normal-appearing hepatocytes in nodules partly surrounded by fibrous bands
- Bile ductules and thick walled muscular vessels in fibrous tissue

Fibrous bands

Bile ductular proliferation

Not too tough a diagnosis when you see the whole thing.....

But much more difficult in a needle biopsy!
The usual difficulty is distinguishing FNH from cirrhosis in a needle biopsy, when the only history is "liver biopsy"!

Fibrous bands and bile ductules
Clinical setting
Imaging studies
Characteristic enough that distinction from HCC is not an issue.

Focal Nodular Hyperplasia

- Rare hepatocellular neoplasm, almost exclusively in young women
- Rarely occurs in patients with metabolic disorders (tyrosinemia, glycogen storage, familial diabetes mellitus) or in persons on anabolic steroids

Hepatic adenoma

Uniform population of hepatocytes that may be the same size, larger, or smaller than normal hepatocytes
Hepatic adenoma

Arranged in plates 1 to 3 cells thick

Hepatic adenoma

Sinusoids separating trabeculae often compressed, giving sheet-like arrangement

Hepatic adenoma

Usually eosinophilic cytoplasm, sometimes have glycogen or fat
Differentiating adenoma from well differentiated hepatocellular carcinoma

**Clinical Setting**

<table>
<thead>
<tr>
<th>Hepatocellular carcinoma:</th>
<th>Adenoma:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older/male patient, with cirrhosis or predisposing condition for HCC</td>
<td>Young female patient on OCP, without cirrhosis</td>
</tr>
</tbody>
</table>

**Histology—architecture**

<table>
<thead>
<tr>
<th>Hepatocellular carcinoma:</th>
<th>Adenoma:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thick cords</td>
<td>2-3 cell cords</td>
</tr>
<tr>
<td>Pseudoglandular spaces</td>
<td>Lack of pseudoglandular spaces</td>
</tr>
</tbody>
</table>
HCC

Open sinusoids

Pseudoglandular spaces

Adenoma

No pseudoglandular spaces

Compressed sinusoids

HCC

Irregular, wide trabeculae

Adenoma

Trabeculae 2-3 cells thick

HCC
The histologic diagnosis of hepatocellular carcinoma

Hepatocellular differentiation

Malignant features

What immunostains can help in the diagnosis of hepatocellular carcinoma?

What immunostains are useful in diagnosing hepatocellular carcinoma?

The stains we choose depend on which problem we are facing.

This is clearly malignant, but is it hepatocellular?

This is clearly hepatocellular, but is it malignant?

For the poorly differentiated carcinoma, we would like to prove it is hepatocellular

Markers of hepatocytes?

- **Hep Par 1** (hepatocyte paraffin 1) and **Hepatocyte** recognize an epitope that is part of hepatocyte mitochondria, so marks both normal and neoplastic hepatocytes.

About 75% of HCC are positive for Hep Par 1, but carcinomas of other types may also occasionally be positive.

Poorly differentiated HCC less likely to be positive.
Variable staining from one field to another.

We can take advantage of the fact that only hepatocytes make bile canaliculi.

- Polyclonal CEA and CD 10 highlight bile canaliculi in normal liver.

Bile canalicular staining is present in some cases of HCC—unfortunately, not always the poorly differentiated ones!
CD 10 immunostain does the same thing, only better!
In poorly differentiated HCC, bile canicular staining with pCEA can be very focal.

The CD 10 is often works better than pCEA to find bile canicular staining.
Be aware, though, that CD 10 (and sometimes pCEA) may stain the entire periphery of cells, looking like a membranous staining pattern.

This membranous pattern has been noted in as many as a third of HCC!

For the very well differentiated carcinoma, we would like to prove it is neoplastic.

In benign liver, the sinusoids are lined by specialized endothelial cells. They lack basement membrane. They are also CD 34 negative.
The cells lining the sinusoid-like spaces in HCC are endothelial cells without these specialized features. They stain with CD 34. Sometimes they stain diffusely.
Sometimes the stain is patchy.

Liver cell adenomas may also have patchy CD 34 positivity.

So, sinusoidal CD 34 positivity can support the lesion being neoplastic, but not necessarily malignant.

Glypican-3 is a new antibody touted as “specific for HCC”

*Best for identifying poorly differentiated carcinoma in liver as HCC*

<table>
<thead>
<tr>
<th>Liver lesions</th>
<th>Total positive</th>
<th>Diffuse positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign hepatocellular lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhotic nodules (n=35)</td>
<td>4 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Macroregenerative nodule (n=10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hepatic adenoma (n=6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Borderline and malignant lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade dysplastic nodule (n=7)</td>
<td>3 (43)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Extremely well-differentiated HCC (n=10)</td>
<td>5 (50)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>HCC, well differentiated (n=10)</td>
<td>9 (90)</td>
<td>5 (51)</td>
</tr>
<tr>
<td>HCC, moderately differentiated (n=18)</td>
<td>15 (83)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>HCC, poorly differentiated (n=24)</td>
<td>22 (92)</td>
<td>20 (83)</td>
</tr>
<tr>
<td>Fibrolamellar HCC (n=11)</td>
<td>7 (64)</td>
<td>4 (36)</td>
</tr>
</tbody>
</table>

A panel of 3 immunohistochemical stains has recently been promoted as useful in the distinction of HCC from regenerative and dysplastic nodules in the setting of cirrhosis.

Heat Shock Protein 70
Glypican 3
Glutamine Synthetase

The percentages differ by study, but each of these has a 30-70% rate of positivity in HCC, but less than 10% positivity in dysplastic or regenerative nodules.

Diagnostic accuracy of a panel of HSP 70, GPC 3, and GS in benign and malignant nodules (study did not include adenomas).

<table>
<thead>
<tr>
<th></th>
<th>At least 1+</th>
<th>At least 2+</th>
<th>All 3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign nodule</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N=84</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant nodule</td>
<td>86</td>
<td>54</td>
<td>23</td>
</tr>
<tr>
<td>N=92</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Di Tommaso L, et al. J of Hepatol 2009;50;746-54

I can find varying results for each of these in adenomas—HSP 70 usually negative, others variable, depending on study.

Notes on other immunostains:

**AFP**: So insensitive as to be useless—we never order it

**MOC 31**: + in most adenocarcinomas, including cholangioca, rarely + in HCC

**CK 5/6**: + in about half of pancreatic adenoc, and 20% of cholangioca, negative in HCC
Notes on other immunostains:

**p63**: Positive in cholangiocarcinoma

**p53**: positive in 35% of HCC; negative in benign liver

**Proliferation markers (Ki-67)**: useful in diagnosing carcinoma if >15-20% of nuclei are positive

How grade hepatocellular neoplasm in young woman on oral contraceptives….should be a liver cell adenoma.

Sheet-like arrangement of bland hepatocytes…should be an adenoma.
What about the history of colectomy for familial adenomatous polyposis?

Are there any immunostains that might help?

- Hepatocellular differentiation
- Hepatocyte/HepPar1
- pCEA/CD10
- p53
- Ki67
- CD34
Given the history of a risk factor for hepatocellular neoplasm, and the prominent pseudoglandular spaces:

**Diagnosis:**
**Well-differentiated hepatocellular carcinoma.**

**Case # 8 History:**
A patient presented with signs and symptoms of acute appendicitis.

The surgeon found a large, cystically dilated appendix with mucus adherent to the tip, mucus in the pelvis surrounding the right fallopian tube and ovary, and small mucus implants on the serosa of the small bowel. She performed an appendectomy, and right salpingo-oophorectomy, and biopsied several of the peritoneal implants.
Many, many sections of appendiceal wall are examined.
Big, dilated lumen, mostly surrounded by fibrous wall.

Epithelium lining still present here and there.

Most of the epithelium is pretty bland.
But, in some areas there is epithelium that is more atypical.

On one slide there are irregularly shaped tubules in the appendiceal wall.
The epithelium in this pelvic mucus is bland, like most of the epithelium in the appendix.

My first dilemma:
What is the name for this neoplasm?

Depending on the book or paper I read, I might consider a number of ways to sign out this case……
Appendiceal adenocarcinoma with peritoneal carcinomatosis
Mucinous cystadenoma of the appendix with pseudomyxoma peritonei
Disseminated peritoneal adenomucinosis
Low grade mucinous neoplasm of the appendix with peritoneal spread
Appendiceal mucinous neoplasm of uncertain malignant potential (UMP)

What is the correct name?
This is clearly a mucinous neoplasm of the appendix with spread to the peritoneal cavity.

What do we know about appendiceal mucinous neoplasms?

This is a typical example…
Let’s sample the wall
First 5 blocks

Typical mucus extravasation rxn

10 blocks later…

Eventually…

Characteristic appendiceal adenomatous epithelium
Undulating surfaces
Tall cells with abundant cytoplasmic mucin

Circumferential proliferation villi

Progressive dilatation
Replacement of lamina propria, lymphoid follicles, muscularis mucosae, submucosa, muscularis propria by collagen

Low grade epithelium

High grade epithelium
This is an example of the adenoma-carcinoma sequence.

Adenoma → Carcinoma

Extravasated mucus on the tip.
This might be just mucus....

...or could include epithelium

How does the mucus get there?
2 routes....

Mucus tracking throughout dilated, thinned wall
All the way to the peritoneal surface...

OR...

By way of an appendiceal diverticulum.

There is an association between appendiceal mucinous neoplasms and diverticula....

Diverticulum
May rupture and result in spread of mucinous neoplasm to peritoneal surfaces.
Then how do we recognize invasive carcinoma?

Desmoplastic stromal reaction
High grade epithelium floating in mucin pools

Naked neoplastic tubules imbedded in the muscular wall without desmoplasia? This can be diagnostically tough.

The surgeon found:

And mucin on small bowel serosa.

Where is the primary?
Mucinous tumors in both appendix and ovary: which is the primary?

7 studies between 1991 and 1999
Looking at synchronous mucinous tumors of ovary and appendix, many with pseudomyxoma peritonei:

Based on clinicopathologic and immunohistochemical data, all but one conclude that appendix is by far the most common primary site.

Mucinous tumors in both appendix and ovary: which is the primary?

7 studies between 1991 and 1999
Looking at synchronous mucinous tumors of ovary and appendix, many with pseudomyxoma peritonei:

Genetic studies among these confirm that, in almost all cases, these synchronous tumors are the same.

Appendiceal Mucinous Neoplasms—how do they behave?

<table>
<thead>
<tr>
<th></th>
<th>#</th>
<th>Epithelium</th>
<th>Peritoneal spread</th>
<th>Survival with peritoneal spread</th>
<th>3 year</th>
<th>5 year</th>
<th>10 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMN</td>
<td>88</td>
<td>Low grade</td>
<td>56%</td>
<td>100%</td>
<td>86%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>MACA</td>
<td>16</td>
<td>High grade</td>
<td>75%</td>
<td>90%</td>
<td>44%</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Discordant</td>
<td>3</td>
<td>LG in app HG in perit</td>
<td>All</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

But stage is important too:

No pt with LAMN confined to the appendix died.
2 of 3 with LAMN and localized periapp spread died.

LAMN: low grade appendiceal mucinous neoplasm
MACA: mucinous adenocarcinoma

# Epithelium

Peritoneal spread

Survival with peritoneal spread

3 year

5 year

10 year

LAMN 88 Low grade 56% 100% 86% 45%
MACA 16 High grade 75% 90% 44% No data
Discordant 3 LG in app HG in perit All No data

No pt with LAMN confined to the appendix died.
2 of 3 with LAMN and localized periapp spread died.
What about the peritoneal mucin and epithelium in our case?

**Pseudomyxoma peritonei**
*(literally means 'false mucinous tumor of the peritoneum')*

is described as a slowly progressive disease process characterized by copious amounts of mucoid fluid and tumor that, over time, fills the peritoneal cavity.

What happens to patients with Pseudomyxoma Peritonei?

108 of 109 cases with epithelium, not all appendiceal

<table>
<thead>
<tr>
<th>EPITHELIUM</th>
<th>APP PRIMARY</th>
<th>ORGAN INVASION</th>
<th>NODE METS</th>
<th>5 YR SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPAM</strong> (low grade)</td>
<td>Scant, low grade like appendiceal adenoma</td>
<td>57% known</td>
<td>12% usually ovary</td>
<td>84%</td>
</tr>
<tr>
<td><strong>PMAC</strong> (high grade)</td>
<td>Abundant, high grade or carcinoma</td>
<td>45% known</td>
<td>97% Intestine</td>
<td>7%</td>
</tr>
<tr>
<td>Indeterminant</td>
<td>Mixed</td>
<td>79%</td>
<td>79%</td>
<td>21%</td>
</tr>
</tbody>
</table>

**DPAM**: diffuse peritoneal adenomucinosis

**PMAC**: peritoneal mucinous adenocarcinoma

Patients with appendiceal mucinous neoplasms with localized extra-appendiceal mucin devoid of epithelium are unlikely to develop disseminated peritoneal disease and do not die of their disease.

However, even scant mucin present in such deposits indicates the patient is at risk to develop disseminated disease and die from disease.

Submit all extracellular mucin from such localized deposits to examine for presence of epithelium!

Conclusions based on these studies:

Low grade appendiceal mucinous neoplasms are likely to stay confined to the appendix, or may spread to peritoneal surfaces. They have a good prognosis.

High grade appendiceal mucinous neoplasms are likely to spread to the peritoneum and have a worse prognosis.

Conclusions based on these studies:

Pseudomyxoma peritonei with low grade epithelium has a protracted clinical course.

Pseudomyxoma peritonei with high grade (carcinomatous) epithelium has a bad prognosis.

What does this suggest about our case?
In our case the appendiceal tip was dilated and filled with mucus... and there was a partial epithelial lining.

Most of the epithelium was low grade... (good prognosis)

but some was high grade.. (bad prognosis)
There were invasive tubules in the wall.
(bad prognosis)

There was also peritoneal mucus with strips of low grade epithelium (bad)

Is this a good prognosis or a bad prognosis case?
Diagnosis:
Appendix, resection:
Low grade appendiceal mucinous neoplasm, with extra-appendiceal mucin (pseudomyxoma peritonei), containing low grade neoplastic epithelium.

Terminologies for neoplastic peritoneal mucin accumulations

• **Pseudomyxoma peritonei**
• Disseminated peritoneal adenomucinosis (DPAM) and Peritoneal mucinous carcinomatosis (PMCA)
• Mucinous adenoma/ neoplasm of uncertain malignant potential/ neoplasm of uncertain malignant potential/ carcinoma

Where did the term “Pseudomyxoma peritonei” come from?

• Werth, in 1884, first described pseudomyxoma peritonei as the presence abundant gelatinous material in the peritoneal cavity as a result of perforation of an **ovarian** mucinous cystadenoma.
• Frankel, in 1901, described the association of PMP with a ruptured "mucocoele" of the **appendix**.
Pseudomyxoma peritonei
What’s wrong with this term?

• The term has been used too broadly, to include low grade appendiceal neoplasm, neoplasms from other sites, and also mucinous carcinomas.
• It does not sufficiently describe the findings.

Solution:
Invent new terms!

DPAM and PMCA
Disseminated peritoneal adenomucinosis
Peritoneal mucinous carcinomatosis

• Ronnett and colleagues classified 109 cases of multifocal peritoneal mucinous tumors according to a set of criteria….


DPAM
Disseminated peritoneal adenomucinosis

“A clinicopathologic entity characterized by mucinous ascites and noninvasive mucinous implants with a characteristic distribution and containing histologically benign mucinous epithelium derived from an appendiceal mucinous adenoma and having an indolent course.”
DPAM
disseminated peritoneal adenomucinosis

Peritoneal mucin
Low grade epithelium
Noninvasive implants
Appendiceal adenoma
PMCA
Peritoneal mucinous carcinomatosis

“cases with histologically malignant peritoneal tumors derived from appendiceal or intestinal mucinous carcinomas”

PMCA
Peritoneal mucinous carcinomatosis

Peritoneal mucin
High grade (carcinomatous) epithelium
Invasion
Appendiceal or intestinal mucinous adenocarcinoma
Terminology akin to that for ovarian surface epithelial tumors

**Mucinous adenoma**
Sessile, circumferential, not extending through wall or present in peritoneum
Simple to stratified columnar cells, slight to moderate cytologic atypia
Appendix dilated, may perforate and extravasate mucin
Clinically benign


**Mucinous neoplasm of uncertain malignant potential**
Features of mucinous adenoma, but.....
Proximal margin involved, or...
Epithelium in wall, but not clearly invasive, or...
Uncertain if epithelium in peritoneal mucin
Clinical behavior uncertain
Terminology akin to that for ovarian surface epithelial tumors

**Mucinous neoplasm of low malignant potential**
- Features of mucinous adenoma, but....
- Neoplastic cells penetrate wall and are present in peritoneal mucin
- Abundant peritoneal mucin, may be extensive, but....
- No lymph node, lung, liver mets

Protracted clinical course

<table>
<thead>
<tr>
<th>DPAM</th>
<th>PMCA</th>
<th>MNUMP</th>
<th>MNLMP</th>
<th>PMP</th>
</tr>
</thead>
</table>

**Mucinous adenocarcinoma**
- Infrequently associated with PMP—when present should be called peritoneal carcinomatosis
- Cytoarchitectural features of frank carcinoma
- Lymph node, lung, liver mets

Clinically malignant with poor prognosis
Peritoneal mucin accumulations with low grade epithelium are primarily treated surgically, often followed by various types of chemotherapy…

So, what language do the surgeons understand?

PubMed search using terms

- Appendiceal mucinous neoplasms peritoneal
- Peritoneal adenomucinosis

Looking for the diagnostic terms used in article titles……

Subtracted pathology journals:

- PMP 20
- Descriptive 8
- DPAM 3

Subtracted journals:

- PMP 17
- Descriptive 8
- DPAM 2

My conclusion:
(yours may be different)

- Tell them exactly what is there **descriptively**
  - Grade of neoplasm in appendix
  - Grade of epithelium in peritoneal mucin

- The term *pseudomyxoma peritonei* should appear somewhere in the report for low grade lesions, since that is what the surgeons call it.

- The term *carcinoma* or *carcinomatosis* should appear for high grade (carcinomatous) cases
Case #9
An appendectomy specimen in a patient with appendicitis-like symptoms:

At low power there are pale areas in the thick muscularis propria

Clusters of goblet cells mixed with other cells
Paneth cells

Nests of cells that look endocrine

This is an uncommon component of such neoplasms.

Chromogranin immunostain
Many names have been used or proposed for this tumor:

- Adenocarcinoma
- Goblet cell carcinoid tumor
- Mucinous carcinoid
- Intermediate type of carcinoid
- Crypt cell carcinoma
- Microglandular carcinoma
- Adenocarcinoid tumor
- Carcinoid tumor NOS

The accepted name (WHO) for this is

—Goblet cell carcinoid tumor”

Patients generally present with acute appendicitis, and neoplasm is seldom suspected preoperatively. Some examples are so small and subtle that it is easy to miss them.

Calling this a carcinoid tumor contributes to confusion as to its significance and management.
Goblet cell carcinoid tumor of the appendix

*Is this a type of carcinoid tumor, a type of adenocarcinoma, or what?*

*How does it behave?*

Endocrine cells are a minor component of this tumor

There are 3 questions that often are asked when these tumors are found:

1. Is this really a type of carcinoid tumor?
2. How will it behave?
3. Should a more extensive resection be done, and under what circumstances?

*Ideally, we would answer these questions using solid data.*
Until recently, most of the literature about this tumor consists of case reports or tiny series, as well as a few review articles by surgeons who did not understand the histologic variations.

The first question....

Is this really a carcinoid tumor?

**WHO classifies this as an endocrine tumor**

*Why has it been categorized this way?*

Its presence at the base of the mucosa is taken as evidence that it originates in the mucosa (like a carcinoid tumor).
There are endocrine cells, but they are never the dominant cells; they are always a distant second to the goblet cells.

Is this really a carcinoid tumor?

Goblet cell carcinoids share a number of genetic abnormalities with ileal carcinoid tumors, including allelic loss of chromosomes 11q, 16q, and 18q, suggesting similar events in the pathogenesis of these tumors.


In fact, these are heterogeneous tumors

One of the proposed names:

Crypt cell carcinoma that differentiate along a number of epithelial lines
However, WHO classifies this as an endocrine tumor and calls it goblet cell carcinoid.

But it has some adenocarcinoma-like features:

- Mucin production
- Paneth cells
- A propensity for spread to ovaries and peritoneal surfaces
- May cause death!

So, if this tumor can be aggressive...

What is known about the long term results following appendectomy?

Two large studies have dealt with this issue:

The authors identify 2 types of goblet cell carcinoid tumors, a pure form and a form that had a mixture of pure areas and carcinoma.
Goblet cell Carcinoids and Related Tumors

<table>
<thead>
<tr>
<th>Type</th>
<th>Extent</th>
<th>Mets</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure GCC</td>
<td>App</td>
<td>NO</td>
<td>A &amp; W</td>
</tr>
<tr>
<td>Mixed GCC/Adenoca</td>
<td>App/Invasion</td>
<td>Yes</td>
<td>80% Fatal AdenoCA</td>
</tr>
</tbody>
</table>


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Study of 63 cases of appendiceal goblet cell carcinoid tumor by Tang, et al, from MSK and AFIP

<table>
<thead>
<tr>
<th>Goblet Cell Carcinoid</th>
<th>MORPHOLOGIC CRITERIA FOR CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well differentiated goblet cells arranged in clusters or in a linear pattern</td>
</tr>
<tr>
<td></td>
<td>Minimal cytologic atypia</td>
</tr>
<tr>
<td></td>
<td>Minimal desmoplasia</td>
</tr>
<tr>
<td></td>
<td>Degenerative change with extracellular mucin is acceptable</td>
</tr>
</tbody>
</table>

| Adenocarcinoma Ex GCC, Moderately Differentiated | Recognizable GCC tumor cells arranged or fused into irregular clusters;                                    |
|                                                  | Recognizable GCC tumor cells with easily identifiable single file or single cell infiltration;           |
|                                                  | Significant cytologic atypia                                                                           |
|                                                  | Marked desmoplasia                                                                                     |

| Adenocarcinoma Ex GCC, Poorly Differentiated     | Requires at least focal evidence of goblet cell morphology;                                            |
|                                                  | A component (> 1 high power field or >0.5 mm²) is not otherwise distinguishable from a poorly adenocarcinoma;|
|                                                  | confluent sheets of signet ring cells or undifferentiated cells                                        |
|                                                  | malignant or infiltrating glands or glandular epithelium                                              |
Study of 63 cases of appendiceal goblet cell carcinoid tumor by Tang, et al, from MSK and AFIP

<table>
<thead>
<tr>
<th>All</th>
<th>GCC</th>
<th>WD Ca ex GCC</th>
<th>PD Ca ex GCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>61</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>F/U (mo)</td>
<td>49</td>
<td>66</td>
<td>35</td>
</tr>
<tr>
<td>Mean survival (mo)</td>
<td>43</td>
<td>119</td>
<td>43</td>
</tr>
<tr>
<td>NED</td>
<td>28 (46%)</td>
<td>24 (86%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>AWD</td>
<td>19 (31%)</td>
<td>3 (11%)</td>
<td>15 (58%)</td>
</tr>
<tr>
<td>DOD</td>
<td>44 (23%)</td>
<td>1 (4%)</td>
<td>7 (27%)</td>
</tr>
</tbody>
</table>

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30 cases of appendiceal goblet cell carcinoids that presented with ovarian metastases
25 involved both ovaries, and all were large masses
Appendices all had transmurally invasive tumors
All had mixed patterns, including GCC pattern and adenocarcinoma
Follow up on 25 patients:
17 DOD, 8 AWD
Median survival 19 months
1- and 2-year survival rates 63% and 34%
Conclusion: Should be reported as metastatic appendiceal adenocarcinomas, rather than GCC to reflect prognosis

This means that high grade, high stage tumors have a bad prognosis.

Stage matters, too:

**Mayo Clinic study of 57 patients with goblet cell carcinoid**

<table>
<thead>
<tr>
<th>5 year survival (%)</th>
<th>Recurrence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T 1 or 2</td>
</tr>
<tr>
<td>Stage II</td>
<td>T 3</td>
</tr>
<tr>
<td>Stage III</td>
<td>T 4</td>
</tr>
<tr>
<td>Stage IV</td>
<td>100</td>
</tr>
</tbody>
</table>

Pure low grade GCC confined to the appendix do very well.

GCC that have a component of frank adenocarcinoma, and those that are advanced at presentation do worse.

If it looks like a duck, and quacks like a duck, then it must be a duck!

The third question...

Should a more extensive resection be done, and, if so, under what circumstances?

This is a great question and one that commonly accompanies our consults on this tumor.

Unfortunately, there are no hard data and no controlled studies.

The primary treatment is surgical.

Which patients need a hemicolectomy is the issue, and there are no universally accepted guidelines.
Which patients require a hemicolecctomy?

*In general, there seems to be consensus on the following:*

- Extension outside appendix (no clear appendiceal margin, peritoneal or ovarian involvement, lymph node mets)
- Clear adenocarcinomatous component

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What do we need to tell the surgeon about a goblet cell carcinoid?

- Pure GCC or adenocarcinoma
- TNM
- Appendiceal margin
- Other staging information, if we have the tissue: lymph nodes, ovaries, peritoneal spread