A lecture on Gastric Mucosal Bumps should never take more than half an hour
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Gastric mucosal bumps are histologic challenges for us when compared to polyps in the colon because......
they are much less common, so we have less exposure to them and experience with them
their literature is often pretty bad.

The 2 most common gastric polyps are unique: they have no counterparts in other organs:
hyperplastic fundic gland
The third most common polyp, the adenoma, is rare in our part of the world, but more common in other parts, like Asia.

Let’s start with adenomas. In the stomach, dysplasias that produce polyps are called “adenomas”. Flat dysplasias are simply called “dysplasias”.

There are 2 types of gastric epithelial dysplasia, and thus 2 types of adenoma. Intestinal type, supposedly the more common. Gastric or foveolar type, actually more common?
Intestinal type: identical to colonic adenomas: Pencillate nuclei, undiff cytoplasm, occ goblets

Low-grade foveolar dysplasia, a caricature of normal: uniform larger nuclei, ±nucleoli, partial stratification, apical pink mucin

Things are not so simple. Some adenomas have both intestinal and foveolar epithelia.
Both types can have all grades of dysplasia, including carcinoma invading the lamina propria.

High-grade intestinal dysplasia: Bigger nuclei, nucleoli, complete stratification, less mucin (cytoplasmic maturation)....pleomorphism when bad

High-grade foveolar dysplasia, a poor caricature of normal Bigger nuclei, nucleoli, complete stratification, less mucin (cytoplasmic maturation)....pleomorphism when bad
How many of you have seen a gastric adenoma? How many years of practice did you have to endure before you found one?

10 year old data. I am not sure this is still true........
For intestinal-type adenomas:
- most arise in a background of atrophic gastritis with intestinal metaplasia
- approximately 40% have high-grade dysplasia
- nearly ¼ have adenocarcinoma mostly confined to lamina propria (intramucosal).

Modified from Abraham, et al, Mod Path, 2003

Foveolar-type adenomas
- tend to occur in normal, nonatrophic gastric mucosa
- rarely have high-grade dysplasia or carcinoma.

Modified from Abraham, et al, Mod Path, 2003

Adenomas are not common cancer precursors
In Japan, adenomas are the most common gastric manifestation of familial adenomatous polyposis (FAP)
In the West, fundic gland polyps are the most common by far
How do we manage a patient with a gastric adenoma?

Adenomas have malignant potential, and this risk correlates with size and older patient age. Patients with adenomas should have complete excision and surveillance endoscopy. The specifics of this surveillance are not defined.

One more kind of adenoma: the pyloric gland adenoma
These occur mainly in the stomach, but also elsewhere, especially in the gallbladder and duodenum. The background mucosa generally has some kind of chronic inflammation with about half being autoimmune gastritis. Recent study from Hopkins found an unusually high prevalence in familial adenomatous polyposis.
Apical mucus in gland epithelium

Pink mucus in gland epithelium

MUC5AC stains normal surface and pit cells but not the adenoma cells
MUC6 stains the adenoma cells

Dysplasia and carcinoma can occur in these adenomas. The carcinomas seem to be mainly intramucosal, but some are deeply invasive.
During the 1960s and 1970s, the most common gastric polyp at the time had 3 aliases:

- Regenerative, 1965
- Hyperplastic, 1971
- Hyperplaseogenous, 1973

**Part 2**

What is the definition of a hyperplastic polyp?

Hardly anyone defines it.
In these 3 recent encyclopedic GI pathology texts, there are no definitions, just descriptions

Finally a useful definition from Greg Lauwers, in Greenson’s book, 2016

“Benign polyp formed by elongated and distorted pits lined by foveolar epithelium and edematous stroma”

Does everyone who has published studies of HPs adhere to the same definition?

Study 1: Only polyps showing well-developed foveolar hyperplasia with or without increased inflammatory cells in the lamina propria or surface erosions were included.

Study 2: Elongated, cystic, and distorted foveolar epithelium, marked regeneration; stroma with inflammation, edema, and smooth muscle hyperplasia

These 2 studies may not deal with the same polyps?
They are mostly single large polyps

A few people make more than one polyp

Complex surface architecture
Cysts
Excess stroma
Typical gastric hyperplastic polyp

Coarse nodular and villiform surface
Edematous, inflamed lamina propria
Distorted pits everywhere but no glands

Distorted, cystic pits
Inflamed edematous lamina propria
Coarse projections or villi on the surface which are commonly eroded with underlying granulation tissue.

Different types of pit epithelium:
- Normal
- Hypertrophied
- Regenerative

Similar changes occur on the tops of big folds in any polyp in overhanging ulcer edges.
“Hyperplastic polyps of the stomach have no counterpart in other parts of the GI tract and are thereby organotypical.”

Elster, 1976, re-emphasized by Hattori, 1985

This is a [colonic style hyperplastic polyp](#) which never occurs in the stomach

Why do these two polyps that look nothing alike have the same name?

Simply to annoy us
Normal body glands deep

HPs arise in the pit area, so they look like they are tacked on to the surface of the mucosa.

There is a fact (rumor?) that HPs occur in inflamed stomachs, as much as 40% with *H pylori*, and others with atrophic gastritis, including autoimmune. The non-inflammatory chemical (reactive) gastropathy also is common.

Maybe this is true, but the adjacent mucosa is rarely biopsied, so how can anyone know?
These inflammatory associations led to the assumption that HPs are exuberant reparative lesions.

There is no proof!

Some have atypical gastric type epithelium with apical mucus. Is this low-grade dysplasia or is it reactive?

YES!!!!

Dysplasia is reported to occur in 1-20% of HPs, mainly size related. Cancers in a tiny percent.

1-20%?

This is useless information!
Component 1: Hyperplastic polyp

Component 2: LGD like adenoma
Component 2: LGD like adenoma

If this component is considered the dominant and is called hyperplastic polyp, then this becomes a HP with dysplasia statistic.

If this component is considered the dominant and is called adenoma, then this becomes an adenoma statistic, and the HP part is not important.
How do HPs develop?

Undoubtedly, they start small and get bigger. But what is the stimulus? More stroma and distortion.

There are small polyps composed of elongated pits, that do not have the architectural complexity or expanded stroma of hyperplastic polyps.

From a resection
An orgy of pits

Focal or Polypoid foveolar hyperplasia

Typical biopsy of such a polyp

Is this FFH the precursor of this HP? Some say yes, some say no
Summary: Hyperplastic Polyps

- There are no minimal diagnostic criteria
- Not all studies have studied the same polyps
- The results of these studies cannot be pooled
- We do not know how they evolve
- We do not know the precursors

The dysplasia and carcinoma risk is not settled

Don’t give up hope!
There will be a gene!

Part 3

Beginning in the mid 1970s, we started seeing a different gastric polyp which also had little published information. We now call this the fundic gland polyp (FGP)
They looked like this: cysts, glands, pits, smooth muscle.

**FGPs these days**
are the most common sporadic gastric polyps, as much as 7:1 over the next one.
commonly occur in a syndrome (FAP) that includes cancers.
May carpet the fundus and body.
FGPs are tacked on to the top of normal oxyntic mucosa.

So, FGPs develop in the pit area, just like hyperplastic polyps.
Audience: What are the **minimal**
established diagnostic criteria for
a fundic gland polyp?
a. Cysts?
b. Disorganized oxyntic glands?
c. Short pits?
d. Any combination of these?

What are the **minimal**
diagnostic criteria?
I showed a polyp to my
colleagues who constitute
our GI diagnostic service
The polyp had these features:
I asked my colleagues to name this polyp

Everyone called it a “fundic gland polyp”

Then I asked them why they made that diagnosis

The answers: a variety of reasons, including: “Because it looks like it!”

I showed it to a bunch of our residents

They also called it a fundic gland polyp for the same reasons
In other words, this is a fundic gland polyp, because I say it is!

Historical perspective

FGPs first named by Elster in 1976 as “cysts of gastric glands” and then in 1977 as “fundic gland cysts”


Watanabe, et al: Gastric lesions in FAP

Probably the first use of the FGP name. No definition of FGP just pictures and descriptions, like “simple hyperplasia of the fundic glands..”

Hum Pathol. 9:269, 1978
They mentioned that the glands were irregular, tortuous, sometimes branching. In other words, they were disorganized.

As with hyperplastic polyps, there are no established minimal criteria that allow a bump in oxyntic mucosa to be called a FGP!

Do protein pump inhibitors (PPIs) cause FGPs?

20 years ago, FGPs were curiosities.

There has been a striking increase in incidence of FGPs that seems to coincide with the increased use of PPIs.
Do (PPIs) cause FGPs?

Several studies have addressed this issue and have come up with opposite results.

Because of the suggestion that some FGPs are caused by PPIs, FGPs may be divided into 3 clinical groups:

1. FAP-associated: these are the pure form. Theoretically these should be the role models and they should be uniform.
2. Sporadic: occurring in people not taking PPIs. Are these the same as those in the syndrome?
3. Sporadic: occurring in people taking PPIs. Are these the same as those in the first 2 categories?

Fundic gland polyps occur in 3 settings:

1. FAP-associated: these are the pure form. Theoretically these should be the role models and they should be uniform.
2. Sporadic: occurring in people not taking PPIs. Are these the same as those in the syndrome?
3. Sporadic: occurring in people taking PPIs. Are these the same as those in the first 2 categories?
Same size polyps in 2 FAP patients are different

Short pits
many glands
gland cysts

Long pits
few glands
pit cysts

2 polyps in one FAP patient don’t look much alike

FGPs in FAP have disorganized pits and glands and cysts, but the architectural changes differ in intensity and in whether the pit or the gland abnormalities dominate.

Typical FGPs have many variations
FGPs in FAP

APC gene alterations in at least one FGP in 9 of 11 patients with known germ-line APC gene mutation

Only one APC gene alteration in each patient


Most sporadic FGPs have β-catenin mutations

52 of 57 (91%) FGPs from 40 pts.  
No mention if pts took PPIs.  

29 of 45 (64%) FGPs from 35 pts.  
No pts on long term PPIs.  

Both studies: different mutations in different polyps from the same patients.

Appelman’s concepts:

FGPs are architecturally complex but cytologically simple lesions.

Architecturally complex: the entire mucosa is structurally altered when compared to normal

Cytologically simple: all cells are mature gastric epithelial cells.
FGPs have both Epithelial and Stromal abnormalities

The epithelial aberrations involve both pits and glands

Pit changes
Normal pits

Shorter pits

Normal pits

Longer pits

Cystic pits
Gland changes

Normal: Glands extending down in uniform rows

FGP: Clustered glands under the surface epithelium

FGP: Haphazard budding and branching glands
Cystic glands

Many cysts are mixed pit-gland cysts

The biggest polyps are full of cysts, suggesting FGPs enlarge by increasing the number and size of the cysts.
Stromal (lamina propria) changes

Normal:
There is a little stroma between the pits, but there is hardly any stroma between the glands.

FGPs
Collagen, edema, inflammation
Smooth muscle
Dysplasia on the surface occurs in some FGPs

This is common in FAP where it is usually low-grade

In contrast, high-grade dysplasia is rare in FAP FGPs
Every so often, it occurs in sporadic fundic gland polyps

Alterations in the \textit{APC gene} were present in about half of sporadic FGPs with dysplasia/indefinite, like FAP-associated FGPs.


Summary

FGPs occur in FAP.

Sporadic FGPs are the most common gastric polyps

FAP and sporadic FGPs are architecturally complex and cytologically simple
There is no proof that PPIs induce polyps with the same architectural complexity that occurs in FAP FGPs.

Sporadic and FAP FGPs have different genetic changes.

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Summary of HP and FGP:

Both hyperplastic polyps and fundic gland polyps are poorly and inconsistently defined in our literature and in our textbooks.

We seem to know what they look like in spite of this.