Digestive System

University of Jordan

Faculty of Medicine

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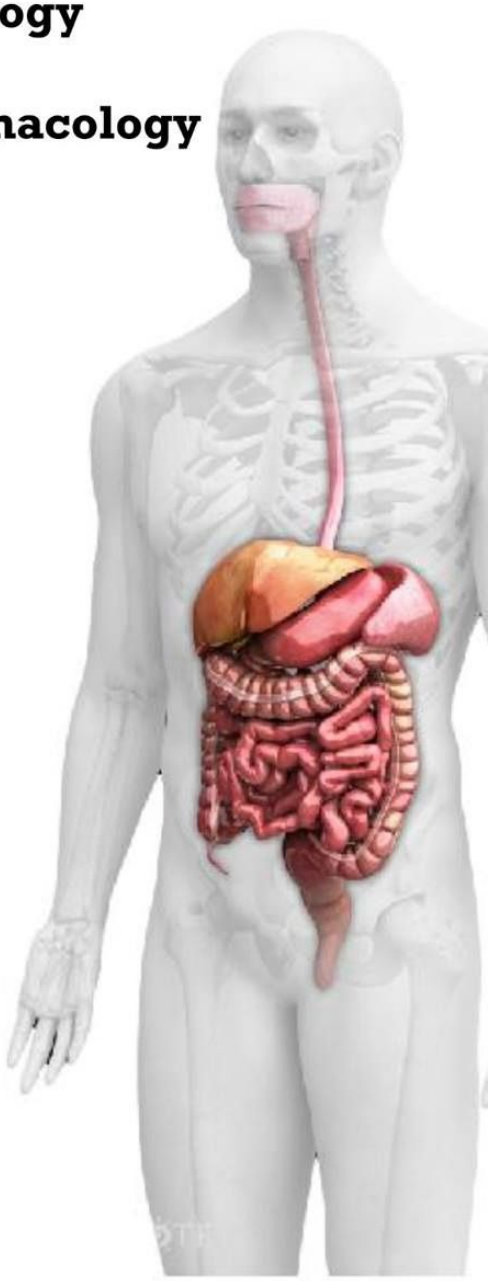

Sheet #: 1

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ESOPHAGUS

Be aware, during the lecture I will be giving you morphology as well. So for your practical part, you will be seeing morphology during the lecture and those pictures will be included in your practical examinations or pictures that are representative of what I'm showing you here they don't necessarily have to be the exact same pictures.

PLEASE REFER TO THE SLIDES FOR IMAGES

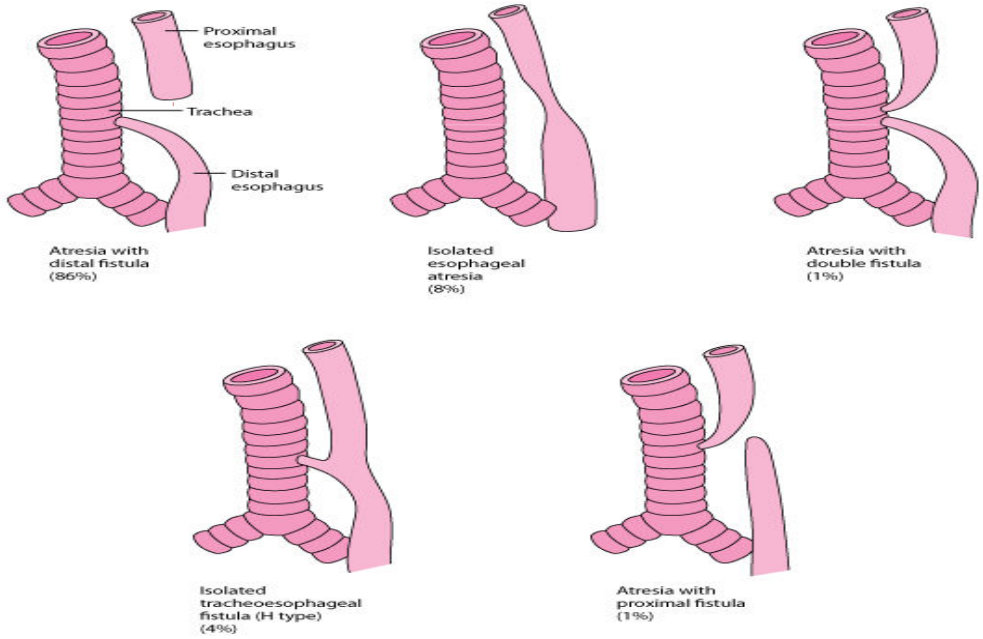
Obstructive and Vascular Diseases of the Esophagus

Mechanical Obstruction

Let's start with esophageal obstruction: **agenesis and atresia** which are typically found very **early after birth** while the child is trying to breast feed when the child will **regurgitate** or not be able to breast feed.

Agenesis is very rare i.e. the esophagus is not there at all. **Atresia** is a thin noncanalized cord replacing part of the esophagus. In either case the child cannot feed properly.

Artesia occurs typically **at the bifurcation of the trachea** and it is **associated sometimes with a fistula** either proximally or distally or both. The problem with a fistula is this child is now at risk for aspiration, pneumonia, and if it is a complete blockage where no food is coming through the child is going to be dehydrated, electronic imbalances so this is something that needs to be recognized and treated immediately.



Stenosis (Narrowing of the esophagus) occurs later on in life, and is typically associated with **inflammation and scarring** so you're not going to find this in a child. Causes for this inflammation and scarring commonly include: **gastroesophageal reflux disease** (we'll talk about that as we go through the lecture), **radiation** (people who have received radiation therapy can also get inflammation and scarring which could lead to esophageal Stenosis and obstruction), or **caustic injury**: the idiots who try to kill themselves by drinking bleach end up rather than killing themselves, debilitating their selves for life.

Stenosis- associated Dysphagia usually is progressive. Dysphagia is difficulty in swallowing. Difficulty in swallowing starts with solids long before it reaches difficulty of swallowing of liquids; so it's harder for you to swallow something solid than it is for you to swallow something liquid.

Functional Obstruction

Functional obstruction of the esophagus also occurs. Food or liquid goes down from your mouth to your stomach by **peristalsis**; there is a coordinated contraction of your esophageal muscles starting from the top moving down to the bottom. So if there is a dis-coordination of that peristalsis you could have functional obstruction there is nothing structurally wrong with your esophagus, but there is something functionally wrong with your esophagus. Because of this dis-coordinated contraction you may have certain areas of the esophagus contracting while the bottom part is also contracting accordingly you have an **increase of intra-luminal pressure** and this could lead to **outpouching or a diverticulum** to occur. There are various types, and when you go to your clinical years you will learn their signs and symptoms, clinical exams, and characteristic shape on Barium ***swallow.***

Achalasia is defined as a triad of:

1. **Incomplete lower esophageal sphincter relaxation**; for food for liquids to go in to your stomach, your lower esophageal sphincter between your stomach and your esophagus has to relax and allow the food or liquid to pass by.
2. **Increased lower esophageal sphincter tone**
3. **Lack of peristalsis**, this typically results in a functional obstruction and a dilation of the esophagus proximal to the obstructed area. Now achalasia could be **primary** i.e. it is a disease on its own there is no underlying condition that led to it, and this is a result of **failure of the inhibitory neurons in your nerve plexuses (myenteric) at the LES. Secondary** i.e. there is an underlying disease that caused achalasia like **Chagas disease** which is caused by **a trypansoma that destroys these nerve plexuses.**

Other diseases can mimic achalsia where you are affecting either the plexuses themselves or the vagus nerve or the dorsal motor nuclei of the vagus nerve so **polio or surgical ablation**,etc can also mimic achlasia.

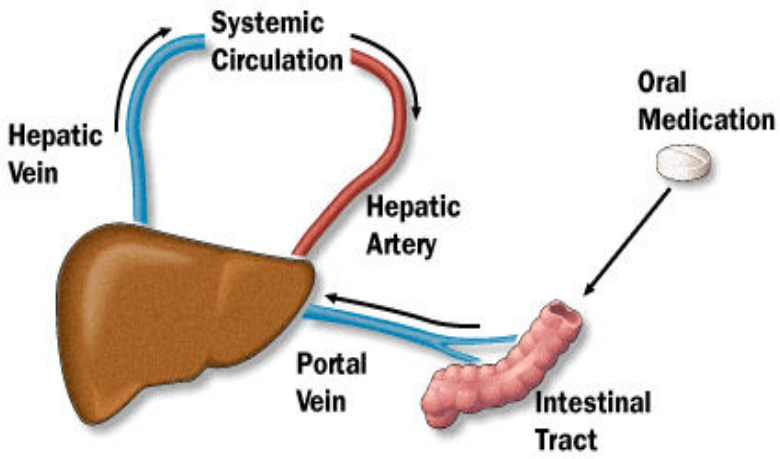
Ectopia

Ectopia is very common in the gastrointestinal tract and is essentially a **developmental rest** of cells that were supposed to move on but stayed in their place rather than reach their final destination. This is very common in the **upper third of the esophagus** and it is called in this case an ***inlet patch*** where there is an **ectopic gastric tissue** at the upper third of the esophagus it is most commonly asymptomatic but if this gastric tissue produces acid you could have symptoms of dysphagia, acidity, ulceration, even as severe as Barrett esophagus, intestinal metaplasia and carcinoma.

Gastric heterotopia is just another name for this ectopia and this is gastric tissue that occurs in the **small bowel or colon** again manifestations could result from excess acidity and ulceration of the surrounding mucosal tissues.

Esophageal Varices

First pass effect is venous circulation from your intestine that's goes to the portal vein (liver); everything that you absorb whether it is drugs, or anything you eat, anything you drink is going to first pass by the liver that's the first pass effect. Although it's commonly for primary metabolism of drugs that are absorbed form the gastrointestinal tract, everything that is absorbed by the gastrointestinal tract passes through the liver, and if you obstruct that portal circulation, this will lead to **portal hypertension**. There are areas where the portal and systemic circulation anastamose, portosystemic anastamosis, **the three major locations are: umbilicus, lower third of the esophagus, and retina.**

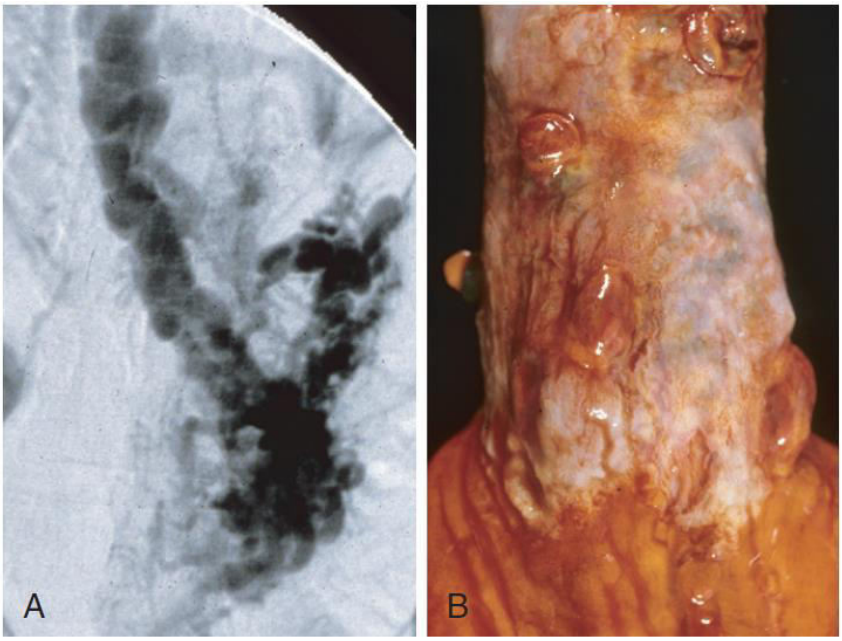


We are talking about **esophageal varices** for the lower third of esophagus, **Capid medusa** "head of medusa" is a symptom of severe portal hypertension where you find a bulging around the umbilicus and veins tortuous around the lower third of the esophagus. A common symptom that is not life-threatening is **hemorrhoids.**

If you have portal hypertension and you increase this shunting from the portal circulation to the systemic circulation or from the splanchnic to the caval you are going to induce the dilatation and tortuousness of the venous plexus where this anastomosis occurs in the lower third of the esophagus. That means there is going to be a lot blood flowing through there and if there is going to be ulceration or a rupture that patient is going to bleed a lot. 50% of patients who bleed through esophageal varices die despite medical intervention. And the ones that do survive another half of those will have a repeat bleed.

Causes: liver cirrhosis; worldwide we are talking about alcoholic liver cirrhosis, less common in our region. Hepatic **schistosomiasis** or what we talked about last lecture Balharzia, is the second most common cause of portal hypertension and esophageal varices.

To make things a bit clearer: everything from your intestine goes to your liver and then from the liver to your systemic circulation. If you cause an increase in the portal system pressure, blood is going to try to find an area of lesser resistance. Areas of lesser resistance are going to be these portosystemic anastomosis.



(The molecular pathology of why the portal blood pressure increases will be explained later.)

While they are often asymptomatic, if they do bleed it is a medical emergency. They can be detected by **angiography**; you will see tortuous veins on angiography of the lower third of the esophagus. If the patient is unlucky and you are the pathologist who is supposed to check why this patient died you will see the tortuous veins at necropsy they won't be full they won't be dilated because there is no pressure but they can still be seen at the lower third of the esophagus often with an area of rupture and necrosis.

Although this microscopic slide does not show rupture and necrosis there is intact epithelium you can see a massive space here with red blood cells that's a lot of blood in a very small area.

That's esophageal varices.

Esophagitis

Esophagitis: inflammation of the esophagus. (–itis typically inflammation) Inflammation results from things that can damage cells and we mentioned last semester that it can be caused by mechanical and chemical agents.

Laceration

First we are going to talk about **mechanical causes**: lacerations.

Two major types of lacerations: the more common being the ***Mallory-Weiss* syndrome** lacerations, second lesser common ***Boerhaave syndrome*. Both** essentially have the same underlying cause which is that you are retching or vomiting severely and constantly.

While typically under vomiting conditions, your **lower esophageal sphincter is going to relax and an antiperistaltic wave** i.e. peristalsis backwards is going to occur to expel whatever you want to expel.

If vomiting goes on for a long time as in people for example who have overindulged in drinking alcohol this is common in Western societies, lower esophageal sphincter will not properly relax, peristalsis will be discoordinated and you can end up with **superficial tears especially at the lower esophageal sphincter.** These are linear, superficial and typically rapid in complete healing. If it's much more severe vomiting or retching you could end up with **transmural** i.e you get perforation of the esophagus and this could lead rarely to mediastinitis where you will osculptate a crackling sound for example in the pericardium because there is air now there and this is a medical emergency.

Anything that can cause constant vomiting could cause you to tire out your sphincter and esophagus, this can occur, like Bulimia.

Hematemesis is vomitting of blood (hemat-blood, emissis- to emit) this is a symptom, because of laceration you've got some blood coming out

Chemical Causes of Esophagitis

Alcohol damages the esophagus, extremes of pH, extremes of temperature, iatrogenic i.e. medically-induced like pill-induced esophagitis.

Whenever you see on an insert, drink/take with plenty of fluids that's not just to ease the swallowing. That's to make sure that the pill doesn't get lodged in the esophagus and the **chemicals in the pill** don't cause problems. People on **chemotherapy and radiotherapy** can also have esophagitis, it is one of your labile tissues, it's supposed to wear and tear, those tissues are more susceptible to chemo and radio therapy.

Graft vs. host disease (GVHD)

Can occur in bone marrow transplantation where there is not a perfect match where now your new graft (your new transplanted material) thinks your tissues are foreign which is a bad outcome for bone marrow transplantation. Esophagitis is one of the symptoms of the graft vs. host disease.

And **heavy smoking**, yes, smoking even though smoke is not going down that way can cause esophagitis. Now chemical esophagitis is usually **self-limiting**; you have **odynophagia** (pain on swallowing) which is different from dysphagia which is difficulty in swallowing. If it continues, you could end up with **stricture,** (remember we mentioned mechanical obstruction through stricture underlying previous inflammation) or in severe cases, **perforation**, which is typically asymptomatic.

There are non-specific morphologic changes where you will see some neutrophils infiltrating and you may see some ulceration but histology is not going to be very helpful to you.

To make things clearer: If you have a problem in your bone, like lymphoma for example, and they decide to ablate your bone marrow because it's diseased, and you get a transplantation from a donor who isn't going to be a perfect match. What does your bone marrow contain? RBCs, WBCs and their progenitors. White blood cells can detect the transplant as a foreign body because they're from somebody else. And this leads to various autoimmune diseases because now your graft is producing immunity against the transplant.

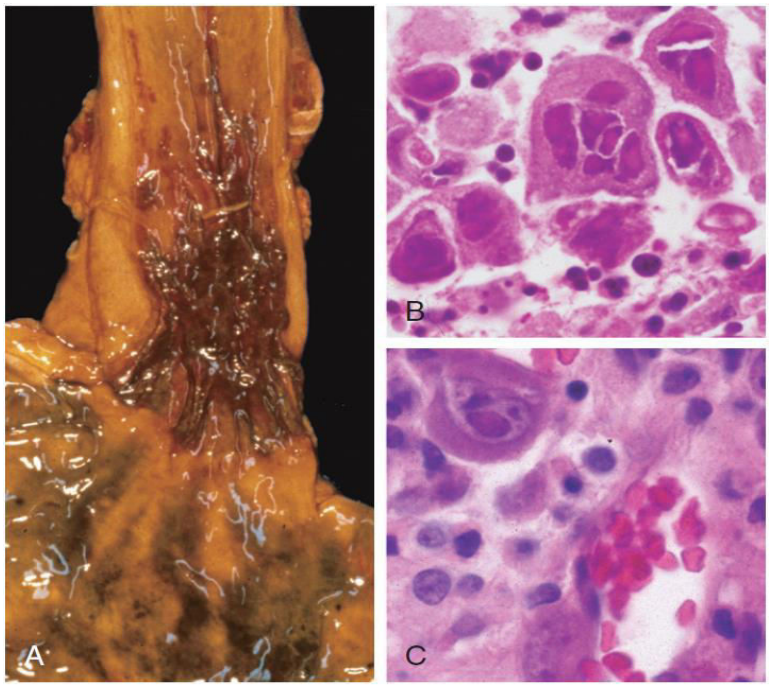
Infectious Esophagitis

Infectious esophagitis: we're talking viruses, we're talking fungi, and we're talking bacteria. They could either be **primary infections or secondary** to ulceration. To typically these occur in immunocompromised doesn't mean they

don't occur in immunocompetent people. Secondary to ulcer infections could happen in immunocomprimised or immunocompetent patients because you have a compromised epithelial barrier. Ulcers simply mean the epithelial barrier is gone making it easier for any infection to occur, because your first line of immunity is not your antibodies and not your white blood cells—it is your epithelial barrier.

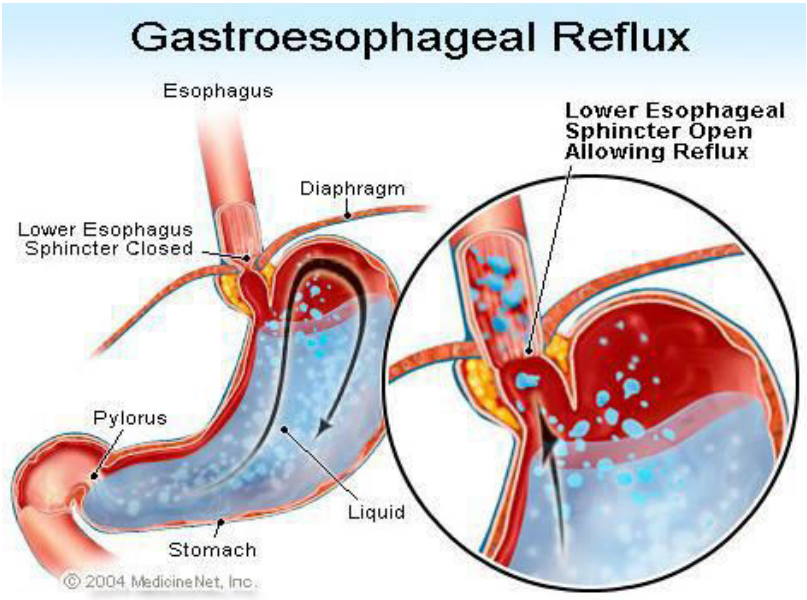
For fungal infections, we're talking more commonly about **candidiasis. In** severe cases, you will get grey white **pseudomembranes** that are all essentially fungal hyphae, very common in immunocompromised patients. For viral infections, if you do take a biopsy on these patients, or through the endoscope you will be able to distinguish between **herpetic and CMV (Cytomegalovirus) infections**. Typically for herpetic the ulcers are **punched out** not very clear on the screen here but if you can have a look at it in the book, and when you do have a look under the microscope you will find **multinucleation** i.e. one cell with multiple nuclei, and you will find inside those nuclei **inclusion bodies** these darker bit that's characteristic of herpetic infections.

Whereas **CMV infections**, the inclusion **bodies both in the cytoplasm and in the nucleus** and the **ulcers are typically on endoscopy shallower** than herpetic ulcers.



Gastroesophageal Reflux (GERD)/ Eosinophilic Esophagitis/ Barrett Esophagus

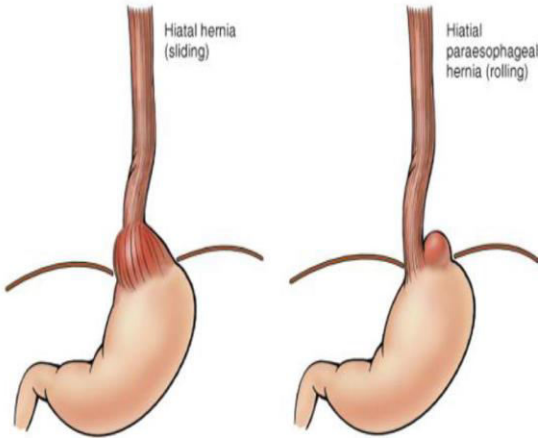
This is a combination of **reduced lower esophageal sphincter tone and an increased abdominal pressure.** Stratified epithelium, which lines your esophagus, is resistant to mechanical stresses. However, it is not very resistant to chemical stresses, and glands in your esophagus also produce some mucus and bicarbonate so if there is some amount of acid that regurgitates it somewhat protects it, but if you have a combination of a reduction in that tone and increased abdominal pressure where you have constant chronic reflux of acid into the esophagus, that's a problem, this causes heartburn.



This is associated with: alcohol and tobacco, obesity (increase intrabdominal pressure), CNS depressants (their side effects affect LES tone), pregnancy increase intraabdominal pressure), hiatal hernia and changes in gastric dynamics (prolonged emptying, over distended stomach) all this can lead to gastroesophageal reflux.

In severe cases, bile reflux from the duodenum can also occur which is also very bad.

A **hiatel hernia** is characterized by separation of the diaphragmatic crura, resulting in sliding of stomach into your chest or a part of your stomach can slide up next to the esophagus and both of these can result in (GERD).



Symptoms: heartburn, if it's frequent and increases when you're sleeping it's not letting you sleep and you've got that annoying taste in your mouth maybe it's time to go see a doctor.

Dysphagia, regurgitation of that sour tasting material which is essentially your stomach acid and it's a differential diagnosis in severe cases for other causes of chest pain, it can cause chest pain in severe cases.

Complications of GERD: your esophagus is not equipped for this kind of pH so:

- **Ulceration**
- **Hematamesis**, because if you ulcerate and you've got some bleeding you can vomit blood.
- **Melena** which is black tarry stools because any bleeding that occurs goes through the stomach and the acidity of the stomach digests it and you end up with black tarry stools. So depending on which way the blood goes: hematemesis or melena. **If bleeding occurs after the stomach you're not going to get have melena**, but if it's stomach or above bleeding and it does pass through your gastrointestinal tract it's going to manifest as melena if there is enough amount of blood.
- **Stricture** we already mentioned that.
- **Barret esophagus**.

Histologically, the tissue may look edematous and in more severe cases you may see some eosinophils here and there especially if you are surveying the lower third of the esophagus which is where (GERD) will be most severe. These few scattered eosinophils are not normal. You could also have **basal zone hyperplasia**, you know the bottom layer of your epithelium is what regenerates, that means that in this particular epithelium injury has been induced and it is trying to regenerate. If that bottom layer exceeds 20% of the total thickness this means that you have basal zone hyperplasia and this is a sign of more severe (GERD) and you may have **elongation of the lamina propria papillae** where it protrudes into even the upper third of the epithelium.

Treatment is **proton pump inhibitors:** you stop the stomach from producing acid, the reflux may still be there but the injurious agent extreme pH is no longer there.

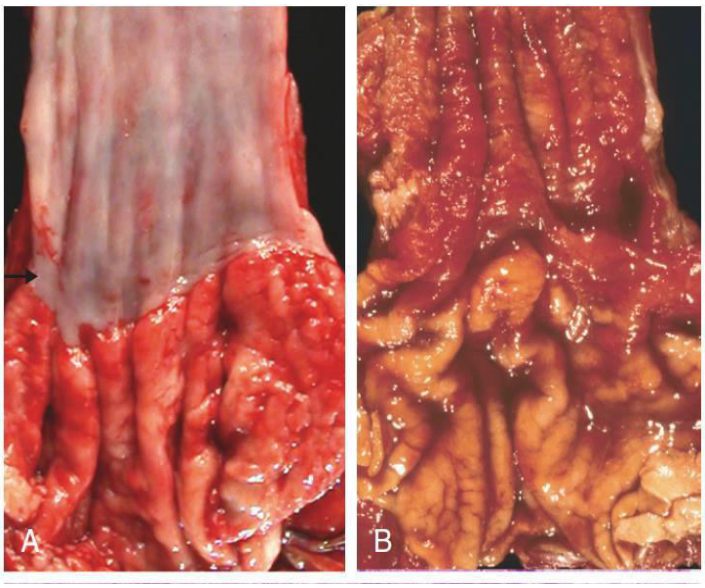
A differential diagnosis for (GERD) is **eosinophilic esophagitis** and the incidence for this type of esophagitis is on the rise. When you look for eosinophils in (GERD) you will find a few scattered here and there. In eosinophilic esophagititis you will find a lot more eosinophils and they will be **a lot more superficial than in (GERD)**. Additionally, they may not be in the lower third they may be throughout the esophagus which is uncommon in (GERD).

Symptomatically, these patients may not have acidity. If they do complain of reflux and they have been put on proton pump inhibitors in the past and proton pump inhibitors have failed, also if you don't find excess acidity in the esophagus (absence of acid reflux) these may be flags to tell you this may not be acidity related (GERD) but maybe eosinophilic esophagitis especially if this patient is **atopic** i.e. has history of being allergic to different things for example: atopic dermatitis,

allergic rhinitis, asthma, and maybe even if you do a CBC some modest eosinophilia.

Treatment for these patients (eosinophilic esophagitis patients) is **food restriction** to whatever they are allergic to that will reduce their symptoms, reduce the severity of the disease and in some causes these patients could be treated **topical or systemic corticosteroids.**

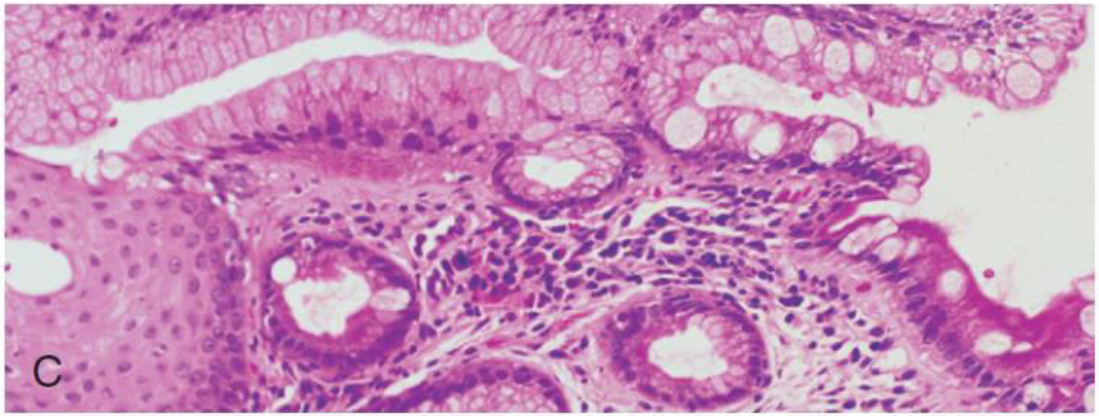
A complication of (GERD) is not eosinophilic esophagitis, it is **Barrett esophagus**, which is a complication of about 10% of (GERD). On necropsy that is what a normal gatroesophageal sphincter or junction looks like, when you have extension of this red velvety tissue which is the stomach tissue up into the esophagus that's when you know that you have a problem.



Remember what we talked about in the very first lecture in pathology first semester, intestinal metaplasia, which is an adaptive cellular response of the lower esophagus to try to cope with the excess acidity.

In **intestinal metaplasia** you will find a transition from this stratified epithelium to columnar and goblet cells producing mucus. As you already know this is preneoplastic lesion, it doesn't mean inevitability but there is an increased risk for adenocarcinoma. So it is the metaplasia- dysplasia -cancer pathway we talked about

last semester.



Diagnosis requires **endoscopy and a biopsy** to show intestinal metaplasia and endoscopy to have a look at that sphincter. Now once diagnosed different centers have different modalities for treatment.

In the past, when we find multifocal adenocarcinoma or carcinoma in situ, resection is the course of treatment .Now we have new modalities: laser ablation, heat therapy ,etc. Whichever hospital you end up at pull up their recommendations for dealing with Barrett's esophagus.

Which brings us finally to esophageal tumors, two major types: adenocarcinoma and squamous cell carcinoma.

Adenocarcinoma

As you already know Barrett esophagus and (GERD), carry with them an increased risk of developing adenocarcinoma; this is good and bad at the same time. Bad because these patients may develop adenocarcinoma, but good because these patients are under surveillance being treated which means if adenocarcinoma does arise it will be caught early. And the earlier you catch a cancer the better off you are able to treat. Adenocarcinoma is associated in addition to (GERD) and Barrett to:

- Dysplasia (there is an increased risk with dysplasia) so if Barrett esophagus has gone on to dysplasia there is an increased risk for adenocarcinoma
- Tobacco
- obesity
- radiation
- And for some reason white males, being a white male increases your risk if you have underlying risk factors already.

Adenocarcinoma is more common in developed countries and the incidence is increasing. Chromosomal abnormalities in TP53 "guardian of the genome" are frequently found early on lesions.

Adenocarcinoma most common as you can notice here in the distal because gastroesophageal reflux and Barett esophagus occur there so that's where the changes are going to occur.

You will frequently find Barett's esophagus adjacent to the tumor and the tumors themselves typically produce mucin from glands.

Symptoms:

Well, if the patient has gastroesophageal reflux disease you already know what the symptoms are. If it's not associated with GERD although the vast majority of adenocarcinoma of the esophagus are associated with (GERD) and Barrett esophagus;the other symptoms are pain, dysphagia, weight loss, and vomiting, which are very nonspecific symptoms, this is why if they are severe enough and the patient presents with these and you find a tumor it is are more likely than not that this tumor is so advanced that we are talking single digit percentage five year survival.

Squamous Cell Carcinoma

Squamous cell carcinoma is unfortunately not **associated with a premalignant condition**: not associated with Barrett esophagus, not associated with (GERD) so these patient when they do present they typically **present late**. There is an **increased risk again with alcohol and tobacco**, are you seeing a pattern emerging here?? Most cancers increased risk with alcohol and tobacco.

Heat and caustic injury, this particular cancer is associated with drinking ridiculously hot beverages so think twice when you get that really hot coffee before instantly drinking it. **There is an increased risk of squamous cell carcinoma with drinking very hot beverages.** Plummer Vincent syndrome that's homework please look it up I'll give you a hint it's more common in females.

From Wikipedia:

Is a rare disease characterized by difficulty in swallowing, iron deficiency anemia, and esophageal webs. Nowadays, this syndrome has become extremely rare. It generally occurs in postmenopausal women. Its identification and follow-up is considered relevant due to increased risk of squamous cell carcinomas of the esophagus and pharynx.

Previous radiation therapy; people who get previous radiation therapy are at an increased risk of getting squamous cell carcinoma and so are **black males**. So if you notice the guys among you are at higher risk of getting esophageal cancers than the girls among you whether you are white or black. I don't know if this applies to our societies or not, these are mostly US numbers.

It is more common in **under developed areas** whereas previously the adenocarcinoma is more common in developed regions of the world. Pathogenesis is not completely understood and there may be a role for **HPV** in this pathogenesis but we don't fully understand why or how.

Squamous cell carcinoma unlike adenocarcinoma is more likely to occur in the **middle third** rather than the lower third of the esophagus and you can find some early squamous dysplasia if you are lucky.

But typically these patients when they present you'll find **local invasion** that can result in:

- Pneumonia
- catastrophic bleeding
- Pericardial/mediastinal invasion anywhere in the esophagus where it is attached to the mediastinal structures invasion can occur.

When you look under the microscope rather than seeing intestinal metaplasia and dysplasia you will see still squamous, what looks like squamous tissue typically moderate to well differentiated.

Now lymph nodes that are affected depend on where in the esophagus the cancer occurs:

- **upper third:** we're talking about **cervical**
- **middle third:** we're talking about **mediastinal**
- **lower third:** we're talking about **abdominal: gastric and celiac.**

Symptoms: again symptoms are not terribly specific and when they do occur it's typically already too late:

- Dysphagia
- Odynophagia
- obstruction (that's a really late symptom)
- Weight loss

- Bleeding & sepsis with from tumor ulceration (a really really late symptom) aspiration from fistula it's already invaded and there's a channel to the respiratory tract.