Digestive System

University of Jordan

Faculty of Medicine

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Medical Committee
The University of Jordan

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☐ Anatomy ☐ Embryology

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Acute and chronic gastritis &peptic ulcers

Today we will continue discussing the topic of acute and chronic gastritis what continues after chronic gastritis. Peptic ulcer disease has the same deficiencies in the mucosal defenses that we mentioned last lecture (leading to chronic/acute gastritis), adding to that we are starting with chronic gastritis advancing to a peptic ulcer (so it's a chronic disease), and also hyperacidity.

Peptic ulcers are more common in males and can be found anywhere in the gastrointestinal tract, it is 4 times more common in the proximal duodenum than in the stomach, in the stomach its most common between the antrum and the body. It can occur at any point in the GI tract that is exposed to acidity, remember in the esophagus, there's ectopia and hetrotopia (where there could be eptopic gastric mucosa and the small intestine and if that produces acidity it can induce ulceration in the normal surrounding mucosa).

Although rarely, if you do see it on x ray that's typically what it looks like a ring enhancing legion and you will see it by an endoscopy, the ulceration will be obvious.

Peptic ulcers are commonly associated with H.pylori infection, however as these infections are getting under control , the incidence is dropping especially in the western societies and older age populations who take non-steroidal anti-inflammatory drugs , these people take aspirin for a long term for cardiovascular prophylaxis so this is becoming the more common reason for peptic ulcer disease. Unlike acute peptic ulceration these are solitary regions, also we can find scaring, granulation tissue and angiogenesis.

Peptic ulcers are also associated with steroids and people with (COPD) chronic obstructive pulmonary disease because they use steroids for a long time, so what do steroids do? Steroids inhibit prostaglandin, prostaglandins enhance bicarbonate secretion, tissue regeneration and blood flow thus inhibiting them induces the formation of ulcers.

Smoking: affects blood supply and regeneration of cells thus ulcer formation increases.

Alcoholic cirrhosis: the pathogenesis leading to peptic ulcer disease isn't clear.

Hyperparathyroidism & chronic renal failure are characterized by hypercalcaemia; high levels of calcium can stimulate gastrin release, excess gastrin causes excess acidity leading to ulceration

Psychological stress has been associated with peptic ulcer disease,(remember Zollinger-Ellison syndrome from last lecture which is a tumor that releases excess gastrin so even if the patients present with peptic ulcer disease or acute/chronic gastritis giving them proton-pump inhibitors wont help as the level of gastrin is extremely high so great doses of proton-pump inhibitors are administered, yet the tumor should be resected .

So the ulcerations are solitary, classily round to oval sharp punched-out defect, ie the surrounding mucosa will appear normal next to it, however the base is going to be clean due to the digestive enzyme, and you can see lots of granulation tissue that is richly vascular you but it's not shown in the picture on the slides, but you can see new blood vessel formation in the granulation tissue.

Patients can present with complications of peptic ulcer disease, they don't always present before complications manifest which are:

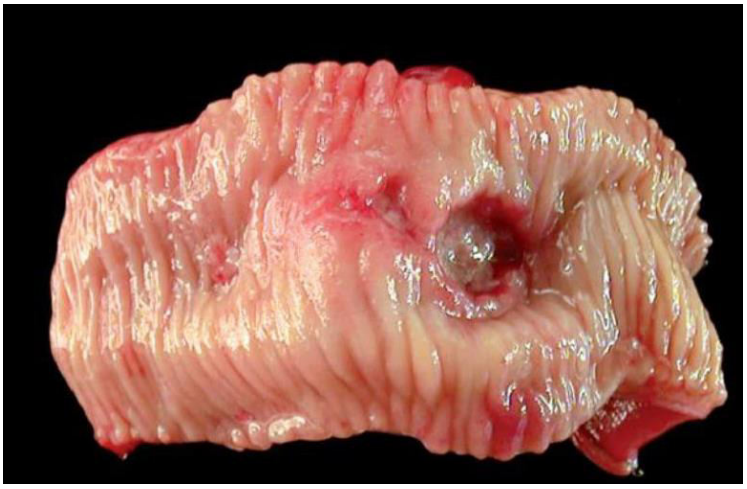
Bleeding (can be presented as hematemesis (vomiting blood) or melena (black tarry stool from blood being exposed to acid).

Perforation which is a medical emergency as gas, acid and digestive enzymes are expelled into the peritoneum which is a disaster. If the bleeding has gone for long enough the patient will present with iron deficiency anemia.

If patients don't have these previously mentioned symptoms, they can present with epigastic burning. Pain is typically 1-3 hours after meals, it is typically worse at night and can be relieved by alkaline food which decrease the stomach acidity and doesn't cause further injury to the injured area. (alkalis like milk of magnesia, anti-acid tablets, gaviscon very popular here)

Nausea, vomiting ,bloating and belching are all also commonly found

Many patients present with all of what we mentioned.



This is a duodenal ulcer very clean base, sharp demarcated edges

Treatment as most of them are H.pylori associated, it includes eradicating the bacteria using antibiotics. For the other causes you treat the underlying condition , so if the patients are under long term use of non steroidals you need to find an alternative or stop using them.

Also proton-pump inhibitors are given to decrease the acidity and the damage that occured.

Surgical techniques are available but they are less commonly used nowadays unless there is massive bleeding or perforation.

Nowadays , because we recognize the underlying diseases, we have better ways to prevent high acidity, medications … peptic ulcer disease is more associated with morbidity (having the disease) than mortality (death caused by the disease). Rarely do people die from peptic ulcer disease.

Now we will continue with stomach problems.

A student asked about the location of the peptic ulcers the doctor said although peptic ulcers are common, but anywhere within the GI tract that's exposed to acid can be ulcerated. So if it is found at the esophagus then it will be associated with acid reflux, upper esophagus will be associated with inlet patch, Intestinal ulcer would be associated with ectopia.

The duodenum is the most common site but don't exclude other sites in the GI.

Neoplasia of the gastrointestinal tract :

Polyps (is the colloquial term), meaning they could be neoplastic ,hyperplasic or inflammatory or ectopic (ectopia) so all of these can be found as they are lumped in with neoplastic diseases of the stomach but not all polyps have to be neoplastic as you know.

The most common polyps are the inflammatory and hyperplastic polyps which are essentially the same when talking about stomach polyps,

They are common with older patients 50-60 years, underlying chronic gastritis, typically small , multiple oval shaped and have a smooth surface however microscopically you will find that the surface is not smooth and you see that the foveolar glands are elongated, underneath you can see cystic dilatation

They are the most common polyps and are associated with H.pylori because h.pylori gastritis is the most common cause of chronic gastritis.

As they are not neoplastic we shouldn't worry about neoplastic transformations obviously but you need to recognize them and if they are hyperplastic you need to treat the underlying cause h.pylori, gastritis …ect) rather than cause cancer panic.

Fundic gland polyps can occur sporadically or with patients with (FAP) familial adenomatous polyposis which is a genetic disease related to "apc" mutations, these too have no neoplastic potential but we mention them because they are becoming more common as they are associated with proton-pump inhibitors use , and as "PPI's" are now given over the counter . They are multiple well circumscribed, typically found at the body of the fundus. Most importantly they look like inflammatory&hyperplastic polyps but less anti-inflammatory cells will be present and the foveolar glands are not as nearly elongated as in the hyperplastic polyps. Again as these don't have any neoplastic potential, most of these polyps are asymptomatic and might cause vomiting ,nausea and some epigastric pain; nonspecific symptoms.

Gastric adenoma:

These do have the potential to become neoplastic

The incidence increases with age and the peeks(50-60 years old) are similar to the nonneoplastic polyps so you need to be able to recognize each type, again like the hyperplastic polyps there is a background of chronic gastritis, however you will find atrophy and intestinal metaplasia(changing one cell type with another so if you observe it without knowing the origin of the sample, it appears to be normal), and by definition adenomas have dysplasia(obviously abnormal, hyperchromatic, increased mitotic figures, polymorphic) with them. Adenomas are most commonly found at the antrum.

The risk of neoplastic transformation increases with the size of the mass, so if they are more than 2cm in size, the risk increases dramatically. You will find intestinal type columnar epithelium, these cells will be crowded so you will find pseudostratified columnar epithelium (which looks stratified but isn't, as only one layer of cells is present however their nuclei arrangement implies otherwise).

Dysplasia associated with these can be of low, medium or high grade, the more bizarre it looks the higher the grade. They are associated with a cribriform structure,where the cells are not only abnormal but create an abnormal architecture as you can see there is gland within a gland. The higher the grade of dysplasia the higher the risk of developing adenocarcinoma.

A question: why does the risk of developing these disease increases with age? Well with age our mucosal defenses weaken so the risk of developing gastritis of getting a H.pylori infection increases for example older people produce less mucin which means that when they take nonsteroidals or get a H.pylori infection the chances of developing a problem is higher than younger people.

As for adenomas or neoplastic polyps the older you grow the more likely your cells have or may have accumulated some genetic damage along the way that could lead to neoplastic transformation.

Gastric adenocarcinoma:

The most common malignancy of the stomach, the problem with it is there are no specific early stage symptoms, the symptoms are commonly similar to chronic gastritis and patients who have advanced to chronic gastritis typically have ignored the milder symptoms and they might not recognize the gradual advancement of these symptoms until it is too late.

There are 2 types:

Intestinal gastric adenocarcinoma (its in the stomach not the intestines it indicates the morphology) the second type is diffused.

Intestinal adenocarcinoma is present in high incidence areas (high risk). These people have a lot of metaplasia/ h.pylori infections meaning that these people are under surveillance (medically) or if they are in an endemic areas there are screening measure that would recognize any early changes. So intestinal type in high risk areas (endemic areas) that have screening programs will be detected earlier and treated earlier so the prognosis in these endemic areas is much better than in other areas with no screening tests (last semester example gastric carcinoma is more common in Japan (endemic area) than in the united states, accordingly the survival rate in Japan when caught early is more than 90% whereas the survival rate for people with the same cancer in the us is barely 30% as they don't have the intensity of screening Japan has and cant afford to screen the public as their incidence is too low (not cost effective).

So what are the presenting symptoms when there are no screening tests?

Weight loss, anorexia, altered bowel habits, anemia and hemorrhage all are very late presenting symptoms, so the survival rate is low (4-5 years).

The pathogenesis is different for the 2 types

Diffused type: either a CDH1 or E-cadherin mutations or silencing by methylation occurs, loss of cell junctions and loss of e-cadherin causes epithelial to mesenchymal change, apparently loss of e-caherin is a fundamental step in formation of the diffused type gastric adenocarcinoma, these cells diffuse and infiltrate in the layers of the stomach rather than creating a cohesive tumor whereas the intestinal type looks more like an ulcer (bunched up).

People with (FAP) who have germ line "APC" mutations have an increased risk of intestinal type, so (FAP) patients who are under surveillance are more likely to get diagnosed early and treated earlier, while sporadic intestinal type ie: there is no inherited gene mutation are associated with "beta catenin" mutations have essentially the same pathway as APC so they will both end up with the same gastric adenocarcinoma of the intestinal type.

Microsatellite instability (typically silent as they are in noncoding regions) and a defect in one of the mismatch repair genes have a higher risk to intestinal type gastric adenocarcinoma.

Hypermethylation which turns off certain genes (TGF-beta receptors, BAX (proapoptotic so when inhibited it will lead to cell proliferation and higher risk of cneoplasia) ,Insulin-like Growth Factor Receptor 2 (IGFR2), P16/INK4a remember the locus cdkn2a also associated with this adenocarcinoma .

Whether it is intestinal or diffused type you will find TP53 mutations as well.

H.pylori pathogenesis, we talked about it in the last lecture: increased production if proinflammatory proteins (interleukin 1, TNF alpha) as well as some host polymorphisms, (polymorphisms are the same normal genes but the proteins are more/less effective or expressed than the general population) so if a polymorphism increases these proinflammatory proteins that are already increased by H.pylori, the risk of developing gastric adenocarcinoma.

Finally in pathogenesis, EBV you will take EPV next year.

It causes gastric adenocarcinoma of not the diffused type but one that has the same morphology so its kind of like diffused but has a lot of lymphocytic infiltrate unlike the diffused type and no TP53 mutations, so EBV can cause gastric adenocarcinoma but we are not sure how it does it ,and it typically affects the proximal part of the stomach.

Morphology

Intestinal type: bulky lesions if you look under the microscope you will find glandular structures this is typically found in the intestine not the stomach and neoplastic cells have apical mucin vacuoles so under higher resolution you can see them.

The diffused type the growth is more infiltrative, you won't find distinct lesions (discohesive cells) as they lost e-cadherin, they have large mucin vacuoles called signet ring (a ring that has a little stone on top), it pushes the nucleus to the top to give that appearance.

Because these cells infiltrate into the stomach wall, they induce a desmoplastic reaction “a fibrotic reaction” meaning there will be a disposition of a lot of collagen deposition and fibrosis thus the stomach will lose its folds hardening the wall (becoming leather like) linitis plastica. So basically, infiltrating cells cause a fibrotic reaction.

Carcinoid tumors are similar to cancer and theyre called that because they’re slow growing tumors.

They arise from neuroendrocine organs/cells so from the pancreas or from terminally differentiated neuroendrocine cells (G cells). So if the g-cells produce gastrinoma (type of Carcinoid) they will produce hyperacidity, because we are talking about neuroendrocine cells they can produce many hormones, if this happens in the GI about 40% most commonly in the small intestine most of these hormones undergo first pass effect and you won’t get systemic effects. However if you do get systematic effects for example from vasoactive amines (excess) you get the Carcinoid syndrome flushing palpitations…. What ever those vasoactive amines can activate, we are producing an excess of them. If we are talking about GI Carcinoid syndrome and you have these manifestations, this means that this Neoplasia has metastasized outside the GI and is no longer under first pass effect. Other locations are tracheobronchial tree and lungs. These especially in the GI can also result in a desmoplastic reactions so the patients will present with obstruction especially in the small intestine making the wall rigid and peristalsis there becomes useless.

If it is a high grade tumor it is called a neuroendrocine carcinoma which looks like a polyp but it’s not a polyp (polypoid) under the mucosa, sub-mucosal legion. If you look at the cells they look uniform pink and have stippled (dots) nuclei so the nuclei are not homogenous.

These tumors peak in older people (age60) and the symptoms depend on the hormone being produced. If confined to GI then they will under go first pass effect and rarely produce symptoms.

If we are talking about GI Carcinoid, if symptoms do occur they are strongly associated with metastasis because they have escaped first pass effect.

Prognosis is strongly based on GI location:

Foregut; from the mouth and ends in the middle of the duodenum at the level of ligament of treitz : metastasis is rare and resection (surgical excision) is curative

Midgut; extends to the transverse colon: tumors are large multiple and invasive giving a poor prognosis.

Hindgut; includes the rest of the transverse colon and the descending colon: if it occurs in the appendix most of the time it is benign with no serious complications and resection is curative, if they occur in the rectum which has a good blood supply: portacaval anastomosis. Unlike other GI tumors, his can lead to Carcinoid symptoms with systemic effects because the hormones can escape the first pass effect and enter the systemic circulation this is an exception. Metastasis is occasional, not as frequent as the foregut but more than the midgut.

GIST (gastrointestinal stromal tumor)

Is the most common mesenchymal tumor in the GI tract , not the only one.

Other mesencymal tumors: Fibromoa, leiomyoma, shcwannoma… we're not covering them because there are too many to cover.

GIST typically produces a solitary well circumscribed fleshy sub-mucosal mass, it rarely goes beyond the wall. There is 2 different morphologies to the cells either

Spindle shaped or epitheloid. Again, the peek is in older males .

There are activating tryrosine kinase mutations most commonly the c-kit tyrosine kinase which is a stem cell factor receptor or less commonly the platelet derived growth factor receptor mutation.

They can metastasize and commonly to the liver however spread outside of the abdomen is not common.

GIST presents with mass effects, which is a growing **mass** that results in secondary pathological effects by pushing on or displacing surrounding tissue. In oncology, the **mass** typically refers to a tumor,

If the size of the tumor is less than 5 cm the prognosis is good. These tumors rarely metastases but if the tumor has a big diameter (10cm huge), this can cause mass effect and the prognosis is much worse and the risk of metastases is higher. Other prognosis factors are:

- Mitotic index: which is **defined** as the ratio between the number of cells in a population undergoing **mitosis** to the number of cells not undergoing **mitosis**. So the higher the index the worse the cancer (faster/more replication) and is more likely to metastasize.

- Location: if it is in a location which is highly innervated or is surrounded with lymph nodes the prognosis is worse.

Treatment:

Surgical resection is typically done however if the location prevents that or there is a recurrence, they respond to a drug called imantinib.

They also respond to tyrosine kinase inhibitors brcause they have tyrosine kinase activating oncogenetic mutations. However patients using imantinib can relapse as the cancer develops immunity where the tumor isn't addicted to this tyrosine kinase as CML is or as a result of a secondary mutation.

Imatinib (INN), marketed by Novartis as **Gleevec** (Canada, South Africa and the USA) or **Glivec** (Australia, Europe and Latin America), and sometimes referred to by its investigational name **STI-571**, is a tyrosine-kinase inhibitor used in the treatment of multiple cancers especially leukemia which has addiction to the BCR-ABL protein (chromosome 9:22 translocation) , most notably Philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia (CML).

THE END.

Sorry no annoying quote or dedications ☺