GERD, Peptic ulcer disease, Tumors of esophagus and stomach

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GASTROESOPHAGEAL REFLUX DISEASE

Introduction - terminology

- **GER (Gastroesophageal reflux) = reflux of gastric contents into the esophagus**
  - Physiological x patological ???

- **GERD (gastroesophageal reflux disease) = condition that develop when the reflux of stomach contents cause reflux-associated symptoms**
  1. Erosive ezophagitis – GERD with present visible mucosal breaks in the distal esophageus based on upper endoscopy result
  2. NERD (Non Erosive Reflux Dissease) = GERD with absent visible mucosal breaks in the distal esophageus

Epidemiology

- **One of the most common gastroenterological problems**
  - 10-30 % of the Western population
  - More often in pregnancy (25%)

Pathogenesis

- **Imbalance between aggressive and protective factors and mechanisms**
- **<u>Agresive factors</u>**
  - Hiatal hernia – particularly if it is large (over 5cm)
  - Character of reflux – pH, composition (bile acid, pancreatic fluid)
  - Esophageal dysmotility
  - External influences: diet composition, drugs, smoking, coffeine, lifting
  - Delayed gastric emptying
  - Operations
  - Increased intraabdominal pressure (obesity, pregnancy,…)
  - Dysfunction of LES (hypotensive)
    - Basal pressure between 5-6mmHg (fyzio 8-20mmHg)
    - TLERS

Pathogenesis

- **Protective factors**
  - Adequate function of LES
  - Sufficient length of intraabdominal part of the esophagus
  - Anatomical conditions: adequate function of diafragm and frenoesophageal ligament, Hiss angle
  - Esophageal clearence: salivary secretions, primary (swallowing) and secondary (cleaning in sleep) peristalsis
  - Esophageal mucosal defense mechanisms
    - Mucous and bicarbonate layer, cell membranes, intercellular junctional complexes, adequate mucosal blood flow

Clinical presentation

- **Typical x atypical**

- **Esophageal x extraesophageal**

- Worsen: lying position, leaning forward and lifting loads
- No correlation: the extent of pathological reflux - clinical presentation - complications - endoscopic and histological picture

Clinical presentation

1. **Esophageal**
   - Typical: Heartburn, regurgitation
   - Atypical: Dysphagia, chest pain, odynophagia, vomiting, upper abdominal pain, nauzea, globus sensation
2. **Extraesophageal**
   - Proven: Chronic cough, laryngitis, asthma, dental erosion
   - Expected: sinusitis, recurrent otitis, idiopathic pulmonary fibrosis, pharyngitis, hoarseness

- **The warning signs = complications**
  - Dysphagia, odynophagia, anemia, haematemesis, melaena, anorexia

Diagnostic methods

- **Anamnesis**
- **Physical examination**
- **Upper endoscopy**
  - Degree of esophageal mucosal injury, complications and tissue sampling
  - Erosive esophagitis x NERD – negative endoscopic findings

Diagnostic methods

- **Ambulatory 24-hour esophageal pH monitoring**
  - gold standard method
  - Ambulatory continuous measurement of the pH in the distal esophagus with a thin tube + correlation with the difficulties of the patient
  - Indications: symptoms with negative upper endoscopy (NERD), extraesophageal symptoms before surgery, after surgery with persistent symptomatology, no effect of PPI treatment
  - Ambulantory 24-hour multichannel impedance with pH monitoring
    - Diagnosis of: all types of reflux (acidic, weakly acidic, weakly alkaline), refluxed fluid type (water, air), determine the height of pathological reflux

Diagnostic methods

- **Manometry**
  - Other diseases (achalasia), before antireflux surgery
- **PPI test**
  - Short course of high dose PPI (Omeprazol 40mg/day) → effect ???
  - Sensitivity 66-89%, Specificity 35-73%
- **Barium esophagogram**
  - Hiatal hernia, complications of GERD (stricture, ulceration)

Treatment

- **Lifestyle and diet modification**
- **Medications**
  - Antacids
  - Procinetics drugs
  - PPI, H_2-blocators
- **Antireflux surgery**
  - fundoplication

Lifestyle and diet modification

- **Usually not enough - importance in reducing the dose maintenance therapy and prevention of relapses**

- Eat more often + smaller portions, eating 2-3 hours before going to sleep
- Ex-smoking, ex coffee and chocolate, weight reduction
- elevation of head of the bed at night
- EX Risk drugs (theophylline, progesterone, BKK, nitrates, antidepresives)

Medications

- **PPIs – proton pump inhibitors**
  - Omeprazole, pantoprazole, lansoprazole
  - Allow an effective control of reflux symptoms, high rate of healing of erosive esophagitis, reduction of complications
  - good tolerability, minimal ADRs
- **Antacids**
  - Short-term symptomatic relief (effect lasts 1 hour)
  - Does not improve mucosal healing
  - Sodim bicarbonate, calcium carbonate, aluminum hydroxide and magnesium alginate suspension with bicarbonate

Medications

- **H2-blockers**
  - Ranitidine, Famotidine
  - Lesser efficacy than PPI, toleration
- **Prokinetics**
  - Drugs stimulating the prograde motility
  - Frequently itopride, cisapride withdrawn (arrhythmias, sudden death)
- **TLERs reducers**
  - Baclofen
  - Increase basal LES pressure, reduce TLERS, accelerate gastric emptying
  - refractery GERD
  - ADRs - somnolence, confusion, dizziness, lightheadedness, drowsiness, weakness, and trembling.

Antireflux surgery

- **Fundoplication according to Nissen-Rossetti**
- Causal therapy
  - Result to augmentation of LES basal pressure

  and decrease in the rate of TLERs
- **indications:**
  - Younger patients with future lifelong pharmacotherapy (anatomical abnormalities)
  - lack of effect of pharmacotherapy - poorly treatable, recurrent esophagitis
  - Aspiration symptoms associated with GERD
  - Complications esophagitis (ulcers, stenosis) – CAVE do not solve Barretts esophagus
- **CAVE - postfundoplication syndrome**

Treatment strategy

- Acute (short-term 6-8 weeks) ± maintenance therapy (continuous treatment x short-term cures on demand in case of complaints of the patient)
- **3 types**
  - Step up: antacids → H2-blockers → PPI (from the least effective modality)
  - **Step down: PPI → H2-blockers → antacids (from the most effective modality)**
    - **TODAY prefer, especially in terms of reduction in PPI, the temporary use or on demand (at least 4 days)**
  - **Step in: initiates and maintains patients on the most potent antireflux modality**

- **Last option: SURGERY**

Complications

- **Barretts esophagus, adenocarcinoma**
- **Esophageal stricture**
  - Prolonged reflux with subsequent fibroproductive changes
- **Ulcerations of the esophagus**
  - Upper GI bleeding

Barrett´s esophagus

- Occurs as a **complication of chronic GERD** and characterized by **incomplete intestinal metaplasia in the epithelium of the esophagus**
  - Metaplastic changes: replacement of squamous epithelium of the esophagus by columnar epithelium ± metaplastic intestinal type
  - Sequence: intestinal metaplasia → dysplasia → adenocarcinoma
- **Epidemiology**
  - 10-15% of patients with GERD (increases with duration of GERD)
- **Pre-malignant condition:** The risk of developing adenocarcinoma (30-40x) - 0.5% of patients with GERD per year

Barrett´s esophagus

- **Clinical presentation**
  - Reflux symptoms or asymptomatic
- **Diagnosis:**
  - GFS + biopsis
    - Multiple biopsies = evaluation of intestinal metaplasia and dysplasia – HISTOLOGICAL DIAGNOSIS

Barrett´s esophagus - therapy

- PPIs – decrease development of dysplasia
- Antireflux surgery
  - No firm documented reduction in cancer risk
- Endoscopic eradication therapy
  - Endoscopic mucosal resection
  - Radiofrequency ablation
  - Hybrid APC

Barrett´s esophagus

- Dispensarization:
  - Necessary
  - Based on histology and BE length

ESOPHAGEAL CANCER

Benign tumors of the esophagus

- **Types:**
  - Epithelial: papilloma, adenoma,

    x
  - Mesenchymal: leiomyoma (75%), fibroma, lipoma - intramural
- **Symptomatology:**
  - Mostly asymptomatic (incidental finding) x dysphagia, bleeding
- **Diagnosis:**
  - GFS with biopsy, EUS (mesenchymal), CT + MRI
- **Therapy:**
  - dispensarization

    x
  - endoscopy x surgery - large (symptomatic), can not clearly identify the biological nature

Malignant tumors of the esophagus

- **Classification**
  - Histological:
    - Squamous cell carcinoma
    - Adenocarcinoma - incidence increases (to 50%)
    - Other - leiomyosarcoma

Carcinomas

- **Squamous cell carcinoma or adenomarcinoma**
  - different risc factors
- **The incidence**
  - SCC declined in Western countries +USA (3-5/100000) x Asian countries (100/100000)
  - ACA – rising incidence in Western countries +USA

Carcinomas

- **Etiopatogenesis**
  - Risc factors
    - SCC: alcohol, tobacco, dietary factors (hot food, spicy food), nitrosamines, mycotoxins, toxic alkaloids, thermal trauma, HPV
    - ACA: Barretts esophagus, obesity, NSAIDs long term
  - Precanceroses: Barrett's esophagus, corrosive stricture, achalasia
- **Symptomatology: LATE**
  - Dysphagia, odynophagia, weight loss, cachexia, regurgitation, gastrointestinal bleeding, retrosternal pain, cough, aspiration
  - Metastasis early to lymph nodes, hematogenous to lung + liver + kidney

Carcinomas

- **Diagnosis**
  - Anamnesis – GERD, tobacco and alcohol use
  - Physical examination – lymphadenopathy, cachexia, fecal occult blood, hepatomegaly
  - Laboratory: anemia, hypoalbuminemia,
  - Barium esophagography
  - GFS + biopsy
  - EUS of the esophagus
  - CT, PET / CT

Carcinomas

- **Therapy**
  - Depedent on staging
    - Surgery – esophagectomy ± lymfadenectomy (stage II+III)
    - (Neo)adjuvant RT+CHT
    - Endoscopy:
      - endoscopic mucosal resection (T1m)
      - Endoscopic submucosal dissection
  - Paliative therapy: RT, brachytherapy, PEG, metal stent, laser therapy - (stage IV)

Carcinoma

- **Prognosis**
  - 50% of patient are incurable at diagnosis

- **Prevention:**
  - Lifestyle modification (smoking-…)
    - Reduce risc factors
  - routine screening is not cost-effective, except in the highest risk groups

PEPTIC ULCER DISEASE

Introduction

- **Ulcer** = mucosa defect which penetrates through the lamina muscularis mucosae

- German internist Schwarz in 1910: „No acid, no ulcer.„
- relatively frequent
- Prevalence: 5-10%
  - people with Helicobacter pylori positive 10 to 20%
- Incidence: 0.1% per year

- <u>Trend to decrease:</u> prevalence of peptic ulcer and gastric cancer, number of hospitalizations for peptic ulcer and peptic ulcer lethality because of complications

Etiopathogenesis

- **Imbalance of protective and aggressive factors**

Etiophatogenesis

Protective factors:

- The normal composition of gastric mucus
- The alkaline bicarbonates secretion
- Intact microcirculation in the gastric mucosa and regenerative capacity of the epithelium
- Normal secretion of endogenous prostaglandins

Aggresive factors:

- HCl, pepsin
- Helicobacter pylori
- Ulcerogenic effect of drugs - NSAIDs
- duodenogastric relfux
- Smoking, stress
- Fault microcirculation in the mucosa and submucosa
- Slow gastric evacuation

Etiopathogenesis

- **Etiology:**
  - Common causes
    - Helicobacter pylori
    - NSAIDs
  - Uncommon causes
    - Crohns disease
    - Conditions causing acid hypersecretion (Z-E sy, multiple endocrine neoplacia, mastocytosis)
    - Severe physical stress (ICU,..)
    - Mucosal ischemia (vascular disease, radiation)

Helicobacter pylori

- In developed countries - 10-20% of the population
  x
  In developing countries - 90% of the population

- oro-oral or oro-fecal transfer

- Role in VCHGD cancer, stomach MALT lymphoma
  - the most common cause of peptic ulcer
- Mucosa colonization by H. pylori leads to the development of diffuse antral gastritis (also known as chronic gastritis type B or hypersecretory gastritis)

Symptomatology

- Variable intensity of difficulties
- The most frequently:
  - pain, abdominal discomfort, weight loss, nausea and vomiting, loss of appetite
- often asymptomatic in elderly patient and patients with DM

- seasonal course with exacerbations in spring and autumn

- 10-20% of patients are asymptomatic peptic ulcer - symptomatology of complications

Complications

- **Bleeding from ulcers:**
  - Bleeding in the upper GI – the commonest cause (60%)
  - Indicated to urgent endoscopy or angiography or surgery
  - Hematemesis, melena, shock
  - Therapy:
    - Endoscopy (adrenaline injection, clipping, heat-based or light-based coagulation)
    - PPI intravenous
    - Ex NSAIDs and aspirin, H.pylori eradication
  - 8% mortality

Complications

- **Penetration ulcer:**
  - gradual deepening of the ulcer
  - penetrates the wall of stomach into nearby organs
  - the most common is the penetration of duodenal ulcer into the pancreas

Complications

- **Ulcer perforation:**
  - More common in duodenal ulcer
  - Symptoms: signs of peritoneal irritation, hypotension, shock
  - Diagnosis: plain radiography
  - Treatment: strictly surgical
  - 10% mortality

Complications

- **Stenosis of the pylorus or the duodenum:**
  - Relatively uncommon (2% of patients with ulceration))
  - Symptomatology:
    - vomiting and epigastric pain
  - Diagnosis:
    - Radiographic findings, endoscopy + biopsies
  - Treatment:
    - NGT (to derivate fluids), rehydration, PPI
    - Surgery
    - Endoscopic baloon dilatation

Diagnostic methods

- **Laboratory:**
  - Gastrin (Z-E sy), complications
- **Endoscopy:**
  - Method of choice
  - Biopsy
    - Helicobacter pylori
    - exclusion of malignant etiology
  - patients with gastric ulcer should be endoscopically observed until the ulcer will be completely healed, duodenal ulcer is no need to monitor the healing
  - Forrest classification

Diagnostic methods

- **Helicobacter pylori diagnostics**
  - Invasive methods: during gastroscopic examination and biopsy
    - Urease test and cultivation, histology
  - non-invasive methods: particularly suitable to evaluate the effectiveness of treatment of infection (eradication of Helicobacter pylori)
    - Breath test
    - Determination of the Helicobacter pylori antigen in feces
    - Serological detection of antibodies against Helicobacter pylori
    - Stimulation of pentagastrin
    - Serum gastrin

Therapy

- **Dietary restrictions**
  - Ex smoking and coffee

- **Ex NSAIDs**

Pharmacotherapy

- **PPI**
  - omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole
  - prophylactic therapy for patients at risk for long-term NSAID therapy
- **Misoprostol**
  - Synthetic analogues of PGE1
- **Pentoxifylline**

Pharmacotherapy

- **Eradication of H. pylori, if positive**
  - heals ulcers and prevents recurrence
  - after successful eradication of the ulcer, the risk of disease recurrence ranges between 0-10%
  - CAVE resistence to ATB
  - combination therapy
    - Amoxicillin - 2x1000mg / day for 7 days
    - Clarithromycin (azithromycin) - 2x500mg / day for 7 days
    - PPI - e.g. omeprazole 2x20mg / day

Therapy

- **Endoscopy**
  - At gastrointestinal bleeding
- **Surgical treatment**
  - Rarely use
  - Indications: complications, resistance to pharmacotherapy, multiple ulcers
  - Resections - operation according to Billroth I and II. resection of endocrine-active tumor (ZE syndrome)
  - Nonresections performances - vagotomy, supereselective vagotomy (broken n.vagus)

TUMORS OF THE STOMACH

Benign tumors of the stomach

- **Epithelial**
  - adenomas
    - risk of carcinoma
    - Clinic: often asymptomatic, dyspepsia
- **Mesenchymal**
  - Hemangiomas, lipomas, fibromas
  - Submucosal tumors bulge the mucosa

- **Diagnosis**: GFS with biopsy, EUS

- **Therapy**: polypectomy, CHIR

Malignant tumors of the stomach

- **Epithelial**
  - Adenocarcinoma
- **Non-epithelial**
  - Lymfoma, GISTom

Adenocarcinoma

- **Most frequently observed malignant gastric disease (up to 95% of gastric neoplasms)**
- **Epidemiology**
  - 2x more in men, increase with age
  - Worldwide decrease in prevalence and death rate
  - high incidence: Japan, Korea, China, South America, Eastern Europe

Adenocarcinoma

- **Etiology**
  - Multifactorial – genetic factors + external factors
  - RF: chronic atrophic gastritis (H. pylori), excess salt, nitrates/nitrites, smoking, EBV, st.p. gastric surgery, blood group A
- **Histological types (Lauren classification)**
  - Intestinal type - older people, more men
  - Diffuse type - as well as younger people, worse prognosis

Adenocarcinoma

- **Pathogenesis:**
  - Intestinal type:
    - Sequence: chronic atrophic gastritis - intestinal metaplasia - dysplasia – carcinoma
  - Diffuse type:
    - mutations in adherin E, gene polymorphisms (IL1, ...)

Adenocarcinoma - symptomatology

- **Early gastric cancer**
  - asymptomatic or nonspecific symptoms

- **Advanced gastric adenocarcinoma - variable**
  - asymptomatic for a long time

    x
  - epigastric pain, dyspepsia (fullness, discomfort, ..) without relation to food (also responds to PPI), loss of appetite, nauzea and vomiting, weakness, weight loss, aversion to meat

    x
  - Advanced disease: vomiting, bleeding, anaemization

Adenocarcinoma - complications

- **Bleeding**
  - Symptomatology
    - Chronic occult bleeding – result in anemia

      x
    - Acute profuse bleeding
  - Therapy:
    - Endoscopic therapy, angiographic therapy, pharmacotherapy, surgery

- **Perforation**
  - Unusual
  - Symptomatology:
    - manifestations of peritoneal irritation, shock
  - Diagnosis:
    - Plain radiology
  - Therapy:
    - surgery

Adenocarcinoma - complications

- **Obstruction**
  - Uncommon
  - Symptomatology
    - Nausea, vomiting, dysphagia, weight loss
  - Diagnosis
    - Plain radiology, endoscopy
  - Therapy
    - Nasogastric tube, endoscopic stenting and palliative surgical resection

Adenocarcinoma - diagnosis

- **Anamnesis**
- **Physical examination** - resistance of the epigastrium, lymphadenopathy (Virchow's node, node Sister Mary Joseph, Irish node), ascites, symptoms of metastatic disease, paraneoplastic processes (dermatomyositis, acanthosis nigricans, GN, hemolytic anemia, hypercoagulation), thrombophlebitis (Trousseau sign) ovarian metastases (tumor of Kruckenberger), signs of metastasis (liver – jaundice+pain, lungs – cough+hemoptysis)
- **Gastroscopy** - macroscopic finding (variable appearance) and localization, biopsy (6-8x - edge and base of the ulcer)
- **LAB** - CRP, ALB, CB, iron deficiency anemia
- **EUS** – assess the extent and stage of tumour, help guide aspiration biopsies of lymph node
- **CT, MR** – detecting distant metastasis
- **Oncomarkers** - CEA, CA 125, CA 72-4

Adenocarcinoma - Therapy

- **DEPENDS ON STAGING**
- **Surgery**
  - Only chance for cure gastric adenocarcinoma
    - Subtotal or total gastrectomy
  - Palliative care – relieve symptoms
- **Endoscopy**
  - EMR or ESD
  - early cancer (only epithelium), palliative (metallic stent)
- **Chemotherapy**
  - advanced gastric cancer
  - Neoadjuvant, adjuvant, palliative
- **Radiotherapy**
  - Resistance – no survival benefit

Adenocarcinoma

- **Screening**
  - In Japan, since 1960
  - early detection

- **Prognosis**
  - The staging and TNM classification is the best prognostic indicator
  - 5 years, only 10% (after CHIR 30%)

Gastric lymphoma

- **Primary gastric lymphoma**
  - defined as a lymphoma that is predominantly located in the stomach
- **Generally**
  - 1-5% of all gastrointestinal malignancies
  - 10% of all lymphomas
- **The most commonly primary extranodal NHL (according to the REAL classification, WHO classification)**
  - MALT lymphoma, diffuse large B-cell lymphoma
- **Pathogenesis**
  - The role of H. pylori infection, HIV, autoimmune diseases

Gastric lymphoma

- **Symptomatology:**
  - NONSPECIFIC:
    - Epigastric pain, dyspepsia, anorexia, nausea, vomiting, weight loss, ... Up to anemia or gastrointestinal bleeding, obstruction or perforation

- **Diagnosis**
  - Gastroscopy(NONSPECIFIC) with biopsies (histology, immunohistochemistry)
  - EUS – depth of invasion and locoregional lymph node involvement
  - CT or MR – extent of disease evaluation = staging

Gastric lymphoma - therapy

- **According to histological and imunohistochemical type and staging**
  - LG-MALTom + positive for H. pylori → H. pylori eradication
    - FOLLOW-UP
  - LG-MALTom resistant to H.pylori eradication → locoregional radiotherapy or single agent chemotherapy (CHOP mode)
  - DLCBL → chemo-immunotherapy (rituximab, CF, doxorubicine, vincristine,…) + radiotherapy

Gastric lymphoma

- **Prognosis**
  - MALT lymphoma is an indolent disease with a very good prognosis
    - Depends on disease stage
  - DLCBL has a worse prognosis than MALTom
  - 5-year survival of:
    - Early stage MALTom – 85%
    - DLCBL – 60%

Gastrointestinal stromal tumor

- **Mesenchymal tumors - from Cajal cells**
- **Uncertain biological nature**
- **Symptomatology:**
  - gastrointestinal bleeding always
- **Diagnosis**
  - Gastroscopy with biopsies, EUS, PET/CT or CT
- **Therapy**
  - CHIR - basic part of therapy
  - Imatinib, sunitinib, VEGF - generalization
- **Prognosis**
  - only in the stomach = 5 years survival 100%