Pathology of pancreas

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Exocrine pancreas

The exocrine pancreas produces trypsin, lipase, phospholipase, amylase, elastase. These enzymes, with the exception of lipase, are in a form of inactive proenzymes and they are activated in the duodenum

Most of the proenzymes are activated by trypsin, which itself is activated from inactive trypsinogen by enteropeptidase in the duodenum

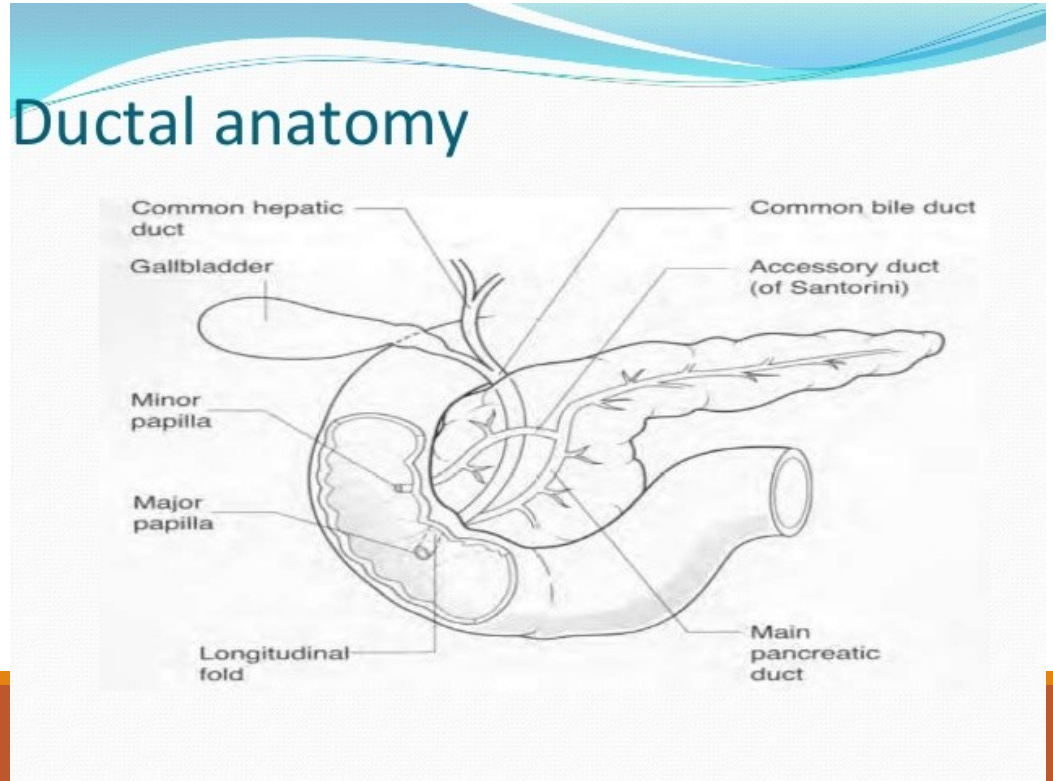
Acinar and ductal cells produce protease inhibitors

Congenital anomalies of pancreas

Usually as a result of failure of migration and fusion of dorsal and ventral parts of the pancreas

May cause stenosis of duodenum, increase the risk of pancreatitis

- Annular pancreas
- Pancreas divisum
- Ectopic pancreas (stomach, duodenum, jejunum,...)
- Congenital/dysgenetic cysts of pancreas



Cystic fibrosis (mucoviscidosis)

- AR inherited disease caused by the presence of mutations in the *CFTR* gene (7q 31.2)
- *CFTR* gene encodes the chloride channel protein, it also participates in the regulation of other ion channels (Na, K) and cellular processes (transport of ATP, bicarbonate and mucus secretion)
- Leads to abnormal transport of ions and water through membranes
- Effect of *CFTR* is tissue-specific:

- *Sweat glands:* chloride and sodium reabsorption; loss of *CFTR* function → hypertonic sweat (with excessive NaCl – „children with salty-tasting skin“)
- *Respiratory and instestinal epithelium*: *CFTR* ensures active luminal chloride secretion; loss of *CFTR* function → reduction of luminal choride secretion and increased reabsorption of sodium and water from the lumen → dense viscous mucus which obstructs ducts of the glands

Cystic fibrosis (mucoviscidosis)

Disorder with a wide degree of phenotypic variation

5 classes of mutations of *CFTR* gene:

- combination of 2 „severe mutations“ → severe („classic“) phenotype of CF

- combination of less severe mutations → mild phenotype of CF

+ modifier genes

(e.g. polymorphisms in genes, whose products modulate neutrophil function in response to bacterial infections)

Cystic fibrosis (mucoviscidosis): pathological features in organs

Pancreas

- viscous mucus obstructs ducts, which leads to dilatation of ducts, atrophy of the parenchyma and fibrosis

- exocrine pancreatic insufficiency (fat malabsorption and avitaminosis A,D,E,K)

- endocrine pancreatic insufficiency (diabetes associated with cystic fibrosis)

Lungs

- airway obstruction, recurrent and persistent infections

- bronchitis, bronchiectasis, bronchopneumonia, abscess

- *Pseudomonas aeruginosa, Haemophilus influenzae, Staphylococcus aureus, Burkholderia cepacia, Strenotrophomonas maltophilia*, atypic mycobakteria

Meconium ileus

Bile ducts obstruction (with the development of biliary cirrhosis)

Impairment of salivary glands (analogical to pancreatic impairment)

Azoospermia and infertility (resulting from congenital bilateral abscence of vas deferens)

Impairment of sweat glands

Pancreatitis

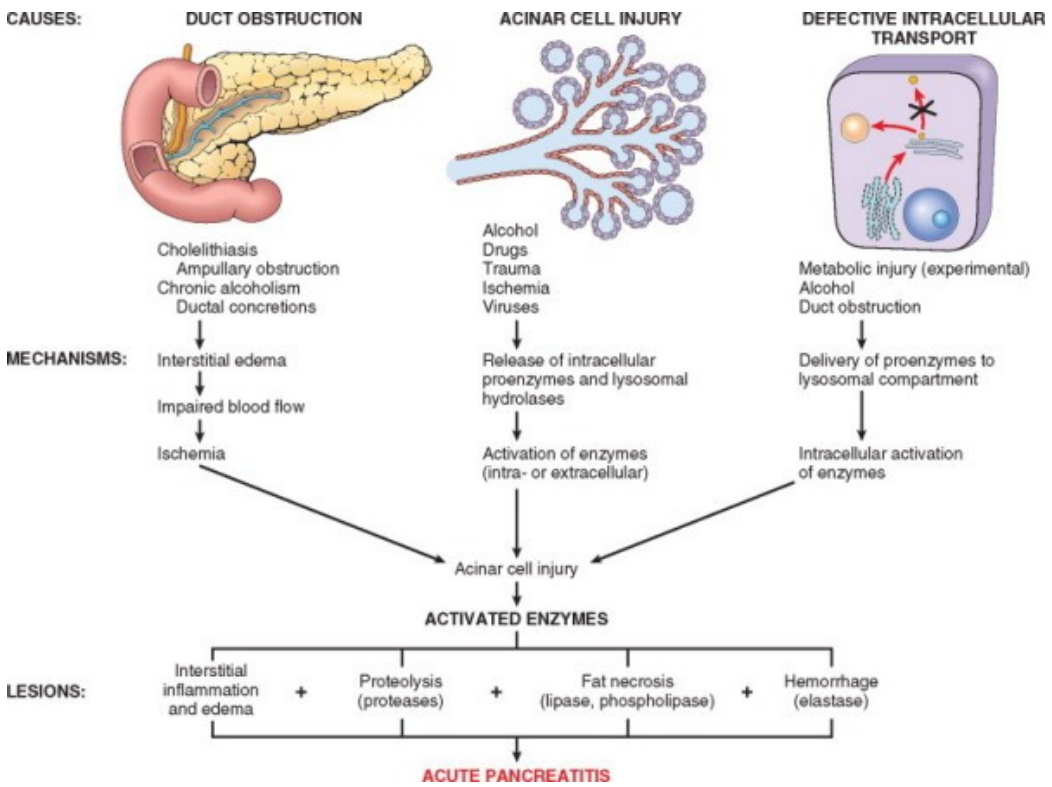
- Acute (AP)

Systemic inflammatory response to **autodigestion of the pancreas and peripancreatic tissue** by inappropriate release and activation of its own enzymes.

- Chronic (CP)

Prolonged inflammation of the pancreas, during which functional parenchyma is gradually replaced by fibrotic tissue with the development of irreversible destruction of exocrine, later endocrine pancreas.

Etiology of acute pancreatitis



Initation of AP:

Inappropriate and massive activation of trypsinogen

Activation of elastase and phospholipase → damage of cell membranes and hemorrhage, ARDS (phospholipases interact with the surfactant)

Activation of other enzymes, activation of complement, kallikrein-kinin system, coagulation and fibrinolytic system → DIC, shock (with mortality of 2-4 %)

Main pathways of pathogenesis of AP:

- duct obstruction

- primary acinar cell injury

- primary defective intracellular transport of proenzymes

The most common causes of AP are **alcoholism and billiary tract disease**

Acute pancreatitis – etiologic factors

80 % of acute pancreatitides is associated with alcoholism and disorders of bile ducts

Metabolic

- Alcoholism
- Hyperlipoproteinemia (type I a V)
- Hypercalcemia (hyperparathyroidism etc.)
- Drugs (thiazide diuretics, azathioprine, estrogens, sulfonamides, furosemide, metyldopa, pentamidine, procainamide)
- Genetic

Mechanical

- Trauma
- Obstruction (gallstones, pancreas divisum, tumors, parasites(*Ascaris lumbricoides*)), spasms
- Iatrogenic injury (perioperative injury, ERCP)

Vascular, ischaemic

- Shock, trombosis, embolism
- Vasculitis – polyarteriitis nodosa

Infectious

- Mumps
- Coxsackievirus
- *Mycoplasma pneumoniae*

+ idiopatic AP (10-20 %)

Focal oedema and necrosis of fat tissue → Diffuse necrosis of pancreatic parenchyma and hemorrhage

Acute pancreatitis

The basic alterations of morphology of the pancreas include:

- **Interstitial oedema** caused by microvascular leakage
- **Necrosis of fat** caused by lipolytic enzymes
- **Acute inflammatory reaction**
- **Protelolytic destruction of pancreatic parenchyma**
- **Destruction of blood vessels** caused by elastase with **interstitial hemorrhage**

Clinical features

Pain in the upper abdomen, anorexia, nausea, emesis; severe cases cause acute abdomen

DIC, ARDS, shock

Hypocalcemia, elevated levels of amylase and lipase in plasma

Postnecrotic pseudocysts, secondary infections, abscess

Clinical-pathological subtypes of AP

- **Acute interstitial pancreatitis**

moderate inflammation, interstitial oedema and focal necrosis of fat tissue of pancreas and peripancreatic tissue

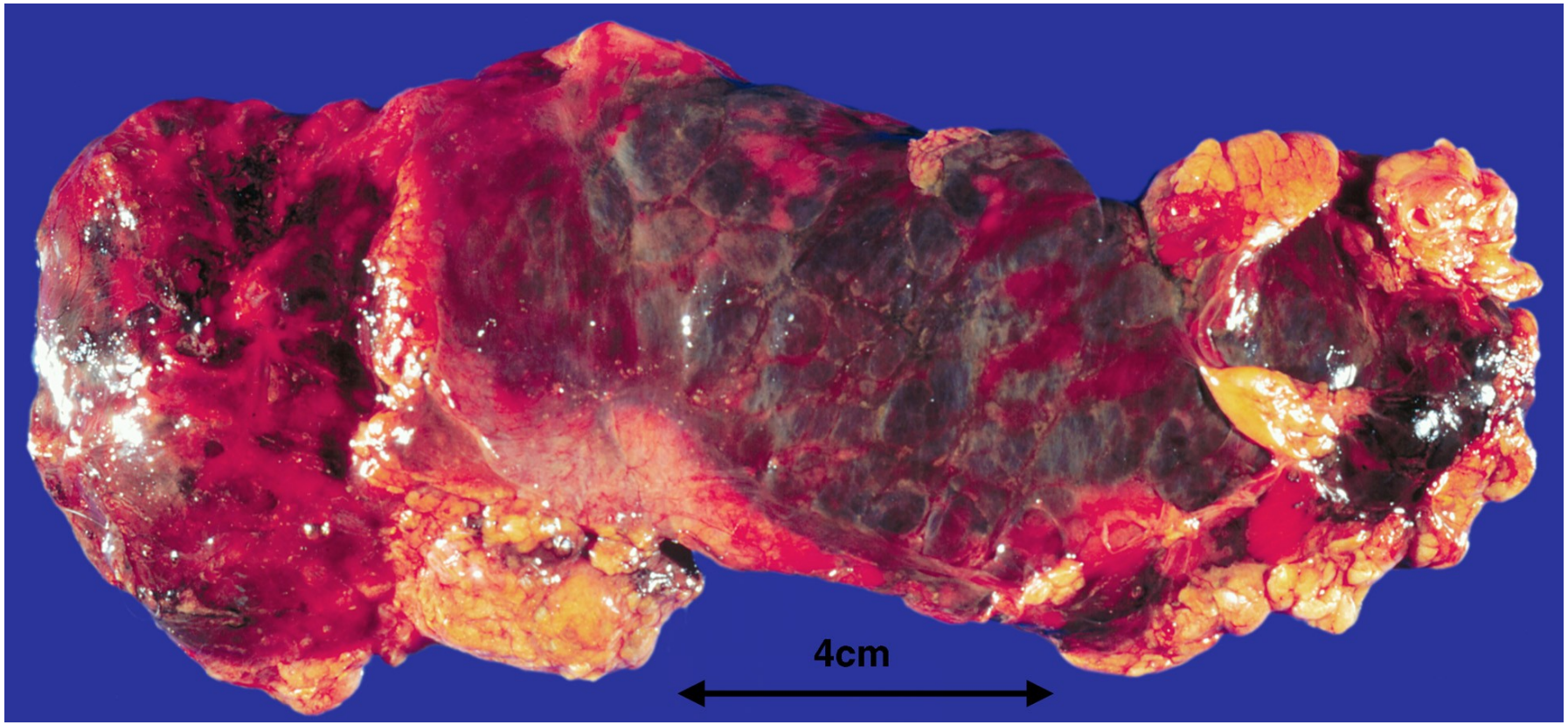
- **Acute necrotizing pancreatitis**

necrosis of fat tissue of pancreas and peripancreatic tissue (Balser‘s fatty necrosis, Ca bound to necrotic tissues, hypocalcemia of blood), colliquation of necrotic areas, destruction of structures of exocrine and endocrine pancreas, interstitial hemorrhage

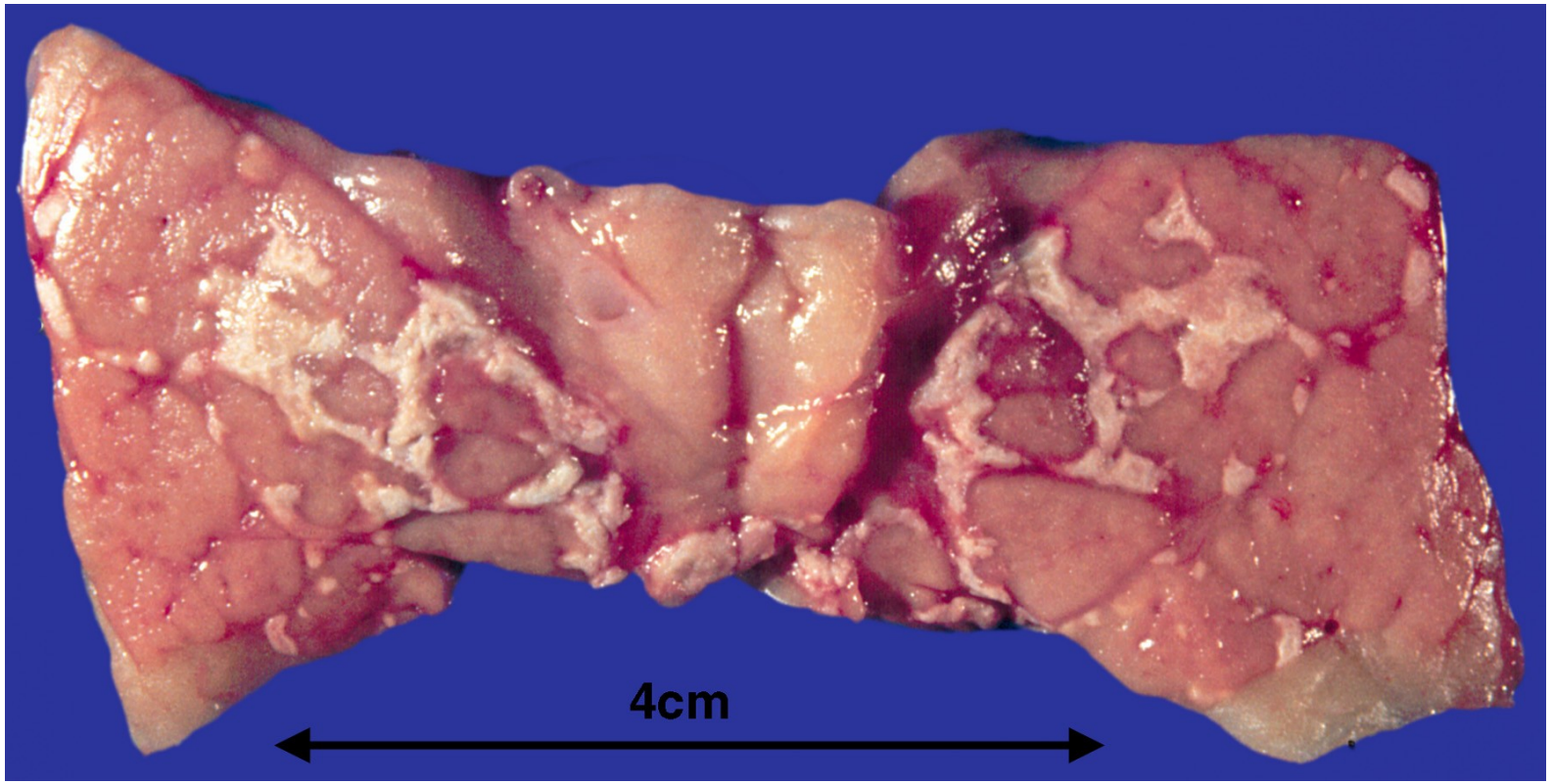
- **Hemorrhagic pancreatitis**

Extensive necrosis of pancreatic parenchyma, hemorrhage

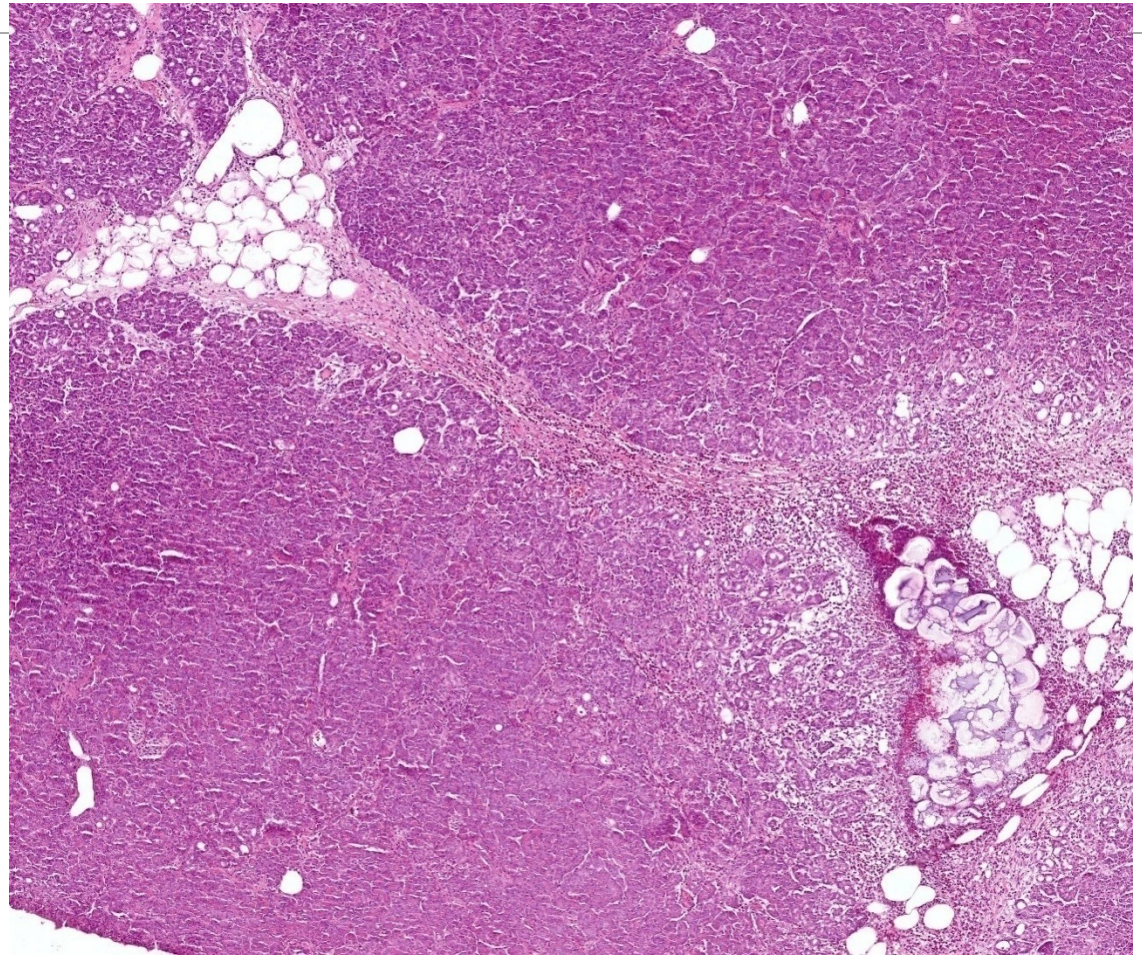
Acute pancreatitis



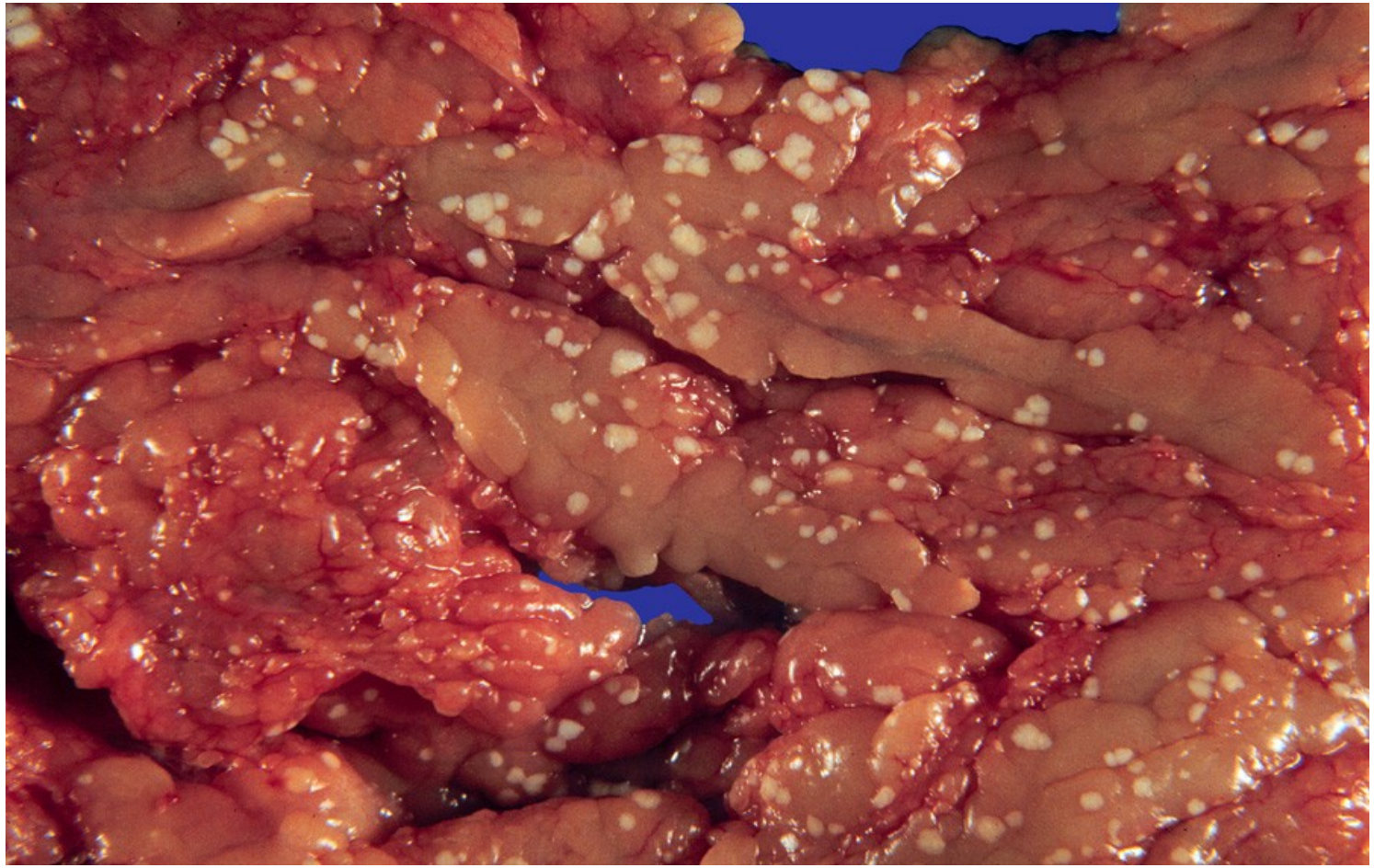
Necrotizing acute pancreatitis



Necrotizing acute pancreatitis



Necrosis adipose tissue of omentum



Chronic pancreatitis (CP)

Pathogenesis of CP

Obstructive causes

Toxic-metabolic causes

Oxidative stress

Necrosis-fibrosis

Etiology of chronic pancreatitis– classification TIGARO

Toxic-metabolic (**alcohol (alcoholic CP)**, nicotine, hyperlipidemia, drugs, uremia, toxins…)

Idiopathic

Genetic

- hereditary pancreatitis, AD (mutation in gene *PRSS1* (trypsinogen 1)), high risk of development of pancreatic carcinoma

- genetically induced pancreatitis (alterations in genes *CFTR*, *SPINK1* (trypsin inhibitor),…)

- alpha-1 antitrypsin deficiency

Autoimmune (imitates carcinoma!)

Recurrent (repeated episodes of acute pancreatitis)

Obstructive (gallstone obstruction, tumor,...)

Clinical features and aftermath:

Atrophy and insufficiency of exocrine and endocrine pancreas, fibrosis.
Chronic pain in the upper abdomen, weight loss, icterus
Pancreatogenic malabsorption syndrome
An increased risk of cancer (pancreatic ductal adenocarcinoma (PDAC))

Chronic pancreatitis (CP)

Associated with extensive architectonical and cytological alterations of pancreas

Destruction of acinar cells

Perilobular and intralobular fibrosis

Distortion of persistent ductal elements → morphologically looks like well-differentiated pancreatic ductal adenocarcinoma (PDAC) – diff. dg. PDAC x CP!!!

Reactive cytonuclear changes of epithelium

Dysplastic ductal lesions – pancreatic intraepithelial neoplasia (PanINs) in CP

Clinical diff. dg. of CP and pancreatic ductal adenocarcinoma (PDAC)

Age (PDAC is rare in younger age (<40 years))

Long-term history of clinical problems of patient with CP

Chronic alcoholic, hereditary and so-called paraduodenal pancreatitis → development on the bases of recurrent acute pancreatitis; formation of pseudocyst

Icterus

- **CP - usually after years of progressive CP**
- **PDAC - sudden manifestation of icterus**

PDAC: disease of older adults (>50 years), without history of CP or alcoholism

* Different in autoimmune pancreatitis!

Gross description (CP in surgical material)

Unevenly distributed fibrosis with foci of fibrotization and lobular parenchyma in CP (alcoholic and hereditary)

Consistency is more elastic in CP, impairment of pancreas is more diffuse

Pseudocyst in CP

Calcificated mucoprotein plugs in CP

Progression of stenosis of major pancreatic duct in CP

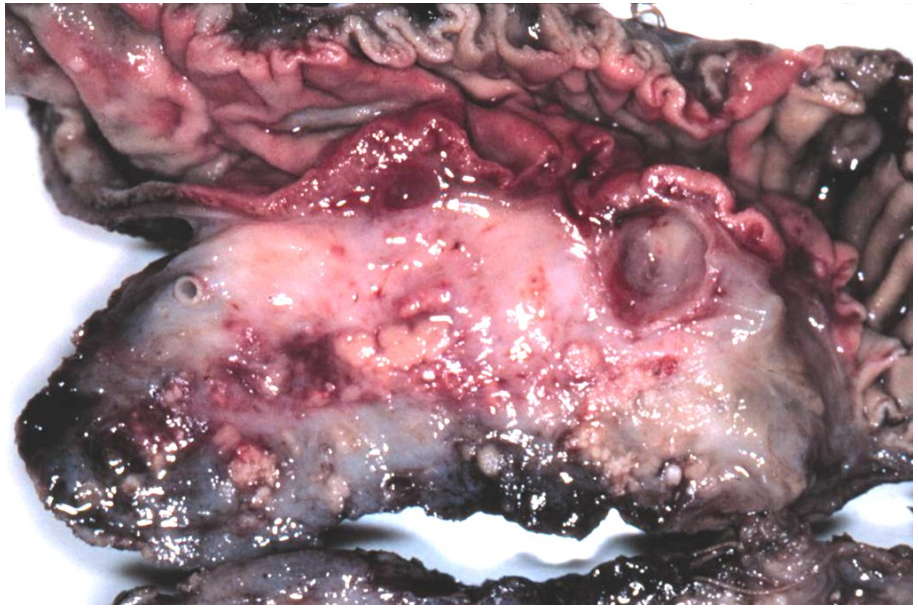
Paraduodenal pancreatitis

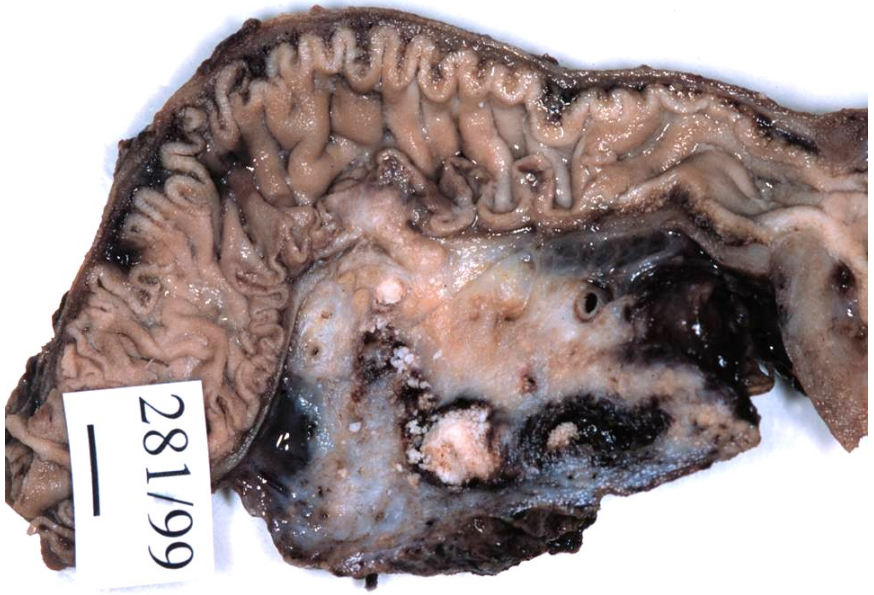
(inflammatory, fibrous and cystic changes in loci of predilection)

Autoimmune pancreatitis

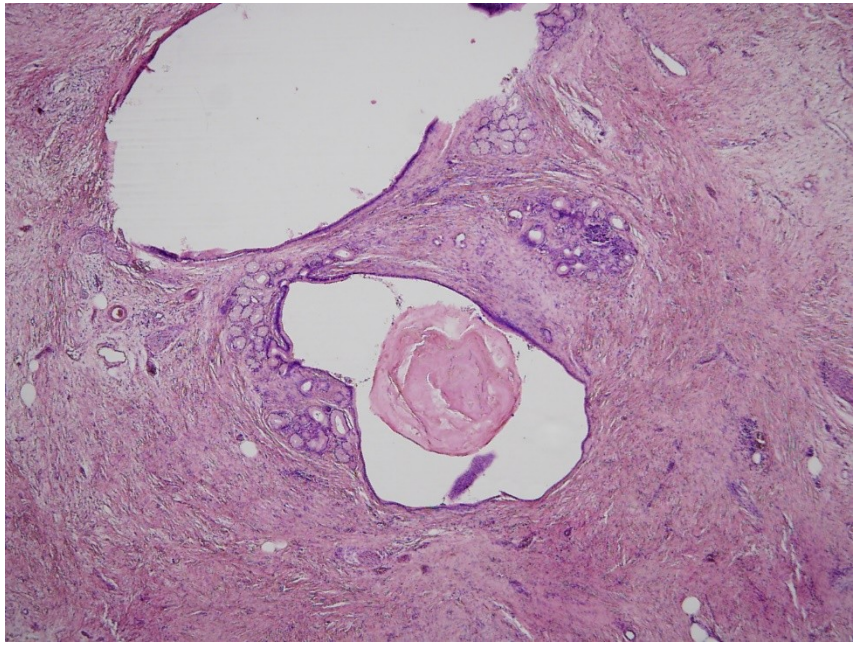
(grossly looks like PDAC, predominantly in pancreatic head, diffuse impairment, stenosis of the major pancreatic duct and damage of extrahepatic bile ducts)

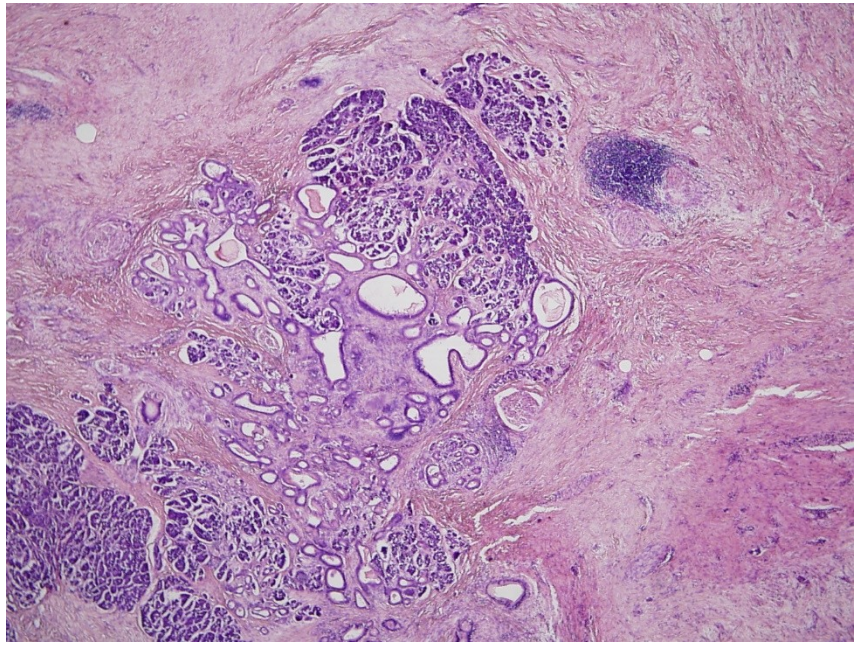
Alcoholic chronic pancreatitis in resection specimen





Alcoholic chronic pancreatitis





Hereditary pancreatitis

Mutations in genes encoding pancreatic enzymes or their inhibitors → increased autoactivation of trypsinogen or resistance to inactivation → autodigestion of pancreatic tissue, recurrent pancreatitis

PRSS1 (cationic trypsinogen gene), AD

SPINK1 (serum protease inhibitor), AR

Fibrosis - perilobular, periductal, sometimes intralobular; diffuse X focal

Dilatation of ducts, inspissation of luminal mucus, calcification (similarity with ACP), hyperplasia, metaplasia and dysplasia of ductal epithelium.

50-70x increased risk of development of pancreatic carcinoma (vs 2-5x increased risk in sporadic CP)

Autoimmune pancreatitis

2 clinicopathologic subtypes of autoimmune pancreatitis:

- **lymphoplasmacytic sclerosing pancreatitis (LPSP, type 1)**
  - often associated with other IgG4-related sclerosing lesions
- **idiopathic ductocentric pancreatitis (IDCP, type 2)**
  - also known as AIP with granulocytic epithelial lesion
  - usually occurs solitary
    - rarely associated with ulcerative colitis
  - dense periductal inflammation with neutrophilic infiltration and destruction of ductal epithelium
  - absence or low IgG4+ plasmocyte count

	LPSP (AIP w/o GEL)	IDCP (AIP with GEL)	Alcoholic CP
Infiltration	Lymphoplasmacytic + eosinophilic + neutrophilic	Lymphoplasmacytic + neutrophilic (ducts, acinar cells)	Few chronic inflammatory cells
Ducts	Dense periductal infiltration w/o destruction	Dense periductal infiltration + GEL	Distortion of ducts, dilatation, w/o infiltration
Mucoprotein plugs and Ca	No	No	Often
Lobuli	Infiltration of acinar cells with destruction	Focal infiltration with neutrophils	Focal lobular atrophy and fibrosis
Veins	Phlebitis obliterans	Rarely phlebitis obliterans	W/o phlebitis obliterans
Arteries	Rarely intensive arterial impairment	Usually w/o arterial impairment	W/o arterial impairment
Pseudocysts	No	No	Yes
Involvement of peripancreatic adipose tissue	Common	Minimal, inflammation restricted to pancreatic tissue	Loci of necrosis
IgG4 IHC	>10 IgG4+ plasmocytes/HPF	few or none IgG4+ plasmocytes	few or none IgG4+ plasmocytes
Clinical features	M >F IgG4 sclerosing lesions	M=F, younger AIP+UC	

Clinical features of AIP

Obstructive icterus

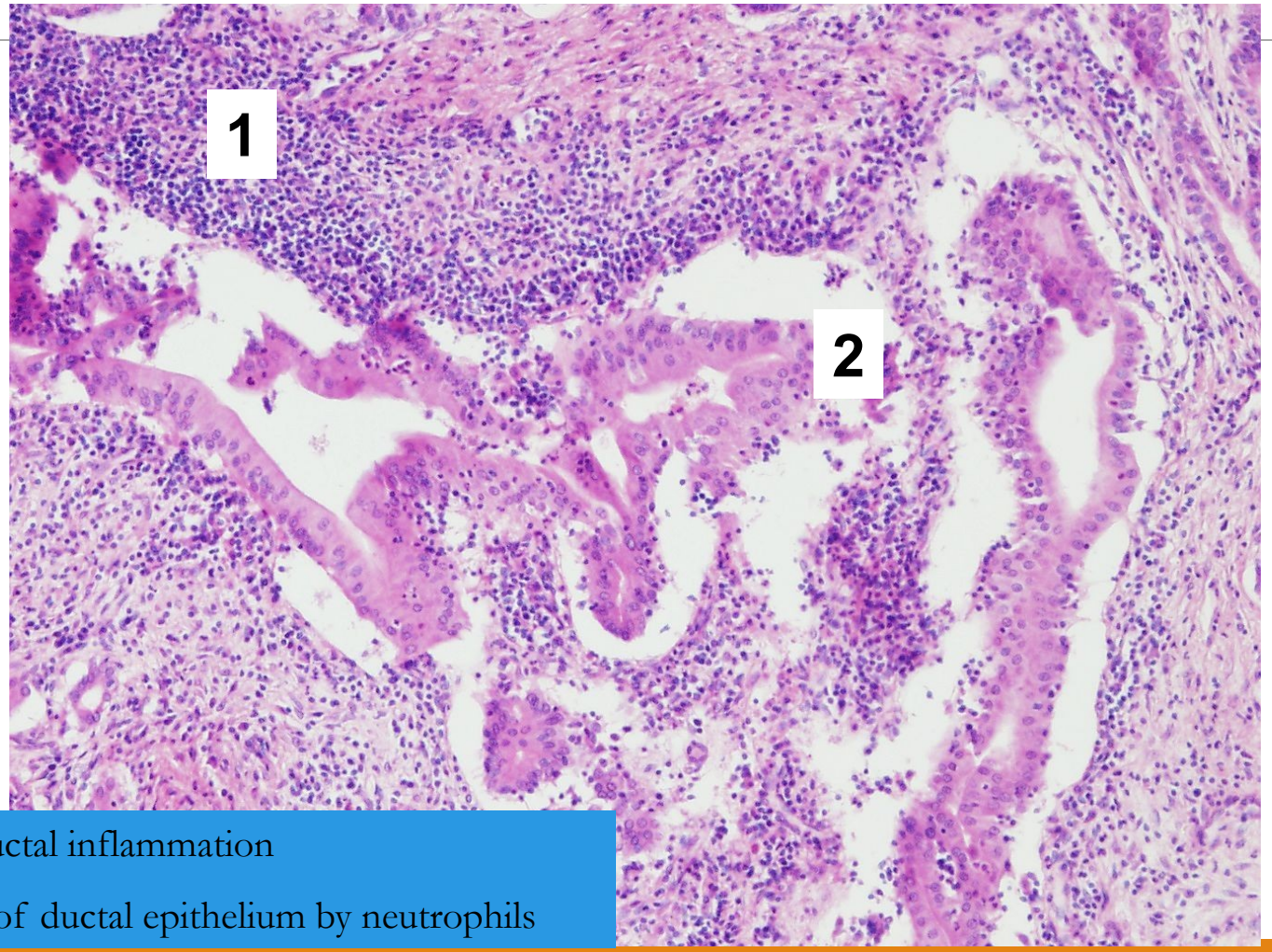
Abdominal pain

Imaging methods – diffuse/focal enlargement of pancreas

ERCP – diffuse irregular major pancreatic duct with stenosis and stenosis of ductus choledochus

Responds to steroid therapy

Autoimmune pancreatitis (IDCP, type 2)



1. Dense periductal inflammation
2. Destruction of ductal epithelium by neutrophils

IgG4-related sclerosing lesions

Autoimmune pancreatitis

Sclerosing cholangitis

Lymphoplasmacytic sclerosing cholecystitis

Sclerosing sialadenitis (Küttner tumor)

Idiopathic retroperitoneal fibrosis (M. Ormond)

Inflammatory pseudotumor of liver, lungs and pituitary gland

IgG4-related tubulointerstitial nephritis

IgG4-related interstitial pneumonia

Sclerosing prostatitis

Sclerosing thyroiditis

Hypophysitis

Pachymeningitis

Sclerosing dacryoadenitis (Mikulicz disease)…….

- M>F; respond to steroid therapy, lymphadenopathy; mimic neoplastic lesions
- sclerosing lesions with diffuse lymphoplasmacytic infiltration, irregular fibrotisation
- may be present: eosinophils, phlebitis obliterans, dense infitration of IgG4+ plasmacytes
- increased risk of development of malignant lymphoma

Obstructive pancreatitis

diffuse perilobular and intralobular fibrosis

dilatation of ducts w/o obstruction, irregularity or signs of destruction of ductal epithelium

w/o signs of inspissation of luminal mucus and calcifications in ducts

hyperplasia of ductal epithelium

necrosis and pseudocysts not present

Paraduodenal pancreatitis

Also known as: cystic dystrophy of heterotopic pancreas (the residue of the dorsal part of pancreas in duodenal wall), periampullary duodenal wall cyst, „groove“ pancreatitis, pancreatic hamartoma of duodenal wall,...

Alcohol comsumption

Clinical features associated with duodenal stenosis, loss of weight, icterus in 20 % of cases

Changes in region of **minor duodenal papilla** (obstruction, pancreas divisum) + impairment of pancreatic head + paraduodenal cystic changes (between the duodenal wall and the pancreas)

Prolonged inflammation in submucosa and wall of the duodenum and the adjacent pancreas, foci of necrosis, myofibroblast proliferation, pseudocystic lesions, granulation tissue, granulomatous response, Brunner gland hyperplasia

„Idiopathic chronic pancreatitis“

3-9 % of all case of CP

Mutation in *CFTR* gene
(cystic fibrosis transmembrane conductance regulator gene)

Mutation v *SPINK1* gene
(PSTI – pancreatic secretory trypsin inhibitor)
+ external factors (smoking, alcohol)

Dysfunction of sphincter of Oddi

Pancreas divisum

Cysts of pancreas

Congenital cysts

- unilocular
- multilocular (AD polycystic disease (cysts of kidney, liver, pancreas), syndrome von Hippel-Lindau)
- (dermoid (mature teratoma))

Benign lymphoepithelial cyst

Mucinous non-neoplastic cyst (v.s. mucinous cystic neoplasm (MCN)??)

Periampullary duodenal wall cyst (in heterotopic pancreas)

Enterogenous cyst

Retention cyst

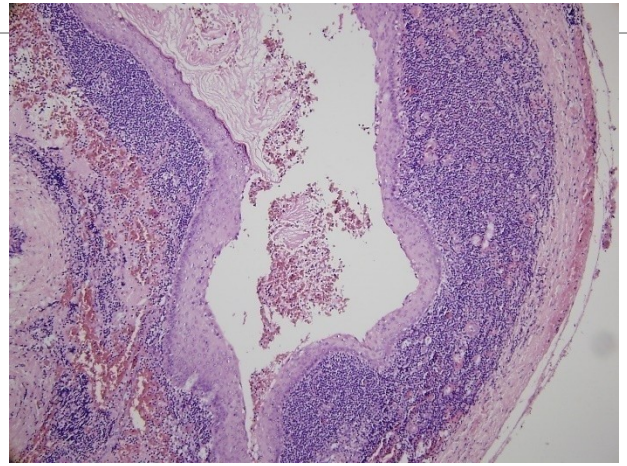
Endometrial cyst - endometriosis

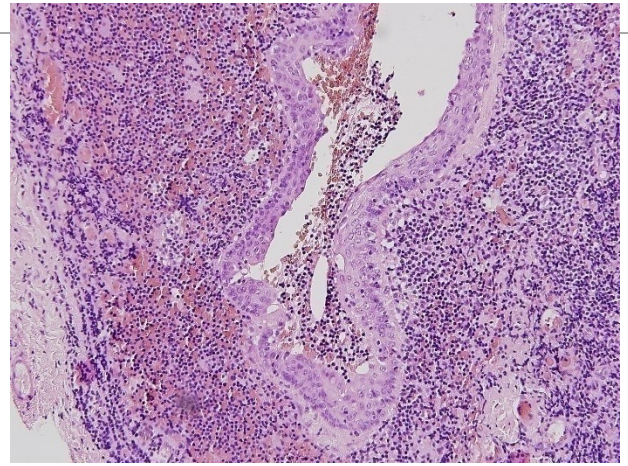
Parasitic cysts (Ecchinococcus granulosus)

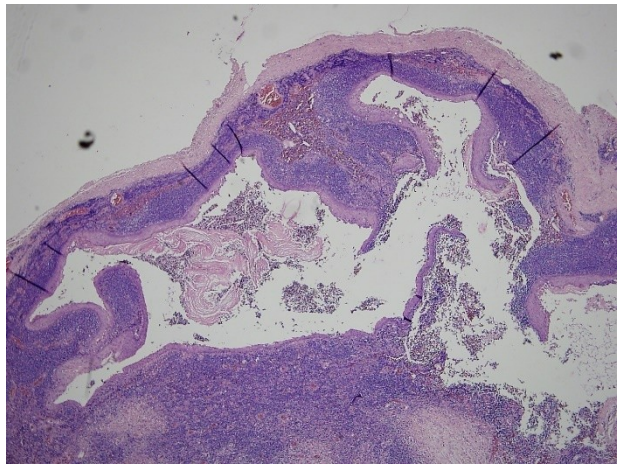
Pseudocysts

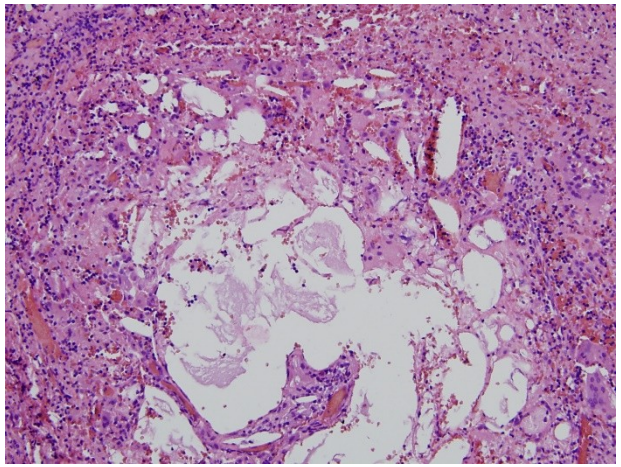
- associated with pancreatitis
- the result of trauma
- **Abscesses**

Benign lymphoepithelial cyst of pancreas









Pancreatic tumors

Epithelial

Non-epithelial

Secondary (metastatic) tumors

Type of neoplasm	Incidence	Location	Features
Ductal adenocarcinoma (PDAC)	**85-90 %**	**H>T**	**solid, poorly defined masses, desmoplastic stroma** **Highly agressive**
Intraductal papillary-mucinous neoplasm	3-5 %	H>T	Cystic, intraductal, progression into carcinoma
Neuroendocrine neoplasia (NEN)/ **Tumors of the endocrine pancreas**	1-2 %	H=T	Solid, pseudocystic*, different degrees of malignancy, see classification of NEN GIT; hormonally active
Mucinous cystic neoplasm	1-2 %	T>>H	Cystic, absence of communication with ducts, , progression into carcinoma, female predominance
Serous cystic neoplasm	1-2 %	H=T	Cystic, absence of communication with ducts, benign
Acinar cell carcinoma	1-2 %	H=T	Solid, pseudocystic*, agressive
Solid pseudopapillary neoplasm	1-2 %	H=T	Solid, pseudocystic*, young women, low malignant potential
Pancreatoblastoma	<1 %	H=T	Solid, in children, malignant

H - head; T - tail; * often with pseudocystic degeneration

Risk factors	
Exogenous risk factors	**Endogenous risk factors**
Age	Familial occurrence
Smoking	Hereditary syndromes
Alcohol*	Chronic pancreatitis
Diet (especially high-fat), obesity	Diabetes mellitus
Exposition to organic substances or radiation	

* Indirect impact by induced chronic pancreatitis

Genetic syndromes associated with PDAC

Syndrome	Type of inheritance	Gene
Lynch sy (hereditary nonpolyposis colorectal cancer)	AD	*MSH2, MLH1,…*
Familial breast cancer; genes of Fanconi anemia	AD	*BRCA2, PALB2, FANCC, PANCG, (BRCA1)*
Familial pancreatic cancer	AD	Unknown
Familial Atypical Multiple Mole Melanoma syndrome (FAMMM)	AD	*CDKN2A* (p16)
Hereditary pancreatitis	AD (*PRSS1*) AR (*SPINK1*)	*PRSS1* *SPINK1*
Peutz-Jeghers sy	AD	*STK11*

Features of PDAC

- 85-90% of all pancreatic neoplasms
- very poor prognosis, the five-year relative survival rate is about 5 %, mortality almost equals to incidence
- incidence is increasing, the highest incidence of pancreatic cancer in Czech republic
- 5th leading cause of cancer related death in Western countries (2nd among GIT malignancies)
- causes of this unfavorable state:

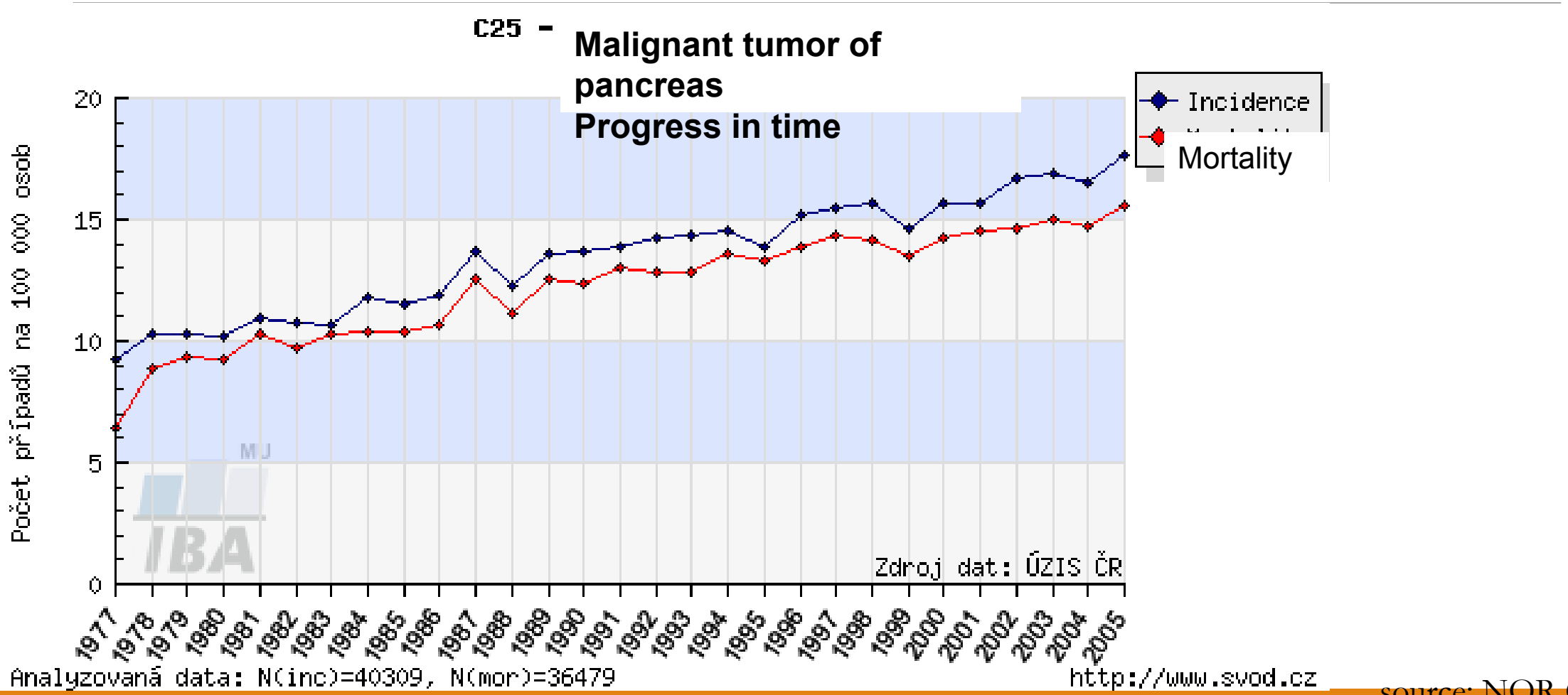
absence of effective screening

diagnosis often made in advanced stage of the disease due to lack of symptoms

molecular-biologic characteristics of PDAC

- radical resection – favourably increases survival rate of patients; at time of diagnosis only 10-15 % patients with PDAC meet criteria for resection; 70 % of patients are presented with metastases in regional lymph nodes. Despite radical resection, reccurence of PDAC in about 90 % of patients within two years after surgery.

Pancreatic cancer



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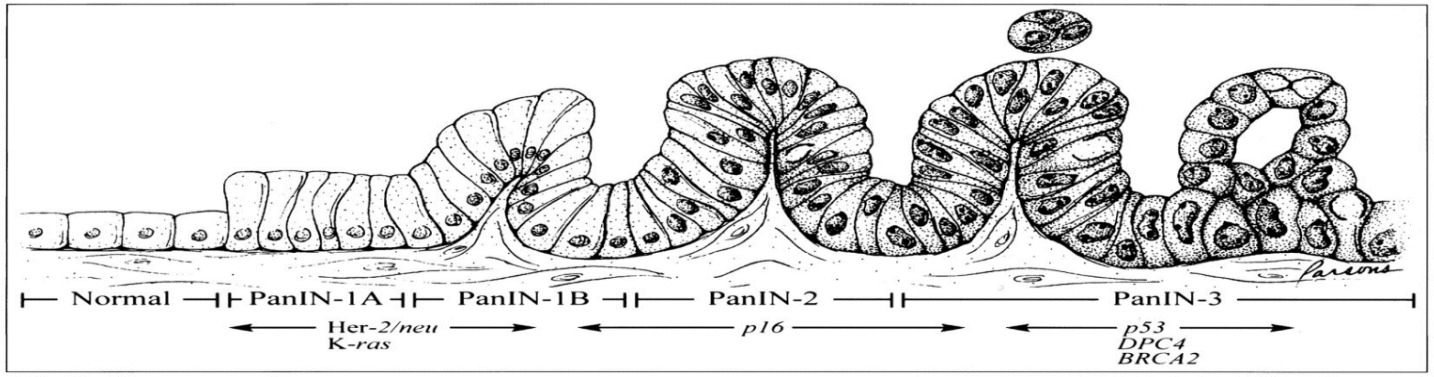
Precursor lesions of pancreatic cancer

Pancreatic intraepithelial neoplasms (PanIN) – precursor of PDAC



Mucinous cystic neoplasms (MCN)

Intraductal papillary-mucinous neoplasms (IPMN)

- multistage process of histologic and genetic progress into invasive cancer
- different clinico-pathological and genetic features

Pancreatic cancer

Disease induced by germline or acquired mutations of germ or somatic cells

Multiple alterations of numerous genes responsible for progression of pancreatic cancer

Knowledge of molecular basis of the disease – revelation of effective marker for early diagnosis + potential target for therapy

Precursor lesions: helpful tool for study of molecular basis of pancreatic cancer

Potentially successfull therapeutic strategy: combination of drugs targeted for pancreatic tumor stem cells and their microenvironment and conventional chemotheurapeutic agents ???

Microenvironment of pancreatic cancer – role of fibrogenesis in pancreatic cancer

Tumor stroma – intergral component of cancerogenesis; provides communication between tumor and stroma cells

Role of activated pancreatic stellate cells (stromal cells with similar behaviour as myofibroblasts):

- Production of extracelular matrix proteins a matrix metalloproteinases (MMPs)
- Source of cytokines and growth factors
- Effect on tumor and other cells favouring tumor progression and fibrosis

Role of proteases produced by stromal cells in DM a ↓BMI

- Biopeptides of glucose homeostasis (+ neuropeptide Y, peptide YY, proline) substrates of these proteases
- Fusion products ↓active/inactive → induction of diabetes associated with pancreatic cancer and loss of body weight (↓BMI)

Stimulation of pancreatic cancer progression by mediators derived from stromal cells

- Induction of cell proliferation
- Inhibition of apoptosis
- Chemoresistance
- Invasive growth

Evolution of therapy targeted on pancreatic stellate cells

Signs of PDAC

Mostly located in the head of pancreas (2/3)

Abdominal pain, loss of weight, suddenly emerged painless icterus, pruritus

Thrombophlebitis migrans

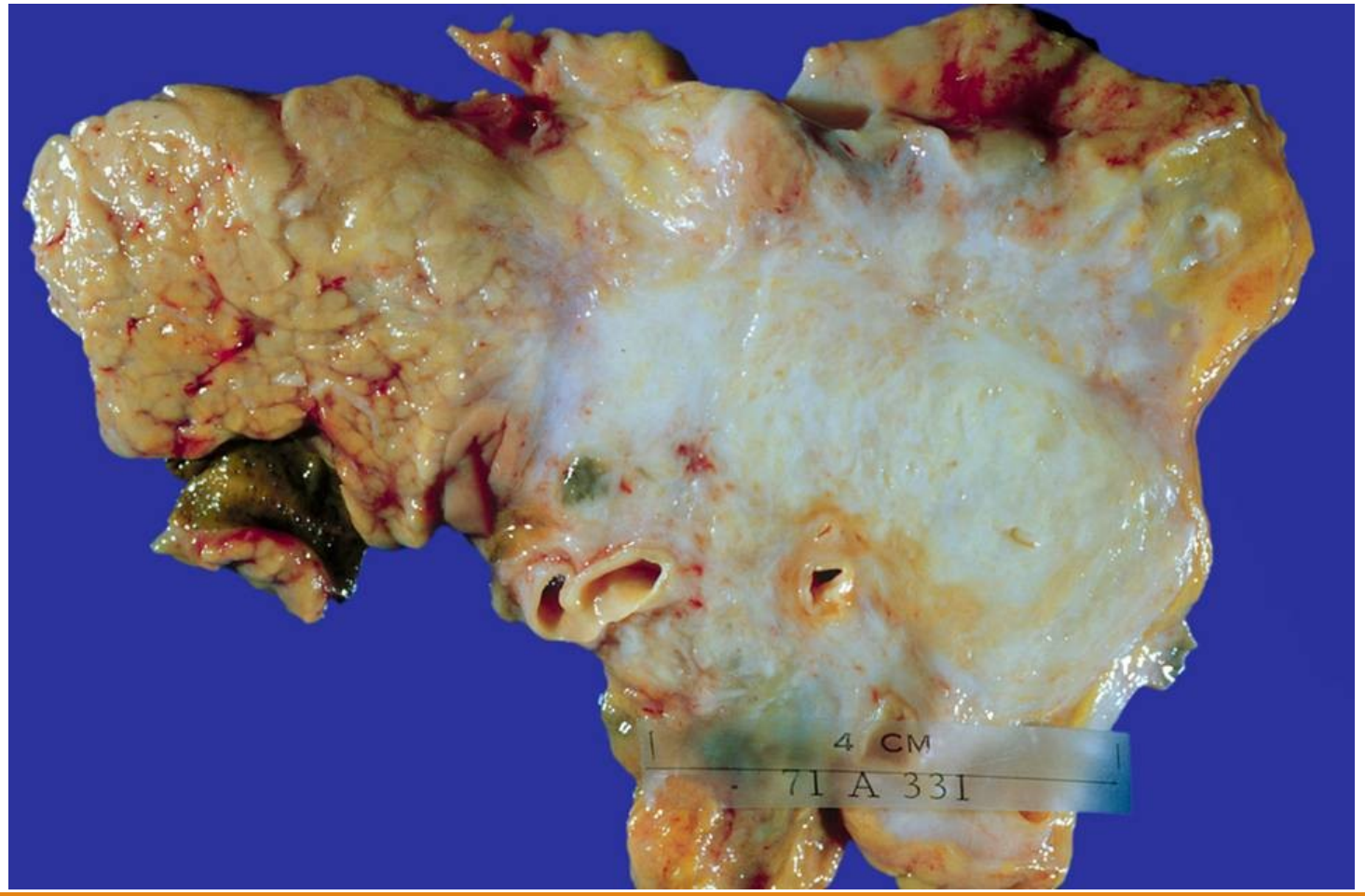
Signs caused by metastates or by affected sorrounding organs

Oncomarkers (CA 19-9, CEA,…non-specific)

DM associated with PDAC (atypical)

- suddenly in advanced age
- absence of obesity, rapid progression requiring insulin therapy
- reccurence of infections including mycotic
- disbalance of homeostasis with repeated hyperglycemia and tendency towards ketoacidosis and kachexia

Ductal adenocarcinoma (head of the pancreas)



PDAC dissemination

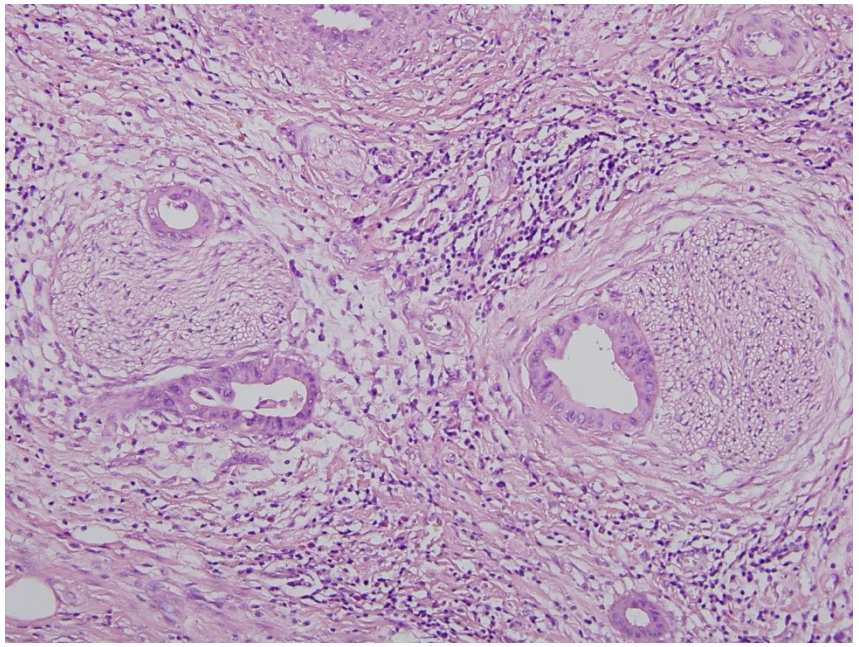
Lymphatic metastases in regional lymph nodes

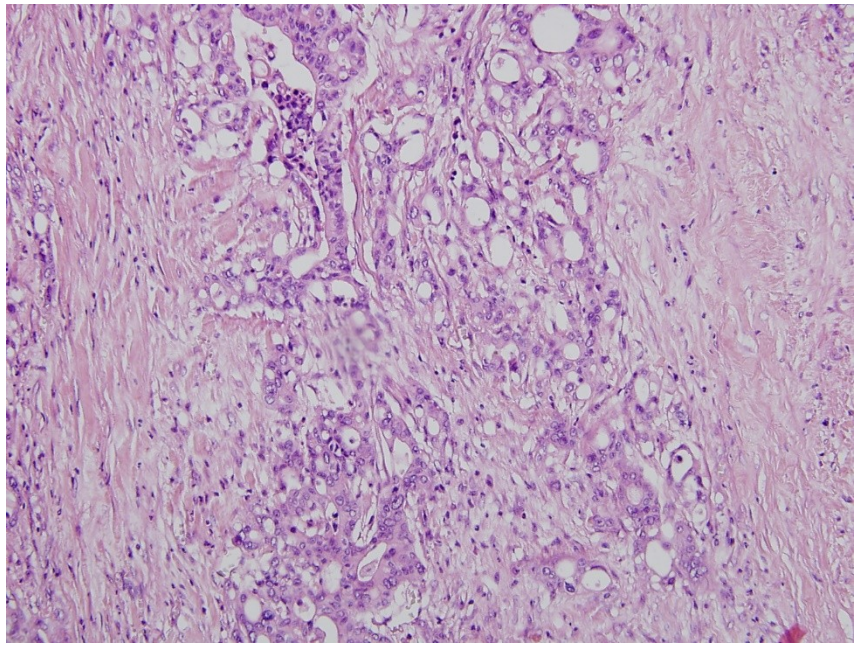
Hematogenous metastases in liver, lungs, bones

Peritoneal carcinomatosis

Perineural invasion

Ductal adenocarcinoma and perineural invasion





Pancreatic Cystic Neoplasms

Mucinous cystic tumors

Mucinous cystic neoplasm (MCN)

Intraductal papillary-mucious neoplasm (IPMN)

Benign, however can progress into carcinoma.

Serous cystic tumors

Almost always benign; some might be associated with Von Hippel-Lindau disease.

Mucinous cystic neoplasms (MCN)

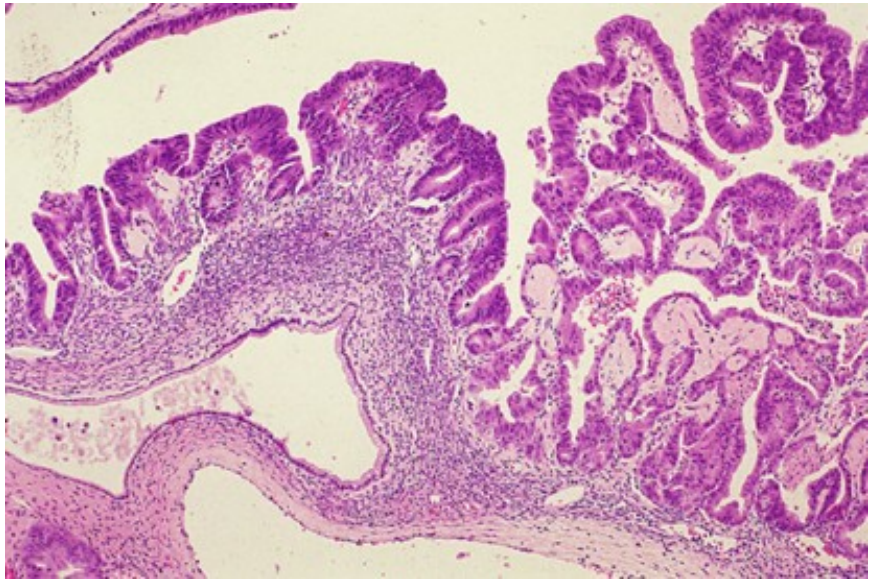
Unilocular or multilocular, no communication with ducts, columnar mucin-producing epithelium supported by ovarian like stroma

90 % in women (5th - 6th decades); body-tale localisation

- Noninvasive

(excellent prognosis)

- Invasive (60 % five-yers survival rate)



• **Genetic alteration in progression of MCN:**
- Early mutation of oncogene *KRAS*
- Inactivation of TSG *TP53* and *DPC4* in invasive MC carcinomas

Intraductal papillary mucinous neoplasms (IPMN)

Mucin producing, growing within the main pancreatic duct or its major branches, papillary architecture

M/F = 60:40; 6th decade

75 % in the head of pancreas; 20 % body and tail + diffuse infiltration

Precursor lesions: IPMN with low grade and high grade dysplasia

Malignant lesions: IPMN associated with invasive carcinoma

Three morphologic types:

- Intestinal type (MUC2+)
- Pancreatobilliary type (MUC1+)
- Gastric type (MUC5AC+; „branch duct type“)

+ intraductal oncocytic papillary neoplasm

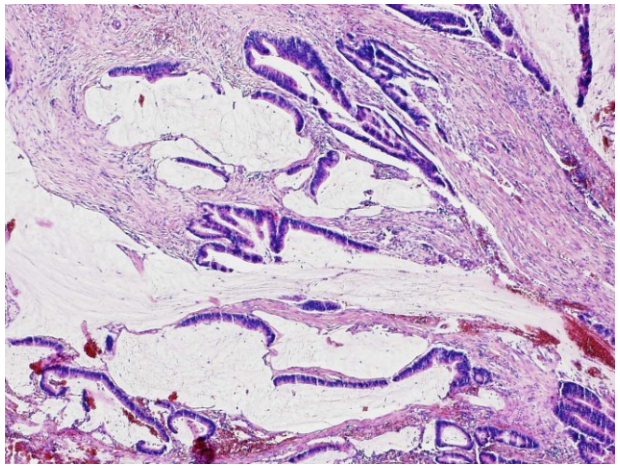
+ intraductal tubulopapillary neoplasm

IPMN

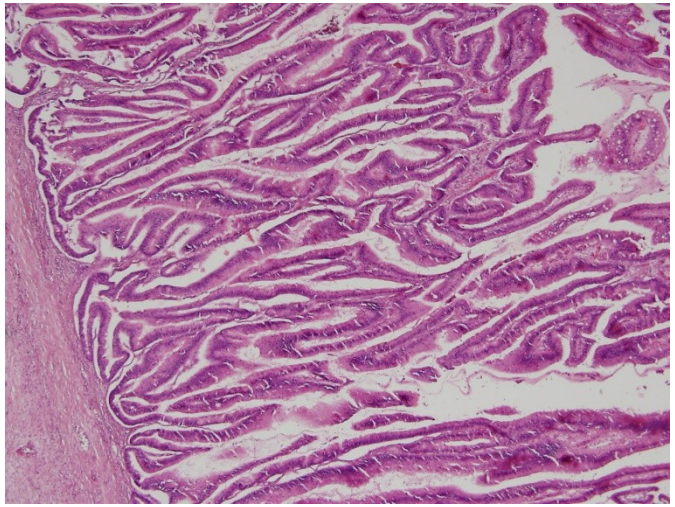
Gastric type IPMN

?

Intestinal type IPMN



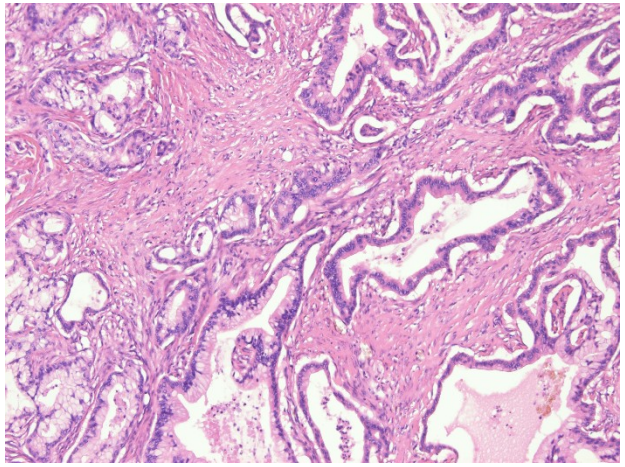
Mucinous noncystic carcinoma (2/3)
Better prognosis



IPMN

?

Pancreatobilliary type IPMN

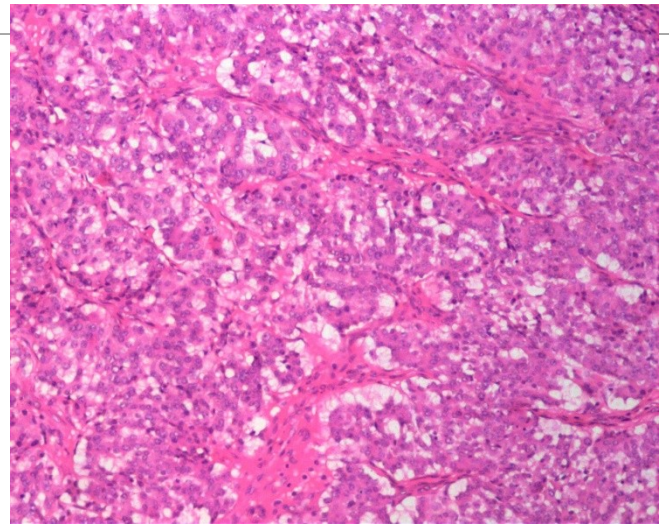


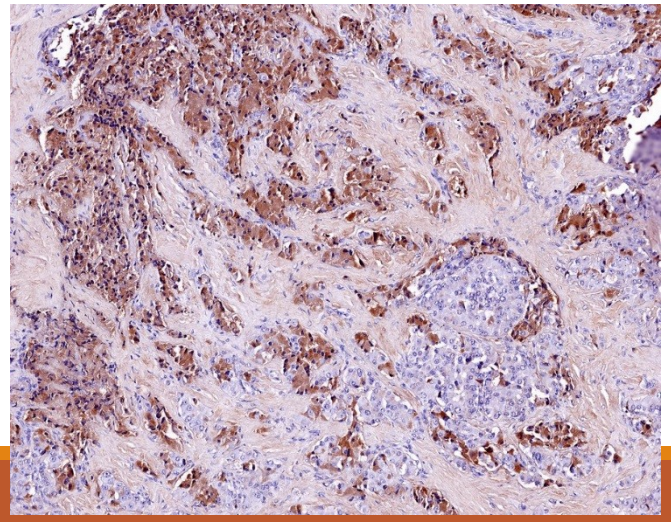
Tubular (PDAC-like) adenocarcinoma (1/3)
Poor prognosis

Genetic alterations in progression of IPMN:

- early mutation of *KRAS*
- late inactivation of *p16* a *TP53*
- inactivation of *DPC4* only in 10 % of IPM invasive carcinomas
- inactivation of *STK11/LKB1* in 1/3 IPMN

Acinar cell carcinoma, trypsine+





Solid and acinar architecture

M>F; adults, rare in children

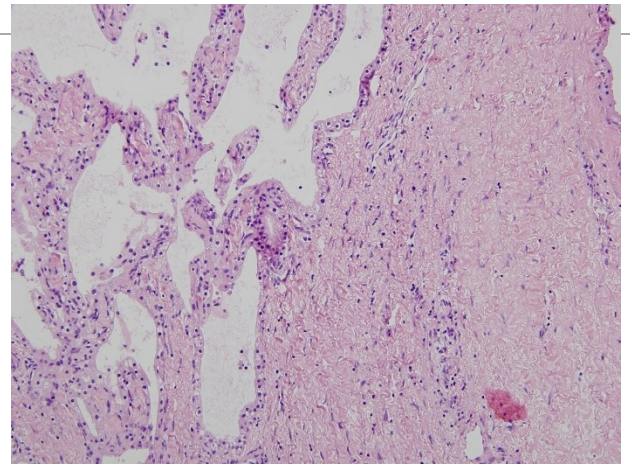
Circumscribed, multinodular, necrosis, cystic degeneration

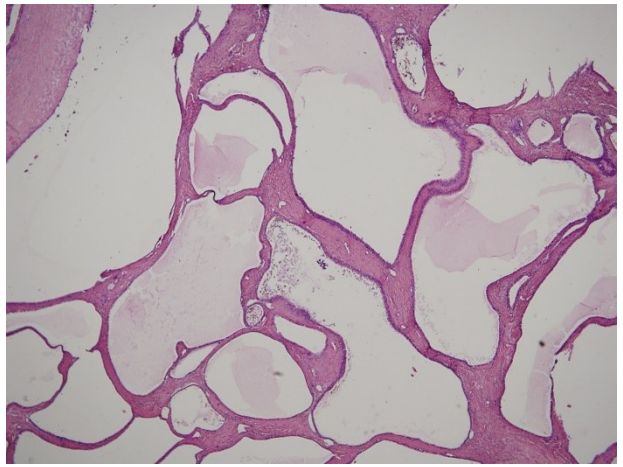
Granular eosinonophilic cytoplasm – zymogen granules

Variants:

- acinar cell cystadenocarcinoma
- mixed acinar-endocrine carcinoma (30 % proportion of more than 1 cell type).

Serous pancreatic neoplasms





Usually cystic, lined by glycogen-rich, ducular type epithelial cells

Serous cystadenoma:
- benign; tail, body > head; central stellate scar; microcystic

Serous cystadenocarcinoma:
- Extremely rare

+ variants:

- Macrocystic serous cystic neoplasm
- Solid serous neoplasm
- SCN associated with Von Hippel-Lindau sy
- Mixed serous neuroendokcrine neoplasm

Solid pseudopapillary neoplasm

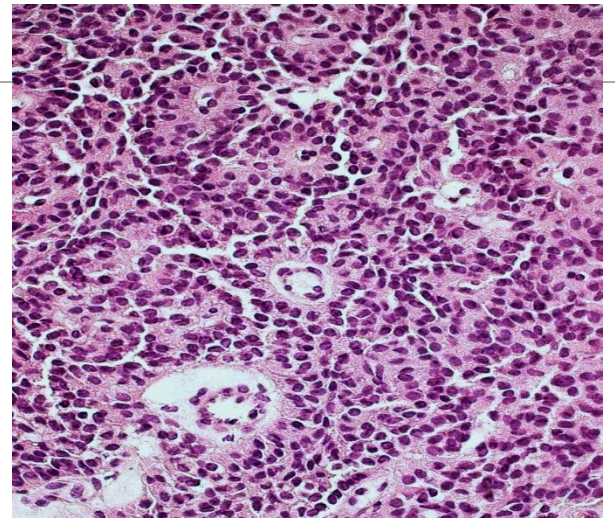
low grade malignancy, with favourable biologic behaviour

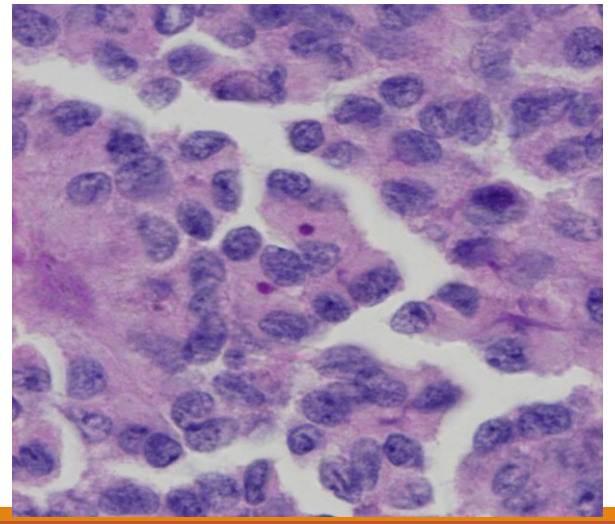
Young women

Monomorphic cells forming solid and pseudopapillary structures; haemorrhagic-cystic changes

Variable expression of epithelial, mesenchymal and endocrine markers

85-95 % cured with surgical resection





Pancreatic neuroendocrine tumors

Functioning (hormonally active)

- insulinoma
- glucagonoma
- somatostatinoma
- gastrinoma
- VIP-producing tumor
- serotonin-producing tumor
- others – producing ectopic hormones (ACTH, calcitonin,…)

Non-fuctioning (clinically asymptomatic without association with hormonal syndrome)

Note: tumors smaller than 0,5 cm – **microadenoma** – usually clinically asymptomatic

Classification of neuroendocrine neoplasms of GIT valid even for pancreas

Neuroendocrine tumor - NET G1/G2/G3

well differentiated neuroendocrine tumor; low grade (G1/G2) and high grade (G3)

(previously called carcinoids and atypical, malignant carcinoids)

Neuroendocrine carcinoma - NEC G3

poorly differentiated neuroendocrine neoplasm

(neuroendocrine carcinomas, high grade malignant tumors)

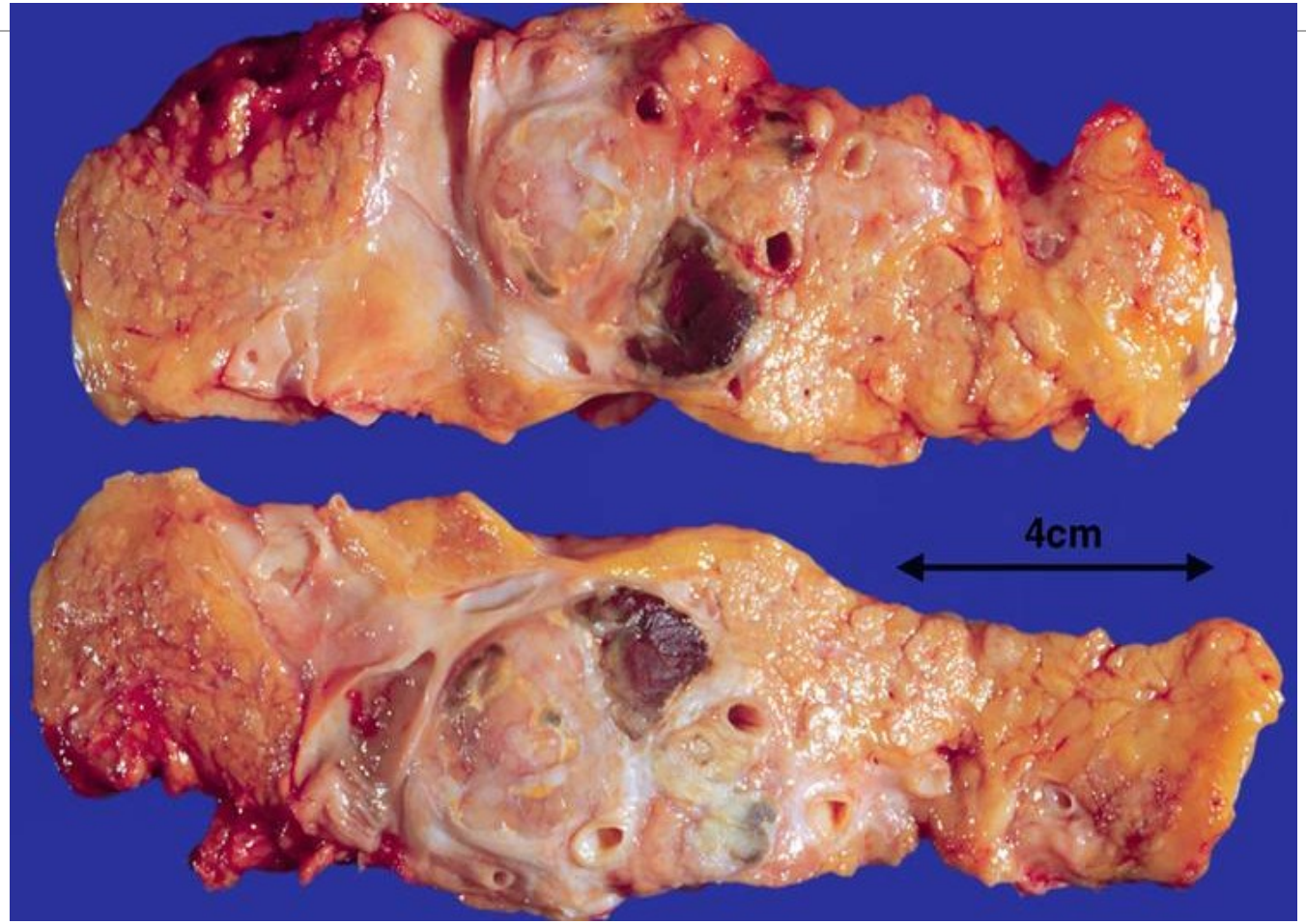
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma

Mixed neuroendocrine nonneuroendocrine neoplasm (MiNEN)

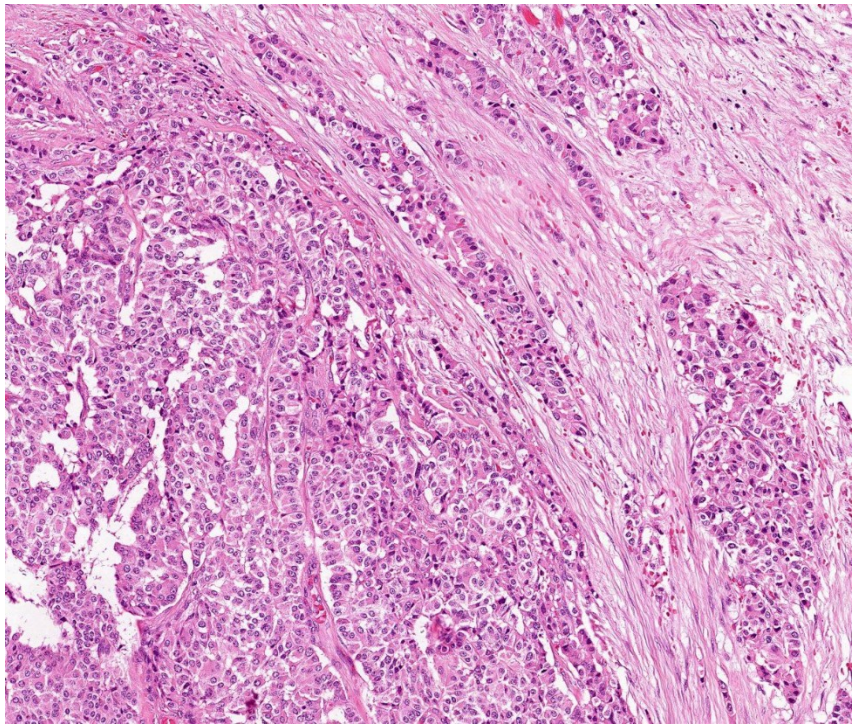
(previously called MANEC)

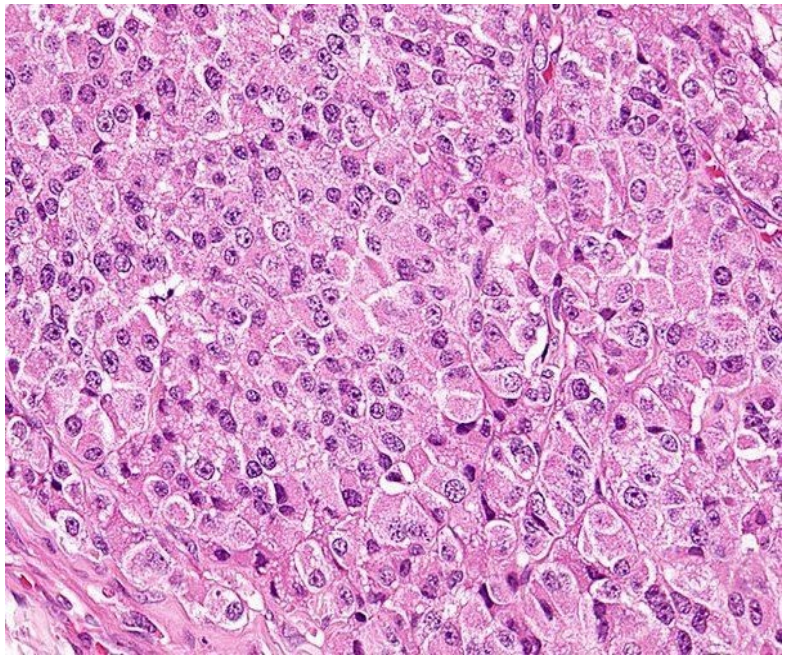
WHO 2010: NET G1/G2; NEC; MANEC)
WHO 2019: NET G1/G2/G3; NEC; MiNEN)

Pancreatic neuroendocrine tumor.



Pancreatic neuroendocrine tumor.





Clinical syndromes associated with functioning neuroendocrine tumors

1) **Insulinoma/hyperinsulinism**…..hypoglycemia

2) **Gastrinoma/Zollinger-Ellison syndrome**……peptic ulcers in atypical localisations

3) **Glukagonoma**….diabetes, erythema migrans, anemia

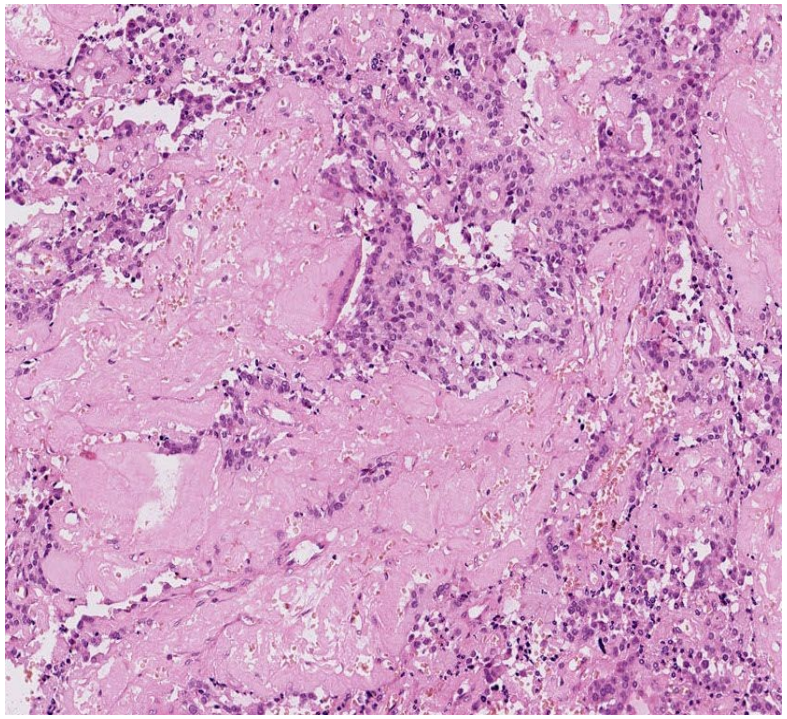
4) **Somatostatinoma**…diabetes, cholelithiasis, steatorhea, hypochlorhydria

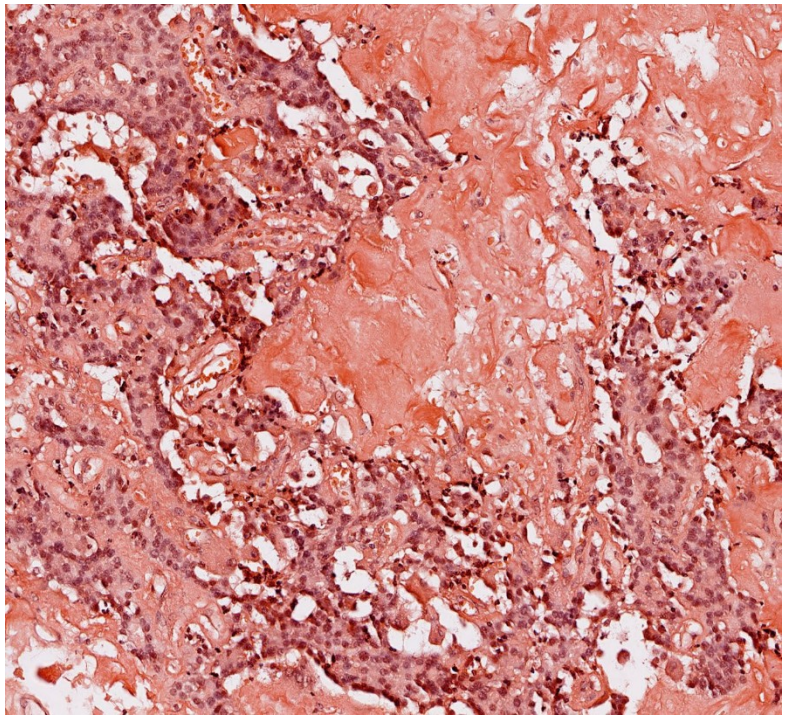
5) **VIPoma/WDHA syndrome**….(„watery diarrhoea, hypokalemia, achlorhydria)

6) **Carcinoid/carcinoid syndrome**

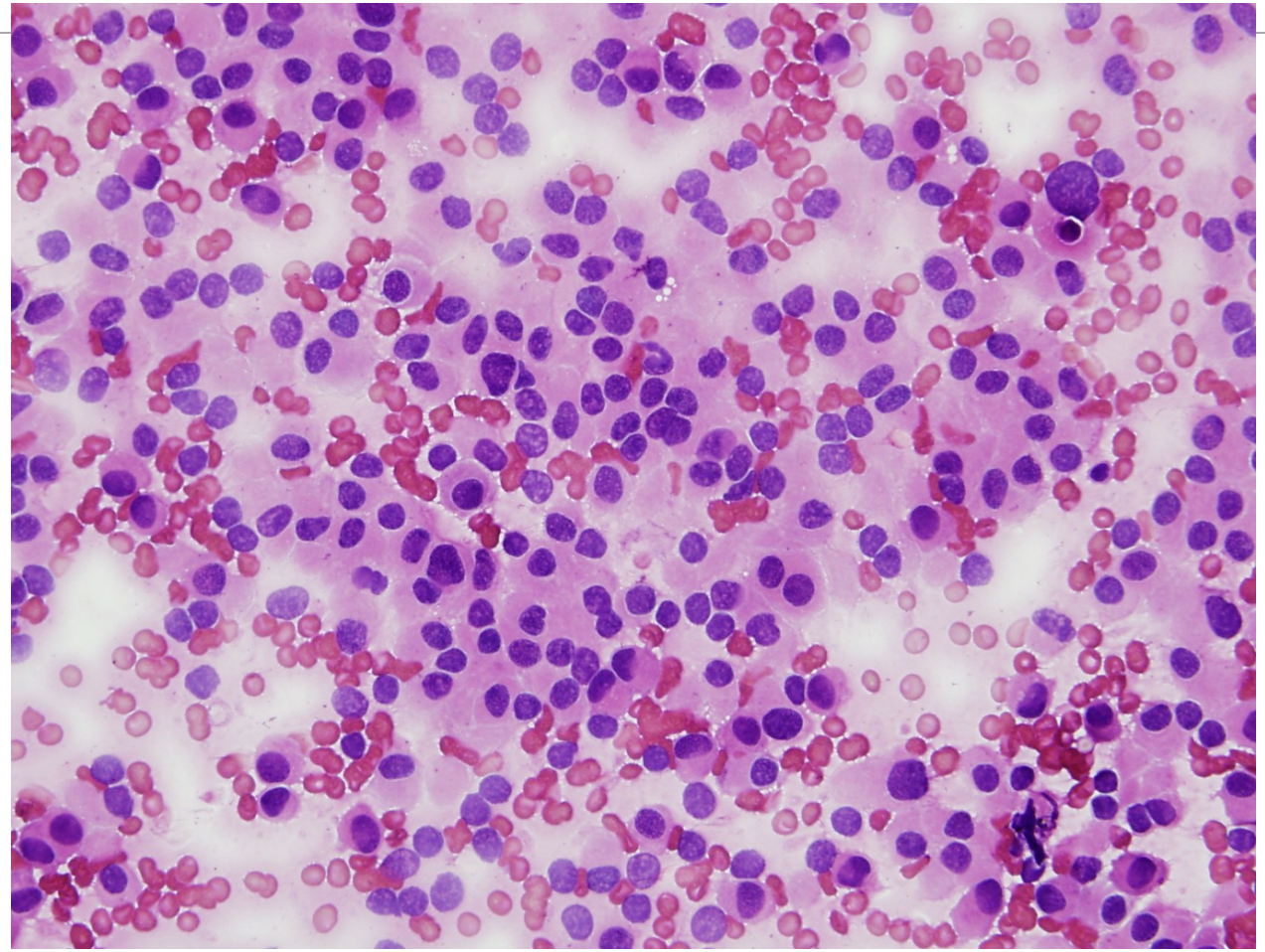
+ tumors with ectopic production of ACTH..Cushing syndrome, MSH..hyperpigmentation, ADH..diabetes insipidus

Amyloid formation in insulinoma.





FNAB – cytology of pancreatic neuroendocrine tumor.



Thank you for your attention….