ORAL/SALIVARY GLAND

TUMORS OF SALIVARY GLAND

→ WHO classification

I Benign epithelial tumors
- i) Pleomorphic adenoma
- ii) Warthin tumor
- iii) oncocytoma
- iv) others (myoepithelioma , basal cell adenoma , keratocystoma , intercalated duct adenoma , striated duct adenoma , sebaceous adenoma)

II Borderline epithelial tumors
- i) Sialoblastoma

III malignant epithelial tumors
- i) mucoepidermoid carcinoma
- ii) Adenocarcinoma
- iii) Carcinoma ex-pleomorphic adenoma
- iv) Adenoid cystic carcinoma
- v) Acinic cell carcinoma
- vi) Salivary duct carcinoma
- vii) Squamous cell carcinoma
- viii) Others (Intraductal carcinoma , clear cell carcinoma , carcinosarcoma , epithelial - myoepithelial carcinoma)

Pleomorphic Adenoma (mixed salivary gland benign tumor)

(mixture epithelial & stromal elements)

small rubbery nodule

- women - 3rd - 6th decade of life
- tumor : solitary , smooth surfaced , nodular , painless , slow growing SSNPS - S³NP
  - ↳ m/c site : parotid region below & front of ear.
- >50% cases : translocation at chromosome 8q12 region involving PLAG1 gene fusion translocation - chromosome 8q12 region → PLAG1 gene fusion

8q12 PLAG1

Pathology :

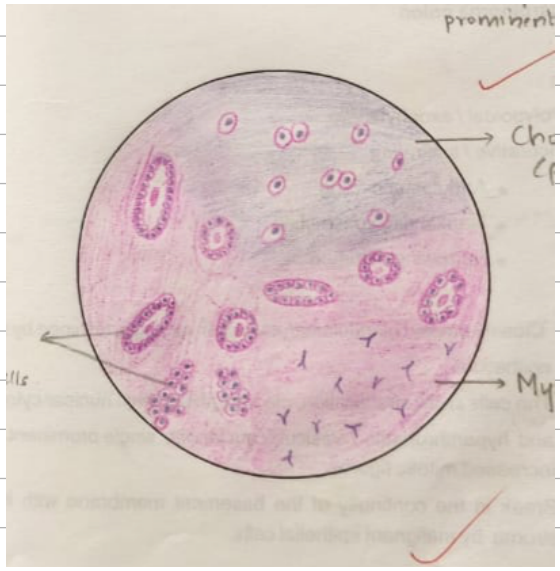
GROSS : Single commonly , rubbery , resilient , rounded , bosselated surface (nodule) well circumscribed (Benign) (pseudocapsule)

C/S : solid , gray white ; semitranslucent , myxoid & shiny areas ; gritch cartilaginous areas
- ↓ resembles mucus ∴ shiny

smooth myxoid cartilaginous → epith, stroma → myxoid matrix

nodule (bosselated surface)

m/s :
- Biphasic - epithelial & mesenchymal (stromal) components
- ducts, acini, tubules, strands & sheets of columnar / cuboidal cells with uniform round or oval nuclei & epithelial
- myoepithelial cells may be present
- myxoid, chondroid, fibrous, osteoid stroma → Stromal tumor

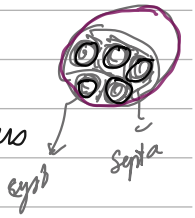


WARTHIN TUMOR

Papillary cystadenoma lymphomatosum or adenolymphoma
- Benign tumor of parotid gland
- Smokers, male, 6th - 7th decades
- Rarely arise in the submandibular or in minor salivary glands.

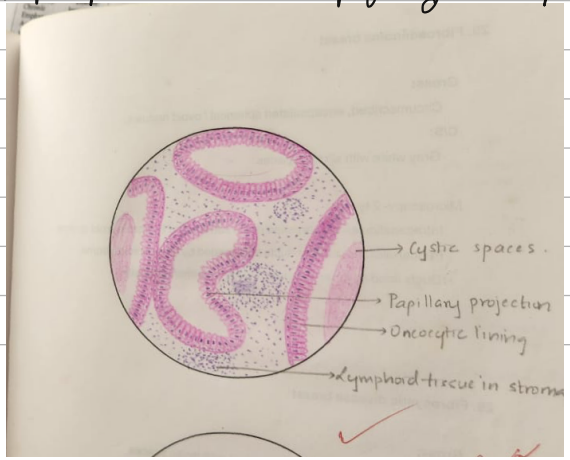
Pathology :

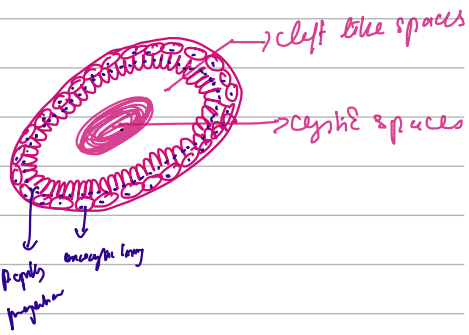
Gross → solitary, well encapsulated, lobulated
round or oval, 3-6 cm, surface pale grey



C/S → multicystic, separated by grayish septa of varying thickness

m/s → cystic spaces & cleft like spaces
oncocytic lining (double layered)
stroma with lymphoid tissue
lymphoepithelial masses projecting into spaces as papillary structures.





GIT SYSTEM

OESOPHAGUS

i) Barrett oesophagus

- Metaplastic condition of lower esophagus
- Stratified squamous mucosal epithelium → columnar epithelium following reflux esophagitis
- m/c - later age
- Caused by factors producing producing gastro-oesophageal reflux disease
- Premalignant condition

→ Barrett epithelium → dysplasia → Carcinoma in situ → oesophageal adenocarcinoma

Pathology :

Grossly : Red & velvety

Hiatus hernia & peptic ulcer at squamocolumnar junction (Barrett ulcer) are frequently associated

Microscopically :

i) Replacement of squamous epithelium by metaplastic columnar cells, along with goblet cells & ~~Paneth cells~~

ii) Accompanied by dysplastic changes of columnar epithelium or glands ranging from low to high grade

iii) Inflammatory changes

iv) ~~Luminal~~ narrowing is the long segment

- High grade dysplasia may progress to invasive adenocarcinoma of oesophagus

STOMACH

i) PEPTIC ULCERS

- Acute peptic (stress) ulcers

- Stress ulcers are multiple, small mucosal erosions.

Etiology :

i) Psychological stress

ii) Pathophysiological stress

- Shock
- Severe trauma
- Septicaemia
- Extensive burns (Curling ulcers)
- Intracranial lesions (Cushings ulcers)

PATHOGENESIS :

* Ischaemic hypoxic injury to the mucosal cells
* Depletion of the gastric mucosal barrier

PATHOLOGY :

Gross → multiple - oval / circular in shape / < 1cm diameter

m/s → shallow - do not invade muscular layer - margins & base may show inflammatory reaction

• Chronic PEPTIC ULCER (Peptic ulcer disease)

- Due to the imbalance b/w noxious influences that damage the mucosa & protective mech that keeps mucosal integrity intact

INCIDENCE - middle aged - m/c in males

ETIOLOGY

* H. pylori gastritis ✓
* NSAIDS - induced ✓
* Acid - pepsin secretions ✓
* Gastritis ✓
* other local irritants - heavily spiced foods, alcohol, cigarette smoking ✓
* Psychological factors - stress, anxiety, fatigue ✓
* Genetic factors - Bl O
* Hormonal factors - eg. elaboration of gastrin by islet - cell tumour in ZES

PATHOGENESIS

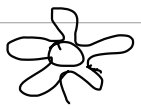
- Duodenal ulcer

↳ high acid - pepsin secretions

* Hypersecretion of gastric acid into the fasting stomach at night which takes place under the influence of vagal stimulation
* Rapid emptying of stomach
* H. pylori gastritis
  - gastric mucosal defence is broken due to urease, protease, catalase
  - Host factors H. pylori - infected mucosal epithelium releases proinflammatory cytokines such as IL's
  - Bacterial factors = cytotoxin - associated gene protein (Cag A) & vacuolating cytotoxin (VacA)

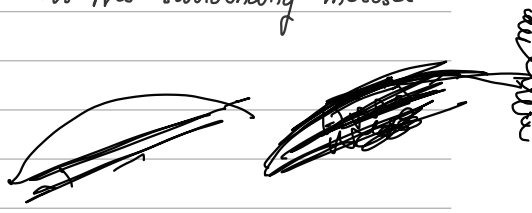
- Gastric ulcer

* Hyperacidity may occur in gastric ulcer due to increased serum gastrin
* Gastritis, bile reflux, smoking etc ↳ ETIOLOGY
* The normally protective gastric mucus 'barrier' against acid - pepsin is deranged.



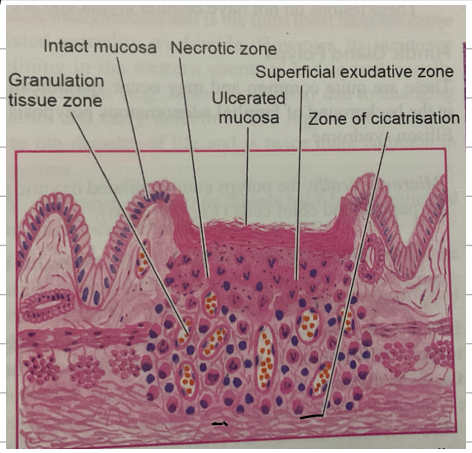
PATHOLOGY

Gross ⇒ solitary, small, round-oval & characteristically 'punched out'.
- Benign ulcers usually have flat margins in level with the surrounding mucosa
- mucosal folds converge towards the ulcer.



M/S ⇒ 4 histological zones

* Necrotic zone : floor of the ulcer
  - composed of fibrinous exudate containing necrotic debris & a few leukocytes
* superficial exudative zone : lies underneath the necrotic zone. The tissue elements here shows coagulative necrosis giving eosinophilic, smudgy appearance with nuclear debris
* granulation tissue zone : merging into the necrotic zone. + fibroblasts + chronic infl cells
  - composed of non-specific inflammatory infiltrate & proliferating capillaries
* Zone of cicatrisation : merging into granulation tissue layer.
  - composed of dense fibrocollagenic scar tissue over which granulation tissue rests.
  - Thrombosed / sclerotic arteries may cross the ulcer which on erosion may result in haemorrhage.



Complications
* Obstruction
* Haemorrhage
* Perforation
* malignant transformation.

	FEATURE	DUODENAL ULCER	GASTRIC ULCER
1.	*Incidence*	i) Four times more common than gastric ulcers ii) Usual age 25-50 years iii) More common in males than in females (4:1)	Less common than duodenal ulcers Usually beyond 6th decade More common in males than in females (3.5:1)
2.	*Etiology*	Most commonly as a result of *H. pylori* infection Other factors—hypersecretion of acid-pepsin, association with alcoholic cirrhosis, tobacco, hyperparathyroidism, chronic pancreatitis, blood group O, genetic factors	Gastric colonisation with *H. pylori* asymptomatic, but higher chances of development of duodenal ulcer. Disruption of mucus barrier most important factor. Association with gastritis, bile reflux, drugs, alcohol, tobacco
3.	*Pathogenesis*	i) Mucosal digestion from hyperacidity most significant factor ii) Protective gastric mucus barrier may be damaged	Usually normal-to-low acid levels; hyperacidity if present is due to high serum gastrin Damage to mucus barrier significant factor
4.	*Pathologic changes*	i) Most common in the first part of duodenum ii) Often solitary, 1-2.5 cm in size, round to oval, punched out iii) Histologically, composed of 4 layers—necrotic, superficial exudative, granulation tissue and cicatrisation	Most common along the lesser curvature and pyloric antrum Grossly similar to duodenal ulcer Histologically, indistinguishable from duodenal ulcer
5.	*Complications*	Commonly haemorrhage, perforation, sometimes obstruction; malignant transformation never occurs	Perforation, haemorrhage and at times obstruction; malignant transformation in less than 1% cases
6.	*Clinical features*	i) Pain-food-relief pattern ii) Night pain common iii) No vomiting iv) Melaena more common than haematemesis v) No loss of weight vi) No particular choice of diet vii) Occurs more commonly in people at greater stress	Food-pain pattern No night pain Vomiting common Haematemesis more common Significant loss of weight Patients choose bland diet devoid of fried foods, curries etc. More often in labouring groups

Gastric carcinoma

- 90% of all gastric malignancy
- 4th - 6th decade of life
- twice more common in women

Etiology ?

i) H. pylori infection

Chronic H. pylori infection
↓
Chronic inflammation of gastric mucosa leading to atrophic gastritis — atrophic gastritis
↓
↓ secretion of acid (hypochlorhydria) & pepsin
↓
favors Bacterial growth & also growth of bacteria that convert nitrate to carcinogenic nitrite. Continuation of chronic inflammation — NO_2 → carcinogenic NO_3
↓
Progression to muscular atrophy — mucosal atrophy
↓
Intestinal metaplasia — metaplasia
↓
Dysplasia — dysplasia
↓
Carcinoma of stomach

ii) Diet & habits
smoked & salted foods

iii) Geographical factors
Japan, Korea, Chile - ↑
US, UK, Canada - ↓

iv) Genetic factors
group A - incidence more

v) Pre-malignant changes in gastric mucosa
- ↑ risk to development of gastric cancer

- Hypo-achlorhydria in atrophic gastritis
- Adenomatous polyps of stomach
- Chronic gastric ulcer

PATHOGENESIS

- mutation in tumor suppressor gene CDH1 (gene encoding for E-cadherin) (autosomal dominant)
  ↳ leads to cell cohesion, infiltration & metastasis

CDH1 → E-cadherin

- Mutation in APC gene leads to increased signalling through the Wnt-β catenin signalling pathway

APC → β-catenin pathway

In familial case ∴ mutation in CDH1 which associated with E cadherin
In sporadic case ∴ loss of E-cadherin due to
- Somatic mutations in CDH1 gene
- Hypermethylation & silencing of CDH1 promoter.

PATHOLOGY

- m/c region of gastric canal formed by lesser curvature, pylorus & antrum.

A) EARLY GASTRIC CARCINOMA
- Cancer limited to mucosa & submucosa
- GROSS: Polypoid, superficial, ulcerated
- HISTOLOGICALLY: It is a typical glandular adenocarcinoma - well differentiated type.

B) ADVANCED GASTRIC CARCINOMA
- Invades muscularis propria
- GROSS:
  i) Ulcerative carcinoma
     - m/c
     - flat, infiltrating & ulcerative growth with irregular necrotic base & raised margin

  ii) Fungating (polypoid) carcinoma
     - cauliflower growth projecting into lumen
     - more often in fundus

  iii) Scirrhous carcinoma
     - Stomach wall is thickened due to extensive desmoplasia
     - Leather bottle stomach

- lumen of stomach reduced
- No ulcus

iv) Colloid carcinoma
- Tumor grows like a mass having gelatinous appearance due to secretion of large amt of mucus

v) ulcer cancer

- HISTOLOGICALLY
(Lauren criteria)

i) Intestinal type : Association with H.pylori gastritis & intestinal metaplasia

ii) Diffuse type

Classification

Intestinal type	Diffuse type
More common	Less common
Elderly	Younger
Male predominance	Male and female equal
Pathogenesis: Mutation of APC gene and beta catenin overactivity + P53 mutation	**Pathogenesis:**CDH1 mutation+P53 mutation
Adhesion (no CDH1 mutation)	Non adhesive(CDH1 mutation)
Gross: polypoid bulky tumor, seen in antrum and lesser curvature	**Gross:** Infiltrate deeply into stomach forming lesion. Flattening of rugal fold and thickening of wall →narrowing of lumen produce leather bottle appearance(linitus plastica)
Microscopy: For cohesive tumor cell forming gland like tubular structure, Apical mucin, vacuoles, mucin present in lumen)	**Microscopy:** Discohesive tumor cell do not form gland. Signet ring cell: Tumor cells contain abundant mucin which expand cytoplasm and pushes nucleus to periphery
Prognosis: Fast prognosis	**Prognosis:** poor prognosis
Spread:	

SPREAD

i) local / direct spread : to muscularis mucosa & serosa

ii) lymphatic spread : supraclavicular lymph node (virchow node) - Troisier's sign
left axillary node (Irish node)
to ovary (Krukenberg)

iii) Blood spread : via portal vein into liver.

3) Carcinoid tumor

Origin : Neuroendocrine organs (endocrine pancreas) & neuroendocrine differentiated epithelial cells of GI tract

Site : GI tract (SI, Stomach)
tracheobronchial tree & lung

morphology :

Gross :- Intramural & submucosal polypoid lesions, ulcerated mucosa, yellow & firm

microscopy : Uniform cells forming islands, trabecular, glands & sheets.
Cells have scanty granular cytoplasm
Min pleomorphism
Anaplasia
Mitotic activity
Necrosis

Clinical features : Carcinoid syndrome
↓
When tumor secretes hormones into non portal venous circulation

flushing of skin, sweating, bronchospasm, colicky abdominal pain, diarrhoea, right sided cardiac valvular fibrosis

4) COLORECTAL CANCER

INCIDENCE : Rise with age , avrg age of patients is about 60 years
M:F - 2:1

ETIOLOGY :

* DIET
  - Low intake of vegetable fibre diet — fibre ↓ animal fat ↑ refined carbohydrate ↑
  - Large amt of animal fat
  - Excessive consumption of refined carbohydrates
* GENETIC SUSCEPTIBILITY - Familial adenomatous polyposis (FAP), hereditary non-polyposis colonic cancer (HNPCC)

i) FAP
  - Autosomal dominant hereditary disease
  - Presence of numerous adenomatous colorectal polyps (1000)
  - Tendency for progression to adenocarcinoma
  - Due to mutations in APC gene located on long arm of chromosome 5

ii) Hereditary non-polyposis colonic cancer (HNPCC) / Lynch syndrome
  - Autosomal dominant
  - Associated with multiple primary cancers @ diff sites including colorectal cancer.
  - mutations in mismatch repair genes (MLH-1, MSH-2, MSH-6, PMS-2) — MSH-2 MSH-6
    ↳ This causes accumulation of mutations in the microsatellite repeats

* HIGH RISK CONDITIONS
  - Inflammatory bowel disease ✓
  - low fibre diet ✓
  - Tobacco ✓
  - Streptococcus bovis

Molecular mechanism : Adenoma - Adenocarcinoma Sequence
- Stepwise progression of normal colonic mucosa into adenomatous polyps.
- Genetic pathways :
  - Mutational pathways
  - Microsatellite instability pathway

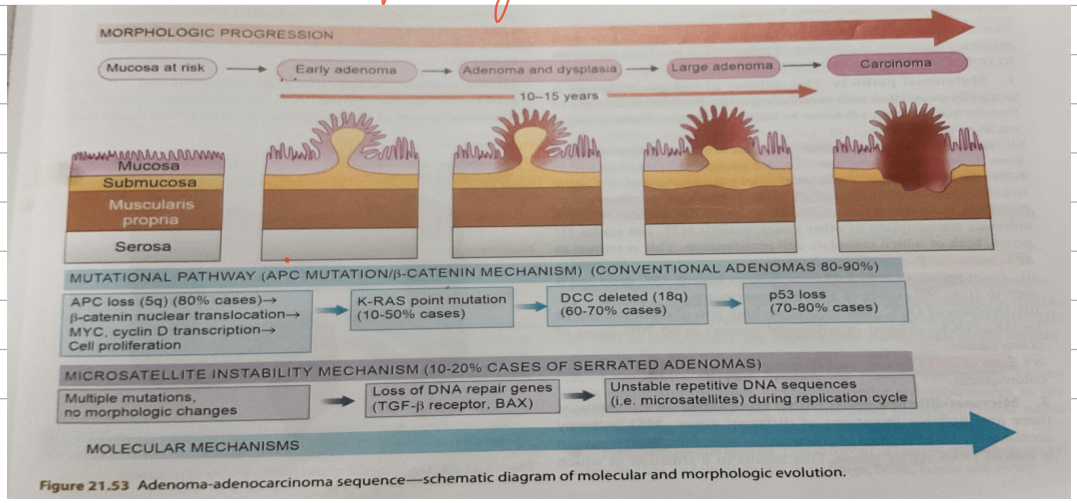


Figure 21.53 Adenoma-adenocarcinoma sequence—schematic diagram of molecular and morphologic evolution.

APC → β catenin

CDH1 → E-cadherin

- mutational pathway
  1) loss of TS - APC ✓

loss of APC ⟶ translocation of β-catenin to the nucleus

↓

Activates transcription of other genes (myc, cyclin D1)

  ii) Point mutation of K-RAS gene ✓
  iii) Deletion of DCC gene
  iv) Loss of TP53 TS gene ✓
  v) Action of telomerase ✓

- microsatellite instability (MSI) mechanism
  - Basic mutation is loss of DNA repair genes
  - TGF-β receptor gene which normally inhibits cell proliferation
  - BAX gene which normally causes apoptosis
    ↳ proapoptotic

} cause unstable repetitive DNA sequences

PATHOLOGY

★ Distribution : Rectum (60%), sigmoid & descending colon (25%), caecum (10%), Ascending colon

★ GROSS :
- Right sided colonic growth : large, cauliflower, soft, friable masses projecting into the lumen (fungating polypoid carcinoma)
- Left side colonic growth : have napkin-ring like annular constriction, ie they encircle the bowel wall & have central ulceration on the surface with slightly elevated margin (carcinomatous ulcers)

★ MIC :
- About 90% of colorectal cancers are adenocarcinomas of varying grades

Familial polyposis colon & Chronic gastritis

SHORT ESSAY

5.Familial polyposis colon (2019)

Autosomal dominant inherited syndrome characterised by 100 to 1000 of polyps through out colorectum.

Mutation of APC gene: which is a tumor suppressor gene and it's product modulate WNT signalling pathway that regulate cell proliferation.

All untreated FAP patients develop colorectal cancer before 30 yrs.

Gardner syndrome: Extraintestinal manifestation of FAP are prominent. , includes osteomas of mandible, skull, long bone, epidermal cyst.

6.Chronic gastritis (2017)

Chronic gastritis is chronic inflammation of stomach associated with mucosal injury.

Causes: H. Pylori infection(most common) , Autoimmune gastritis and less common causes such as radiation injury, chronic bile reflux and mechanical injury.

H. Pylori Gastritis: Transmission by feco-oral route

Mechanism: Flagella, Urease, Adhesins, Cytotoxin.

Host factors: Increase expression of proinflammatory cytokines and Decreased expression of Antiinflammatory cytokines.

Pathogenesis: Antral gastritis and multifocal atrophic gastritis Antral gastritis: localised, lead to increased production leading to peptic ulcer. (H. Pylori infection (urease produced by H. Pylori releases ammonia→ raises gastric pH→ G cells activate→ Gastrin secretion→ hypersecretion of gastric acid))
Atrophic gastritis: With advancing time mucosal atrophy occurs leading to decrease parietal cells and acid production. Leads to production of adenocarcinoma.

Morphology:

Presence of intraepithelial neutrophil and sub epithelial plasma cells.

Loss of parietal cells and chief cells.

Microscopy: lymphoid aggregate

H. Pylori demonstration: Biopsy, special stains(Modified Giemsa stain, Diff- quick stain), Silver stain(Warthin Starry and Genta stain)

Note: H. Pylori positive for catalase, oxidase, urease and culture media includes (Skirrow's media and Chocolate media)

9.Acute Appendicitis

Acute inflammation of appendix.

Etiology: Obstruction, ischemia, infection, hereditary

Pathogenesis: Begin with luminal obstruction →increase intraluminal pressure.

Ischemia injury and stasis favours bacterial proliferation and produce inflammation →produces edema and neutrophil infiltration.

Pressure produced by inflammation and edema lead to development of gangrene and perforation.

Morphology

Swollen and erythematous. Serosa covered by purulent exudate.

Microscopy: Inflammation extent into lamina propria, neutrophil infiltration in lumen. Ulceration can seen in acute gangrenous appendicitis. Fibropurulent reaction in serosa and abscess develop in acute suppurative appendicitis.

Clinical feature: Mc Burney's sign

Complications: perforation, portal venous thrombosis, liver abscess, bacteremia.

11 Gastroesophagal Reflux Syndrome (GERD)

GERD is a chronic diffuse erosive/ulcerative oesophagitis. Normally the oesophageal Lining is protected from acids by

- The abundant submucosal glands in proximal and distal oesophagus which secrete Mucin and bicarbonate
- The tone of LES which prevents reflux of acidic gastric contents

Pathogenesis: Both genetic and environmental factors contribute to cause decreased LES pressure which allows reflux.

Predisposing Factors : Pregnancy, ascites, obesity, delayed gastric emptying and peristaltic disorders, eg: scleroderma

Clinical Features : Heartburn, regurgitation, dysphagia/odynophagia, hypersalivation and atypical intermittent chest pain

Complications: Ulceration, hematemesis, melena, stricture formation and Barret oesophagus **Diagnosis:** X-ray and endoscopy

Feature	Non neoplastic polyps	Neoplastic Polyps
Frequency	More common	Less common
Number	Often sporadic	Sporadic &Multiple
Familial predisposition on	No	YES
Types	Hyperplastic,hamartomatous,Juvanile,Inflammatory,Lymphoid	Tubular,Villous,Tubulovillous and Serrated adenomas
Familial Syndromes	Juvenile polyposis syndrome	Familial polyposis coli
Biological Behavior	Always benign	Shows malignant potential

HEPATOBILIARY SYSTEM

CIRRHOSIS

Structurally abnormal nodules + fibrosis

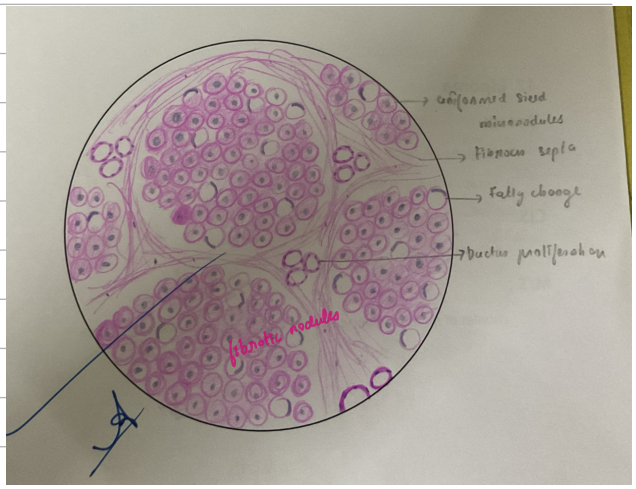
Diffuse process characterized by fibrosis & the conversion of normal liver architecture into structurally abnormal nodules

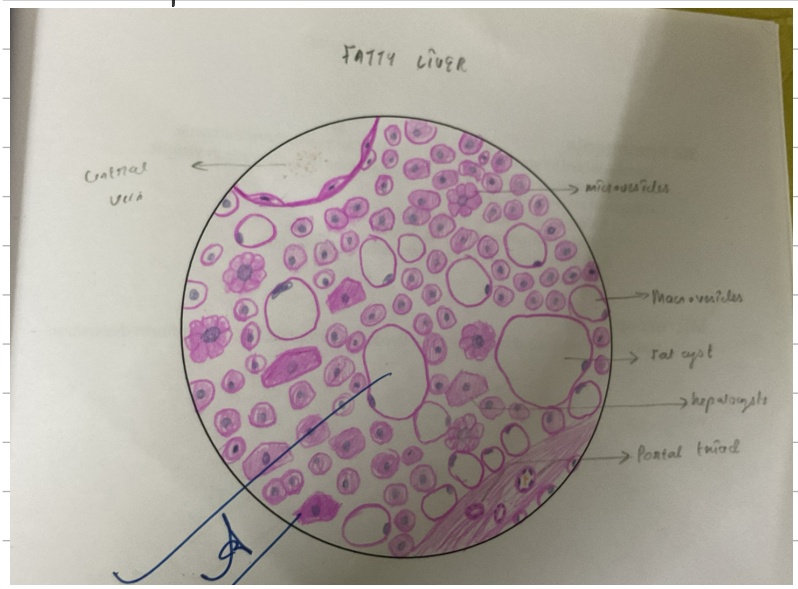
H features ☺
- ★ Involves entire liver
- ★ hepatic parenchyma is disorganized
- ★ formation of nodules separated from one another by irregular bands of fibrosis
- ★ occurs following hepatocellular necrosis of varying etiology

CLASSIFICATION

A) MORPHOLOGICAL
- Micronodular (< 3mm)
- Macronodular (> 3mm)
- Mixed

B) ETIOLOGICAL
- Alcoholic cirrhosis ✓
- Post-necrotic cirrhosis (hep-B & C) ✓
- Biliary cirrhosis ✓
- Pigment cirrhosis in haemochromatosis ✓
- Non-alcoholic fatty liver disease cirrhosis ✓
- Wilson disease cirrhosis ✓
- α-1 AT deficiency cirrhosis
- Cardiac cirrhosis ✓
- Indian childhood cirrhosis ✓
- AI hepatitis cirrhosis ✓





Pathology

i) Alcoholic steatosis (fatty liver)

Gross → enlarged, yellow, firm, smooth & glistening capsule

Microscopically :-

Initial microvesicular droplets of fat → macrovesicular fat

(may develop) fat cysts develop due to rupture of fat containing hepatocytes.

ii) Alcoholic hepatitis (necrosis - mallory → hepatitis)

Histologically :-

- Hepatocellular necrosis : hepatocytes undergo degeneration & necrosis
- Mallory bodies : Intracytoplasmic eosinophilic inclusions seen in perivenular location within
  Swollen & ballooned hepatocytes (aggregates of prekeratin)
  Stained by : Masson trichrome
) Also found in 1° biliary cirrhosis, Wilson disease, Indian childhood necrosis
- Inflammatory response - chiefly consists of polymorphs.

iii) Alcoholic cirrhosis

Gross : micronodular, large, fatty (2ry) liver → even shaped, non-fatty, macronodular
Resembling post-necrotic cirrhosis
Surface of liver studded with diffuse nodules ⇒ hobnail liver

Microscopy :

i) Nodular pattern
ii) Fibrous septa : Divides hepatic parenchyma into nodules
iii) Hepatic parenchyma : hepatocytes in the islands of surviving parenchyma undergo slow proliferation forming regenerative nodules
iv) Necrosis, inflammation & bile duct proliferation

PATHOGENESIS

Cirrhosis ? combⁿ of few processes:

hepatocellular necrosis → healing by fibrosis → formⁿ of compensatory regenerative nodules → changes in vascular pattern

Destrⁿ in hepatocytes

↓

Collapse of normal lobular parenchyma

↓

fibrosis around necrotic liver cells

(portal-central, portal-portal, both)

Fibrosis done by:

↑ed synth of Type I & III collagen

↓

Basement collagen, fibronectin & laminin ↑

↓

deposited in excessive amt in area of liver damage

Stimulants for fibrosis: HF, vasoactive factors, cytokines, lymphokines, chemokines

Regenerative nodules:

Surviving hepatocytes act as stimulants

↓

growth & proliferation of more hepatocytes

(within fibrous nodules - regenerative nodules)

Vascular reorganisation:

Due to damaged hepatic parenchyma & formⁿ of fibrous nodules, new vessels formed in the fibrous septa are connected to the vessels of portal triad.

↓

Blood is drained into hepatic vein

↓

∴ blood bypasses the hepatic parenchyma

PATHOGENESIS

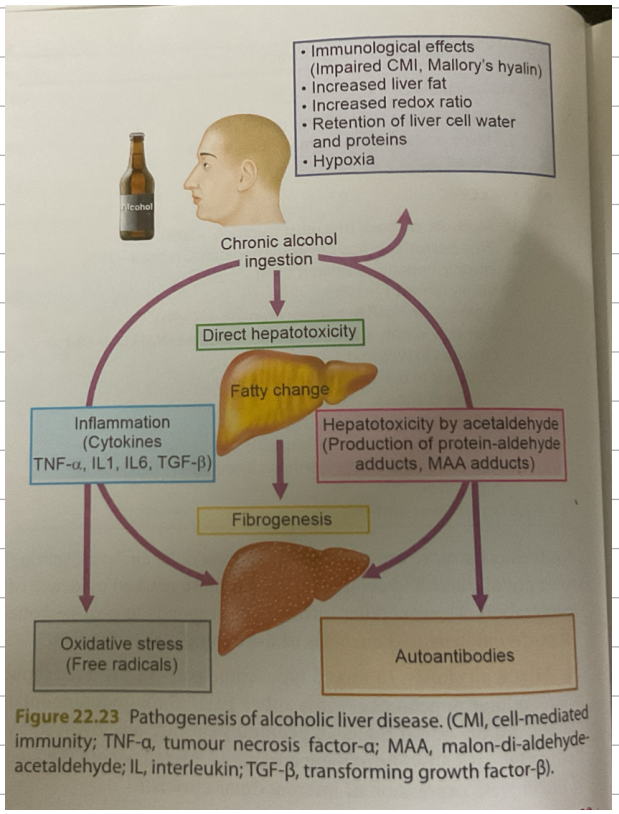


Figure 22.23 Pathogenesis of alcoholic liver disease. (CMI, cell-mediated immunity; TNF-α, tumour necrosis factor-α; MAA, malon-di-aldehyde-acetaldehyde; IL, interleukin; TGF-β, transforming growth factor-β).

GALL STONES / CHOLELITHIASIS

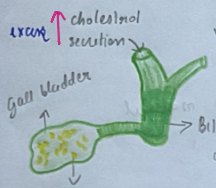
TABLE 22.16 Features of gallstones.

	TYPE AND FREQUENCY		COMPOSITION	GALLBLADDER CHANGES	APPEARANCE
1.	*Pure gallstones* (10%)		i) Cholesterol	Cholesterolosis	Solitary, oval, large, smooth, yellow-white; on C/s radiating glistening crystals
			ii) Bile pigment	No change	Multiple, small, jet-black, mulberry-shaped; on C/s soft black
			iii) Calcium carbonate	No change	Multiple, small, grey-white, faceted; C/s hard
2.	*Mixed gallstones* (80%)		Cholesterol, bile pigment and calcium carbonate in varying combination	Chronic cholecystitis	Multiple, multifaceted, variable size, on C/s laminated alternating dark-pigment layer and pale-white layer
3.	*Combined gallstones* (10%)		Pure gallstone nucleus with mixed gallstone shell, or mixed gallstone nucleus with pure gallstone shell	Chronic cholecystitis	Solitary, large, smooth; on C/s central nucleus of pure gallstone with mixed shell or vice versa

→ Choledocholithiasis (in common bile duct)

3) Outline the underlying pathogenesis

Pathogenesis of cholesterol stones

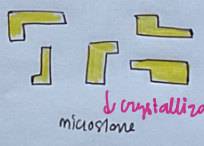


SUPERSATURATION

Promote nucleation
- gallbladder hypomotility
- mucin secretion
- Calcium

Inhibit nucleation
- Apolipoproteins
- lecithins

NUCLEATION → process of molecules to cluster together to form small solid particles



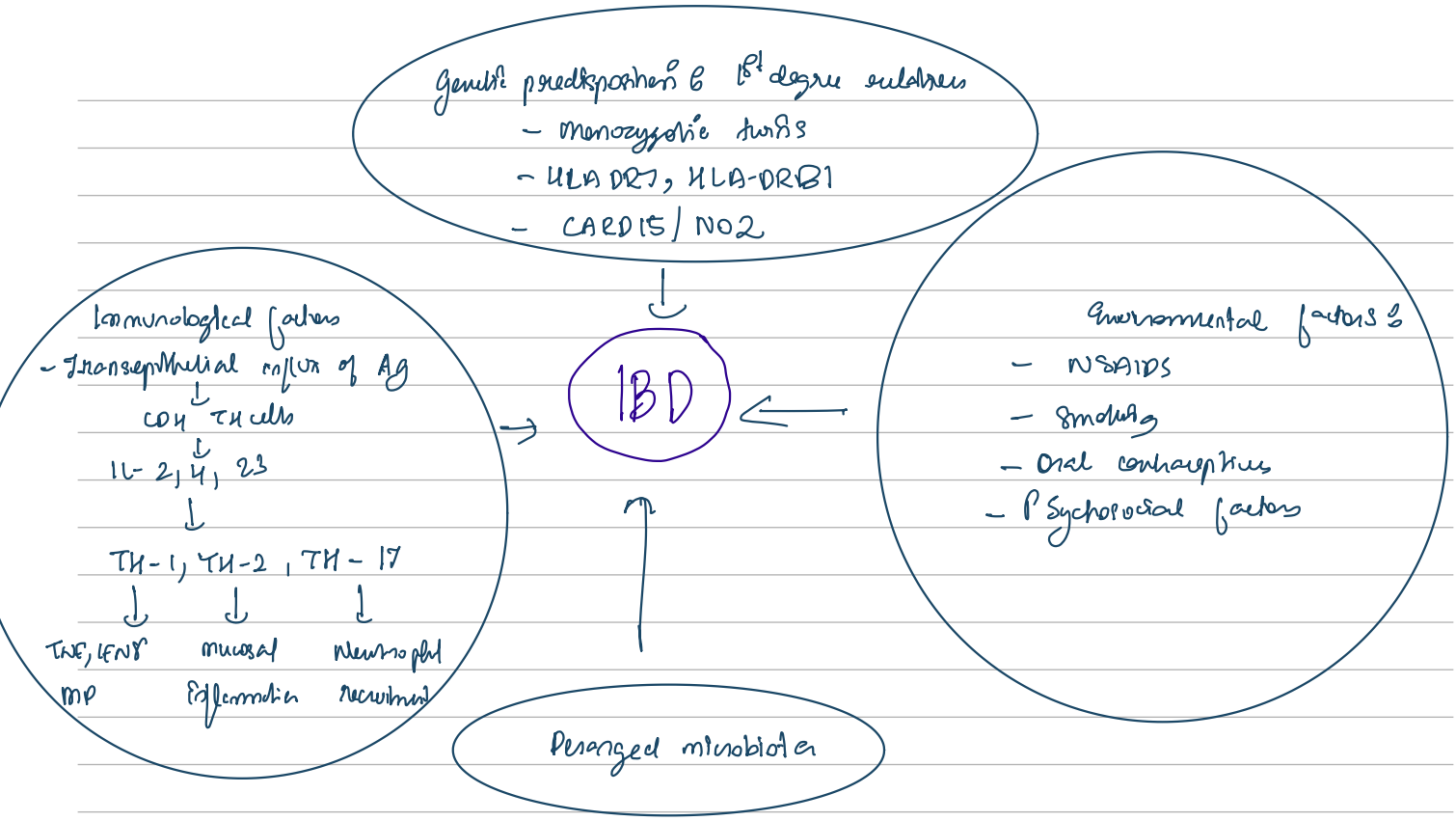
formation of cholesterol monohydrate crystals.

↓ crystallization

microstone

crystallization forming microstones

↓ Accretion (grows in size)


Genetic predisposition & 1st degree relatives
- monozygotic twins
- HLA DR1, HLA-DRB1
- CARD15 / NOD2
Immunological factors
- Transepithelial influx of Ag
CD4 TH cells
IL-2, 4, 23
TH-1, TH-2, TH-17
TNF, IFNγ
MP
mucosal inflammation
Neutrophil recruitment
IBD
Environmental factors
- NSAIDS
- Smoking
- Oral contraceptives
- Psychosocial factors
Deranged microbiota