Vascular Disorders

Arteriosclerosis

Arteriosclerosis means hardening of the arteries
↓
- arterial wall thickening and loss of elasticity.

arteriosclerosis
↓
4 patterns.

- arteriolosclerosis
- atherosclerosis
- Monckeberg medial calcific sclerosis
- fibromuscular intimal hyperplasia.

① arteriolosclerosis

- affects small arteries & arterioles
- 2 types

hyaline arteriolosclerosis
↓
- pink glassy appearance.

hyperplastic arteriolosclerosis
↓
onion skinning
↓
smooth muscle & fibroblasts.
↓
malignant HTN

② Monckeberg's Sclerosis.

- Calcific medial Degeneration.
- Calcification in Tunica media of muscular arteries
- old age - >50 years.
- Calcifications are non-obstructive with no clinical consequence.

③ Fibromuscular Intimal Hyperplasia.

- occurs in muscular arteries larger than arterioles.
- occurs after
↓
① Inflammation
↓
{arteritis, transplant associated arteriopathy}.

② mechanical injury.
{stents, balloon angioplasty}.

④ Atherosclerosis.

- Intimal disease.

Q
Atherosclerosis (Essay)
- definition.
- risk factors
- etiopathogenesis
- morphology (SN)

Atherosclerosis.

- atherosclerosis is defined as hardening and narrowing of medium to large sized vessels due to fat and plaque deposition resulting in coronary, cerebral and peripheral vascular disease, causing significant morbidity & mortality.
- Characterized by intimal lesions called atheromas AKA → atheromatous / atherosclerotic plaques.

Plaque.
- rupture → superimposed thrombosis
- mechanical obstruction to blood flow
- ischaemic injury and weakening of vessel wall → aneurysmal dilatation.

Risk factors

① Non-modifiable risk factors.
- genetic abnormalities ✓
- increasing age ✓
- family history ✓
- male gender ✓

② modifiable risk factors.
- hyperlipidemia ✓
- Hypertension ✓
- diabetes mellitus ✓
- Cigarette smoking ✓

② Additional Risk factors
- ✓ Inflammation
- ✓ hyperhomocysteinemia
- ✓ Lipoprotein A
- ✓ metabolic syndrome
- ✓ ↑ CRP level
- ✓ obesity
- ✓ sedentary lifestyle

✓ Genetic factors
- history of "familial hypercholesterolemia"
- Familial predisposition → polygenic.
  - genetic
  - environmental
  - lifestyle factors.

✓ Age.
- with age, disease progresses.
- becomes clinically apparent between 40-60 years.
- Risk of MI 9 5 times in this age group.

✓ Gender.
- pre-menopausal women are relatively protected compared to men {due to estrogen}.
- post-menopausally, incidence is equal / even ↑ as compared to men.

- Estrogen therapy → young pre menopausal → ↓ risk of atherosclerosis.
- Estrogen therapy → old, post menopausal → ↑ risk of atherosclerosis.

Hyperlipidemia

- major risk factor.

Sr cholesterol.

- LDL. → Ch → peripheral tissue
- HDL. → peripheral tissue → liver → Bile - Excretion.

✓ Omega 3 F.A → Beneficial.

✓ transfat → Bad.

- hypothyroidism ↑ Sr cholesterol.
- obesity & smoking ↓ HDL.

Hypertension (major risk factor)

- can alone ↑ risk of MI/IHD by 60%
- chronic HTN → most common cause of ↑ risk of IHD

Cigarette Smoking

most Impt avoidable cause of Atherosclerosis

x2 risk.

Diabetes mellitus

- Induces hypercholesterolemia.
- MI Incidence is twice as high.
- ↑ Incidence of stroke.

Inflammation

- Intimately linked with atherosclerosis
- CRP is the most reliable marker of Inflammation. → predict risk of MI
- CRP → acute phase reactant made by liver.
- plasma CRP → strong Independent marker for Risk of MI / stroke / PVD.

Hyperhomocysteinemia

- Inborn errors of metabolism. autosomal recessive.
- ↑ circulating homocysteine levels.
- premature vascular disease.

Lipoprotein A

- Independent RF altered form of LDL that contains APO B100 linked to APO-A
- structurally Similar to plasminogen

PATHOGENESIS

- atherosclerosis is a chronic inflammatory & Healing response of arterial wall to Endothelial Injury.

Steps of atherosclerosis.

① Endothelial Injury & dysfunction.

② accumulation of lipoprotein {LDL & it's oxidised form}

③ monocyte adhesion to endothelium.
↓
migrate to Intima
↓
transformation into macrophages & Foam cells.

④ platelet adhesion

⑤ factors release from activated platelets, macrophages

↓

Induce smooth muscle recruitment.

⑥ Lipid accumulation both Extracellularly and within cells. {macrophages & smooth muscle cells}

⑦ Calcification of ECM & Necrotic debris late in pathogenesis.

Endothelial Injury

3 most impt causes

① Hemodynamic disturbance.

② Inflammation.

③ hypercholesterolemia.

pathogenesis

- Atherosclerosis develops as a chronic (inflammatory and healing) response of arterial wall to Endothelial injury

Sequence of pathogenesis.

① Endothelial injury & dysfunction

Causes: Hemodynamic disturbance.
→ branching points
→ posterior wall of abdominal aorta.

Risk factors: hyperlipidemia, hypertension, toxin from cigarette smoke, glycation products in

Effect of Endothelial injury.

→ Leukocyte {mainly monocyte} adhesion to endothelium.

→ Increased vascular permeability.

→ platelet adhesion.

→ movement of LDL across endothelium into intima.

② Migration of Monocytes into Intima

- locally produced chemokines allows penetration of endothelial layer.
- monocytes migrate to Intima.
↓
transformed into macrophages.

③ Lipid accumulation in Intima

penetration of endothelium by LDL from blood
↓
LDL accumulates within the Intima.

- LDL is oxidised by oxygen free radical, produced by macrophages, dysfunctional endothelial cells.

④ formation of foam cells & activation of macrophages.

macrophages engulfs
↓
Lipoproteins & oxidized LDL.
↓ cytoplasm becomes foamy.
foam cells.

- Some foam cells.
  ↓ undergo.
  apoptosis
  ↓
  release lipids.
  ↓ forms.

necrotic core in atheromatous plaque.

- oxidized LDL cause
  ↓
  activation of macrophages.
  ↓ produces.

(1) cytokines (TNF) ↑ WBC adhesion.

(2) chemokine → monocyte accumulation.
{monocyte chemotactic protein 1}

(3) ROS → ↑ LDL oxidation.

(4) Growth factors → Stimulate
① Smooth muscle cell proliferation and.
② extracellular matrix synthesis

(5) migration of smooth muscle cells into intima.
↓ due to.
Growth factors → PDGF.
FGF
TGF-α.
↓
released from
- macrophages
- platelets
- endothelial cells.

(6) Smooth muscle cell proliferation in intima & ECM production

- due to growth factors.
- Smooth muscle cell may also engulf oxidized LDL
  ↓ forms.
  foam cells

(7) Lipid Accumulation

- intracellularly & extracellularly.
- Intra - within macrophages & smooth muscle cells.
- extra - derived from transudation from vessel wall.

Morphology

① fatty streaks

- earliest lesions of atherosclerosis.

GROSS - small flat yellow lesions in intima (~1mm).
↓
which may coalesce to form long streaks (1cm).
↓
only mildly / flat elevated
↓
doesn't disturb blood flow.

MC / lipid filled foamy macrophages in intima.

Atherosclerotic plaque

- Intimal thickening & lipid accumulation.
- yellow, raised lesions
- any superimposed thrombus is reddish brown in colour.
- on Cross section,
  ↓
  eccentric lesions.

GROSS.

① Sites
A
C
P
D T
I
C.

② Size - 0.3 to 1.5 cm d.
8-12 and
↓
advanced lesions

③ shape - irregular with well-defined borders.

④ distribution:
focal / patchy
↓
eccentric on cross section.

Composition: soft, yellow, core of lipid covered by a white fibrous cap.

microscopy

4 principal Components:

① cells → Smooth muscle cells, macrophages, T cells.

② ECM → Collagen, elastic fibres, Proteoglycans.

③ Intracellular & Extracellular lipid.

④ calcification in Later stage of plaque

these Components occur in 3 regions:

① Superficial fibrous cap.

→ Composed of smooth muscle cells & Collagen {Blue in masson's trichrome}.

② Necrotic core.

- deep to fibrous cap & contains:

- lipid - cholesterol, cholesterol esters
  ↓
  empty needle-shaped cleft like spaces.

- debris from dead cells.
- Foam cells
- other: fibrin, organized thrombus

③ shoulder.

- breach side of cap
- more cellular & contains macrophages, SMC, & T cells.

Neovascularization

MORPHOLOGY

GROSS

Site : abdominal aorta
coronary artery. etc.

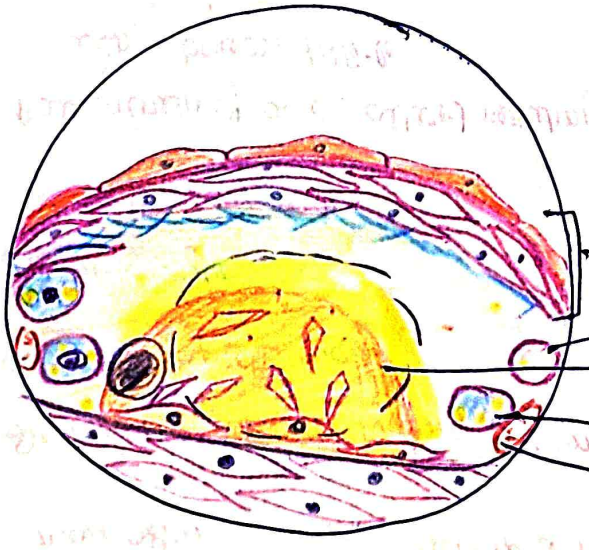
Color : yello-white
red-brown – if thrombus formation

Size : 0.3 – 1.5 cm →
coalesce to form large lesions.

Distribution : focal / patchy.

Cut section : soft, yellow, grumous core of lipid covered by white fibrous cap.

MICROSCOPY



Fibrous cap :

- consists of smooth muscle cells & collagen.

Necrotic core :

Cholesterol & cholesterol esters
→ Needle clefts → cholesterol clefts.

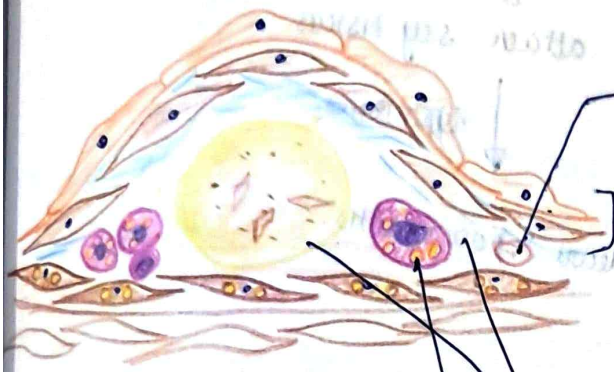
- debri from dead cells.
- foam cells – lipid laden SMC & Ma.

Shoulder :

- cellular area
- consists of SMC, Ma, T-lymphocytes.

Neovascularization

ATHEROSCLEROTIC PLAQUE.



- Neovascularization.
- Fibrous cap. → smooth muscle cells, collagen, elastin.
- Necrotic core → cholesterol & CE in clefts
  - necrotic debris.
  - foam cells.
- Shoulder. Cellular area : macrophages, T cells, SMC.
- foam cells