Pathology of vascular diseases
Lecture 1

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- Vascular disorders are responsible for more morbidity and mortality than any other category of human diseases.
- Although the most clinically significant lesions typically involve arteries, venous diseases also occur.
- Vascular pathology results in disease via three principal mechanisms:

1- Progressive narrowing of the lumen associated with progressive ischemia of the relevant tissues.
2- Thrombosis associated with partial or complete luminal obstruction and/or embolism.
3- Aneurysmal dilatation that may eventuate in rupture with ischemic and destructive consequences.
4- in addition to inflammation (vasculitis) and neoplastic tumors.

Normal histology and anatomy
Basic components of the wall of blood vessels are including;
1. Endothelial Cells (ECs) &Smooth Muscle Cells SMCs
2. Extracellular Matrix (ECM).
(from lumen to outside) These components are arranged into three layers:
Intima: consist of single layer of endothelial cells.
Media: consist of smooth muscle cells.
Adventitia: Consist of connective tissue, Vasa Vasorum & nerve fibers.

According to their size & structure, arteries can be classified into the followings:
1- Large or elastic arteries including: the aorta, the major branches of the aorta subclavian, common carotid, and iliac, and pulmonary arteries have elastic fiber rich media (expand during systole & recoil during diastole)

2- Medium-sized or muscular arteries including: smaller branches of the aorta (e.g coronary and renal arteries), their media is composed predominantly of SMC, which regulate regional blood flow & blood pressure by vasoconstriction & vasodilatation.

3- Small arteries (≤2 mm in diameter) and arterioles (20 to 100 μm in diameter) within tissues and organs.
Their media consist of smooth muscles, contraction cause changes in diameter that regulates systemic arterial blood pressure, (as much as small vessel, the higher resistance & pressure).
So the arterioles are the principals' points of physiologic resistance (control the blood pressure).

Congenital Anomalies:
Among many congenital vascular anomalies, some of them are particularly significant, (although not necessarily common and may be asymptomatic)

1- Berry aneurysms occur in cerebral vessels; when ruptured, these can cause fatal intracerebral hemorrhage.

2-Arteriovenous fistulas they are abnormal, typically small, direct connections between arteries and veins that bypass the intervening capillaries.

Causes: Could be congenital or acquired, acquired causes are:

1- Rupture of an arterial aneurysm into adjacent vein.
2- Penetrating injuries through the wall of artery & vein.
3- Inflammatory necrosis of adjacent vessels.
4- Intentionally created arteriovenous fistulas in treatment of chronic renal failure by dialysis.

Complications:
-Ruptured and cause sever hemorrhage.
-Large arteriovenous fistulas become clinically significant by shunting blood from the arterial to the venous circulations and forcing the heart to pump additional volume result in high-

output cardiac failure.

1- Fibromuscular dysplasia is a focal irregular thickening in medium and large muscular arteries (e.g renal, carotid and vertebral vessels).

The cause is unknown, segments of the vessel wall are focally thickened by a combination of medial and intimal hyperplasia and fibrosis resulting in luminal stenosis, in renal arteries, it can be a cause of renovascular hypertension. Immediately adjacent vessel segments can have markedly attenuated media (a "string of beads" appearance ON ANGIOGRAPHY) leading to vascular *(aneurysms)* that can rupture.

Arteriosclerosis:

This generic term refers to a group of disorders having in common thickening and loss of elasticity of arterial walls and thus leading to sclerosis i.e. hardening of the wall. Under this heading come three distinctive morphological variants, namely:

1- Atherosclerosis the most frequent & important form

2- Monckberg medial calcific sclerosis

3- Arteriolosclerosis: (Disease of small arteries & arterioles). Most often in patients with hypertension & diabetes mellitus.

ATHEROSCLEROSIS

This disease is responsible for more deaths and serious complications than any other disorder (roughly half of all deaths).

This is because its prime targets are vital arteries, namely the coronaries, cerebral arteries, & the aorta so its major consequences are:

1- Myocardial infarction (alone responsible for about 25% of all deaths)

2- Cerebral infarction

3- Aortic aneurysm

- Atherosclerosis is "a disease primarily of large elastic arteries and medium sized muscular arteries. Its basic lesion is the **atheroma.**
- Atheroma (fibro-fatty plaque) is a raised patch within the

intima having a core of lipid (mainly cholesterol and its esters) and a cap of fibrous tissue".

- Examples of large elastic arteries are aorta, carotid, and the iliac arteries, & examples of medium-sized muscular arteries are the coronaries and popliteal arteries.

Risk factors of atherosclerosis:

Risk factors of atherosclerosis are expressed largely in terms of the incidence of deaths caused by ischemic heart disease (IHD). This is because atherosclerosis does not by itself produce signs and symptoms but its prevalence is detected by its effects on the most commonly involved arteries which are the coronaries. Risk factors that predispose to atherosclerosis and the resultant IHD can be divided into two main groups

Major

A. Potentially modifiable (controllable)

1. Hyperlipidemia
2. Hypertension
3. Cigarette smoking
4. Diabetes mellitus
5. Inflammation

Non modifiable

1. Genetic abnormalities
2. Family history polygenic relating to small effects of many shared alleles common to a family or population.
3. Increasing age
4. Male gender

Minor (additional risk factors)

As many as 20% of all cardiovascular events occur in the absence of major risk factors. Also, more than 75% of cardiovascular events in previously healthy women occur with normal LDL cholesterol levels m so additional risk factors re proven or suspected including:

1. Inflammation: (C reactive protein) a strong, independent marker of risk for myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death and its level decrease with smoking cessation, weight loss, exercise, and statin administration.

2. Hyperhomocystinemia

3. Metabolic syndrome: associated with central obesity and characterized by insulin resistance, hypertension, dyslipidemia (elevated LDL and depressed HDL), hypercoagulability and proinflammatory state.
4. Lipoprotein (a)
5. Factors affecting hemostasis e.g., elevated plasminogen activator inhibitor 1, thrombin are potent predictors of risk for myocardial infarction through both procoagulant and proinflammatory effects.
6. Lack of exercise;
7. Stressful lifestyle (type A personality)
8. Obesity

Pathogenesis of atherosclerosis

The most widely accepted theory of pathogenesis is called the response to injury hypothesis.

This theory states that:

- Atherosclerosis is a chronic inflammatory and healing response of the arterial wall to endothelial injury (endothelial dysfunction)
- This injury increases endothelial permeability to plasma lipids as well as permitting blood monocytes and platelets to adhere to the endothelium.
- Monocytes subsequently enter the intima, transform into macrophages and accumulate lipids to become foam cells.
- Factors released from both platelets and macrophages cause migration of smooth muscle cells from the media into the intima with eventual synthesis and
- accumulation of collagen.
- Macrophages produce toxic free oxygen radicals (ROS) that oxidize (modify) LDL in the lesions. This oxidized LDL is considered atherogenic, as it is
  - Chemotactic to blood monocytes
  - Inhibits macrophage motility thus preventing them from leaving the atheroma.
  - Cytotoxic to endothelial cells increasing their permeability

This suggests that antioxidants e.g. vitamin E and ß-carotene may be effective in preventing atherosclerosis by reducing LDL oxidation.

The three most important causes of endothelial dysfunction are

1. Hemodynamic disturbances plaques tend to locate at the ostia of exiting vessels, branch points, and along the posterior abdominal aorta where flow patterns are disturbed and nonlaminar.

2. Hypercholesterolemia: Evidences that hypercholesterolemia important are:

a. The dominant lipids in atheromatous plaques cholesterol

and cholesterol esters.

b. Hyperlipoproteinemia are associated with accelerated atherosclerosis (i.e familial hypercholesterolemia can precipitate myocardial infarctions before age 20 . Similarly, accelerated atherosclerosis occurs in animal models with deficiencies in apolipoproteins or LDL receptors.

c. A significant correlation between the severity of atherosclerosis and the levels of total plasma cholesterol or LDL.

d. Lowering serum cholesterol by diet or drugs slows the rate of progression of atherosclerosis (regression of plaques, and reduces the risk of cardiovascular events)

Inflammation: Accumulation of lipid laden macrophages lead to production of IL1------recruit and activate macrophages &T lymphocytes-------- Activated macrophages release reactive oxygen species-------- LDL oxidation and elaborate growth factors (SMC proliferation.) while

Activated T lymphocytes release interferon-γ which activate macrophages, ECs and SMCs. So many lesions of atherosclerosis related to the chronic inflammatory reaction in the vessel

Pathological features (morphology) of atherosclerosis

Pathology of atherosclerosis passes in stages:

1- Fatty streaks: characterized by intimal thickening & lipid accumulation

- Components of Fatty streaks: These streaks are composed of lipid laden foam cells.
- Gross: multiple yellow, fat spots (fatty dots) less than 1mm in diameter that coalesce into large streaks of 1cm or more.

- Although fatty streaks regards as the precursor of atheroma, not all fatty streaks are tend to become advanced lesions (plaques).
- These lesions found to present in aortas of infants, and are present in virtually all adolescents, even those without known risk factors.

2- Atheromatous Plaques:

- These are raised focal lesions within the intima, also called fibro fatty plaque (atheroma).

These plaques consist of two parts:

I- Core: soft, yellow core, consist of cholesterol & cholesterol esters.

II- Cap: Firm, white fibrous cap.

The above mentioned components may occur in varying proportions in different plaques, for e.g. some plaques may be composed mostly of smooth muscle cells and fibrous tissue (fibrous plaques).

- These plaques are varied in their size from 0.3 to 1.5cm in diameter, sometimes they coalesce to form large masses protrude into lumen.
- Atherosclerotic lesions are patchy and rarely circumferential, usually involving only a portion of any given arterial wall; on cross-section, the lesions therefore appear eccentric

The most heavily involved arteries by atherosclerosis and in descending order are

1- Lower abdominal aorta

2- Iliac arteries

3- The coronary arteries
4- The popliteal arteries
5- The internal carotid arteries,
6- The vessels of the circle of Willis.
Vessels of the upper extremities are usually relatively spared, as are the mesenteric and renal arteries except at their ostia.

Clinical consequence of atherosclerosis (complications)

The principal outcomes depend on the size of the involved vessels, the relative stability of the plaque itself, and the degree of degeneration of the underlying arterial wall:

1. Rupture, ulceration, or erosion of the surface of atheromatous plaques exposes the blood stream to highly thrombogenic substances and leads to

2.Thrombosis, which can partially or completely occlude the vessel lumen (myocardial or cerebral infarction)

3.Hemorrhage into a plaque. a contained hematoma may expand the plaque or induce plaque rupture.

4.Atheroembolism. Plaque rupture can discharge atherosclerotic debris into the blood stream, producing microemboli.

5. Aneurysm formation. Due to pressure or ischemic atrophy of the underlying media causes weakness and potential rupture.

Atherosclerotic plaques develop and generally grow slowly over decades.
The fibrous cap undergoes continuous remodeling that can stabilize the plaque or, conversely, render it more susceptible to rupture.

Stable plaques can produce symptoms related to chronic ischemia by narrowing vessel lumens, whereas unstable plaques can cause dramatic and potentially fatal ischemic complications related to acute plaque rupture, thrombosis, or embolization.
Stable plaques tend to have a dense fibrous cap, minimal lipid

accumulation and little inflammation, whereas "vulnerable" unstable plaques have thin caps, large lipid cores, and relatively dense inflammatory infiltrates.
Critical stenosis occurs when the occlusion produces a 70% to 75% decrease in luminal cross-sectional area leading to chest pain that may develop with exertion (*stable angina*)

Medial calcific sclerosis (Monckeberg's arteriosclerosis)
This variant of arteriosclerosis is of undetermined etiology & is characterized by ring-like calcifications within the media of medium sized to small muscular arteries.
The calcification does not narrow the lumen and thus the condition is of little clinical significance. It may coexist with atherosclerosis in the same artery.
The arteries most commonly affected are those of the extremities (femoral, tibial, radial and ulnar), and those of the genital tract in both sexes.
The condition can be demonstrated in individuals over the age of 5*0 years.*

References:
Robbins Basic Pathology 11th edition