Pathology of cardiovascular interventions and surgery☆

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Abstract

This review describes the histopathology of cardiovascular tissue in patients who have undergone interventions and/or surgery, primarily on coronary arteries, aortas arteries, cardiac biopsies and excisions, and explanted devices. The tissue, prosthesis and/or devices are submitted for surgical pathology or autopsy examination. The anatomic pathologist must provide comprehensive reports on the gross and microscopic findings of the biopsied or explanted specimen, including the condition of any existing prosthesis, the state of the normal and/or diseased host tissue, and complications related to the procedure. The pathologist needs to be well informed of the clinical history, which should include a detailed description of any explanted prosthesis or device. Each report prepared by the pathologist should convey a comprehensive clinical-pathologic discussion to provide useful information to the physicians treating the patient, including cardiologists and cardiovascular surgeons.

Keywords aneurysms; angioplasty; coronary artery disease; endomyocardial biopsies; endovascular repair; prosthetic vascular grafts; stem cells; stents; ventricular assist devices

☆ Excludes valve replacement surgery, heart valve repair and cardiac tumour resection.

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Atherosclerosis

A thorough understanding of the pathogenesis of the atherosclerotic plaque is essential in interpreting plaque findings in numerous cardiovascular interventions and clinical conditions. A useful way to describe pathogenesis is as a series of three clinicopathological stages that can be identified over the course of the growth of the human plaque: (i) a plaque initiation and formation stage, (ii) a plaque adaptation stage, and (iii) a clinical stage.[1] In these stages, many biologically active molecules regulate the function of the cells of the arterial wall as they interact with the wall itself, and with the constituents and physical forces of the blood stream. These molecules may demonstrate atheroprotective and/or atherogenic properties depending on local and systemic conditions.

Stage I: plaque initiation and formation

Injury is considered to be the earliest event in pathogenesis with injury to the endothelium leading to endothelial cell (EC) dysfunction, disruption of endothelial integrity and/or loss of ECs. The state of the endothelial surface should be commented on in pathology reports. Injury may be due to several conditions including hyperlipidaemia, hypertension, microorganisms, toxins, immunologic events, and haemodynamic shear stress, especially at branch points and curves. Intimal lesions initially occur at vascular sites predisposed to atherosclerotic plaque formation. The presence of subendothelial smooth muscle cells (SMCs), in an intimal cell mass (eccentric intimal thickening, intimal cushion) at branch points and other sites is a predisposing condition for plaque formation since it provides a readily available source of SMCs. Human atherosclerotic lesions tend to occur at sites where shear stresses are low but fluctuate rapidly, such as at bifurcations and branch points.[2] Since the location of the plaque is important in pathogenesis, this should be identified in pathology reports. Low shear has been shown to induce expression of cell adhesion molecules on the surface of ECs to promote monocyte attachment, such as vascular cell adhesion molecule (VCAM). The leukocytes first roll along the endothelium mediated by P-selectin and E-selectin and then adhere due to chemokine induced EC activation and integrin interactions with cell adhesion molecules.[3] The leukocytes penetrate the endothelial barrier at interendothelial sites, regulated by platelet EC adhesion molecule (PECAM, CD31). Haemodynamic forces induce gene expression of several biologically active molecules in ECs that are likely to promote atherosclerosis, including fibroblast growth factor-2 (FGF-2), tissue factor (TF), plasminogen activator (PA), and endothelin. However, shear stress also

induces gene expression of agents that are considered anti-atherogenic, including nitric oxide synthase (NOS) and plasminogen activator inhibitor-1 (PAI-1).[2]

Increased lipid entry and subsequent accumulation depend on disruption of the integrity of the endothelial barrier through cell dysfunction, disruption of cell—cell adhesion junctions, and/or cell loss. Low density lipoproteins (LDL) carry lipids into the intima which lead to lipid oxidation. Monocytes/macrophages adhere to activated ECs and transmigrate into the intima also bringing in lipids. Some macrophages become foam cells, due in part to the uptake of oxidized LDL via scavenger receptors. These cells undergo necrosis, release lipids and incite further inflammation. A change in the types and quantity of matrix proteins and proteoglycans synthesized by intimal SMCs enhances binding of lipids. These proteoglycans such as chrondroitin sulphate rich proteoglycans have a high binding affinity for lipoproteins. Versican and biglycan are thus thought to promote atherosclerosis while decorin may be protective.

Macrophages secrete cytokines, including monocyte chemoattractant protein-1 (MCP-1) and growth factors, thereby promoting further accumulation of both macrophages and SMCs. Oxidized lipoproteins and macrophage derived reactive oxygen species induce tissue damage. Monocyte/macrophages synthesize platelet derived growth factor (PDGF), FGF, tumour necrosis factor (TNF), interleukin-1 (IL-1), IL-6, interferon-γ (IFN-γ), and transforming growth factor-β (TGF-β), each of which can modulate the growth of SMCs and ECs. The cytokines IL-1 and TNF stimulate ECs to produce platelet-activating factor (PAF), tissue factor (TF), and PAI. TF expression, an important initiator of the coagulation cascade, is also upregulated by oxidized lipids, thus several conditions promote the transformation of the normal anticoagulant vascular surface to a procoagulant endothelium.

Thrombi may develop on the damaged prothrombotic intimal surface.[4] Numerous biologically active molecules are released from adherent and activated platelets.[5] PDGF, accelerates SMC proliferation, TGF-β enhances the secretion of matrix components and thrombin and adenine diphosphate (ADP) and thromboxane promote further platelet activation resulting in enhanced thrombus growth. Since thrombosis also initiates fibrinolysis and inhibitory factors in the coagulation pathway, the thrombus may alternatively lyse. Organization of the thrombus and incorporation into the plaque may occur in part by TGF-β which regulates secretion of collagen, matrix proteins, and differentiation of SMCs into myofibroblasts. Further growth of the thrombus is now a balance between pro- and anti-thrombotic processes. The histopathology of the plaque should be described and the extent of thrombosis reported.

The deep part of the thickened intima is poorly nourished. Hypoxia promotes HIF-1α translocation to the nucleus of SMCs and macrophages, which binds to the promoter specific hypoxia response element, leading to the transcriptional activation of VEGF and other target genes. Some macrophages and SMCs undergo ischaemic necrosis, as well as apoptosis. Cell death is also promoted by proteolytic enzymes released by macrophages and by tissue damage caused by oxidized LDL and other reactive oxygen species. VEGF initiates plaque angiogenesis with new vessels forming from the vasa vasorum, therefore establishing permanency to the plaque.

The fibroinflammatory lipid plaque is formed, with a central necrotic core and a fibrous cap which separates the necrotic core from the blood in the lumen. The distribution of inflammatory cell infiltration, lipids and SMC and matrix is heterogeneous within the plaque. TGF-β regulates the plaque by increasing several types of collagen, fibronectin and proteoglycans. It inhibits proteolytic enzymes that promote matrix degradation and enhances expression of protease inhibitors. This may reflect a dual effect of TGF-β in promoting plaque growth but also being beneficial by promoting fibrous cap formation and thus plaque stability.[6]

The expression of human leukocyte antigen-DR (HLA-DR) antigens on both ECs and SMCs in plaques suggests immunological activation, perhaps in response to IFN-γ released by activated T cells present in the plaque. Antibodies to oxidized LDL have been identified in the plaque.

Stage II: adaptation stage

As the plaque encroaches upon the lumen, the wall of the artery undergoes remodelling to maintain the original lumen size, likely regulated by haemodynamic shear stress, TGF-β and metalloproteinases (MMP) and their inhibitors (TIMP). Once a plaque encroaches upon about half the lumen, compensatory remodelling can no longer maintain normal patency, and the lumen of the artery becomes stenotic. Thus it is important to comment on lumen size in the pathology assessment, however without perfusion, fixation can only provide an approximation of the true value. Haemodynamic shear stress regulates the expression of a variety of genes that encode for proteins that promote remodelling such as MMPs, collagens, bFGF, TGF-β and inflammatory mediators. SMC turnover characterized by proliferation and apoptosis, and matrix synthesis and degradation modulate remodelling of the vessel and the plaque.[7] This compensatory remodelling is useful because it maintains patency and blood flow in the lumen; however it may delay clinical diagnosis of atherosclerosis since the plaque may be ''clinically silent'' without demonstrating any symptoms. Even though the plaque is small, plaque rupture with catastrophic results may occur at this stage, as noted below.

Stage III: clinical stage

Plaque growth continues as the plaque encroaches on the lumen.[8] Haemorrhage into a plaque due to leakage from the small fragile vessels of neovascularization may not necessarily result in actual rupture of the plaque but may still increase plaque size. Complications develop in the plaque, including surface erosion, ulceration, fissure formation, calcification, and aneurysm formation.[9] It is important to record these complications in the microscopic evaluation of the plaque. Calcification is driven by chondrogenesis and osteogenesis, regulated in part by TGF-β, osteogenic progenitor cells and bone forming proteins. Activated mast cells are found at sites of erosion and may release proinflammatory mediators and cytokines. Continued plaque growth leads to severe stenosis or occlusion of the lumen. Plaque rupture through the fibrous cap leads to thrombosis and occlusion precipitating acute myocardial infarction. Endothelial erosion, ulceration, fistula; thin fibrous cap; decreased SMCs in cap; inflammation; macrophages and SMC foam cells; haemodynamic shear stress; imbalance in matrix synthesis/degradation; and

