Thrombosis and Infarction

Answer Sheet

Q1 Why do you think the endothelium did not act in its usual anti-thrombotic manner in this case?

A1 The local area of inflammation releases mediators, which will activate the endothelial cells, much as described previously in the course for acute inflammation. This leads to the altered expression of adhesion molecules and an alteration in the balance of arachidonic acid metabolites, especially prostaglandins, which has a net pro-coagulant or pro-thrombotic effect.

Q2 What are the risk factors for thrombosis? Can you explain at a cellular / molecular level how each risk factor operates?

A2 Risk factors for thrombosis include: Immobility, recent surgery, trauma, burns and many other disease processes involving tissue damage or inflammation, inflammation local to the site of thrombus, pregnancy, being female, certain oral contraceptive pills, disorders of the coagulation cascade (e.g., inhibitor deficiencies), smoking. The sluggish blood flow that results from immobility allows a “domino effect” to occur in local blood, once thrombosis starts to occur. Mediators released by tissue damage and inflammatory mediators activate the “acute phase response”, in which a number of pro-inflammatory and pro-coagulant proteins are released from the liver in response to circulating cytokines released from the area of tissue damage. These proteins include complement components and clotting factors, which increase the coagulant tendency of the blood. Just as in acute inflammation, the complement and clotting cascades can reciprocally activate each other. Cytokine release will also cause release from the bone marrow of increased numbers of platelets, including younger and more “sticky” platelets. Inflammation local to the site of thrombus formation may activate the endothelium, making it less anti-coagulant, for example causing the expression of adhesion molecules or alterations in the arachidonic acid metabolites produced. In general female hormones make blood more likely to coagulate by increasing levels of clotting factors. This is probably an adaptation to childbirth. Smoking increases the likelihood of platelet activation and degranulation, via a variety of substances contained in cigarettes.

Q3 Where did the original thrombosis occur? What course did this thromboembolus take to reach the lady’s lung?

A3 The original thrombosis most likely occurred in the leg veins, in particular the deep veins of the calf, as a result of immobility causing sluggish leg venous blood flow. Route: leg veins – Iliac Vein – Inferior Vena Cava – Right Atrium – Tricuspid Valve – Right Ventricle – Pulmonary Artery – Lung.

Q4 Why did this lady die within minutes of the onset of symptoms?
Death from a large pulmonary embolus is rapid because the blood flow through the lungs is occluded by the presence of a large thrombus in a major pulmonary artery. The left ventricle will not fill and there will be no cardiac output. Brain death will occur within a few minutes.

Q5 Why does haemorrhage occur into the tissue, given that the pulmonary artery is occluded?

A5 The lung has a **dual blood supply**. Although the majority of blood comes from the deoxygenated pulmonary artery circulation (and most oxygen for the pulmonary tissue is derived directly from air in the lung), a small proportion comes from the bronchial artery circulation. This bronchial arterial system is still intact and vessels rupture around the infarct producing haemorrhage into the damaged area, especially as the damaged tissues in the area of infarction release mediators of vasodilatation.

Q6 What risk factors does this lady have for pulmonary thrombo-embolism?

A6 Risk factors for pulmonary embolus in this patient: Immobility, recent surgery, being female, smoking.

Q7 Name the 2 pathological processes that are the most likely to have caused this infarct and in which blood vessel have they occurred?

A7 The 2 pathological processes are: **atherosclerosis & thrombosis**. These occur in a coronary artery to cause its occlusion resulting in an acute myocardial infarction.

Q8 What further complication may follow from the development of endocardial (mural) thrombosis over the site of a myocardial infarct?

A8 Further complications following the development of endocardial (mural) thrombosis over the site of a myocardial infarct include breaking up of the mural thrombus to form **multiple emboli** that can flow almost anywhere in the systemic circulation leading to one or more **infarcts**, such as infarcts of brain, kidney, gut, spleen, liver or other sites and also to limb ischaemia.

Q9 Which cells secrete the fibrous connective tissue in the fibrous cap of the atherosclerotic plaque?

A9 In atherosclerotic plaques, the fibrous cap is formed from collagenous fibrous tissue and other extracellular matrix proteins secreted by **myofibroblast cells**, which are cells that started off as **smooth muscle cells in the tunica media** and migrated into the tunica intima (as part of the process of atherogenesis), changing their phenotype from a contractile smooth muscle cell to a more secretory myofibroblast in the process.

Q10 Where does the extracellular lipid in the lipid pool come from?

A10 In individuals with high blood concentrations of **Low Density Lipoproteins (LDLs)**, some of the LDLs can infiltrate into the tunica intima at sites of **endothelial damage** or dysfunction (during the early stages of atherosclerotic
plaque formation). Here LDLs can become oxidised and taken up by macrophages (also infiltrate at sites of damage) to form the foam cells (foamy macrophages). Oxidised LDLs often induce cell death of the foamy macrophages causing release of previously intracellular lipid into the extracellular environment of the core of the plaque, generating the lipid pool consisting of extracellular lipid and necrotic cell debris.

Report writing and pathological process identification

Calf veins: organizing thrombus

NDP Image: 21.6: 54.354
Glass Slide: 21.6: 54.354

This slide is from a 73-year-old man who developed leg swelling after a bladder operation.

Organisation of a thrombus

Recent thrombus  Homogenization  New channels invaginate  Organized; converted to fibrous tissue

Gradual shrinkage

This is a cross section of veins and an artery within the calf muscles. The veins developed venous thrombosis that is undergoing organization. Organization of the venous thrombosis is well advanced. There is pale fibrous tissue forming in the granulation tissue, in which there are elongated fibroblast cells with a few lymphocytes and macrophages, the latter sometimes containing golden brown haemosiderin granules (breakdown products of haemoglobin from the red blood cells).

The pathological process is thrombosis within a vein with subsequent organization.

Organisation of a thrombus: Shortly after a thrombus has formed retraction begins, creating spaces between it and the vessel wall. The endothelial lining of the vessel regenerates to line these spaces and then, accompanied by smooth muscle cells, it invades the thrombus itself forming new channels. The process, (which is akin to healing elsewhere), leads finally to the formation of channels, both through and around the thrombus, producing recanalization.