Cancer-related Coagulopathies

Resource: Cancer-related coagulopathies; Levi Marcel, Thrombosis Research 133 S2 (2014) S70–S75.

Basics	• Malignancies are assoc. w. (micro)vascular dysfunction, VTE (venous thromboembolism) and other complications caused by the activation of coagulation (e.g. PE, MAHA/TMA, etc.) They may also be assoc. w. bleeding diatheses (e.g. acquired vWD, thrombocytopaenia, etc.) • Sometimes, **a CVS event may be the first clinical manifestation of the malignancy**. • The most severe manifestation of cancer-assoc. thrombosis is DIC. However, DIC has a less fulminant presentation in cancer than the types of DIC complicating sepsis or trauma.

Pathogenesis	Predisposition to thrombosis:
	• Activation of coagulation and the ensuing procoagulant state in cancer is usually due to (1) cancer-procoagulant, (2) defective anticoagulant and fibrinolytic mechanisms (3) and damaged endothelium.
	  ○ Solid Tu. (e.g. Breast CA) may express different procoagulant molec. incl.
	  ▪ **TF** (tissue factor), which complexes w. F VIIa to activate F IX and FX, and
	  ▪ **Cancer procoagulant (CP)**, a cysteine protease with F X activating properties
	  ▪ Mucinous adenoCA secrete **mucin** that can induce the formation of platelet microthrombi.
	  ○ Endothelial damage can increase the risk of thrombosis as follows:
	  ▪ **↑[vWF]** expression on the EC potentially contributes to the initiation of platelet activation.
	  ▪ Dysfunction of EC results in impaired coagulation (**abnormal expression of TFPI**) and fibrinolysis (**abnormal expression of t-PA and PAI-1**). Moreover, a whole series of adhesion molec. expressed by EC mediate the binding and activation of WBC, resulting in the release of various cytokines that induce activation of blood coagulation.
	  ○ Chemotherapy may enhance the risk of thrombosis due to its damaging effect to the EC. It appears to increase EC reactivity to platelets (mediated by cytokine-induced expression of endothelial adhesion molecules.)
	
	• Some cancers may predispose to thrombosis indirectly, for instance by secreting products into the blood that change the blood's viscosity (e.g. Polycythaemia Vera, Waldenstrom macroglobulinemia, etc.)
	• In the context of Essential Thrombocythemia, Pz. are more likely to experience arterial thrombi due to excess of thrombocytes.
	
	Predisposition to bleeding:
	• Both primary bone marrow malignancies (i.e. leukaemias) and secondary BM malignancies predispose to bleeding by causing thrombocytopaenia.
	• Primary and secondary hepatic malignancies may predispose to bleeding by impairing the hepatic function of producing coagulation factors.

Thromboembolic complications in Pz. w. cancer	• **Trousseau's syndrome**
	  ○ Refers to the occurrence of migratory thrombophlebitis (venous thromboembolism accompanied by inflammation) in the context of malignancy.
	• **DIC**
	  ○ Usually seen in Pz. w.
	  ▪ Mucin-producing adenocarcinoma (clinical picture is dominated by VTE)
	  ▪ Acute leukaemia leukaemia(clinical picture is dominated by bleeding)
	  ▪ Prostate CA (clinical picture is dominated by bleeding)
	• **TMA (Thrombotic microangiopathy)**
	  ○ Encompasses a number of syndromes that closely resemble each other, i.e. HUS, TTP etc. They are characterised by platelet adhesion to EC followed by massive platelet aggregation and activation resulting in consumptive thrombocytopaenia.
	  ○ Usually occurs 9 months after cessation of chemo. and whilst cancer is still in remission.

Disseminated Intravascular Coagulation (DIC)

- Is characterised by **the systemic activation of coagulation and result in the formation of thrombi throughout the microcirculation**. As a result of DIC platelets and coagulation factors are consumed, and fibrinolysis is activated (= consumptive coagulopathy).
- DIC gives rise to:
  - Tissue hypoxia
  - Microinfarcts
  - Bleeding disorders

Pathogenesis	• DIC is usually triggered by: 1. The release of TF or thromboplastic substances into the circulation. Sources incl.: ▪ **Placenta**, in obstetric complications (incl. abruptio placentae, retained dead foetus, septic abortion, amniotic fluid embolism & toxaemia) ▪ **Cancer cells**, in tumour lysis syndrome (TLS) ▪ Infectious foci ▪ WBCs, in SIRS 2. Widespread endothelial damage ▪ Deposition of antigen-antibody complexes (e.g. SLE) ▪ Extreme temperatures (e.g. burn injury, heat stroke) ▪ Infections (e.g. meningococcemia, rickettsiae rocky mountain spotted fever, histoplasmosis, aspergillosis, malaria) • DIC has two consequences: 1. Widespread fibrin deposition within the microcirculation leads to **organ ischaemia** and **thrombotic microangiopathy** (TMA), previously known as microangiopathic haemolytic anaemia (MAHA.) 2. Because of the depletion of platelets and clotting factors and the 2^{o} release of plasminogen activators, there is a **superimposed bleeding tendency**.
Clinical Features	• Acute DIC is dominated by bleeding, whereas chronic DIC by signs and symptoms of thrombosis. • There may be cyanosis, stroke, convulsions, acute renal failure, dyspnoea, shock and coma • Lab evaluation ○ Thrombocytopaenia ○ ↑PTT & ↑PT ○ ↑D-Dimers
Tx.	• Medical emergency that req. immediate administration of anticoagulants (e.g. heparin) or fresh frozen plasma (FFP.)