



A Comprehensive Review on Cancer Associated Deep Vein Thrombosis

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Abstract

Cancer-associated thrombosis accounts for almost one-fifth of all cases of venous thromboembolism (VTE) and is a leading cause of death, morbidity, delays in care, and increased costs. Our understanding of risk factors for cancer-associated thrombosis has expanded in recent years, and investigators have begun to use biomarkers and clinical prediction models to identify those cancer patients at greatest risk for VTE. A thrombus either arises spontaneously or is caused by clinical conditions including surgery, trauma, or prolonged bed rest. In these instances, prophylaxis with low-dose anticoagulation is effective. Diagnosis of deep vein thrombosis relies on imaging techniques such as ultrasonography or venography. Only about 25% of symptomatic patients have a thrombus. Risk factors, cancer associated risk factors, pathophysiology and diagnosis is discussed here under.

Keywords: Cancer, Deep vein thrombosis, Chemotherapy, venous thromboembolism,

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Introduction

Cancer is the second leading cause of death worldwide with an incidence rate of 14.1 million new cancer cases, 8.2 million cancer deaths annually. The close relationship between cancer and thrombosis has been known since the days of Armand Trousseau, who first described the clinical association between idiopathic venous thromboembolism (VTE) and occult malignancy in 1865 [1].

A hypercoagulable or prothrombotic state of malignancy occurs due to the ability of tumor cells to activate the coagulation system. It has been estimated that hypercoagulation accounts for a significant percentage of mortality and morbidity in cancer patients. Today, we know that cancer is associated with a hypercoagulable state and a four-

fold increase in thrombosis risk, with chemotherapy elevating this risk even more. Epidemiologic and population-based studies provide detailed information on the scale of the problem and the identification of VTE risk factors, including those related to the tumor (tumor type, clinical stage, chemotherapy, use of anti-angiogenic drugs or erythropoietic growth factors, and insertion of central venous catheters), and those related to individual patient characteristics (sex, race, age, previous VTE history, immobilization, and obesity). Thrombosis has a significant impact on the morbidity and mortality of cancer; therefore, it is important to identify which patients may be at higher risk than others, especially before starting chemo-radiotherapy or surgery.

Thrombosis and disseminated intravascular coagulation (DIC) are common complications in cancer. Patients with malignancy have a prothrombotic state due to the ability of almost all type of cancer cells to activate the coagulation system. However, none of the haemostatic markers of coagulation has any predictive value for the occurrence of the thrombotic events in one individual patient. The pathogenesis of the prothrombotic state in cancer is complex and, probably, multifactorial. Prothrombotic factors in malignancy include the tumour production of procoagulants (i.e., tissue factor (TF) and cancer procoagulant (CP)) and inflammatory cytokines, and the interaction between

tumour cells, blood (i.e., monocytes/macrophages, platelets) and endothelial cells. Other mechanisms of thrombus promotion include some general responses of the host to the tumour (i.e., acute phase, inflammation, angiogenesis), decreased levels of inhibitors of coagulation, and impaired fibrinolysis. In addition, the prothrombotic tendency of cancer patients is enhanced by anticancer therapy, such as surgery, chemotherapy, hormone therapy and radiotherapy, by in dwelling central venous catheter, and by haemodynamic compromise (i.e., stasis). However, not all of the mechanisms allowing the prothrombotic state of cancer are entirely understood. Therefore, it is presently difficult to rank the relative weight of these multiple interactions on the basis of the well-recognised clinical evidences of enhanced thrombotic episodes in patients with cancer. In this review we attempt to describe the risk factors, diagnostic approaches and management of deep vein thrombosis. A better understanding of these aspects could help clinicians in the developments of more targeted treatment to prevent thromboembolic complications in cancer patient.

Deep vein thrombosis (DVT) can be sub classified into four groups depending on where the thrombus forms:

- Lower extremity DVT- involving the lower limbs
- Upper extremity DVT- involving the veins of the upper limbs, neck and chest.
- Abdominopelvic DVT- involving the venous system of the abdomen and pelvis including the portal venous system, the inferior vena cava (IVC) and iliac vessels and their branches.
- Cerebral vein thrombosis including the venous sinuses.

Risk Factors

A number of risk factors for developing venous thrombosis have been identified with most of the current evidence derived from lower limb DVT and PE epidemiological retrospective studies.

Demographics

Age

VTE development is more likely as an individual ages but it is challenging to conclude that age itself is a factor when it is also associated with deteriorating mobility and co morbidities, such as cancer, which may confound observational cohort findings [2].

Ethnicity

Africans and Europeans appear to have the highest risk of VTE of all ancestries. African-Americans have a five-fold increase in VTE incidence compared with Asian ancestry populations who are low risk. Hispanic populations are moderate risk. These variations are currently not fully explained by genetic and environmental risk factors. Little epidemiological research has taken place outside of North America and Europe to validate previous findings although emerging data from the Asian continent following orthopaedic surgery, suggest that VTE rates may not be as low as once thought. This suggests that clinical suspicion, surveillance and access to healthcare may be confounding factors.

Comorbidities

Medical interventions and Comorbidities

The Worcester venous thromboembolism study investigated risk factors associated with VTE development in their patient population. Immobility for >48 hours in the preceding month (45%), hospitalisation in the last three months (39%), surgery in the past three months (34%), infection in the past three months (34%) and current hospitalisation (26%) were the most commonly associated risk factors in the 587 patients diagnosed with VTE.

Renal disease

In all patients with chronic kidney disease thrombotic risk is higher than the general population with the estimated glomerular filtration rate and the urinary albumin-creatinine ratio associated with VTE risk [3].

Respiratory disease

PE may exacerbate the symptoms of chronic obstructive pulmonary disease (COPD). In a systematic review and meta-analysis, one in four in patients with COPD were diagnosed with PE, although the studies examined were heterogeneous with regards to design and selection criteria [4].

Cardiovascular disease

Conflicting results have been published regarding cardiovascular disease and VTE risk. VTE and intracardiac thrombi, and is a prominent risk factor for death as an inpatient and within 30 days of a VTE event [5].

Obesity

DVT and PE are both increased in obese patients (two-fold) with the impact greater in individuals younger than 40 years of age [6].

Smoking

The contribution of smoking to VTE is controversial with many large studies reporting conflicting results. It is possible that smoking, in combination with other risk factors

Surgery and trauma

Major vascular, orthopaedic, neurosurgical and cancer surgery appear to carry the greatest risk of venous thrombotic complications. Older age and anaesthesia were also shown to be associated with VTE [7].

Inherited thrombophilias

Approximately 60% of cases of VTE in patients with inherited thrombophilia are associated with Factor V Leiden and the prothrombin gene G20210A mutation. A family history of thrombosis or recurrent miscarriage may or may not be evident. The lifetime probability of developing thrombosis compared with those with no defect in a study of 150 pedigrees was 8.5 times higher in patients with protein S deficiency, 8.1 with antithrombin deficiency, 7.3 in protein C deficiency and 2.2 in Factor V Leiden deficiency [8].

Cancer Associated Risk Factors

VTE and cancer primary site

VTE risk varies with primary cancer site as well as tissue type further emphasising the importance of understanding tumour biology characteristics. State of California law, in the United States of America, requires all cancer patients to be identified and clinical information logged and reported. This California Cancer Registry (CCR) has provided important information with regards to VTE events in cancer patients. Wun et al. linked the registry to patient hospital discharge data and analysed all cases of cancer and VTE diagnosed between 1993 and 1999. Outpatient management of VTE with low molecular weight heparin was seldom used during this time period and so it was possible to minimize case ascertainment bias and allow the investigators to link virtually all cases of cancer associated thrombosis to the relevant patient's cancer stage and clinical outcome.

High grade gliomas, such as glioblastoma multiforme, and upper gastrointestinal cancers, such as gastro-oesophageal junction, gastric and pancreatic cancers had a high risk for VTE occurrence. Hematological malignancies, such as acute myeloid leukemia were also ranked as high risk whereas lower incidences of VTE occurred in cancers of the colon, breast, prostate [9]. Similar findings have also

been reported in other studies including a large Dutch database [9].

Tumor histology and VTE

Adenocarcinoma, especially mucinous adenocarcinoma histology, appears to correlate with thrombus development in cohorts of patients with colorectal but not breast cancer [10]. In patients with lung cancer, adenocarcinoma histology was significantly associated with symptomatic PE but not DVT [11]. Ovarian, gastrointestinal and prostate adenocarcinomas have also been associated high incidences of VTE with patients diagnosed with pancreas adenocarcinoma faring worst of all [12]. A recently published retrospective analysis of 641 patients with epithelial ovarian, fallopian and primary peritoneal cancers, however, did not associate mucinous tumours with VTE but found that serous, clear cell and high grade undifferentiated histologies were associated with the highest VTE risks. Transitional cell histology was also associated with VTE but patient numbers in this subgroup were small. In breast cancer, undifferentiated carcinoma histology, is associated with increased two-year mortality in those with VTE [13].

Cancer stage

Studies, to date, have provided conflicting opinions on the association between cancer stage and VTE risk. Patients with advanced cancer (metastatic or stage IV cancer) were at higher risk for VTE than their peers with localised disease according to a large Dutch database [14]. Their risk was also higher when hospitalised or undergoing surgery [15]. Metastatic disease was also found to be a strong risk factor for VTE in retrospective analyses of colorectal, breast and ovarian cancer patients [16]. Those patients developing VTE within one year of cancer diagnosis were more likely to have metastatic disease which was an independent risk factor for VTE development in that first year. A positive correlation between cancers with high one-year mortality rates (e.g. pancreas, lung) and VTE incidence has also been reported suggesting biological aggressiveness (e.g. tumour cell doubling time or rate of metastatic spread) rather than cancer stage may influence VTE risk [17].

VTE and survival of cancer patients

Sorensen et al. first described the negative impact of VTE occurrence on survival in cancer patients. The one year survival reduced from 36% in cancer patients without VTE to 12% in those that had developed VTE [18]. This study did not stratify for

cancer stage but a retrospective analysis of the California Cancer Registry did and concluded that VTE was indeed an independent predictor of poorer survival in cancer patients [19]. Development of VTE was also an independent risk factor for poorer survival in the first few months of chemotherapy treatment regardless of cancer type, cancer stage, age, gender, ethnicity, performance status, body mass index (BMI), and comorbid conditions [20]. This has been shown in a cohort of irrespectable locally advanced and metastatic pancreatic cancer patients [21].

Pathphysiology of Thrombosis in Cancer

The vascular endothelium

The endothelial lining of blood vessels is the thin, single cell-thick layer which comes into direct contact with the blood. It is anchored to the basement membrane of the surrounding tissue by pericytes and smooth muscle cells. These anchoring cells penetrate the basement membrane and make direct contact with the endothelial cells (ECs) allowing communication via signaling messengers. Under physiological conditions ECs are stable, rarely undergo apoptosis (turnover rate of months to years) and form an unbroken layer separating the blood and its constituents from the sub endothelial extracellular matrix (ECM).⁽²⁵⁾ The blood travels unimpeded over this layer and is not induced to undergo coagulation as is the case when blood contacts other surfaces. ECs form a barrier to the passage of substances through them by adherens and tight junctions (cell to cell contacts) consisting of transmembrane proteins including VE-cadherin, N-cadherin, claudins and occludin. These adherens and tight junctions also allow cell to cell communication and Vary in different vascular tissue beds, meaning that there is variable permeability in different tissues. Brain vasculature has many tight junctions which significantly reduce permeability (the blood-brain barrier), while post capillary venules have relatively few tight junctions to allow increased permeability and leukocyte transmigration. Gap junctions allow the intercellular passage of small molecules [26].

The endothelial lining, therefore, allows smooth, laminar flow and regulates all substances, cells and pathogens that may potentially pass across from the blood into the extracellular matrix or vice versa. Stimulation of ECs by pro-angiogenic factors or cell damage will significantly alter this control and may induce thrombosis as well as support easier passage of substances between the blood and the ECM.

Blood flow

Blood flow is normally unidirectional and laminar due to the pumping action of the heart, the subendothelial muscle contractions of the blood vessel wall, the venous muscle pump of the lower limbs and the actions of venous and cardiac valves. Anything that disrupts flow may induce thrombosis. This may be due to the presence of an intrinsic or extrinsic mass/process narrowing or obstructing the vessel lumen leading to sluggish flow, turbulent flow or stasis. Reflux of blood through damaged valves may also have a similar effect.

Blood Constituents

The blood contains many constituents which are vital for survival and maintenance of the body. At a macroscopic level it appears to be a liquid but, at a microscopic level, is far more complex. The major components of the blood are:

- The liquid component termed serum
- A non-cellular liquid in which all blood constituents, including coagulation factors.

The solid component made up of red blood cells and their precursors, which transport oxygen to the tissues, white blood cells and their precursors, involved in host immune and inflammatory responses, and platelets and their precursors, involved in coagulation and inflammation.

The numbers of mature cells circulating in the blood are usually tightly controlled in the healthy individual but can be upset in disease e.g. infection and cancer. Increasing absolute numbers of premature and mature cells can increase the solid component of the blood and increase the viscosity of the blood leading to sluggish flow and the increased potential for thrombosis (e.g. leukaemic and polycythaemic patients). Functional changes in blood cells (e.g. platelets) will also impact on thrombosis risk even if the absolute number present in the blood appears normal [27].

Malignancy is characterized by a bidirectional interrelationship connecting cancer growth, progression, and metastasis with activation of the coagulation cascade and subsequent thrombin generation and inflammation. Cancer cells can disrupt the haemostatic balance via several different pathways, including production of procoagulant, profibrinolytic, proproteolytic, and proaggregating activities, expression of adhesion molecules that mediate direct interactions with host vascular and blood cells, and secretion of proinflammatory and proangiogenic cytokines [28].

Cancer procoagulant is a cysteine protease expressed only by malignant cells that can directly activate factor X independent of factor VII [29]. Cancer procoagulant identified in a wide variety of cancer types and has been noted to have increased activity at disease onset with a subsequent slow decline. In addition, cancer procoagulant has been demonstrated to activate platelets, further adding to its prothrombotic potential [30].

Tissue factor (TF) is the principal initiator of coagulation protease cascade and is normally expressed as transmembrane glycoprotein on vascular subendothelial Cells. Therefore TF is not normally in contact with blood unless vascular endothelial integrity is compromised or if its expression is induced on endothelial cells by inflammatory stimuli [31]. TF, which can also be produced by cells in the cancer microenvironment depending on cancer type and context, has been associated with cancer initiation, metastasis, progression, and angiogenesis, in addition to activation of coagulation. Tumors with stronger immunoreactivity for TF were more poorly differentiated [32].

TF can drive cancer progression by coagulation-dependent and coagulation-independent mechanisms. The circulating form of TF has been proposed to contribute more significantly to the pathogenesis of cancer-associated VTE than TF expressed on primary cancer cells.

Most patients with cancer have been found to exhibit increased levels of coagulation factors V, VIII, IX, XI, and biomarkers of thrombin generation such as prothrombin fragment 1+2 and D dimer [33] as mentioned previously, elevated biomarkers of thrombin generation have been associated with aggressive cancer biology and worse clinical outcomes [34].

The fibrinolytic system can also be significantly dysregulated in patients with cancer [34]. Malignant cells can express different proteins in the fibrinolytic system, including urokinase-type and tissue-type plasminogen activators (UPA and TPA, respectively) and PAIs. Similarly, plasminogen activators, PAIs, and other proteins that regulate the fibrinolytic system are also expressed by solid tumor cells, and the resulting imbalance in fibrinolysis may contribute to the hypofibrinolytic and procoagulant state seen in some affected patients [35].

Additionally, cancers can be associated with deficiencies in the natural anticoagulants, antithrombin, protein C, and protein S, further promoting the cancer-associated thrombotic state [36]. The degree of activation of the coagulation

cascade and fibrinolysis differs between various tumor types. As noted earlier, some patients with cancer will exhibit clinically evident manifestations of activated coagulation such as DIC and/or venous or arterial thromboembolism, whereas many other patients with cancer will only have laboratory markers of a procoagulant state such as elevated D-dimer.

Cancer cells can also modulate the hemostatic balance in an indirect fashion through their interaction with host immune cells such as monocytes and macrophages, leading to activation of platelets and factors X and XII [37]. Tumor cells can directly produce inflammatory cytokines or indirectly stimulate their production by host cells (leukocytes and endothelial cells), promoting a hypercoagulable state [38]. These inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and vascular endothelial growth factor (VEGF) can induce TF production by endothelial cells and monocytes, stimulate PAI-1 production, and downregulate expression of the natural anticoagulant protein, thrombomodulin, on endothelial cells [38]. In addition, these cytokines can lead to vascular endothelial cell damage and conversion of vascular lining into a thrombotic surface [38]. In addition to activation of TF production by endothelial cells and monocytes, the effects of VEGF include induction of angiogenesis and increased local vascular permeability, therefore increasing the exposure of TF and promoting cancer-associated thrombotic state [38]. The acute phase reactants induced by inflammatory cytokines in patients with cancer include procoagulants such as von Willebrand factor (vWF), factor VIII, and fibrinogen, therefore favoring a thrombotic hemostatic milieu.

Tumor cells can also promote nonenzymatic activation of factor X through the sialic acid moieties of mucin produced by adenocarcinomas [38]. Although increased levels of factor VIII, vWF, fibrinogen, PAI, and markers of thrombin generation and fibrin degradation have been associated with more advanced cancers and worse outcomes, these biomarkers have not shown any benefit to date in selecting patients with cancer who might benefit from primary anticoagulant VTE prophylaxis. Tumor cells can also directly aggregate platelets and secrete important platelet aggregation agonists such as thrombin and adenosine diphosphate [39].

In addition to these biochemical procoagulant mechanisms, direct cell-cell interactions and the local mass effect of tumors contribute to VTE pathogenesis in patients with cancer. Vascular invasion and

physical compression by the tumor can mechanically obstruct venous blood flow, leading to venous stagnation, endothelial lining damage, and local activation of the coagulation cascade, all of which predispose to VTE [40]. In patients with myeloma, increased plasma viscosity, elevated levels of circulating immunoglobulins, autoantibodies targeting natural anticoagulants, and secretion of inflammatory mediators with procoagulant activity have all been proposed to contribute to the pathogenesis of VTE [41].

Diagnosis

Duplex ultrasonography allows assessment of the presence and chronicity of DVT and is the current noninvasive imaging investigation of choice [41]. Lack of compressibility of a vein with the ultrasound probe has more than 95% sensitivity and specificity for DVT. Patients with initial negative compression ultrasonography and a high Wells score should have a repeat study performed a week later because up to 2% of patients may have a positive repeat test [42].

Doppler color flow ultrasound reduces the required duration of the study and demands placed on the patient while maintaining accuracy [42]. Important characteristics noted by the ultrasonographer during duplex ultrasound include lack of compressibility of the vein and the change in vein diameter during the Valsalva maneuver, abnormal Doppler color flow, and/or presence of an echogenic band. Compression ultrasonography is less useful for detection of recurrent DVT, proximal lower limb thrombus in the iliac vein, or DVT in patients who have pelvic or arm girdle tumors that may impede flow from distal veins [43].

In the last decade, the story was advanced by the discovery of a complex scenario in which oncogenic events drive the procoagulant conversion of tumor cells. Oncogene and tumor suppressor gene-mediated neoplastic transformation driven by activation of MET, loss of PTEN, induction of K-ras, and/or loss of p53 in several experimental models of human cancers have been associated with activation of clotting pathways as an integral feature of the transformation. Signaling pathways triggered by one or more of these genes can result in activation of blood coagulation and platelet function and/or suppression of fibrinolysis, which in some cases produced thrombosis and/or DIC in these models. Furthermore, a mutation of *EGFR* gene renders cancer cells hypersensitive to the action of

coagulation proteins, such as TF; as a result, a microenvironment promoting tumor growth is generated.

In human malignancies, *PML-RAR* hybrid gene expression in patients with acute promyelocytic leukemia and *JAK2V617F* expression in patients with myeloproliferative neoplasms (MPNs) are associated with expression of a prothrombotic phenotype. Among other properties, platelets from *JAK2*-positive patients with MPN express increased TF on their membranes. With a better understanding of the molecular events associated with cancer thrombophilia, new targets for development of bifunctional drugs (i.e., those capable of attacking both the malignant process and the coagulopathy) may be identified. Perhaps one example of a targeted, bifunctional therapy is ATRA for treatment of APL. Until more specific targeted therapies are available, however, we must rely on anticoagulant drugs for prophylaxis and treatment of thrombosis. In this context, it is worth noting that anticoagulant treatments have been reported to improve survival in cancer patients. Given the limitations of the available studies, the routine use of anticoagulants as primary anti-cancer therapy cannot be recommended. Nevertheless, the data from meta-analyses may provide a stimulus to test the hypothesis in properly designed, large randomized clinical trials. Additional efforts to develop therapies that rapidly correct the hypercoagulable state of cancer are required. As the molecular basis becomes better elucidated, development of drugs that will target both the malignant process and the resultant hypercoagulability is a realistic goal.

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