CANCER ASSOCIATED THROMBOSIS

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INTRODUCTION

Cancer-associated thrombosis (CAT) is the development of blood clots in cancer patients, a leading cause of morbidity and mortality in oncology patients. Approximately 20% of all VTE events occur in individuals with cancer, and patients with malignancy have a four- to seven-fold increased risk of thrombosis compared to the general public. The heightened risk stems from factors including tumor cell secretion of procoagulant substances (e.g., tissue factor), chemotherapy, immobility, and inflammatory responses that promote a higher tendency to create clots. VTE risk is particularly elevated within the first 6 months following a cancer diagnosis. Despite advances in therapy, CAT remains a major clinical challenge due to its recurrence, bleeding risks with anticoagulation, and its contribution to early cancer-related death. CAT commonly occurs in patients with clinically active malignancy; however, there is a subset of patients in whom thrombosis can be the first manifestation of their cancer. The relationship between cancer and Thrombosis was first reported by Bouilland in 1823 and Armand Trousseau later in 1865. Overall, cancer patients comprise 15-20% of patients who are diagnosed with VTE. Thrombosis has become the second leading cause of death in cancer patients.

PATHOPHYSIOLOGY

CAT arises from a multifactorial disruption of the normal hemostatic balance, leading to a hypercoagulable state. Tumor cells directly activate the coagulation cascade by expressing procoagulant proteins such as tissue factor and cancer procoagulant, stimulating thrombin generation and release microparticles rich in tissue factor, further amplifying clot formation. Tumor-derived inflammatory cytokines like interleukin-6 and tumor necrosis factor-alpha induce endothelial injury and promote the expression of adhesion molecules, facilitating platelet activation and leukocyte aggregation. Chemotherapeutic agents, indwelling catheters, and surgery further contribute to vascular injury and stasis. This prothrombotic milieu can lead to venous and, less commonly, arterial thromboembolic events. In some cases, thrombosis may precede the diagnosis of cancer.

CONTRIBUTING FACTORS

Multiple factors contribute to the increased risk of arterial and venous thromboembolism in cancer patients:
1. The tumor's tissue and anatomical factors
2. Patient's comorbidities, including obesity and advanced age
3. Surgical and medical oncological treatment

RISK OF VTE

There is an increased risk of VTE in patients with malignancy, with prevalence as high as 20%. A large case-control study in the Netherlands examined 3220 cancer patients aged 18 to 70 and found the overall risk of venous thrombosis to be 7-fold higher, the highest risk was in the first few months after diagnosis with the highest risk increase seen in patients with hematological malignancies, lung cancer, gastrointestinal cancer, or with distant metastases. In another case-control study in Minnesota, a 4-fold increased risk of VTE was found in patients with cancer, while patients receiving chemotherapy experienced an even higher risk. Cancer patients face an increased risk of arterial thromboembolism. In a large retrospective study with 279,719 pairs of cancer patients and matched controls, the 6-month incidence of myocardial infarction was 2.0% in cancer patients compared to 0.7% in control patients. In contrast, for ischemic stroke, the incidence was 3.0% for cancer patients compared to 1.6% for control patients. The study also found that cancer patients experiencing arterial thromboembolism had a poor prognosis, with a 3-fold increased hazard for death.
The rates of VTE are higher in cancer patients when compared to non-cancer patients (Fig.1).

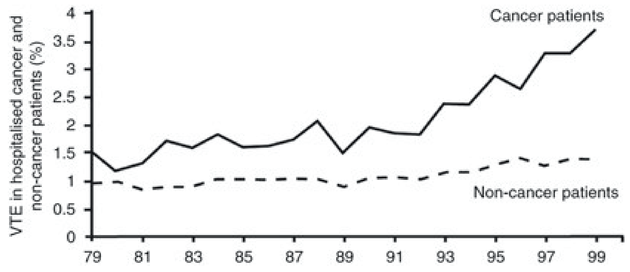

Figure 1: Rates of VTE in cancer when compared to non-cancer patients.

MECHANISM OF CAT

Tissue factor produced by malignant cells triggers the coagulation cascade, leading to the formation of Factor Xa. Some cancer cells can produce cancer procoagulants that act directly on Factor Xa. Chemotherapeutic agents, including methotrexate, and cyclophosphamide increase the risk of VTE and mortality. Other causes include venous stasis due to compression of blood vessels by tumor or prolonged immobility in critically ill cancer patients.

ORGANS AFFECTED BY CAT

CAT can affect several organs, causing VTE (Figure 2). The pancreas is most commonly affected, followed by mesothelioma, the lung, and the brain.

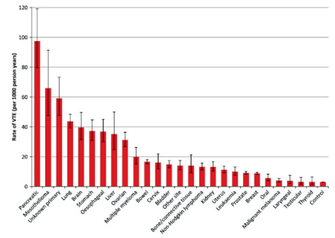

Figure 2: Rates of VTE caused by various types of cancer

MORTALITY

CAT often leads to an earlier, untimely death. The survival rate post-diagnosis can be as low as 6.3 months.

DIAGNOSIS

1. History and physical
2. Imaging

MANAGEMENT

1. Thromboprophylaxis decreases the incidence of VTE.
2. Anticoagulation with UFH or LMWH.
3. Warfarin and DOACs (apixaban, rivaroxaban).

PATIENT EDUCATION

1. Patients with active malignancy are at risk of developing VTE and arterial thromboembolism, and need to be educated, including unilateral leg swelling, palpitations, chest pain, dyspnea, and stroke.
2. For non-cancer patients with unprovoked VTE, age-appropriate cancer screening to evaluate for hidden malignancy needs to be performed.

CONCLUSION

CAT is one of the leading causes of morbidity and mortality. Factors contributing to CAT are obesity and old age. The rates of VTE are higher in cancer vs non-cancer patients. Common organs affected are the pancreas, the lungs, and the brain. Treatment of CAT includes thromboprophylaxis, mechanical prophylaxis, warfarin, LMWH, and DOACs.