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Review of Trousseau phenomenon - pathomechanism, diagnosis, treatment and risk of cancer

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Abstract

Introduction: Trousseau's phenomenon, also referred to as malignancy-associated thrombosis, represents a hypercoagulable state commonly encountered in oncology patients, contributing substantially to morbidity and mortality. This review examines the underlying mechanisms of Trousseau's phenomenon, including the release of tumor-derived procoagulants and immune-inflammatory interactions, alongside contemporary diagnostic methodologies and emerging biomarker candidates. Additionally, therapeutic strategies, with a focus on anticoagulation management, are discussed, highlighting the clinical and prognostic significance of Trousseau's phenomenon in evaluating cancer progression and risk stratification. The evolving understanding of this condition underscores the necessity of interdisciplinary collaboration in its clinical management and ongoing research efforts.

Aim of these study: The aim of this study was to explore the issue of hypercoagulability in the cancer patient population and to investigate the underlying mechanisms contributing to its development.

State of knowledge: It is well-established in scientific literature that oncology patients are at a significantly increased risk for thromboembolic events. Neoplasms promote a hypercoagulable state and its associated complications through diverse and complex pathophysiological mechanisms.

Conclusions: Cancer-associated thrombosis is a significant clinical challenge in oncology patients. Understanding the underlying mechanisms, identifying specific risk factors, and ensuring early diagnosis are essential for improving prognosis and optimizing therapeutic outcomes.

Key words: Trousseau's syndrome, thrombosis, cancer-associated thrombosis, cancer,

1. **Introduction**.

Trousseau’s syndrome (cancer-associated thrombosis) is well known among clinicians, especially oncologists. In 1865 Armand Trousseau described this syndrome, few years later he diagnosed this syndrome on himself. Forthcoming, he died from gastric cancer [1,2]. Since its identification, the association between malignancy and hypercoagulable states has been commonly referred to as Trousseau’s syndrome, with Trousseau’s original report recognized as the earliest documented link between cancer and thrombotic events.

The definition of Trousseau’s syndrome remains ambiguous and is applied across various clinical contexts, reflecting its diverse presentation and underlying pathophysiological mechanisms. The original term Trousseau’s sign of malignancy refers to the occurrence of an inflamed and thrombosed vain ahead of or concomitant with diagnosis of cancer. However, the term Trousseau’s syndrome was extended to a more complex paraneoplastic syndrome with systemic coagulation activation. Currently, in clinical practice, the term "Trousseau's syndrome" is used to describe nearly all clinically significant clotting abnormalities in cancer patients [3,4,5].
This emphasize the potentially profound effect that occult malignancies can exert on the haemostatic system.

Despite of well-known correlation between cancer and thrombosis, the mechanisms are not clear and appear to be multifaceted. It is well-established that cancer patient are frequently in a hypercoagulable or prothrombotic state, defined by dysfunction across all components of Virchow’s triad, which collectively facilitate thrombus formation [6]. These mechanisms remain poorly understood and may be tumor-specific, as different cancer types exhibit varying levels of risk for cancer-associated thrombosis.

The clinical manifestations of cancer-associated thrombosis encompass venomous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as arterial thrombosis and chronic DIC associated with nonbacterial thrombotic endocarditis (NBTE). Numerous studies have demonstrated that thromboembolic events are linked to poorer prognosis in cancer patients,

particularly during chemotherapy [14]. The repercussions of thrombosis in this patient population can be severe, with arterial thrombosis most commonly resulting in stroke, which may significantly impair health and, in some cases, directly lead to mortality [7]. This article describes the issue of cancer-associated thrombosis, identifies possible mechanisms, and outlines diagnostic and treatment methods.

2. Epidemiology.

It is well known that tumors substantially elevate risk, with patients undergoing chemotherapy experiencing an even higher predisposition. This thrombotic tendency is now widely acknowledged, with venous thromboembolism (VTE) developing in up to 20% of cancer patients over the course of their disease [11]. The exact timing of thromboembolic events in these patients remains largely undetermined. Certain tumors demonstrate a particularly strong association with thrombosis; research indicates that cancers of the pancreas, brain, lung, ovary and haematological malignancies present the highest thrombotic risk [8-10]. Additionally, epidemiological studies have also identified stomach, uterine, kidney, and metastatic cancers as being strongly linked to thrombosis [13].

3. Risk factors and pathophysiology.

The development and risk factors for cancer-associated thrombosis are classified into three main categories: factors related to the patient, those associated with treatment, and those specific to the cancer itself [17-19].

Patient-related factors encompass advanced age, female sex, prolonged immobility, a previous history of thrombosis, obesity, elevated leukocyte and platelet counts, acute infections, and comorbidities such as cardiovascular disease [20,22,76].

Regarding treatment-related factors, it is well established that anticancer drugs elevate thrombosis risk. Additionally, specific chemotherapy drugs, including platinum-based compounds, hormonal therapies, tamoxifen, growth factors (such as granulocyte colony-stimulating factor and erythropoiesis-stimulating agents), and antiangiogenic drugs, further contribute to this risk [77,78]. Surgical procedures and the use of central venous catheters are also recognized as mechanical treatment-related causes of thrombosis [20,78].

The third category, related to cancer type, is determined by the specific characteristics of the malignancy. Studies have shown that malignant tumors, including those of the brain, pancreas, and lungs, are associated with a higher risk of developing venous thromboembolism (VTE) [20,22,79]. Additionally, the compression or direct invasion of large blood vessels represents another significant risk factor. Furthermore, metastatic and higher grade tumors have been shown to carry a higher risk of thrombosis compared to primary tumor sites [15,21].

The mechanisms underlying Trousseau syndrome are complex, involving both tumor-derived factors and host responses, which together contribute to a hypercoagulable state and increased risk of thrombosis. Several mechanisms have been proposed to explain the heightened coagulation in cancer patients. Evidence points to significant roles of tissue factor (TF), microvesicles (MV), cancers procoagulant (CP), inflammatory cytokines, podoplanin and several other factors. In this study, we aim to present the factors most commonly identified in the articles analyzed during our review [23-54, 62-64, 73-75]. However, further studies are required to elucidate its role and mechanism.

1. Tissue factor (TF) functions as the physiological trigger for coagulation in vivo. Studies have documented increased TF levels in the circulation of cancer patients and animal models. [23,24]. It is a 47 kDa transmembrane protein that serves as a critical initiator of the extrinsic pathway in the coagulation cascade, facilitating thrombin generation, platelet activation, and subsequent hemostatic clot formation. [25] It has been discovered that in certain malignancies, such as chronic myeloid leukemia, chronic lymphocytic leukemia, and acute promyelocytic leukemia, heightened procoagulant activity is associated with tissue factor (TF) expression. [26,27] Conversely, research on lymphoid-derived malignancies has revealed that, despite the heightened incidence of thrombosis, tissue factor (TF) is not expressed on the surface of malignant cells. [28] At present, a significant relationship between tissue factor (TF) expression and both cancer progression and unfavorable survival outcomes has been identified in various malignancies, including breast [34], bladder [35], colorectal [36], gastric [37], kidney [38], ovarian [39], lung [40], pancreatic [41], and prostate [42] cancers. Although this correlation has been supported by further research, certain studies have reported a lack of such an association in specific cases.

Additionally, elevated levels of TF have been observed in the urine of patients with cancer and inflammatory diseases. [29] Mutations in K-ras and TP53 result in the constitutive activation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) signaling cascades, which directly promote the transcriptional upregulation of tissue factor (TF) [30]. Furthermore, other well-characterized oncogenes, including the epidermal growth factor receptor (EGFR), MET proto-oncogene, and erb-b2 receptor tyrosine kinase 2 (ERBB2), are extensively implicated in the regulation and increased expression of TF, underscoring their significant role in oncogenesis and the associated procoagulant phenotype.[31-33]

2. Microvesicles are small fragments released from the plasma membrane of various cell types, such as tumor cells, blood cells, and endothelial cells, in response to stress. They function as mediators facilitating communication between cells.[43] These vesicles frequently exhibit strong procoagulant properties; for example, those derived from platelets have been shown to possess procoagulant activity that is 50 to 100 times greater than that of activated platelets [44]. Cancer chemotherapy can potentially induce the release of microvesicles (MVs) from tumor cells, blood cells, or endothelial cells [45]. An additional source of MVs is red blood cell and platelet transfusions administered to cancer patients. MVs and exosomes (a subtype of MVs measuring 50–100 nm in diameter) may play a critical role in tumorigenesis, cancer progression, metastasis, and cancer-associated thrombosis [46-50]. Among these, TF-bearing microvesicles are particularly significant. In cancer patients with high levels of TF-positive microvesicles, the cumulative incidence of VTE was 27% compared to 7% in patients with low levels [51]. Exosomes, whether spontaneously released or induced by doxorubicin treatment of the B16 melanoma cell line in vitro, have been shown to promote the production of thrombin and fibrin in plasma, even when inhibitory antibodies against tissue factor (TF) were present [52]. In a breast cancer mouse model, tumor-derived exosomes collaborated with neutrophils activated by tumor-secreted G-CSF, facilitating the formation of neutrophil extracellular traps (NETs) and increasing thrombosis, as discussed later [53]. Additionally, exosomes released by prostate cancer cells, referred to

as prostasomes, were observed to stimulate thrombin generation in vitro in a dose-dependent manner and to induce fatal pulmonary embolism in mice [54].

3. Cancer procoagulant (CP), a cysteine proteinase produced by tumor cells, directly activates factor X. Elevated CP levels correlate with increased fibrinogen in gastrointestinal adenocarcinoma, implicating its role in malignancy-associated thrombosis [75].

4. PAI-1, a critical regulator of fibrinolysis, has been found to be highly expressed in pancreatic cancer cells [62]. Elevated plasma levels of PAI-1 lead to diminished fibrinolytic activity, thereby increasing the risk of thrombosis [63]. The study of Anndén-Sandberg demonstrated that pancreatic cancer patients exhibited excessive PAI-1 levels, which were significantly associated with thromboembolic occurrences [64].

5. Certain malignancies are characterized by the production of aberrantly glycosylated mucins, which interact with selectins to facilitate the formation of platelet-rich microthrombi. These interactions, mediated by leukocyte L-selectin and platelet P-selectin, promote platelet activation and the release of cathepsin G, a potent agonist of platelet aggregation [73,74].

4. **Biomarkers**. The risk of VTE in cancer patients may be reflected by elevations in specific biomarkers. Remarkably, thrombocytosis has been strongly associated with an increased risk of VTE, with one study demonstrating that a platelet count $\geq 443 \times 10^9$/L is associated with a 3.5-fold elevated risk of thromboembolism [55,56]. Additional hematologic biomarkers implicated in VTE risk include leukocytosis and reduced hemoglobin levels, both of which are commonly observed in this patient population [57,58].

Patients with cancer constitute a distinct population with specific clinical and physiological characteristics. Biomarkers are often altered due to the inflammatory response associated with malignancy. Moreover, their clinical presentation is frequently atypical. Notable biomarkers discussed in the literature include increased levels of soluble P-selectin, prothrombin fragment 1+2 (F1+2), D-dimer, and C-reactive protein (CRP) [59,60,61].

5. Treatment.

The goal and the treatment options for primary prevention and acute treatment of VTE in cancer patients are the same as in other populations of patients. In this patient population, however, significantly more therapeutic challenges exist. For instance, in cancer patients, treatment with vitamin K antagonists (VKAs) is associated with a higher risk of recurrence and bleeding compared to non-cancer patients. Cancer patients receiving VKA therapy have approximately a threefold increased risk of VTE recurrence and a two- to sixfold higher risk of bleeding [66,67].

Treatment guidelines from organizations such as the American College of Chest Physicians, American Society of Clinical Oncology (ASCO), British Committee for Standards in Haematology (BCSH), European Society of Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and International Clinical Practice Guidelines advocate for the use of low-molecular-weight heparin (LMWH) for both short-term and long-term management of VTE in cancer patients [68-72]. Despite minor variations in guidelines due to regional practices and clinical trial interpretations, there is a consensus that cancer-associated VTE should be treated with LMWH for at least 3 to 6 months. In remission, treatment can stop after six months, but in active cancer, therapy may extend beyond six months with LMWH or oral anticoagulants, based on patient preference.Furthermore, the CHEST guidelines and expert panel report recommend LMWH as the preferred therapy over vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, or edoxaban [68].

For the prevention of VTE in medical cancer patients is not recommend thromboprophylaxis for outpatients with cancer deemed at low risk for VTE [73]. However in select population with solid tumours or in myeloma patients receving immunomodulatory agents, prophylaxis could be considered.

6. Conclusion.

The phenomenon of Trousseau's syndrome highlights the extensive and multifaceted impact malignancies can have on the hemostatic system. Cancer patients represent a distinct population with a heightened predisposition to developing venous thromboembolism (VTE). In recent

years, significant advances have been made in elucidating the molecular mechanisms underlying the increased risk of VTE in this patient group. However, many aspects of these processes remain poorly understood.Early recognition and targeted management are paramount, requiring clinicians to maintain a high index of suspicion for malignancy-associated thrombosis, especially in cases of recurrent or idiopathic thrombotic events. Further research is necessary to understand the pathophysiology of cancer-associated thrombosis and optimize therapeutic interventions aimed at reducing mortality in this vulnerable population.

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