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The association of cancer and venous thrombosis :yes, Trousseau is right.. again!

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The association between cancer and venous thrombosis was first recognized more than 140 years ago by Armand Trousseau.¹ He wrote that "spontaneous coagulation is common in cancerous patients" because of a "special crisis of the blood." Later studies have confirmed that cancer significantly increases the risk of venous thromboembolism, which is particularly high during the first few months following diagnosis and in the presence of distant metastasis.² Thrombotic complications are frequently observed in patients with solid tumors, such as cancer of the pancreas, lung, stomach, breast, ovaries and the brain.^{3,4} In a study by Prandoni et al an almost 10-fold increased risk of overt cancer was observed in patients with recurring idiopathic deep vein thrombosis.⁵ Furthermore in a study by Sørensen et al. a diagnosis of cancer at the same time as or within one year after an episode of venous thromboembolism was associated with an advanced stage of cancer.⁶ In addition, patients with an unprovoked venous thromboembolism are more likely to have an underlying occult malignancy when compared to those with a known risk factor for venous thromboembolism.⁵

The mechanisms for venous thromboembolism in cancer are multifactorial, and include hypercoagulability, vessel wall injury, and stasis.⁷ The coagulation system is activated in patients with malignancy. The prothrombotic mechanisms often relate to the host response to the tumor, including inflammation, necrosis, and hemodynamic factors, that can also be exacerbated by chemotherapy. In addition, tumor-specific clot-promoting mechanisms, such as expression of procoagulant and fibrinolytic activities by the tumor cells, and interaction with endothelial cells and blood cells, play a role in the pathogenesis of thrombosis in patients with cancer. Venous vessel wall injury can be caused by surgery and by cell-to-cell interactions. Finally, venous stasis predisposes to thromboembolism by diluting and reducing the clearance of activated coagulation factors, and may cause endothelial cell damage.

The most important consequence of venous thromboembolism in cancer patients is its effect on mortality. The occurrence of deep vein thrombosis or pulmonary embolism in the general population is associated with a decreased survival.⁸ Patients with cancer and a venous thromboembolism have much higher mortality compared to cancer patients without thrombosis.⁹ In a study by Sørensen et al. when analysing prognosis, the group with cancer at the time of venous thromboembolism, had a one-year survival rate of 12 percent, as compared with 36 percent in the control group ($P < 0.001$).⁹ Furthermore, patients in whom cancer was diagnosed within one year after an episode of venous thromboembolism had a significantly inferior survival at one year. In a prospective observational study on 4,466 cancer patients

receiving chemotherapy, causes of death were analyzed, and among non-cancer causes of death, 9% of the patients died due to thrombosis, making in the leading contributor of death.¹⁰

In the study by Anderson et al in the present issue of *Leukemia and Lymphoma*, the authors evaluated how and to what extent concomitant or antecedent diagnosis of deep vein thrombosis affected overall survival among more than 400,000 males with cancer.¹¹ They make two important observations. Firstly, patients with a concomitant deep vein thrombosis and cancer had significantly 38% higher risk of dying, compared to cancer patients without deep vein thrombosis. Those patients with lung-, gastric-, prostate-, bladder-, and renal cancer had the highest excess mortality. This may be caused by differences in tumor stage, as well as underlying co-morbidity and life-style factors. Secondly, risk of death was significantly increased among cancer patients diagnosed with deep vein thrombosis one-, one to five and even more than five years prior to their cancer diagnosis. As the authors discuss, this indicates that deep vein thrombosis is not only a serious consequence of a cancer diagnosis but that similar genetic or environmental risk factors may be associated with deep vein thrombosis and poorer cancer survival.

We have come a long way since Trousseau. However, the association of prognosis in cancer and venous thromboembolism is complex and not completely understood. Thorough analyses on causes of death among cancer patients with a concomitant and antecedent thrombosis could elucidate the underlying mechanism behind the findings of Anderson et al.¹¹ It can not be emphasised enough the importance of anticoagulation therapy in cancer patients. In addition, future studies will hopefully increase our understanding on the mechanisms and biology of hypercoagulable state, cancer and its prognosis and help us to better define those patients with idiopathic venous thrombosis that should be subject to in-depth clinical examination for cancer.

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