Editorial Focus

Inside the two way association between malignancy and alteration of haemostasis

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In the few last years, we have learnt to identify several conditions associated with alterations of haemostasis that predispose towards thrombotic disorders, including thrombophilia, hypercoagulable state and thrombosis. Clinical thrombosis is, in fact, a multifactorial disease in which several pathophysiological mechanisms are involved. From this point of view, we can include all thrombotic risk factors (inherited and/or acquired) (1) that may trigger a hypercoagulable state in the first place with the development of vascular thrombosis. Inherited, as well as acquired, risk factors may contribute equally in this way. Underlying systemic diseases, such as different types of cancer, are frequently involved in the pathophysiology of thrombosis, particularly deep venous thrombosis (DVT) (2). Moreover, anti-cancer therapies are also well-recognised thrombotic risk factors (3), such that cancer and diverse treatment modalities represent the most common acquired condition associated with hypercoagulable state and DVT. Although the association between cancer and thrombosis was already described in 1865 by Trousseau for the first time (4), only in the last 20 years we observed an increased interest on this topic with a growing body of data and the accumulation of numerous reports.

A thrombotic event can occur at any time during the history of oncological / oncohaematological disease and may affect arterial and/or venous vessels (5–6) or can culminate as systemic syndrome such as disseminated intravascular coagulation (DIC) (7). Furthermore, we also learned that indications of thrombosis could be the first clinical signs of an underlying malignancy (6, 8). As previously noted, anticancer strategies may contribute to thrombotic symptoms, and an increased rate of DVT has been frequently reported after oncological surgery (6). Also, implantation of central venous catheter or port-a-cath to simplify chemotherapy have been associated with thrombosis not only of a lower limb, but also of the upper extremities (9). Moreover, chemotherapy is also involved in thrombogenesis, because several drugs or chemotherapeutical regimens exert *per se* a prothrombotic action such as hormonal or growth factor therapy (2, 10–11). Although combined thalidomide treatment appears to be promising as anti-tumorangiogenic therapy (12), insufficient reliable data are available at present to predict an association between this therapy and thrombosis (13).

Cancer *per se* represents a high thrombotic risk situation and several molecular mechanisms may contribute to a hypercoagulable state in certain tumor patients. Cancer procoagulant and tissue factor have been described as most common procoagulant factors produced by cancer cells that provide a link between the tumor burden and alterations in haemostasis (14). Other pathways such as fibrinolysis or pericellular proteolysis are significantly altered in certain tumors with an overall increase in plasminogen activators and their inhibitors; these parameters present reliable prognostic factors as well (15). Conversely, antithrombotic and anticoagulant interventions have been documented to reduce the outcome of tumor angiogenesis in patients with different kinds of cancer (16, 17). In experimental models, platelets and their proangiogenic release products (such as vascular endothelial growth factor or lysophospholipids) have been identified as major triggers for (tumor-) angiogenesis (18–20). Altogether, about 20% of oncological patients present a life-threatening DVT, and the survival rate for patients with a diagnosis of cancer within one year after venous thromboembolism is poor as compared to oncological patients without previous DVT (21).

In this issue of *Thrombosis and Haemostasis*, Sase et al. report on the clinical association between oncohaematological disease, such as the different types of malignant lymphoma, and thrombophilia in several ways (see pages 156-62). A hypercoagulable state of the described patients was shown by increased levels of fibrinogen, D-dimer and fibrin degradation products in accordance with previous reports. Furthermore, a clear association between some particular histological types of malignant lymphoma, the advanced stage of the disease and thrombotic disorders such as DIC and interstitial pneumonia was described, confirming and extending the few data available in the literature on this topic. This point is particularly interesting because oncological patients frequently show life threatening thrombotic complications in advanced stage (21), and this could explain the increased rate of pulmonary embolism in an autoptical study on critically ill patients (23): In this study, there was a significant discrepancy between ante-mortem and post-mortem diagnosis related to cancer myocardial infarction and pulmonary embolism that were the most commonly missed diagnoses in described patients (23). Moreover, besides plasma determination

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of tissue factor antigen, Sase et al. (22) reported an increased tissue factor expression in vascular endothelial cells surrounding lymphoma tissue.

This approach could promote another trend not frequently explored to study the molecular alterations of haemostasis present in the tumor tissue itself that is flanked by analysis of plasmatic, serological and genetic abnormalities in oncological patients. Based on such a combined diagnostic approach, a reliable and safe antithrombotic and / or anticoagulant therapy may not only help to prevent a DVT situation, but may also provide a reduction in the tumor burden of patients.

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