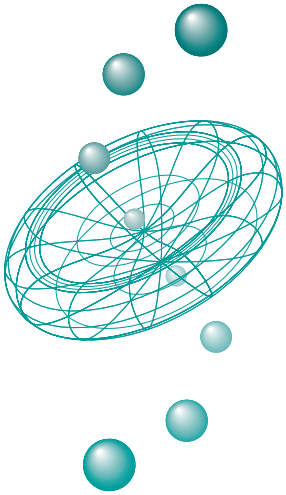
REVIEW ARTICLE



Coagulation Abnormalities and Oncology

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INTRODUCTION

More than 100 years ago Trousseau described for the first time hemostatic abnormalities in stomach cancer. Many decades later in recognition of his work the stimulation of blood coagulation by tumors is still generally described as Trousseau's syndrome.

Three types of evidence support the idea of an important relationship between blood coagulation and tumor homeostasis: clinical, histologic, and pharmacologic.

Clinical and laboratory evidence is based on the well known phenomenon of patients with certain forms of cancer to develop thromboembolic disease and/or disseminated intra-vascular coagulation (DIC). Histologic evidence is provided by the observation of platelet and fibrin thrombi in vessels draining tumors. Finally the positive results of pharmacologic intervention with anticoagulant drugs and/or anti-platelet agents in animal tumor models and in human cancer have also supported the thesis that a "hypercoagulable" state associated with cancer is disadvantageous for the host. Today it is well accepted, that local or systemic activation of blood coagulation can be produced by tumor products, e.g. receptors, surface matrix, and cytokines. While this activation favors tumor spread, interruption of blood coagulation reactions, in general, favors the host and impairs tumor metastasis.

TUMORS AND THROMBOEMBOLIC DISEASE

Increased incidence of thromboembolic disease in tumor patients has led to the examination of various aspects of the coagulation system in these patients. Abnormalities of routine tests of blood coagulation have been reported to occur in as many as more than 92% of patients suffering from cancer[1]. There is also a clear correlation of the risk for thromboembolic diseases with certain tumors[2]. For instance, is the relative risk for thrombosis in bronchial carcinoma, pancreatic, stomach and colon cancer higher than in other malignant diseases.

The activation of coagulation in patients with cancer contributes significantly to morbidity and mortality rates and may play a fundamental role in the host response to growing tumors[3]. Thereby, patients suffering from cancer are at high risk for the development of venous thromboembolism (VTE), particularly during chemotherapy, adjuvant immunotherapy or following surgery. In many cases, even, VTE is the first manifestation of cancer. According to Monreal the incidence of newly diagnosed malignancy is increased significantly among patients with unexplained VTE during the first 6-12 months after the thromboembolic event. Several studies have shown, that the frequency of underlying cancer in idiopathic VTE can be more than 20%, with up to 38%[4].

PATHOPHYSIOLOGY OF THROMBOEMBOLIC STATE IN CANCER PATIENTS

The hypercoagulable state of malignancy is due to a complex interaction of tumor cells and their products with host cells. Tumor cells can activate directly the clotting cascade and cause thrombosis or can induce pro-coagulant properties and inhibit anti-coagulant properties of vascular endothelial cells, platelets, monocytes, and macrophages[5]. Clotting activation in cancer may be at least partly related to expression of tissue factor by circulating blood monocytes, which can be induced by tumor associated cytokines, like TNF α or IL-1 β. The activation of the clotting process in cancer, however, is a multifactorial process. This includes a variety of nonspecific mechanisms such as tissue damage and inflammatory response that lead to exaggerated tissue factor expression[6]. Tissue factor (TF, thromboplastin) is a membrane protein found in many normal body tissues and, although lacking protease function itself, greatly enhances the ability of Factor VII to initiate extrinsic blood coagulation by activation of Factor X. Elevated expression of TF has been described in numerous solid tumors, like gastric[7], ovary[8], and kidney tumors[5]. Furthermore, a wide variety of tumor cells release plasma membrane vesicles with procoagulant activity, which behave largely like TF. These vesicles may also act as surfaces for the prothrombinase complex generation.

PROLONGATION OF SURVIVAL OF PATIENTS WITH CANCER

Recent studies have suggested that heparin (UFH) or low molecular weight heparin (LMWH) administered to patients with malignant disease may prolong their survival[9]. A significant survival advantage was shown for patients with colorectal cancer who had received UFH.
Lebeau, et al. observed, that in patients with small cell lung carcinoma administration of subcutaneous UFH led to higher complete response rates to chemotherapy and longer median survival when compared to control patients[10]. LMWH also appear to prolong survival in patients with malignant diseases[11]. The evaluation of LMWH as a direct cancer agent is still in progress.

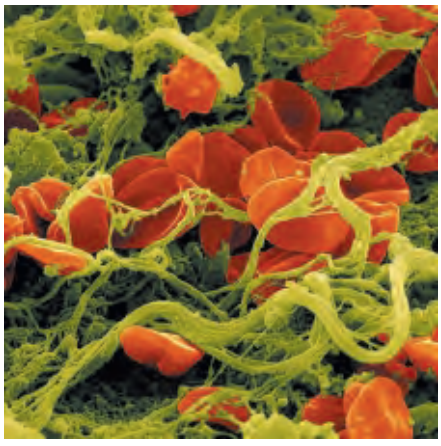

Fig. 1 *Fibrin clot with erythrocytes (photo is courtesy of eye of science, Germany)*

DIAGNOSTIC ASPECTS

Molecular markers of haemostatic activation in cancer patients

In general, routine coagulation tests such as for prothrombin time (PT) and activated partial thromboplastin time (APTT) are not helpful in demonstrating hypercoagulability in cancer patients. Some may exhibit decreased clotting times, others may have moderate prolongation. A status of hypercoagulability is best demonstrated with sensitive molecular markers of clotting.
Duncan, et al. have used the term “markers of coagulation and haemostasis activation” (MOCHA) to describe these kind of tests. They also suggested that particularly high levels of these MOCHA are suspected for undiagnosed malignancy in thrombophilic patients[12].

Some examples for elevated D-dimer, F1+2 and TAT in tumor patients

Prothrombin Fragment 1+2 (F1+2) and Thrombin-Antithrombin (TAT) complex have been studied in cancer patients with broadly similar results.
High levels of TAT and D-dimer seemed to be associated with poor prognosis in lung cancer[13]. Comparing patients with limited disease to those with extensive disease, there were significant differences in TAT and D-dimer. Those patients who achieved complete or at least partial remission to subsequent tumor treatment had significant lower baseline level samples than non-responders to therapy. High levels of TAT in lung cancer are obviously a sign for an unfavorable prognosis. In a later study, D-dimer was even found to be an independent predictor of survival in patients with lung cancer[14,15].
Similar results were observed for breast cancer patients and for kidney cancer patients. Plasma D-dimer levels correlated with clinical stage and axillary lymph node status in operable breast cancer patients. Elevated plasma D-dimer levels were markers for lymphovascular invasion of the tumor. This suggested that detectable fibrin degradation, as measured by plasma D-dimer, is a clinically important marker for lymphovascular invasion and early tumor metastasis in operable breast cancer[16] and for renal cell carcinoma[17].
Geenen, et al. found that D-dimer values were significantly higher in prostatic carcinoma patients having metastases when compared to patients with benign hyperplasia or local malignant disease[18].
Plasma levels of the fibrin degradation fragment, D-dimer, may also be very useful in assessing the tumor burden, as the levels of D-dimer correlated with the stage in colorectal cancer[19]. According to Oya and colleagues D-dimer is considered to be useful for the preoperative staging of colorectal cancer[20].
The measurement of plasma D-dimer levels in patients

with ovarian cancer revealed that D-dimer correlates with the clinical course of this disease[21]. D-dimer and fibrinogen levels, but not Antithrombin, Protein C and PAI were found to be significantly correlated with the FIGO stage (a particular tumor stage classification system) in a study on patients with ovarian malignancy. They were significant risk factors for reduced overall survival[22].
In another study with gynaecological tumors van Wersch observed , that the group of patients with a metastatic disease differed from the non-metastasized tumor group in Prothrombin F1+2, TAT and D-dimer. In the non-metastasized malignant tumor group solely F1+2 was significantly higher than in the benign tumor group. Thus, these parameters seem to be indicative for high risk gynaecological tumors[23]. Very interestingly the same group found that in metastasized gynaecological tumors Factor XIII levels were significantly lower than in the non-metastasized malignant group or in the benign tumor group. From a clinical point of view, in this circumstance the measurement of FXII activity might be helpful in diagnosing metastases in patients with a gynaecological tumor[24]. A summary on these examples is provided in ***Table 1.***

COAGULATION MARKERS PREDICT SURVIVAL IN CANCER PATIENTS

Various clinical investigations during the last two decades have provided meaningful examples for the usefulness of specific coagulation markers for the risk assessment in cancers. However, very recently Beer and colleagues published a paper, which for the first time provides clear evidence, that coagulation markers can even predict survival time in cancer patients. From January 1995 until November 1996 consecutive (n = 268) ambulatory cancer patients at the University Hospital of Bern in Switzerland, were included in this study and followed over a maximum of 3 years. 99 out of 268 patients died during the observation period. Patients with active disease had a significant, 1,5 to 5-fold, increased marker concentration compared to patients in documented remission (***Table 2)***. The authors conclude that a single determination of coagulation markers, particularly of TAT, FM, and D-dimer is capable to strongly predict survival in cancer patients over the following 1-3 years after first diagnosis of the tumor.
Taking all these findings together, there is little doubt

Table 1 *Abnormal coagulation markers in various cancers*

Tumor entity	Elevated markers utilized for staging or prognosis	References
Breast cancer	D-dimer	Blackwell 2000
Prostatic carcinoma	D-dimer	Genen 1997
Ovarian cancer	D-dimer	Gaducci 1995
	Fibrinogen	von Tempelhoff 1997
	Tissue factor	Mussoni 1986
Gynaecological tumors	Prothrombin Fragment F1+2, Thrombin Antithrombin (TAT) Complex, D-dimer	van Wersch 1995
	Factor XIII (decreased)	van Wersch 1994
Kidney cancer	Tissue factor, D-dimer	Petri 1997, Petri 1998
Gastric cancer	Tissue factor	Sakuragawa 1997
Colorectal cancer	D-dimer	Edward 1993, Oya 1998
Lung cancer	TAT, D-dimer	Seitz 1993, Bucheri 1997, Taguchi 1997

Table 2 *Marker concentrations of coagulation in active tumor disease and in remission (Enzygnost TAT micro, F1+2 and D-dimer micro, all Dade Behring, Roche Enzymun Test FM, taken from Beer,et al., 2002)*[25].

	Patients with active disease (n = 196)	Patients in Remission (n = 71)	P (Wilcoxon Rank sum test)	Healthy controls (n = 20)
TAT [ug/L]	3.3 ± 4.3	1.6 ± 2.4	< 0.0001	1.59 ± 0.55
F1+2 [nmol/L]	1.40 ± 1.02	0.97 ± 0.45	< 0.0006	0.77 ± 0.21
D-dimer [ug/L]	199 ± 615	40 ± 81	< 0.0001	21.1 ± 15.6
FM [ug/mL]	26.6 ± 83.6	4.9 ± 8.9	< 0.0001	1.58 ± 1.03

that investigation of the coagulation abnormalities in tumor patients can provide additional important information for prognosis and for individual risk stratification. Hopefully, these diagnostic efforts may help to improve patient care and the quality of life of tumor patients by helping to optimize treatment in the follow-up period after removal of a primary tumor.

SUMMARY AND CONCLUSION

- The coagulation cascade may be activated by several mechanisms in cancer patients
- Coagulation markers may be useful tools to assess the malignant potential of tumors
- Frequently tumors are detected after idiopathic VTE or incidentally by elevated coagulation markers
- Coagulation markers like D-dimer, Prothrombin F1+2, Thrombin/Antithrombin III complex, and Fibrin monomer have shown their diagnostic potential for utilization in oncology, as they may represent suitable tools for risk stratification and for selection of adequate therapeutic regimens.

Sysmex and its global partner Dade Behring offer a variety of assays for use in clinical routine and in oncology research. By providing these particular coagulation marker assays both companies support this interdisciplinary field of clinical medicine with the necessary tools.

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