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Clinical characteristics of disseminated intravascular coagulation in patients with solid and hematological cancers

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ABSTRACT

Malignant disease can be complicated by disseminated intravascular coagulation (DIC). DIC is defined as systemic intravascular triggering of coagulation (resulting in intravascular fibrin clot formation) and concurrent depletion of clotting factors and platelets (increasing the risk of hemorrhage). The clinical presentation of DIC in patients with cancer has usually a less fulminant presentation than DIC that may accompany other underlying disorders, such as sepsis and trauma. A more insidious, but also more protracted, diffuse activation of coagulation can proceed without any symptom. Ultimately this may lead to deficiency of platelets and clotting factors and hemorrhage (often at the site of the tumor or metastases) may be the first clinical symptom indicating the presence of DIC. An alternative presentation may be thrombosis, ranging from overt venous thrombo-embolism to microvascular disease and thrombotic microangiopathy. The therapeutic foundation of DIC is management of the underlying condition but in some cases supportive interventions, specifically targeting the hemostatic system may be needed.

1. Introduction

There is a clear connection between the presence of malignancy and thrombosis. Patients with cancer are at high risk to present with venous thrombosis or pulmonary embolism, which in some cases may manifest before a diagnosis of cancer has been made. However, thrombotic complications of cancer are not restricted to venous thromboembolism, and other manifestations of a procoagulant state, in its most fulminant appearance manifesting as disseminated intravascular coagulation (DIC), may occur as well [1,2]. The clinical manifestation of DIC in cancer may be bleeding, thrombosis or a combination of these two conditions [3]. In addition, thrombotic microangiopathy may occur [4].

The pathways that contribute to activation of hemostasis and the ensuing prothrombotic state associated with malignant disease are for an important part understood. Tissue factor- and (possibly) cancer-procoagulant-initiated activation of coagulation, cytokine-mediated dysfunctional anticoagulant systems and deranged fibrinolysis play a crucial role and pathological processes may evolve at the surface of endothelium injury caused by radio- and chemotherapy.

It is not clear to what extent the manifestation of a clinically overt coagulopathy and thrombosis can be ascribed to malignancy-associated DIC. There is ample evidence for a prohemostatic state in practically all patients with advanced cancer, however, the incidence of clinically detected DIC seems to be much less frequent [5]. The incidence of DIC in consecutive patients with solid cancer was approximately 7% in clinical studies and in patients presenting with acute hematologic malignancy, in particular acute lymphoblastic leukemia, DIC could be diagnosed in 15–20% of patients [6,7]. A number of studies showed that the occurrence of DIC in patients with acute leukemia further surged during initiation of chemotherapy [8]. In patients with acute promyelocytic leukemia (AML M-3 according to the FAB classification) DIC can be detected in over 90% of patients at the time of presentation [9,10].

2. Bleeding in patients with cancer and DIC

Contrary to patients who present with fulminant DIC as a complication of sepsis or trauma, the coagulopathy in patients with malignancy may manifest with relatively mild or insidious clinical symptoms of consumption or even non-symptomatic disease characterised by laboratory abnormalities only [11–13]. The clinical presentation of subacute to protracted forms of DIC usually occurs in association with mucin-producing adenocarcinomas and some types of acute hematological malignancies. The latter, in particular in case of acute promyelocytic or monocytic leukemia, is often dominated by a hemorrhagic presentation, whereas thromboembolic manifestations are more common in case of solid tumors, especially in adenocarcinomas, such as

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prostate, pancreatic or other digestive tract cancers.

In a series of 182 patients with cancer and DIC, major and profuse hemorrhage was seen in 75 cases, whereas thrombotic complications were more frequently present, in the form of venous thrombosis (123 cases), migratory thrombophlebitis (in 96 patients), and arterial thrombosis and embolism caused by nonbacterial thrombotic endocarditis (31 patients) [14]. In addition, multifocal hemorrhagic cerebral infarctions, caused by microemboli were described. A unique feature of patients with cancer and a prohemostatic state, in particular in those with mucin-producing carcinoma, is nonbacterial thrombotic endocarditis with systemic embolization [15]. In patients with malignant disease and protracted DIC, laboratory abnormalities are exceptionally variable. Some patients have all of the classic abnormalities of thrombocytopenia, prolonged global clotting assays, elevated fibrin split products, and low levels of fibrinogen whereas other patients will present with moderate thrombocytopenia only or nearly normal coagulation laboratory results, due to sufficient compensation for the consumption of coagulation factors and platelets.

3. Venous thromboembolism as a manifestation of systemic coagulation activation in cancer

The association between cancer and venous thrombosis was first described in the 19th century and is often linked to the French doctor Armand Trousseau (1801–1867) [16]. In fact, the acronym 'Trousseau's syndrome' is regularly used for the manifestation of venous thromboembolism as a first sign of the presence of cancer. It was, however, not before 1935 that thrombosis as a first symptom of until then undetected cancer was unequivocally reported [17]. Since this publication, many reports have appeared on the incidence of venous thrombosis and pulmonary embolism in patients with diagnosed or occult malignant disease [18].

The occurrence of malignancy in consecutive patients with a diagnosis of venous thromboembolism can be inferred from 14 observational studies including almost 5000 patients [18]. The mean prevalence was 15.2% with a very wide range of 4.7 to 30.7%, presumably caused by differences in the various study populations. It is unclear, however, whether screening for malignancy in patients with unexplained thrombosis is of clinical benefit [19]. The presence of malignant disease caused an almost 4-fold increased risk of venous thromboembolism. Upon administration of chemotherapy the relative risk further surged to 6.5 [20]. Studies in breast cancer patients treated with chemotherapy, often in combination with hormone treatment, confirmed a 5-years incidence of thrombosis of 1–10%. Risk factors for developing thrombosis in patients with malignant disease are the tumor type, the extent of the cancer, treatment with chemotherapy, and the presence of central venous catheters.

Mucin-secreting tumors, such as pancreas, lung, and stomach malignancy, or metastasized adenocarcinomas from unknown origin, are associated with the highest risk of thrombosis [14]. Prospective studies have demonstrated that thrombosis is a particular risk in patients with brain tumors, ovarian cancer and pancreatic carcinoma [21,22]. In absolute terms, due to their relatively frequent occurrence lung carcinoma, colon cancer and prostate malignancies, are most frequently observed [23].

Chemotherapy may increase the thrombotic risk presumably due to its harmful effect to endothelial cells. Anti-angiogenic drugs, especially when combined with chemotherapy, may significantly augment this risk. Administration of thalidomide in combination with chemotherapy for renal cell carcinoma or multiple myeloma caused very high complication rates of thrombosis in 43% and 28% of patients, respectively [24,25]. Other anti-angiogenic agents have been related to an enhanced risk of both venous and arterial thrombosis, likely caused by their effect on endothelial cells [26,27].

Indwelling catheters may represent a surface on which thrombosis in patients with cancer may assemble and this risk is further enlarged when catheter-related infection occurs. Previous studies have estimated the risk of symptomatic catheter-associated thrombosis in patients with cancer to be 4–15% [28,29]. A trial in patients with a hematological malignancy, however, showed a much lower incidence of thrombosis and no beneficial effect of prophylaxis with low molecular weight heparin [30].

4. Microangiopathy in cancer

Thrombotic microangiopathy may be another manifestation of cancer or cancer-related treatment [31]. This coagulopathy seems to occur in an increasing number of patients following high-dose chemotherapy in combination with autologous or allogeneic stem cell transplantation [32,33]. A relatively large number of case has been reported in > 30 articles and a prospective study demonstrated that the incidence of thrombotic microangiopathy ranged from 2 to 8% of patients on high-dose chemotherapy [34–37]. Thrombotic microangiopathy encompasses a number of syndromes which are characterised by enhanced platelet-vessel wall interaction, in its most typical form represented by thrombotic thrombocytopenic purpura (TTP). In addition, some of the features of veno-occlusive disease (VOD) that can occur in stem cell transplantation patients are similar to those seen in thrombotic microangiopathy. Thrombotic microangiopathy is a consequence of massive platelet adhesion, aggregation and activation (resulting in consumptive thrombocytopenia and formation of thrombi in the (micro)vasculature causing impaired organ function (for example resulting in kidney failure or cerebrovascular symptoms) and red cell fragmentation due to microangiopathic hemolysis. Historically, this complication only occurred in association with specific types of chemotherapy, such as mitomycin-C, but in recent years a large number of different types of chemotherapy seem capable of eliciting thrombotic microangiopathy [38,39]. The dose of the chemotherapy appears to be of relevance, which may explain the rising incidence since the widespread clinical application of stem cell transplantation permits much higher doses of chemotherapy. Furthermore, total body irradiation and the use of immunosuppressive medication (such as ciclosporin-A) have been implicated with the higher incidence of post-chemotherapy thrombotic microangiopathy [40,41]. The prognosis of thrombotic microangiopathy in cancer is poor: Of all affected patients mortality was about 30% and the direct thrombotic microangiopathy-related mortality > 20% [37]. In addition, survivors may develop persistent or even end stage renal insufficiency. The pathogenesis of thrombotic microangiopathy is not completely clear. It is widely assumed that endothelial injury caused by chemotherapy plays a crucial role, but definitive evidence is lacking.

5. Pathogenetic features of DIC in cancer

Malignant cells can express various procoagulant molecules such as tissue factor (TF), which binds circulating factor VII(a) and subsequently activates factors IX and X. Another initiator of coagulation is cancer procoagulant (CP), a cysteine protease with factor X activating properties [42], although some authors argue that in the absence of protein or gene sequence data and specific antibodies and/or assays recognizing this protein, its existence is controversial and may be due to contamination in earlier experiments. A number of studies demonstrate the presence of functionally active TF on vascular endothelial cells as well as tumor cells in breast cancer, while not detectable in tissue from patients with benign fibrocystic breast disease [43,44]. It should be noted that the role of TF in the pathogenesis of cancer besides its role in coagulation is only partly understood. TF appears to be involved in tumor metastasis and angiogenesis [45–47], factors that may directly influence the course of malignancy [48]. Cancer procoagulant is an endopeptidase that is found in extracts on neoplastic cells but also in the plasma of patients with solid tumors. The exact role of CP in the pathogenesis of cancer-related DIC has not yet been completely