REVIEW

An overview of coagulation disorders in cancer patients

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Abstract
A diversity of coagulation disorders in cancer patients arise from tumor-specific growth characteristics, neangiogenesis with impaired endothelial lining, defective myelopoiesis, hypoproteinemia or metastatic lesions growth with organ dysfunction. Recent investigations have found a clinically relevant correlation of coagulation disorders and tumor growth. These prompted new therapeutic strategies focused on growth factors with the aim to control tumor metastasis, particularly if used for the treatment of micrometastatic disease. However, such treatment may lead to the life threatening coagulation imbalance.

A coagulation homeostasis may become further impaired after nonsurgical cancer therapy, especially after preoperative irradiation, which produces lesions precipitating both bleeding and thrombosis. Anticancer chemotherapy may affect liver function and decrease the synthesis of both procoagulation and anticoagulation factors. The most of chemotherapeutic protocols affect platelet synthesis, which arises as a principal dose-limiting side effect. It was observed both during combined systemic chemotherapy and local antitumor therapy. Although the side effects produced by chemotherapy are reversible, endothelial lesions may persist for many years after the anticancer treatment.

Instead of cancer patients, there's a growing cohort of patients with nonmalignant diseases who use cytostatics in the perioperative period, and are candidates for surgical procedures not related to their malignant disease, i.e. hernia repair. In this patient population a special attention must be paid to the preoperative evaluation of coagulation status and thromboprophylaxis.

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Introduction

Clinically evident coagulation disorders are commonly the first sign of malignancy [1,2]. The incidence of subsequent occult cancer was 2.2–12% in the group of patients with symptomatic idiopathic venous thromboembolism (VTE). If the extensive screening for malignancies was performed in the patients with VTE, malignancies may be identified at an earlier stage, and the mean delay to diagnosis can be reduced from 11.6 to 1.0 month [3]. Independent risk factors for a cancer diagnosis are older age at the time of the venous thrombosis and an idiopathic thromboembolism [3]. The elevated risk of newly diagnosed cancer after the first episode of VTE is present during at least the following two years [4].

Various laboratory signs of coagulation activation in cancer patients are caused by tumor growth, neoangiogenesis and affected organ dysfunction. Anticancer chemotherapeutic agents may further aggravate patient’s general condition and precipitate coagulation disorders. Despite an increased risk for thrombo-embolic events in overall cancer patient population, these drugs may enhance the risk of bleeding complications. This article emphasizes critical points in the cancer growth and treatment that may result in the coagulation disorders.

Tumor growth and angiogenesis

While growing, malignant tumors usually produce intratumoral proteolytic enzymes involved in the tumor cell invasion, numerous stromal reactions and new blood vessel formation [5–8]. One of the enzymes involved in this process is a membrane type 1 matrix metalloproteinase (MT1-MMP) which is exposed at the abluminal endothelial cell surface. It is engaged in direct proteolytic digestion of vascular basement membranes, which is essential for out-sprouting and tubulogenesis of novel capillaries and tumor growth [6]. Matrix metalloproteinases participate in the extracellular degradation of type IV collagen, gelatin, and elastin, and in the tumor–stroma interactions [7].

Tumor cells stimulate angiogenesis by releasing stimulatory growth factors, like vascular endothelial growth factor A (VEGF-A) [8]. VEGF-A is a multifunctional cytokine that is widely expressed by tumor cells. It acts through receptors (VEGFR-1, VEGFR-2, and neuropilin) that are expressed at the abluminal, basal surface of vascular endothelium and on some other cells. VEGF-A up-regulates the expression of endothelial cell proteases that degrade vascular basement membranes, and induce pericyte detachment. It stimulates spreading and thinning of endothelial cells to cover a greatly
expanded vascular surface area, acting as the most potent proangiogenic factor [8]. A resulting microvessel density is significantly higher in the tumor than in normal tissue (Fig. 1).

It plays a key role in the pathophysiology of several tumors, and is an indirect procoagulant which alters the hemostatic properties of endothelial cells [9]. VEGF-A increases microvascular permeability, reprograms gene expression, and promotes endothelial cell survival [8]. In the case of minor local endothelial damage, VEGF-A produced locally probably contributes in endothelial lining reparation [8,10].

Morphology and pathophysiology of tumor endothelium

Neoangiogenesis is the process by which new tumor blood vessels are derived from preexisting host microvessels, primarily venules. Morphological and functional features of tumor blood vessels are the main source of tumor procoagulative activity. Tumor blood vessels are not arranged in a hierarchical pattern but are irregularly spaced and structurally heterogeneous [8]. The vasculature in the tumor microenvironment presents multiple morphological and functional defects. Basement membrane in tumor vessels has conspicuous abnormalities, including irregular thickness, and loose association with endothelial cells and pericytes [12]. Thin-walled tumor vessels can be distinguished from normal arteries and veins by their inappropriately large size, by their thinner and often asymmetric muscular coat [8]. Such vessels lacking pericyte and having basement membrane with profound structural abnormalities are subject to thrombosis or collapse (Figs. 1–3). They are irregularly lined by actively dividing endothelial cells forming defective inner coat, especially in aggressive tumors [8] (Figs. 1 and 2). Tumor blood vessels may undergo a process of bridging, in which endothelial cells form transluminal bridges into and across vascular lumens (Fig. 3). That process divides blood flow into multiple smaller-sized channels expressing endothelial markers [8].

A leakage of plasma protein through highly permeable tumor blood vessels may activate an inflammatory response and tumor-induced extrinsic pathway of coagulation (Fig. 4). An exposure to inflammatory stimuli can induce a procoagulant behavior of the tumor endothelial cells, with endothelial activation/apoptosis. Another important coagulation trigger is collagen that typically proliferates in the tumor stroma. Through multiple holes in the endothelium it reaches blood stream (Fig. 5), and activates platelets within the tumor vessels [9]. Upon the activation platelets release growth factors and associate with fibrinogen in aggregates, resulting in the elevated fibrinogen degradation products (FDPs) levels in malignant diseases. Consequently, an increased platelet turnover in the cancer patients occurs [9]. Kuenen et al. observed that 40% of patients with malignancy (in small series) had an elevated platelet count [10]. In the same manner cancer cells may form tumor emboli with fibrinogen, platelets, and red blood cells and enter vasculature (Fig. 4). Tumor emboli, depending on their size, may precede the metastatic process or result in the pulmonary tumor embolism [13].

The tumor microenvironment influences the induction of angiogenesis by increasing the production of VEGF-A. Endogenous angiogenesis inhibitors are molecules proved to have antiangiogenic activity, potentially offering a counterbalance for the VEGF-A. Endogenous angiogenesis inhibitors thrombospondin-1 and endostatin are thus maintaining a physiological angiogenesis balance. Endostatin was recently found to be stored in platelets and released in response to thrombin. It inhibits endothelial cell migration and induces apoptosis, leading to the reduced vascularization of tumors. Endostatin suppresses both tumor growth and angiogenesis in mice by blocking both VEGF and its receptors. It could block the activities of certain tumor-associated pro-matrix metalloproteinases. This observation may explain some of its antitumor effects [14,15]. An alteration within the angiogenic balance due to a reduction

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Figure 1  Blood vessels in the invasive ductal breast cancer, immunohistochemical staining of endothelial cells with antibodies against CD34, magnification 630×. Endothelium of blood vessels (block arrows) and clusters of salient endothelial cells without obvious lumen are shown in the brown color. Endothelial cells are activated in three blood vessels in the centre of the micrograph.

Figure 2  A glioblastoma micrograph with defective endothelial lining in two blood vessels and perivascular tumor infiltration (arrowheads). CD34 staining, magnification 630×.
in the levels of individual endogenous inhibitors of angiogenesis leads to increased tumor growth, as shown in thrombospondin-1 and endostatin deficient mice [15]. In the light of this observation antiangiogenic therapy is a promising approach for anticancer treatment.

**Antiangiogenic therapy**

A suppression of tumor angiogenesis targeting VEGF and MMP is in the focus of numerous preclinical and clinical investigations. Inhibitors of VEGF receptor-1 and -2, specific monoclonal antibodies are new modalities of anticancer chemotherapy [10,16]. Anti-VEGF antibody bevacizumab is a standard front-line treatment for patients with metastatic colorectal cancer, alone or combined with other cytostatics [17]. Recently it was approved by FDA for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer and as a first line treatment administered in combination with carboplatin and paclitaxel in non-small cell lung cancer, too [16,18].

Several studies on the effects of MMP inhibitors did not confirm that drugs effective in preclinical studies will inhibit tumor growth and dissemination in the clinical setting. MMP inhibitor prinomastat was evaluated in combined modality therapy with irradiation in the patients with resectable oesophageal cancer. Unfortunately, early termination of the study due to the unexpected thromboembolic events precluded any conclusions regarding clinical activity of this combined therapy [19]. The patients in the both prinomastat and placebo arm developed thrombo-embolic complications in the preoperative and post-operative period. The patients developed deep vein thrombosis (DVT) in an upper extremity, superior vena cava, and pulmonary embolism (PE) [19]. Despite earlier observation that prinomastat combined with chemotherapy in patients with advanced cancer approximately doubled the risk of developing venous thromboembolism [20], the synergism with irradiation cannot be underestimated [19].

An inhibition of angiogenesis was observed with less specific anticancer drugs. Docetaxel treatment inhibits angiogenesis in both *in vitro* and *in vivo* models. PEG-interferon-α and docetaxel suppress the local production of proangiogenic molecules by tumor cells, inhibiting thus neoplastic angiogenesis. This combination therapy results in increased apoptosis of tumor-associated endothelial cells in prostate cancer [21]. As expected, the endothelial stimulating factors, VEGF and the basic fibroblast growth factor are able to protect endothelial cells from antiangiogenic properties of docetaxel [22].

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**Figure 3** Recidive cancer of the colon with early diffuse postirradiation lymphocyte infiltration. Thin-walled blood vessels with endothelial cell bridging (arrows) and endothelial necrosis or disruptions with perivascular bleeding (triangles) are stained with hemalaun/eosin (HE), magnification 100×.

**Figure 4** Metastatic planocellular (squamous) neck cancer with irregular luminal surface in the blood vessel; HE 200×. Tumor embolus with central necrosis (arrow) completely obstructs blood flow. Tumor infiltration and destruction of the blood vessel wall (block arrow), with perivascular inflammation (oval arrow).

**Figure 5** Invasive breast cancer tissue, noncellular collagen fibers (green) are in the close contact with activated endothelial cells. Tumor cells are shown with arrowheads. Red blood cells within small tumor vessels with endothelial bridging (arrows) and diffuse bleeding (triangle). Mallory’s stain, magnification 630×.
Procoagulative factors in cancer

Multiple vascular lesions in the tumor microvasculature promote plasma coagulation cascade activation through the extrinsic coagulation pathway. Microvascular lesions are the sites of intravascular coagulation and flow occlusion, and sites of extravasations and bleeding, too (Figs. 1–6). A resulting tumor vascular supply is typically aberrant. An enlarged tumor mass, neoangiogenesis and metastasis correlate with concentrations of procoagulation factors. The tissue factor (TF, factor III) is protease initiating coagulation cascade. TF is procoagulant expressed on various normal cells, i.e. endothelial, and on tumor cells. It reacts with clotting factor VIIa and with other extravasated plasma-clotting proteins, resulting in thrombin generation. Thrombin (FII) is a powerful proteolytic enzyme and procoagulant compound. It activates pro-MMP-2, which destroys the basal membrane (Fig. 7), allowing proliferation of endothelial cells in the novel tumoral fibrin matrix. Thrombin induces the degradation of fibrinogen to fibrin monomer and forms an extracellular fibrin barrier [29]. After fibrinogen is converted to fibrin, a fibrin stabilizing factor or FXIII introduces new peptide bonds and makes a fibrin clot mechanically stronger and resistant to the activity of fibrinolytic enzymes (Fig. 7). The cross-linked fibrin shows similar distribution with TF in the vascular endothelial cells of the malignant tumors i.e. in the breast cancer, and not in the breast fibrocystic disease [23]. The presence of extravascular fibrin deposits strongly implies that tumor blood vessels are hyperpermeable to fibrinogen and therefore to other plasma proteins, especially at the tumor-host interface [8]. Other elements of tumor stroma are also indicative of leakage: increased amounts of plasma protein-rich interstitial fluid; structural proteins not normally found in mature stroma such as fetal forms of fibronectin, tenascin, abnormal proteoglycans, and variable numbers of inflammatory cells, etc. [8,9]. TF-dependent activation of extravascular coagulation was found in active angiogenic sites in invasive human breast cancer [23] and in gastric cancer [24]. In the cancer population increased levels of circulating soluble TF have been associated with increased thrombogenicity [9,10].

As a result of enhanced procoagulative activity, the serum levels of plasma soluble fibrin monomer complex, fibrinogen and fibrin degradation products (D-dimer) values are significantly higher in cancer patients than in nonmalignant disease and healthy controls [9,30,31]. The median DD level reflecting local thrombin and fibrin formation stepwise increases with the tumor stage and is higher in patients with either a large-sized tumor or a tumor showing deep wall penetration [20,32]. Lymphatic invasion, metastasis to lymph node or liver and peritoneal dissemination are all associated with higher DD and CEA levels in colorectal cancer [33]. Such patients are at risk for thrombotic events due to the combined increase in fibrinogen plasma levels and thrombin formation.

von Willebrand factor (VWF), a large glycoprotein expressed by endothelial cells and megakaryocytes, is involved in the platelet aggregation and adhesion to the
subendothelial matrix. VWF antigen was demonstrated in the small stromal blood vessels particularly near the host—tumor interface [24]. High VWF is associated with tumor-related angiogenesis and is critical to the hematogenous tumor cell metastasis [25]. An increased synthesis of VWF correlating with tumor progression was observed in various types of cancer in contrast to their normal counterparts such as squamous cell cancer of the larynx, the cervix, the colorectal cancer [26], and in the metastatic osteosarcoma tumor samples, suggesting endothelial cells activation [27]. These values tend to increase with the tumor progression [26]. VWF in malignant patients may be even higher due to the deficient activity of von Willebrand factor-cleaving protease (VWF-cp, ADAMTS-13), as observed in the study comparing patients with localized and disseminated solid tumors [28].

Multiple vascular microinfarctions and inadequate blood flow may lead to the increased apoptosis ratio and necroses in the tumors [16] (Fig. 4). During the apoptotic process anionic phospholipids, usually cardiolipin but also phosphatidylserine are displaced from inner to the outer leaflet of the cell membrane [34]. This disarrangement results in the increased production of antiphospholipid antibodies. The presence of antiphospholipid antibodies may identify a subset of cancer patients with a high risk of developing thrombotic complications [18,35].

Coagulation inhibitors in cancer

A decreased production of coagulation inhibitors or its consumption may intensify procoagulative activity in cancer patients. Antithrombin III (AT III) and vitamin K-dependent coagulation inhibitors, protein C and S counterbalance against enhanced procoagulative activity (Fig. 7). AT III appears as the most important natural thrombin inhibitor. It inactivates thrombin in the irreversible reaction, resulting in the formation of thrombin—antithrombin complexes (TAT). Increased levels of TAT referring to the coagulation activation and AT III consumption were observed in the patients with acute lymphatic leukemia (ALL) [36,37]. A decrease in AT III concentration without increase of TAT complexes in the patients with disseminated malignancy suggests a decrease of production [38].

Protein C is an inhibitor of the coagulation cascade observed on the cancer cells surface and small blood vessels of tumor [24]. Activated form of protein C (APC) neutralizes activated factor V and activated factor VIII. Although levels of protein C are significantly increased in cancer, tumor-induced coagulation activation results in hypercoagulability, particularly in disseminated malignancies [25,39]. The cancer-related hypercoagulability may be influenced by tissue-factor-based APC resistance, disturbance of the hemostatic balance observed in various malignant diseases. It can be quantified by APC resistance test, measuring the effect of APC on thrombin generation initiated via the extrinsic coagulation pathway. Acquired APC resistance is present in almost one-quarter of newly diagnosed myeloma patients contributing to the increased risk of DVT [39]. The significant resistance to APC was found in the breast cancer patients as compared to the healthy control subjects and correlates with D-dimer levels [32,38].

Another coagulation inhibitor protein S, was observed in the tumor vascular bed, and was significantly elevated in patients with metastases compared with patients without metastases and healthy control subjects [32].

Fibrinolytic system

During the tumor growth, angiogenesis and coagulation cascade activation, the components of fibrinolytic system are activated, too. This process is directed to solubilize an abundance of fibrin clots and to prevent thrombosis in the defective tumor blood vessels. Tumor endothelial cells act in the fibrinolysis by synthesizing, storing, and binding fibrinolytic proteins. The mean global fibrinolytic activity as often increased in the plasma samples taken from patients with cancer [31,40].

A fibrinolytic process depends mostly on the plasmin proteolytic activity (Fig. 7). Plasmin occurs in plasma in the inactive form, plasminogen, which is activated via cleavage by the tissue plasminogen activator (tPA), prourokinase or urokinase plasminogen activator (uPA) [5,30,32,41]. Plasmin solubilizes fibrin, factor V and VII. Two types of plasminogen play different roles in the tumor coagulation cascade. Plasminogen 1 down-regulates the function of TF in 1-LN human prostate tumor cells. Plasminogen 2 is involved in the regulation of matrix metalloproteinase-9 expression by these cells [41].

The activity of plasminogen activators is controlled at two levels: by the existence of specific receptors, and by a group of specific plasminogen activator inhibitors (PAI-1) that prevent the activation of plasminogen (Fig. 7). The components of plasminogen activator system are higher in cancer patients due to local tumor production [5], as observed tPA in gastric cancer patients [32]. uPA and uPA receptor (uPAR) are significantly higher in tumor than in paired normal tissue, correlating with pathological staging and TNF values [30]. The cancer patients showing over-expression of uPA and uPAR had a trend towards poorer survival than those who did not express it [5,42]. Baker et al. observed significantly higher uPA, uPAR, and PAI-1 values in oral squamous cell carcinoma samples than in paired normal tissue. Tissue concentrations of components of the plasminogen activator system correlate with the clinical and pathological indexes of tumor aggression, including differentiation and T-stage [42].

Coagulation disorders related to specific malignant processes

Particular malignant diseases are prone to develop specific coagulation disorder. Real incidence and the best treatment of this complication are still a matter of debate, because diverse asymptomatic disorders are present in single patient [1]. Bleeding disorders are frequent in the cancer population with advanced malignancy, and were observed in 2.7% of patients during a 1-year period [43]. Bleeding is the most common complication in the DVT [44] or disseminated intravascular coagulation associated with malignancies like acute promyelocytic leukemia, low-grade malignant NHL or prostate cancer [36,45].
Thromboembolism

The cancer types associated with a significantly elevated thrombosis incidence ratio are acute myelogenous leukemia, non-Hodgkin lymphoma, and renal cell, ovarian, pancreatic, gastric, and lung cancer. Thrombo-embolic events may occur in rare myeloproliferative diseases with high platelet count, like essential thrombocythemia and polycythemia vera [46]. Patients with essential thrombocythemia have associated risk of cerebrovascular disease, acute coronary syndrome, peripheral arterial or venous thrombosis and hemorrhagic complications [46]. In the patient with acute myelogenous leukemia (AML) the two-year cumulative incidence of VTE was 5.2%. Sixty-four percent of the VTE events occurred within three months of AML diagnosis [47]. Patients with colorectal and gastric cancer are prone to develop VTE, mostly DVT and PE [26,48]. Prostate cancer is somewhat specific due to the relatively low risk of DVT but an intermediate risk of PE (1:4 ratio) [49,50]. Risk factors for VTE are presence of a central venous catheter, older age, and number of chronic co-morbidities [47]. In the ALL patients the development of VTE is associated with a 40% increase in the risk of dying within one year [47].

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) in the malignant diseases presents in the acute, subacute or chronic form. It results from the release of stimulatory factors (VEGF/VPF) from cancer cells, activation of coagulation cascade in defective cancer blood vessels and surrounding tissue with high production of fibrinogen and fibrin degradation products. The local fibrinogen and platelet consumption in rapidly growing tumors result in the systemic fibrinogen and platelet deficiency. The bleeding is common manifestation of DIC in the patients with aggressive malignancies [51]. The clinical suspicion of DIC must be confirmed by laboratory tests. A decrease in fibrinogen levels and platelet count, increase of D-dimer, fibrinogen degradation products, and soluble fibrin monomer support the diagnosis [45,52]. Diagnosis should always be confirmed by finding abnormalities in at least 3 of these laboratory values.

DIC that usually has subclinical course can be observed in 20% of acute leukemia patients, mostly as acute or subacute form in AML, and chronic in ALL patients. In the majority (>80%) of acute leukemia patients TAT, D-dimer and plasmin–antiplasmin complexes are elevated [36].

DIC is the most frequent coagulation disorder associated with prostate cancer. The chronic form of DIC is characterized by increased bleeding tendency and excessive prothrombin time prolongation. In the patients receiving anticoagulant drugs this coagulation abnormality should be included in the differential diagnosis of occult prostate cancer [45]. Thrombosis can be observed in less than 10% of acute cases but more frequently encountered in chronic DIC associated with prostate cancer. Other coagulopathies in this population are thrombocytopenic thrombotic purpura and Trousseau’s syndrome. The most common preoperative signs of coagulation activation in the prostate cancer are TAT, D-dimer, fibrinogen, and F1+2 fragment over normal range [30,50]. Those values increase significantly during the post-operative period in the patients undergoing radical retropubic prostatectomy [50].

Acquired hemophilia A

Acquired hemophilia A is uncommon coagulation disorder characterized by spontaneous formation of neutralizing antibodies (inhibitors) to factor VIII in patients with solid cancers or hematologic malignancies [53]. Approximately 10% of patients with FVIII inhibitor have an underlying malignancy, as observed by Sallah and Wan in a study of 41 patients with cancer and acquired hemophilia [2]. A production of FVIII inhibitor was described in the series of patients with solid organ tumors, with prostate cancer being the most common, followed by lung cancer patients and chronic lymphocytic leukemia [2].

A bleeding was also described due to acquired prothrombin (factor II) deficiency resulting from non-inhibitory antibody to prothrombin that interacted with a calcium dependent epitope in a patient with a low-grade lymphoma [54]. The treatment of cancer or surgery accelerates the eradication of the inhibitors in some of the patients [2].

Treatment-related coagulation disorders

Postirradiation disorders

Perioperative irradiation alone or in the combination with biochemotherapy is one of treatment modalities targeted to reduce preoperative tumor size, tumor growth and dissemination during surgery and in the post-operative course [55,56]. Enhanced toxic effects on tumor growth especially inhibition of tumor angiogenesis can be measured during simultaneous combined chemotheraphy and irradiation protocol in vitro, where it showed a greater than 90% decrease in neovascularization [57].

High-dose preoperative external beam radiotherapy and intraoperative radiation therapy decrease the local recurrence rates and improve survival in the patients with locally advanced primary or locally recurrent rectal cancer. It significantly correlates with severe hemorrhage during or after the operation and with the development of adult respiratory distress [58]. In patients with esophageal cancer acute treatment-related toxicities consisting of hematological, bleeding and infectious disorders are also increased with chemoradiotherapy. Outcomes are still comparable to results achievable by surgery alone [59]. Acute radiation-induced epithelial damage is the most pronounced on 4th day postirradiation as observed in the animal model of whole body irradiation [60]. Such vascular lesions after preoperative radiotherapy may increase the incidence of thromboembolism as observed in the rectal cancer patients [55]. In the combined chemoradiotherapy the incidence of thrombo-embolic events may further raise [19].

A delayed radiation injury is a complication persisting after radiotherapy, constituting of radiation vasculopathy and radionecrosis. Morphologic changes in late cerebral radionecrosis observed many years after irradiation were typical coagulation necroses with occlusion of the lumina.
and poorly active inflammatory areas with many inflammatory ghost cells, focal perivascular lymphocytes, hyalinized vessels, and telangiectatic vascularization near and in the necrotic tissue [61]. It is very likely that the first event in the coagulation necrosis is vascular endothelial cell damage, because fibrinoid necrosis is a main feature and prevailing multiple lesion in the late radionecrosis [61] (Figs. 8–10). Such fibrous vessels may exhibit severe endothelial and contractile dysfunction characterized with intensive bleeding.

Lee et al. described a delayed radiation injury presenting as lobar hematoma and cystic lesion due to radiation vasculopathy and radionecrosis in two patients. Both had previously received external brain radiation for malignant diseases before 27 and 19 years respectively [62].

The postirradiation bleeding was commonly observed from pelvic organs: rectum, vagina and urinary bladder (Fig. 3). Radiation cystitis is a complication presenting with hematuria. Baker observed microscopic abnormalities in the bladder consisting of irregularly shaped and arranged aggregates of epithelial cells in the lamina propria. The cells showed a mild to severe pleomorphism, and ulceration of the overlying epithelium. Edema, fibrosis and chronic inflammation of the lamina propria were also observed. Atypical fibroblasts and vascular ectasia presenting with hematuria are typical changes in such pseudocarcinomatous proliferations [63].

The risk of rectal bleeding in the irradiated prostate cancer patients directly correlates to the dose and percentage of rectum receiving >60 Gy (recommended mean rectal dose is 50 Gy and 42% of rectum irradiated) [64]. Colonoscopy with fulguration for rectal bleeding was needed in 23.4% of patients 4–45 months after radiotherapy [65]. After exclusion of other coagulation abnormalities hemorrhagic postirradiation lesions can be treated successfully using non-contact argon plasma coagulation technique, too [66].

The effects of chemotherapy

Chemotherapeutic drugs are the first line therapy in particular cancer types, after organ transplantations, and in some autoimmune diseases. Chemotherapeutic agents act by targeting different points in the cell cycle, i.e. decrease cell division and increase tumor cell apoptosis, or suppress tumor neoangiogenesis [16]. The coagulation disorders in cancer patients may be the main safety concern in this population [67]. The intensity and type of coagulation disorder depends on the type of agent, dose and other therapies applied concomitantly [67].

The most of chemotherapeutic agents produce coagulation disbalances through induction of endothelial injury, 

Figure 8  Hyalinized small vessel with fibrinoid degeneration of vascular wall, subintimal and perivascular deposition of connective tissue elements in the lymph node 1 year after irradiation, HE 1000 ×. Activated endothelial cells are bulging into the vessel lumen.

Figure 9  Fibrous thickening of the vascular wall in the irradiated lymph node with abundant collagen fibers (green) disrupting endothelial integrity and entering into the vessel lumen. A process of scarring in the adventitia and media replaces a loss of smooth muscle cells, staining Mallory, 430 ×.

Figure 10  Late irradiation changes in the blood vessel in the lymph node from Fig. 9, smooth muscle actin immunostaining, 430 ×. Smooth muscle actin is shown in brown, cellular nuclei in blue. See discontinuities of smooth muscle due to the broad interstitial fibrosis shown on Fig. 9.
decrease of coagulation factors synthesis in the liver, or platelet dysfunction [68,69].

An increased apoptosis ratio in the tumor endothelium during chemotherapy is strong procoagulative factor, prompting platelet activation, local intratumoral adherence and microthromboses within the tumor tissue [70]. An activation of intratumoral coagulation and microvessel occlusion is tumor selective, as observed during cisplatin-based chemotherapy [70]. A significant increase in the endogenous thrombin potential and of the parameters reflecting endothelial cell activation (von Willebrand antigen, soluble tissue factor, and soluble E-selectin) was observed in patients during the treatment with angiogenesis inhibitor SU5416 [10]. The signs of endothelial lesions can be observed more than ten years after chemotherapy. The patients after cisplatin-based chemotherapy with increased plasma levels of endothelial and inflammatory marker proteins can progress to more severe endothelial dysfunction, overt atherosclerosis and may have higher risk of cardiovascular diseases, i.e. myocardial infarction [71].

In various chemotherapy protocols DVT occurred in 5.7%–10.6% during chemotherapy [72]. The incidence of thrombotic events may arise to 36.7% in the ALL patients who receive L-asparaginase [73]. Bleeding mostly due to thrombocytopenia was observed in about 10–15% of patients in the single agent therapy [74], and in almost half of the patients treated with combined chemotherapy protocols [75]. These severe bleeding complications may completely disappear, and coagulation parameters normalize after the chemotherapy of malignant disease was completed [2,36].

A single agent anticancer chemotherapy is used in malignant diseases, like high-dose methotrexate administration in ALL [76] and topotecan in ovarian cancers [74]. Antitumor effect may be enhanced in high-dose chemotherapy protocols compared to standard-dose for some patients, but more coagulation disorders are usually expressed [77]. A large cohort study conducted by Behrendt and Ruiz found that combination of MMP inhibitor (primo-mastat) with chemotherapy enhances the hazard of VTE approximately twice among patients with advanced lung cancer [20]. Some protocols pronounce both bleeding and thrombosis, as observed in busulphan and cyclophosphamide therapy, causing veno-occlusive disease and hemorrhagic cystitis [78]. Despite more systemic coagulation disorders produced by combined chemotherapy regimens, antitumor effects were not always additive [75,79].

The addition of bevacizumab to oxaliplatin-based chemotherapy significantly improves progression-free survival [17]. Similar results were registered in a phase II trial comparing the addition of bevacizumab [18] to standard carboplatin/paclitaxel chemotherapy in patients with advanced metastatic non-small cell lung cancer. Serious tumor-related bleeding episodes appeared as the main safety concern in these patients. Two distinct clinical patterns of bleeding were observed: minor mucocutaneous hemorrhage in 33–44% and major hemoptysis in 10% of patients [18]. Gastrointestinal bleeding, epistaxis, CNS hemorrhage, and ocular bleeding were observed during combination therapy with another monoclonal antibody, gemtuzumab ozogamicin with cytarabine as continuous perfusion in elderly AML patients [75].

**A systemic preoperative chemotherapy**

A systemic preoperative (or neoadjuvant) chemotherapy aimed to reduce tumor size, lymphatic tumor extension of the primary tumor, diminish positive lymph node status and increase overall survival, can also produce more perioperative coagulation disorders in cancer patients [80,81]. It may be applied locally or as systemic chemotherapy. Bleeding disorders due to the thrombocytopenia, treatment delays and infections are common in the patients undergoing neoadjuvant chemotherapy, as observed in patients with stage III melanoma [81].

**Local and intraarterial chemotherapy**

Intraarterial chemotherapy is aimed to reduce systemic toxic effects and tumor size in patients with locally advanced or metastatic cancer, both as the neoadjuvant or a palliative treatment [82]. Thrombocytopenia, a manifestation of systemic toxicity is still significant during intraarterial neoadjuvant chemotherapy. Coagulation disorders observed after targeted arterial chemotherapy are both bleeding and thrombosis [83]. Thrombosis is mostly local toxic phenomenon occurring within an artery into which a catheter was placed. Bleeding complications after the intraarterial treatment of liver metastases are intestinal bleeding and gastric and duodenal stress ulcerations [58]. A survival advantage of intraarterial chemotherapy is not clear. Bleeding can be observed after intralesional instillation of chemotherapeutics in the bladder cancer [84].

**Systemic toxic effects of chemotherapy**

The most observed systemic toxic effects in various chemotherapy protocols are leukopenia and thrombocytopenia, clinical manifestations of myelosuppression [18].

**Thrombocytopenia** is an acute dose-limiting hematologic toxicity, occurring in the treatment of potentially curable malignancies such as leukemia, lymphomas, pediatric cancers [36], and during the treatment of patients with locally advanced or metastatic cancer [18]. It may be observed in more than 70% of patients after transcatheter arterial infusion of cisplatin, doxorubicin, mitomycin, and 5-fluorouracil for uterine cervical cancer [58]. Bleeding disorders are common problem of thrombocytopenia, especially in chemotherapeutic protocols known to produce skin and mucosal lesions [57,78]. 5-fluorouracil (5-FU) and mitomycin C may present with gastrointestinal bleeding [58], whereas gynecologic cancer patients receiving bleomycin, ifosfamide with mesna, and cisplatin may exhibit grade 3 vaginal bleeding [79]. The patients at high risk of bleeding during chemotherapy are those having prior episodes of bleeding, treatment with a drug affecting platelet function, bone marrow metastases, a baseline platelet count <75,000, and genitourinary or gynecologic malignancy [85].

**Platelet reactivity** may be diminished without development of thrombocytopenia during some chemotherapy protocols [86]. An acquired decrease in a platelet aggregation may be responsible for various hemorrhagic manifestations such as mucositis, epistaxis and hemorrhagic cystitis following therapy with cyclophosphamide, methotrexate and 5-FU (CMF) [69]. In the CMF protocol a significant reduction in platelet factor-3 (PF3) availability with impaired platelet aggregation was observed on the 8th day.
of chemotherapy and a progressive suppression in platelet aggregation was noted during subsequent follow-up. These changes precede the onset of thrombocytopenia [69]. Contrary, the platelet reactivity increases during the cisplatin-based chemotherapy contributing to the pathogenesis of thrombotic complications [70,87].

Vitamin K-dependent synthesis of coagulation factors and inhibitors may decrease in the majority of chemotherapeutic protocols. The CMF-chemotherapy decreases vitamin K-dependent synthesis in the liver. Fibrinogen, FVII, FIX, FX, plasma protein C, protein S and AT III were significantly decreased during combined chemotherapy or during high-dose methotrexate therapy, resulting in prolonged prothrombin time, APTT and higher D-Dimer after chemotherapy compared to the baseline values [68,69,76]. The effect may be more pronounced after oral versus intravenous application of drugs due to the first pass effect [88]. Those hemostatic parameters began to improve on day 7 after chemotherapy [76,77], and may return to the pretherapy values 2 months after the completion of CMF-chemotherapy protocols [68]. The manifestations of hepatic toxicity should not obligatory produce clinically evident thrombocytopenic or hemorrhagic complications and can be alleviated by a reduction in the drug dose [76].

Decreased synthesis of anticoagulant factors in liver and fibrinolysis parameters (α2-antiplasmin and plasminogen) which are synthesized in a number of tissues can be observed during chemotherapy. It results in the decreased potential of clot lysis by plasmin and imposes a caution in patients with other thrombosis risk factors [37].

The effects of hormonal chemotherapy

Coagulation disorders related to hormonal chemotherapy are commonly observed. Although antiestrogen tamoxifen produced more favorable outcome in secondary prevention of the breast cancer, the incidence of endometrial cancer, stroke, PE, and DVT are higher in women during such treatment [89]. A long-term treatment with tamoxifen for 2 or more years tends to reduce both AT III and protein C, a situation possibly predisposing towards thrombosis [90]. This was the main reason to introduce a third-generation of antiestrogen drugs, i.e. letrozole, anastrozole, and exemestane which target the aromatase enzyme, producing a more favorable quality of life and resulting in the lower incidence of thromboembolism and vaginal bleeding [91].

Some randomized trials demonstrated an oncological benefit of neoadjuvant hormonotherapy before radical prostatectomy, but an increased surgical difficulty [80]. An underlying disorder for such enhanced bleeding in prostate cancer patients may be a hepatotoxicity of flutamide [92], or development of acquired coagulation factor VIII inhibitor [2].

Post-operative coagulation disorders in cancer patients

The incidence of post-operative thrombo-embolic disorders in cancer patients depends on the type of malignant disease, operative procedure and therapies applied. The PE was observed in 0.87% of patients after TURP [49] and DVT in the range from 8.3% of patients with ovarian malignancy between the 8th and 29th post-operative day and in 10.6% during post-operative chemotherapy [72]. The incidence of TE complications is lower after laparoscopic than after conventional colorectal resections despite similar effects on the post-operative intravasal fibrinolytic capacity [93]. This may result from minor surgical trauma and minor exogenous coagulation pathway activation.

The post-operative hypercoagulability may be attributed to cancer disease, immobility, and surgical trauma prompting exogenous coagulation cascade with thrombin activation. In the most of the cases an increase in fibrinogen, plasma VWF concentrations, F1 + 2 fragment, TAT and D-dimer may be observed during the post-operative period. PT, aPTT and levels of hemostatic markers AT III, PC, total and free PS showed the most substantial changes towards baseline hypercoagulability on the 1st post-operative day [50,94]. Ayala observed a post-operative protein C deficiency which resulted in post-operative free flap thrombosis in a cancer patient after microvascular head and neck reconstruction [95].

Post-operative hypoproteinemia is characterized by the deficient synthesis of both coagulation factors and coagulation inhibitors. The procoagulative state in hypoproteinemic patients may result as a consequence of decreased production of AT III (α2-globulin). On the contrary, a decreased Ca2+ which correlates with albumin concentrations and serves as cofactor for most of the coagulation factors may lead to bleeding diathesis.

The mean global fibrinolytic activity observed in the patients after major cancer surgery is enhanced, resulting in the low-grade post-operative DIC when compared to controls [40]. It is a physiologic reaction to the surgical trauma in the early post-operative period.

The post-operative bleeding occurrence depends on the type of surgery. It was observed in almost 6% of patients after duodenopancreatectomy [96], and in 23% of the irradiated patients with overall mortality due to hemorrhage about 56% in this group [97]. Post-operative hypoproteinemia and low platelet count should be considered and treated in affected population. Neurosurgical oncologic patients are population at special risk to develop deleterious space-occupying post-operative hemorrhage. Risk factors of post-operative hematoma development in this population are age (patients >70 years have a six-fold increased risk), lower post-operative PT, decreased fibrinogen and platelet count immediately after surgery and at day 1, platelet dysfunction and decreased FXIII activity [98].

Conclusion

Coagulation disorders in the rapidly growing cancer population may appear as a consequence of tumor growth, chemotherapy, radiotherapy or due to the surgical trauma. Awareness of underlying mechanisms should point to preventive strategies, early diagnostics, and appropriate treatment of cancer and coagulation disorders associated. Those may have a significant impact on the clinical outcomes in this susceptible population [44].
Coagulation disorders in cancer patients

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