Review

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Solid Tumors, Liquid Challenges: The Impact of Coagulation Disorders

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Abstract: Coagulation disorders are increasingly recognized as significant complications in patients with solid tumors, affecting morbidity and mortality outcomes. Solid tumors can provoke a hypercoagulable state through the release of pro-coagulant factors, endothelial activation, and inflammation, leading to a heightened risk of coagulation disorders. These coagulation disorders may manifest as venous thromboembolism, arterial thromboembolism, thrombotic microangiopathy, or disseminated intravascular coagulation. These disorders can complicate surgical interventions and impact treatments, including chemotherapy and immunotherapy efficacy, leading to poor outcomes. Understanding the implications of coagulation disorders in solid tumors is essential for optimizing patient management, including identifying high-risk patients and implementing prophylactic measures. This review aims to provide insights into the current knowledge surrounding coagulation disorders in solid tumors and their clinical implications.

Keywords: coagulation disorders; solid; tumors; venous; arterial; thromboembolism; thrombotic microangiopathy; disseminated intravascular coagulation

Introduction

Coagulation disorders in patients with solid tumors represent a significant clinical challenge, influencing both the course of malignancy and the efficacy of treatment interventions. The interplay between malignancies and the hemostatic system is complex and multifaceted. Tumor-derived factors, particularly tissue factors, play a pivotal role in activating the coagulation cascade, thereby increasing the risk of thromboembolic events. Additionally, the release of inflammatory cytokines, the activation of endothelial cells and the activation of platelets further contribute to this dysregulation of hemostasis [1–3]. This hypercoagulability increases the risk of thromboembolic events in solid tumors, including venous thromboembolism, arterial thromboembolism, thrombotic microangiopathy, and disseminated intravascular coagulation [4]. Apart from tumor, patient and treatment-related factors, some biomarkers increase the risk of thrombosis (Table 1) [5].

Table 1. Factors associated with thromboembolism in solid tumors.

Tumor-related factors	• Tumor site: Highest risk with pancreas, stomach, lung, kidney, uterus and brain tumors. • Stage of cancer: Highest risk with metastatic disease. • Time from diagnosis: Highest risk in the first 3 months of diagnosis.
Patient-related factors	• Obesity • Ethnicity: More in Black Americans • Prolonged immobility • Family or previous history of thromboembolism

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	• Inherited thrombophilia disorders • Comorbidities: renal disease, respiratory disease, acute infections.
Treatment-related factors	• Surgery. • Chemotherapy: Platinum - based drugs like cisplatin. • Immunomodulatory drugs: thalidomide, lenalidomide • Vascular endothelial growth factor inhibitors like bevacizumab, sunitinib, sorafenib and pazopanib • Immune check point inhibitors. • Erythropoiesis-stimulating agents. • Blood transfusions. • Central venous catheters.
Biomarkers	• High D-dimer levels • Leukocytosis and Thrombocytosis

Thrombosis can be the first clinical manifestation of a solid tumor and is considered the second leading cause of death in patients with cancer [6,7]. Various studies have shown a significant correlation between the incidence of thromboembolic events and worse prognosis in solid tumors, proposing the fact that activation of blood coagulation has an impact on tumor metastasis and aggressiveness [8–10]

Understanding the implications of coagulation disorders is vital for improving patient outcomes. This review aims to highlight the significance of coagulation disorders in the context of solid tumors, emphasizing the need for a comprehensive approach to patient care that addresses both cancer treatment and associated thrombotic risks.

Solid Tumors and Venous Thromboembolism

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant complication in patients with solid tumors. Patients with cancer have a 4- to 6-fold increased risk of developing vein thrombosis compared to patients without cancer. Acute idiopathic VTE can be the first manifestation of an occult malignancy when it develops in less common sites such as the neck or the vena cava, and portends a poor prognosis [6,7,11,12]. However, there is little evidence to support routine cancer screening in patients with unprovoked thrombosis. Certain solid tumors have an increased risk of VTE, like cancer of the pancreas, lung, stomach, uterus, kidney, and brain tumors, with pancreatic cancer displaying the highest risk [13]. These findings highlight the importance of risk stratification tools, such as the Khorana score introduced in 2019, which aids in identifying patients who may benefit from thromboprophylaxis (Table 2) [14].

Table 2. Khorana Risk Score.

Variable	Score
Very high-risk tumor (stomach, pancreas)	2
High-risk tumor (lung, gynecologic, genitourinary excluding prostate)	1
Hemoglobin level < 100g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11x10)9/L	1
Prechemotherapy platelet count 350x10)9/L or greater	1
Body mass index 35 kg/m2 or greater	1

A score of 0 = low-risk category, 1-2 = intermediate-risk category, >2= very high-risk category.

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The risk of VTE in patients with a high-risk Khorana score was 11.0%, significantly higher than in those with a low-risk (5.0%) or intermediate-risk (6.6%) score. Despite the availability of such tools, there still needs to be a consistent implementation of prophylactic measures in clinical practice, suggesting a need for enhanced education and awareness among healthcare providers [14].

Routine pharmacological thromboprophylaxis is not recommended for all outpatients with cancer. Anticoagulation is the cornerstone of VTE management in cancer patients. The choice of anticoagulant depends on the patient's clinical scenario, including cancer type, presence of metastasis, and overall health status. Low Molecular Weight Heparin **(**LMWH), such as enoxaparin (1 mg/kg, twice daily), is the preferred treatment for cancer-associated VTE, especially in hospitalized patients. Direct oral anticoagulants (DOACs) such as apixaban or rivaroxaban may be preferred over LMWH for ambulatory patients and those at low risk of bleeding. The duration of anticoagulation therapy for VTE in cancer patients typically depends on the presence of active malignancy and the risk of recurrence. For patients with active cancer and ongoing treatment, the American Society of Hematology guideline panel suggests long-term anticoagulation for secondary prophylaxis (>6 months) rather than short-term treatment alone (6 months) [15].

In patients with renal insufficiency (CrCl <30/ml), apixaban, DOAC with the most minor renal clearance, may be an appropriate choice [16].

Solid Tumors and Arterial Thromboembolism

Patients with solid tumors are at an increased risk of arterial thromboembolism (ATE). While much of the research has centered on VTE, ATE has gained attention due to its significant morbidity and mortality. Patients with cancer have a 2-fold increased risk of developing ATE compared to patients without cancer. The strongest predictor of ATE risk is the clinical stage and the site of solid tumor, with metastatic disease and pancreatic and lung cancers conferring the highest risks [16]. ATE in cancer is associated with a worse prognosis, a 3-fold increase in overall mortality risk, and a probability of recurrent thromboembolism of 37% at six months [17,18]

Arterial thromboembolism typically occurs with endothelial damage, unlike VTE. High flow and high shear arterial circulation, in contrast to the low venous shear in the venous circulation, along with the procoagulant materials in the ruptured plaque, leads to the formation of a thrombus [19]. Other factors like marantic endocarditis, secondary antiphospholipid syndrome, tumor embolization, tumor arterial invasion, or tumor arterial compression can also contribute to ATE in solid tumors [20]. Some chemotherapeutic agents like cisplatin and vascular endothelial growth factor (VEGF) inhibitors (bevacizumab, sorafenib, sunitinib, pazopanib) can be prothrombotic [21]. In a recent sizeable genomic tumor profiling registry of patients with solid cancers, alterations in *KRAS* and *STK11* were associated with an increased risk for ATE independent of cancer type [22].

ATE can manifest as acute coronary syndrome (ACS), stroke, or peripheral arterial disease, and these may be the first manifestation of solid tumors when their cause is not clear [23]. The risk of cryptogenic strokes is higher (30 *vs.* 50%) in cancer patients, and a study suggests thrombotic endocarditis is a possible cause of stroke in cancer patients [18]. Another potential mechanism for stroke in cancer is paradoxical embolism, taking into consideration that about 20% of cancer patients develop venous thromboembolism or septic embolism [24].

The management of ATE in patients with solid tumors represents a tough clinical challenge because of the higher risk of bleeding than the general population, thrombocytopenia, and significant drug-drug interactions. The diagnosis of ACS in solid tumors follows the same diagnostic algorithm as in general patients. The clinical practice guidelines for the management of ACS are mainly derived from observational data and expert consensus. These guidelines propose that invasive approaches for the management of ACS are recommended in patients with an expected survival of six months or more. In patients with an expected survival of less than six months or at very high bleeding risk, conservative, non-invasive management strategies should be considered. Since cancer patients are at a higher risk of bleeding, the shortest course of dual anti-platelet therapy is recommended [25]. The management of stroke and peripheral arterial disease follows the same principle as in non-cancer patients.

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Solid Tumors and Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) refers to a group of disorders characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction due to the formation of small blood clots in capillaries and arterioles. While TMA can arise from various causes, its association with solid tumors has gained attention in recent years. The exact mechanism by which solid tumors induce TMA is complex and multifactorial. Several factors contributing to this condition include procoagulant substances, such as tissue factors, direct damage to the endothelial cells lining blood vessels, inflammatory cytokines, hypoxia, and platelet activation. TMA can also be triggered by other overlapping conditions such as infections or, more frequently, as an adverse effect of anticancer drugs due to direct dose-dependent toxicity or a drug-dependent antibody reaction [26,27].

The clinical spectrum of TMA may vary widely from asymptomatic abnormal laboratory tests to acute severe, potentially life-threatening forms due to massive microvascular occlusion. Patients with TMA associated with solid tumors often present symptoms indicative of hemolytic anemia, including fatigue, pallor, and jaundice. Thrombocytopenia may lead to easy bruising and bleeding complications. Organ dysfunction is also common, with the kidneys frequently being affected, leading to acute kidney injury. Diagnosis typically involves a combination of laboratory tests, including complete blood count that reveals hemolytic anemia and thrombocytopenia, peripheral blood smear showing schistocytes, elevated lactate dehydrogenase, non-conjugated bilirubin, and reticulocyte count, with reduced haptoglobin suggestive of hemolysis. Coagulation studies are generally normal, distinguishing TMA from disseminated intravascular coagulation (DIC).

While TMA can manifest in various forms, two notable types are often observed in patients with solid tumors [28]:

1. **Atypical Hemolytic Uremic Syndrome (aHUS)**: This rare form of TMA may be triggered by certain solid tumors, particularly those associated with the overactivation of the complement system.
2. **Chemotherapy-Induced TMA**: Certain chemotherapeutic agents used to treat solid tumors, such as mitomycin C and gemcitabine, have been associated with the development of TMA, highlighting the importance of monitoring this complication during treatment.

Hereditary or primary acquired TMA syndromes like thrombotic thrombocytopenic purpura (TTP) which results from a severe deficiency of ADAMTS13 and is the most common cause of TMA among adults without cancer should be excluded. It is also important to exclude secondary TMA due to autoimmune diseases, infections, malignant hypertension and DIC. This distinction is essential to avoid inappropriate use of treatments, mainly plasma exchange, which is associated with significant complications.

The management of TMA in the context of solid tumors requires a multidisciplinary approach. Effective management of the primary malignancy is crucial. This may involve surgery, chemotherapy, or targeted therapy. Transfusions may be necessary to manage severe anemia or thrombocytopenia. Patients should be monitored closely for signs of bleeding or organ dysfunction. Anti-platelet agents or anticoagulants may be considered, but caution is needed due to the risk of bleeding complications. Complement inhibitors, such as eculizumab, have shown promise in treating aHUS and may offer new avenues for managing TMA associated with solid tumors [26]. In patients with cancer-associated TMA, there is no beneficial role for plasmapheresis, steroids, or other immunosuppressive agents used in TTP. Cancer-associated TMA is treating with chemotherapy and supportive treatment. The prognosis of patients with cancer TMA is usually extremely poor due to disseminated cancer [27].

Solid Tumors and DIC

Disseminated intravascular coagulation (DIC) is a complex disorder characterized by the widespread activation of the coagulation cascade, leading to the formation of blood clots in small

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vessels throughout the body. This condition can result in multiple organ dysfunction and bleeding due to the consumption of clotting factors and platelets. While DIC can occur in various clinical contexts, its association with solid tumors presents unique challenges in diagnosis and management. DIC may occur as the first sign of an underlying malignant disease or a late complication of a previously diagnosed and heavily treated cancer [29,30]. Among solid tumors, adenocarcinomas are more prone to trigger both thromboembolic complications and consumption coagulopathy [31]. The prevalence of overt DIC is estimated to be up to 7% in patients suffering from solid tumors [30]. The hypercoagulability of solid tumors increases the risk of DIC [4]. In the context of solid tumors, DIC is often classified as a secondary form, where the tumor itself contributes to the dysregulation of hemostasis.

Patients may present with signs of thrombosis despite low platelets, including deep vein thrombosis (DVT) or pulmonary embolism (PE), which may not always be readily recognized. The bleeding symptoms may include petechiae, ecchymosis, hematuria, or gastrointestinal bleeding due to the consumption of clotting factors, and thrombocytopenia can lead to multi-organ failure, with renal impairment, hepatic dysfunction, and respiratory distress being common [32].

Diagnosing DIC in the context of solid tumors involves a combination of clinical evaluation and laboratory tests. Key laboratory findings include thrombocytopenia, hypofibrinogenemia, prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT) and elevated fibrin degradation products (e.g., D-dimer) [32].

A clinical scoring system, such as the International Society of Thrombosis & Hemostasis (ISTH) DIC score, can also aid in the diagnosis. This score includes platelet count, fibrin markers such as D-dimer, PT, and fibrinogen level, with a score over 5 indicating a high likelihood for overt DIC (Table 3) [33].

Table 3. International Society of Thrombosis & Hemostasis (ISTH) DIC score.

Test	0 points	1 point	2 points	3 points
INR, or **PT prolongation**	INR ≤1.3 < 3 seconds	INR 1.3-1.7 3-6 seconds	INR >1.7 >6 seconds	
Fibrinogen	>100 mg/dl	<100 mg/dl		
D-dimer	<400 ng/dl		400-4000 ng/ml	>4000 ng/ml
Platelets	>100,000/ul	50,000-100,000/ul	<50,000/ul	

≥5 points: Overt DIC.

The management of DIC in patients with solid tumors requires a multidisciplinary approach and is often tailored to the underlying cause, addressing the malignancy with chemotherapy. Successful treatment of the tumor may resolve DIC. Supportive care includes blood product transfusions (platelets, fresh frozen plasma) to manage bleeding and restore hemostatic balance. Anticoagulation may sometimes be indicated, particularly if thrombotic complications are prominent. However, this must be approached cautiously, as the risk of bleeding is significant. Continuous coagulation parameters and clinical status monitoring are crucial in managing patients with DIC, allowing for timely interventions [34].

Conclusion

In conclusion, understanding and managing coagulation disorders in solid tumors is crucial for optimizing patient care. Clinicians must adopt a proactive approach to assess thrombotic risks, implement appropriate prophylactic measures, and consider the implications of anticoagulant therapy in the context of cancer treatment. By addressing these challenges, healthcare providers can enhance the quality of care for patients with solid tumors and mitigate the associated risks of coagulation disorders. Future research should focus on elucidating the underlying mechanisms of coagulation disorders in different tumor types and exploring novel therapeutic strategies.

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