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Cancer-associated thrombotic microangiopathy; a review article

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ABSTRACT

Cancer-associated thrombotic microangiopathy (TMA) is a rare but is a serious complication that can occur in individuals with malignancy. It is characterized by widespread small blood vessel thrombosis (formation of blood clots) in various organs of the body, leading to organ damage and dysfunction. The exact mechanisms underlying cancer-associated TMA are not fully understood. However, several factors may contribute to its development. Cancer cells can release procoagulant substances that promote blood clot formation, since some tumors can directly invade blood vessels, leading to endothelial cell damage and activation of the coagulation system. Additionally, certain chemotherapeutic agents used in cancer treatment can have adverse effects on the endothelium, further increasing the risk of TMA. Clinically, cancer-associated TMA presents with a range of symptoms depending on the organs affected. Common manifestations include microangiopathic hemolytic anemia, thrombocytopenia, and organ-specific symptoms such as neurological deficits, renal dysfunction, or cardiac abnormalities.

Review

Implication for health policy/practice/research/medical education:
Cancer-associated thrombotic microangiopathy (TMA) is a rare complication that can occur in individuals with malignancy. It is characterized by the formation of blood clots within small blood vessels, leading to organ damage and dysfunction. Cancer-associated TMA can affect multiple organs in the body, including the kidneys, brain, heart, and gastrointestinal system. Symptoms may vary depending on the organs involved but can include fatigue, neurological symptoms, kidney dysfunction, and signs of anemia.

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Introduction

Cancer-associated thrombotic microangiopathy (TMA) is a rare but serious condition that occurs in cancer patients. It is characterized by the formation of small blood clots in the small blood vessels throughout the body, leading to organ damage and dysfunction. TMA is a term conducted to describe a group of disorders characterized by microvascular thrombosis and microangiopathic hemolytic anemia (1,2). In the case of tumor-associated TMA, the condition is directly related to the presence of cancer. The t mechanisms that cancer leads to TMA is believed to the capability of cancer cells to release substances that activate the clotting system and promote the formation of blood clots. Additionally, certain chemotherapeutic agents conducted to treat cancers can also contribute to the development of TMA (3,4). This review study aims to provide a comprehensive overview of cancer-associated TMA including its etiology, clinical presentation, diagnostic modalities, treatment options, and prognosis.

Search strategy

We conducted a comprehensive literature search using various databases including PubMed, Directory of

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Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, Google Scholar, and Embase. We used a range of keywords such as thrombotic microangiopathy, cancer, platelet count, renal dysfunction, endothelial cell, microangiopathic hemolytic anemia, schistocytes, cancer-associated thrombotic microangiopathy, peripheral blood smear, von Willebrand factor, and small blood vessels to ensure a thorough search.

Molecular mechanisms of cancer-associated TMA

The molecular mechanisms underlying cancer-associated TMA are complex. However, several factors and pathways have been implicated in the development of this condition. Malignant tumors can directly invade blood vessels, leading to endothelial cell injury and activation. Tumor cells can secrete various factors, such as cytokines, growth factors, and procoagulant molecules, which promote endothelial cell dysfunction. Then damaged endothelium becomes prothrombotic, leading to the formation of blood clots in small blood vessels (5,6). Meanwhile, some cancer cells possess procoagulant properties. They can release procoagulant substances, such as tissue factor or cancer procoagulant, which initiate the coagulation cascade and promote blood clot formation. Tissue factor is a potent activator of clotting factors, triggering the formation of thrombin and fibrin, which ultimately leads to the formation of blood clots (7,8). Further, von Willebrand factor (vWF) is a multimeric glycoprotein that plays a crucial role in platelet adhesion and aggregation during hemostasis. In cancer-associated TMA, there is an imbalance in vWF regulation. Increased release of ultra-large vWF multimers and decreased activity of ADAMTS13 (a metalloprotease responsible for cleaving vWF) have been observed. This imbalance contributes to platelet aggregation and microvascular thrombosis (9,10). Moreover, dysregulation of the complement system, a part of the innate immune system, has been implicated in cancer-associated TMA. Activation of the complement cascade can occur through various mechanisms, including immune complex formation, release of complement-activating substances by tumor cells, and tumor-induced endothelial cell damage. The activated complement system leads to inflammation, endothelial cell injury, and thrombosis (11,12). Finally, there may be chemotherapy-induced endothelial cell toxicity, following the tumor therapy. Certain chemotherapeutic agents used in cancer treatment can cause direct toxicity to endothelial cells. These agents can disrupt the integrity of the endothelium, impair endothelial cell function, and promote procoagulant properties. The resulting endothelial damage and dysfunction contribute to the development of TMA (13,14).

Morphologic lesions of cancer-associated TMA

Morphologic lesions and pathological features observed in cancer-associated TMA can vary depending on the organs involved and the underlying malignancy (15,16). Cancer-associated TMA often presents with microangiopathic hemolytic anemia, characterized by the presence of fragmented red blood cells (schistocytes) on peripheral blood smear. These schistocytes are a result of mechanical damage to red blood cells as they pass through small blood vessels with intravascular clot formation (17,18). Furthermore, malignant tumors can induce a procoagulant state, leading to the formation of blood clots within small blood vessels. Thrombosis can occur in various organs, including the kidneys, brain, heart, and other organs. The presence of fibrin-rich thrombi within the microvasculature is a common pathological finding in cancer-associated TMA (19,20). Likewise, tumor cells themselves or the tumor microenvironment can cause direct damage to endothelial cells lining the blood vessels. This endothelial injury leads to endothelial cell swelling and detachment. The damaged endothelium can become prothrombotic and further contribute to the development of TMA (21,22). In addition, inflammatory infiltrates may be observed in the affected organs cancer-associated TMA. These infiltrates consist of immune cells, such as lymphocytes and macrophages, and are often seen in association with endothelial damage and thrombus formation (2,19).

Renal morphologic lesions of cancer-associated TMA

Cancer-associated TMA can involve the kidneys, leading to renal dysfunction. Renal biopsy may reveal glomerular and arteriolar involvement, including the presence of thrombi within glomerular capillaries or arterioles. Histological features such as fibrinoid necrosis, ischemic changes, and inflammatory infiltrates can also be observed (23,24).

Organ-specific manifestations

Depending on the organs affected, additional pathological features may be observed. For example, in cancer-associated TMA involving the brain, pathological examination may reveal microinfarcts, ischemic changes, and hemorrhages. In cardiac involvement, examination of cardiac tissue may show microvascular thrombosis, fibrosis, or other cardiac abnormalities (25-27). However, the pathological features of cancer-associated TMA can overlap with other microangiopathic disorders, such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Therefore, a comprehensive evaluation incorporating clinical, laboratory, and pathological findings is essential for accurate diagnosis and appropriate management of cancer-associated TMA (3,28).

Diagnosis of cancer-associated TMA

The diagnosis of cancer-associated TMA is often challenging due to its similarity to other conditions, such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. It requires a comprehensive evaluation,

including clinical assessment, laboratory tests (e.g., complete blood count, peripheral blood smear, kidney function tests), and sometimes imaging studies to assess organ involvement (29,30).

Clinical assessment

A detailed medical history, physical examination, and assessment of symptoms are important initial steps in the diagnostic process. Clinical manifestations may include microangiopathic hemolytic, thrombocytopenia, renal dysfunction, neurological deficits, and other organ-specific abnormalities (17,30).

Laboratory tests

Several laboratory tests are employed to evaluate patients suspected of having cancer-associated TMA. The CBC helps assess red blood cell count, hemoglobin levels, and platelet count. Presence of anemia and thrombocytopenia is commonly observed in TMA (31). Examination of a peripheral blood smear can also reveal schistocytes, which are characteristic of microangiopathic hemolytic anemia (32,33). Besides, coagulation tests such as prothrombin time (PT), activated partial thromboplastin time and fibrinogen levels may be performed to assess the coagulation status and rule out other coagulation disorders (34). Accordingly, evaluation of renal function, including blood urea nitrogen, creatinine, and urinalysis, is important to assess the presence and severity of renal involvement (35). In this regard, DAMTS13 is a vWF-cleaving protease, and deficiency or inhibition of ADAMTS13 activity is associated with thrombotic thrombocytopenic purpura (TTP). Testing for ADAMTS13 activity and the presence of ADAMTS13 antibodies can help differentiate TTP from cancer-associated TMA (36). Measurement of complement component levels, such as C3 and C4, can be helpful in assessing complement dysregulation, which may be present in some cases of cancer-associated TMA (37,38). In selected cases, imaging studies may be performed to assess organ involvement and evaluate the extent of TMA-related complications. Imaging techniques such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) may be used to evaluate renal involvement and detect any structural abnormalities (39,40). Furthermore, CT or MRI scans of the brain may be performed to assess neurological manifestations or rule out other causes of neurological deficits (41). Consequently, echocardiography or other cardiac imaging modalities can be utilized to evaluate cardiac function and detect any TMA-related cardiac abnormalities (42,43).

Treatment of cancer-associated TMA

Treatment of cancer-associated TMA primarily involves addressing the underlying cancer and managing the complications associated with TMA. This may include chemotherapy, immunotherapy, or targeted therapy depending on the specific cancer type. Supportive measures such as red blood cell transfusions, platelet transfusions, and plasma exchange may be utilized to manage the hematological abnormalities. In severe cases, more aggressive therapies like immunosuppressive agents or complement inhibitors may be considered (1,44).

Notably, the treatment of cancer-associated TMA requires a multidisciplinary approach involving hematologists, oncologists, and other relevant specialists. The management strategy should be personalized based on the patient's overall clinical condition, cancer characteristics, and response to treatment (1,17). Close monitoring of the patient's hematological parameters, organ function, and symptoms is essential to guide treatment decisions and ensure optimal care. The treatment of TMA induced by tumors involves addressing both the underlying malignancy and managing the complications associated with TMA. The specific treatment approach depends on the individual patient, the type and stage of cancer, and the severity of TMA symptoms (17,45). Treating the underlying malignancy is crucial in managing TMA. The choice of cancer treatment depends on the type and stage of the cancer. This may include chemotherapy, radiation therapy, immunotherapy, targeted therapy, or a combination of these modalities. By reducing tumor burden and suppressing tumor-related factors, cancer-directed therapy can potentially alleviate TMA-associated complications (46,47). Likewise, supportive modalities are important in managing the hematological abnormalities associated with TMA. This may involve red blood cell transfusions to address anemia, platelet transfusions to manage thrombocytopenia, and fresh frozen plasma or cryoprecipitate infusions to replenish coagulation factors. Supportive care also includes close monitoring of organ function and appropriate management of complications such as renal dysfunction, cardiac abnormalities, or neurological deficits (48,49). Correspondingly, plasma exchange, also known as plasmapheresis, is a therapeutic procedure that aims to remove the patient's plasma, which contains the circulating factors that contribute to TMA. It is then replaced with fresh frozen plasma or albumin. Plasma exchange can help remove procoagulant factors, reduce thrombotic tendencies, and improve organ function. However, the effectiveness of plasma exchange in cancer-associated TMA remains uncertain, and its use is often considered on a case-by-case basis (50,51).

Immunotherapy and complement inhibitors

In some cases, immunosuppressive therapies may be considered to manage TMA associated with cancer. Various agents such as corticosteroids, rituximab, or eculizumab (a monoclonal antibody that targets complement component 5) have been conducted in specific situations, particularly when there is evidence of complement dysregulation or autoimmune-mediated TMA. The administration of these agents should be guided by an experienced hematologist or

oncologist and tailored to individual patient factors (3,52).

Prognosis of cancer-associated TMA

Prognosis for individuals with cancer-associated TMA depends on various factors, including the extent of organ damage, response to treatment, and the underlying cancer. Prompt recognition and management of cancer-associated TMA are essential to improve outcomes and prevent further complications (53).

Conclusion

Cancer-associated TMA is a rare complication that can occur in individuals with cancer. It is characterized by the formation of blood clots in small blood vessels, leading to organ damage and dysfunction. Cancer cells can release substances that activate the clotting cascade, leading to the formation of blood clots. Additionally, certain cancer treatments, such as chemotherapy and radiation therapy, can damage the lining of blood vessels, further promoting clot formation. The treatment of cancer-associated TMA involves a multidisciplinary approach, with oncologists, hematologists, and other specialists working together. The management may include addressing the underlying cancer, discontinuing any medications that may be contributing to TMA, and providing supportive care. In some cases, plasma exchange or targeted therapies aimed at suppressing the abnormal clotting may be considered.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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