Thrombotic Microangiopathy in Cancer

Ilene C. Weitz, MD

1 Jane Anne Nohl Division of Hematology, Department of Medicine, University of Southern California-Keck School of Medicine, Los Angeles, California


Abstract

Keywords

Thrombotic microangiopathy (TMA) is a rare but often devastating complication of cancer and cancer treatment. The syndrome is defined by thrombocytopenia (i.e., a platelet count of < 150,000/mL blood, or a reduction in platelet count by > 30% from baseline), evidence of microangiopathic hemolytic anemia, and some evidence of organ damage. Among the nine recognized groups of disorders causing TMA, the focus of this article will be on cancer and cancer treatment-related causes of TMA. This review will discuss the pathophysiology of TMA in cancer, chemotherapy-associated TMA, transplant-associated TMA, and newer therapeutic modalities.

Tumor-Associated Thrombotic Microangiopathy

Almost 50 years ago, TMA was first described in gastric cancer patients. Cancer is known to be associated with both macro- and microvascular thrombosis.1 TMA was reported with mucinous gastric cancers from as early as the 1970s.3–5 Cobalamine deficiency, which can also cause a TMA-like syndrome by itself, can occur in gastric cancer and may contribute to the development of TMA in that setting.6 In most cases, TMA is associated with advanced cancer. It has been identified in patients with metastatic gastric, ovarian cancer, prostate, lung cancer, urothelial cancers, lymphomas, and myeloproliferative neoplasm and acute myeloid leukemia.7–10 Tumor embolization to the small vessels in the lungs, particularly from gastric, urothelial, and lung cancers, is associated with pulmonary tumor thrombotic microangiopathy (PTTM).7–12 In one study, it occurred in 21/690 consecutive autopsies and is reported to occur in 0.3 to 3.3% of autopsies. This syndrome is associated with acute pulmonary decompensation, characterized by worsening dyspnea, and pulmonary hypertension. In addition to hypoxemia, the chest X-ray findings show ground glass opacities, without an infectious etiology. Pathologic findings include small vessel, pulmonary arteriolar occlusion with intimal proliferation, and fibrin deposition in the thrombi.9,10 There is evidence of increased pulmonary vascular resistance.7,11 The syndrome is rapidly fatal.9,10

Pathologic features of tumor-induced TMA include vessel wall thickening at the arteriolar-capillary junction, with
swelling or detachment of endothelial cells from the basement membrane and intraluminal thrombosis. This results in partial or complete obstruction of the vessel lumen. By adhering to the vascular endothelium, the tumor cells are thought to activate the coagulation cascade directly through tissue factor (TF) as well as through the induction of inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor (TNF). Tumor cells, and tumor cell-derived microparticles, express TF on the cell membrane inducing thrombin generation, increasing the risk of thrombosis. In addition to cleaving fibrinogen, increased thrombin generation induces platelet activation and aggregation resulting in the formation of platelet and fibrin-rich microthrombi. Activation of the protease-activated receptors by thrombin may result in endothelial subintimal and smooth muscle proliferation. There is laboratory evidence of DIC, with elevated D-dimers. In addition, platelet-derived growth factor-A and vascular endothelial growth factor-C (VEGF-C) may be increased in PTTM and may contribute to the pathogenesis. Because tumor emboli express TF, there may be the local as well as systemic activation of the coagulation system resulting in vascular occlusion.

Table 1 Cancer-associated TMA

<table>
<thead>
<tr>
<th>Type of TMA</th>
<th>Clinical features</th>
<th>Pathology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor-related TMA</td>
<td>Disseminated intravascular coagulation, Acute respiratory distress</td>
<td>Pulmonary microtumor emboli, platelet, and fibrin-rich microthrombi</td>
<td>Specific cancer treatment</td>
</tr>
<tr>
<td>Chemotherapy associated a. Mitomycin C</td>
<td>Cumulative dose of 40–60 mg, May occur 4–6 months post-treatment, Noncardiogenic pulmonary edema, renal failure</td>
<td>Endothelial damage, Prostacycline inhibition, Increased levels of thrombomodulin, TPA, PAI-1</td>
<td>Drug discontinuation, Complement inhibition</td>
</tr>
<tr>
<td>b. Gemcitabine</td>
<td>Cumulative dose &gt; 22.5 mg/dL (± 14), HTN, proteinuria, hematuria, acute renal failure</td>
<td>Thicken of renal capillary walls, fibrin thrombi, necrotic endothelial cells, and granular deposits, complement C3 deposition</td>
<td>Drug discontinuation, Complement inhibition</td>
</tr>
<tr>
<td>c. Tyrosine kinase inhibitors</td>
<td>HTN, proteinuria, renal failure</td>
<td>Damage to podocytes similar to minimal change nephropathy or collapsing focal glomerulosclerosis.</td>
<td>Drug discontinuation, Complement inhibition</td>
</tr>
<tr>
<td>d. VEGF inhibitors</td>
<td>HTN, proteinuria, renal failure</td>
<td>Segmental glomerular capillary microaneurysms and segmental hyalinosis were typical</td>
<td>Drug discontinuation, Complement inhibition</td>
</tr>
<tr>
<td>Transplant-associated TMA a. CNI/MTOR inhibitors</td>
<td>Onset/worsening HTN, Progressive renal failure, Thrombocytopenia, MAHA, Pulmonary HTN</td>
<td>Separation of the endothelial cell layer arterioles and vascular occlusion with endothelial debris and fibrin, C4d deposition in renal arterioles</td>
<td>Elevated sC5b-9</td>
</tr>
<tr>
<td>b. Complement regulatory protein mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: C4d, complement protein 4d; CNI, calcineurin inhibitors; HTN, hypertension; MAHA, microangiopathic hemolytic anemia; MTOR, mammalian target of rapamycin; PAI-1, plasminogen activator inhibitor-1; sC5b-9, serum Complement 5b-9; TMA, thrombotic microangiopathy; TPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor.

**Role of Complement in Cancer-Associated TMA**

Complement dysregulation has been associated with TMA. In addition to activating the coagulation cascade, a variety of cancers can activate the complement system. DIC is the form of TMA most often associated with cancer. However, complement activation may have a role in the development of TMA. Direct activation of the complement system through the lectin pathway, involving mannan-binding lectin serine protease, may occur in adult T cell leukemia, where galactose-mannose is expressed on the tumor cell membrane. The conversion from a benign tumor to a neoplasm has been associated with increased expression of complement genes in endometriosis-associated ovarian cancer, as compared with benign endometriosis. More intriguing is the highly significant upregulation of complement genes, notable on ribonucleic acid (RNA) sequencing of lung cancer tissue, in patients with thrombosis compared with patients without thrombosis. Complement proteins, C3a and C5a, are essential for the development of neovascularization of tumors by inducing altered endothelial cell VEGF expression. VEGF and platelet-derived growth factor A, as expressed by the tumor cells, might contribute to pulmonary TMA. Increases in the expression of complement proteins and complement activation could cause TMA alone or may contribute to the development of HUS in a susceptible patient, triggered by either chemotherapeutic agents or infection. The interaction of the complement system and coagulation may contribute to the development of TMA. Thrombin generation, increased in certain cancers, can provoke development of cancer-related HUS by directly activating the
complement system through direct C5 cleavage, generating terminal complement complex and C5a. C5a is a potent inflammatory and prothrombotic complement fragment which in turn induces the release of various cytokines including IL-6, IL-8, and TNF. C5a also binds its receptor (C5aR) on monocytes to induce TF expression. TNF and IL-6 further increase endothelial and monocyte TF expression, augmenting formation of microvascular clots. C5a also binds to C5aR on platelets, inducing their activation and promoting platelet aggregation. In a murine mouse thrombosis model, blockade of the platelet C5a receptor, using an inhibitor of C5aR, was able to prevent antiphospholipid antibody-induced thrombosis (B Furie, personal communication). Blockade of complement 1q activation has been shown to result in decrease of both TF and IL-6 messenger RNA expression in the mouse. Improvement or resolution of the cancer-associated TMA may happen with the treatment of the underlying cancer. However, recurrence of the TMA may herald the recurrence of the cancer.

Chemotherapy-Associated Thrombotic Microangiopathy

Induction of TMA syndromes has been associated with multiple chemotherapeutic agents, including mitomycin C, gemcitabine, cisplatin, carboplatin, and the VEGF inhibitor bevacizumab. Moreover, tyrosine kinase inhibitors (TKIs) like sunitinib, dasatinib, and imatinib can induce TTP/aHUS-like syndromes. This may be because of direct toxic effects of chemotherapy (CT) on endothelium or development of antibodies to VEGF or immune complex-mediated endothelial damage. Decreased endothelial prostacyclin production has been reported in response to mitomycin C as well as anti-VEGF treatments in human endothelial cell cultures.

Prostacyclin is an important physiologic inhibitor of vascular tone and platelet aggregation. Thus, deficiency of prostacyclin would promote platelet aggregation and vascular constriction. In cases of mitomycin C-induced TMA, levels of plasma thrombomodulin, a sign of endothelial activation, along with tissue plasminogen activator and plasminogen activator inhibitor-1, are raised and similar to what is seen with aHUS.

Mitomycin C-associated TMA is typically a result of cumulative dosing, often occurring 4 to 8 weeks after the last dose. Most cases occur following 6 to 12 months of CT, representing a cumulative dose of 40 to 60 mg. Patients may be in remission but then die from the TMA complications. Mortality is 72%. The acute development of noncardiogenic pulmonary edema, adult respiratory distress syndrome, a finding not described in TTP, represents the seminal presentation of mitomycin C-induced TMA. The mechanism for the pulmonary edema is unclear but most likely results from pulmonary endothelial toxicity. Pulmonary hemorrhage may occur and is similar to that described with aHUS. Renal failure is prominent and frequently irreversible. There is a poor response to plasma exchange (PEx). A recent report suggest improvements in renal function, thrombocytopenia, and outcomes with the use of complement inhibition.

Gemcitabine can also induce TMA, and like mitomycin C, it is a result of cumulative toxicity. It typically occurs after treatment for 6 to 8 months with a total dose of 22.5 (± 14) mg/dL. In contrast to mitomycin C, the hallmark presentation of gemcitabine TMA is renal insufficiency. The onset, or worsening, of systemic hypertension, proteinuria, microscopic hematuria is present in 66% of patients. Renal biopsies show thickening of capillary walls, fibrin thrombi, necrotic endothelial cells, granular deposits, and complement C3 deposition. The response to PEx is poor. Several recent published reports, documenting successful use of complement inhibition to reverse gemcitabine-induced TMA, support the significant impact of complement activation in this condition.

Treatment with anti-VEGF inhibitors (e.g., bevacizumab) and TKIs are also associated with development of aHUS-like syndromes. While clinical presentation is similar, there appears to be differential effects on the kidney. In a large patient series with biopsy-proven kidney damage during anti-VEGF therapy, intraglomerular TMA occurred more often with VEGF-ligand inhibitors than with TKIs. TKIs instead more often caused podocyte damage, similar to minimal change nephropathy or collapsing focal glomerulosclerosis. A recent analysis found that segmental glomerular capillary microaneurysms and segmental hyalinosis were typical morphological features of anti-VEGF therapy-induced glomerular microangiopathy. Fibrin and platelet thrombi and fragmented erythrocytes were rarely found or completely absent. Occasional immune complexes were found. VEGF stimulates endothelial cells to generate nitric oxide and prostaglandin, which induce endothelial cell-dependent changes in vascular tone. Blockage of VEGF would lead to vasoconstriction. The vasoconstriction has also been hypothesized as a mechanism of the hypertension induced by anti-VEGF therapy. The onset, or worsening, of systemic hypertension may be preceded by the onset of the CT-associated TMA (CT-TMA). Inhibition of VEGF in the glomerular microvasculature may therefore prevent the formation and maintenance of healthy, fenestrated endothelium, and this may then compromise the glomerular filtration barrier, leading to hypertension and renal failure.

Although rare cases of ADAMTS-13 deficiency and ADAMTS-13 inhibitors have been reported, most patients with CT-TMA usually show ADAMTS-13 levels > 5 to 10%, more compatible with aHUS than TTP. CT-TMA responds very poorly to termination of the offending medication as well as to PEx. In a series of patients with CT–HUS, in which all failed drug termination and PEx, resolution of the TMA was accomplished using complement inhibition, indicating the significance of complement activation in this syndrome. In these patients, short-term (12–24 weeks) eculizumab therapy appeared sufficient to reverse the TMA findings.

Transplant-Associated Thrombotic Microangiopathy

Many hematologic and select solid tumors are treated by bone marrow or hematopoietic stem cell transplantation (HSCT), and these patients may develop TMA. Transplant-associated
TMA (TA-TMA) may result due to multiple risk factors, including the use of calcineurin inhibitors (CNIs) or mammalian target of rapamycin (MTOR) inhibitors, graft versus host disease (GVHD), the number of previous transplants, human leukocyte antigen mismatch, opportunistic infections, and conditioning regimen. The end result of these insults is endothelial damage particularly affecting the kidney but other organs as well. A significant role for complement activation contributing to tissue damage has also been indicated.

Transplant-associated TMA has been causally linked to calcineurin and MTOR inhibitors. However, two recent studies suggest otherwise. There does not appear to be any difference in the incidence of TA-TMA in patients receiving cyclosporin/methotrexate versus tacrolimus/methotrexate GVHD prophylaxis unless the tacrolimus level was > 25 ng/mL. In another study, only a sirolimus level of > 9.9 ng/mL was associated with a twofold risk of developing TMA within the first 2 weeks post-transplantation.

Confounding much of this data are the presence of additional risk factors such as acute GVHD, which may worsen with discontinuation of the CNI or MTOR inhibitor and myeloablative conditioning with total body irradiation (TBI). TA-TMA can occur in patients receiving T cell depleted hematopoietic transplant in which a CNI or MTOR inhibitor is not used. In the T cell-depleted patients who received TBI as part of their conditioning regimen, 11/70 developed TMA compared with 0/30 in the nonirradiated group without using a CNI or MTOR inhibitor. Studies have failed to demonstrate any difference in TA-TMA with high dose versus reduced intensity conditioning, unless TBI was added.

TA-TMA has also been reported in autologous stem cell transplants, where immune modulation with CNI/MTOR inhibitors would not be used. This would suggest that the conditioning regimen might have a role. In a study evaluating patients with neuroblastoma receiving different conditioning regimens prior to autologous transplant, the use of carboplatin, + etoposide + melphalan was associated with a significant increased incidence of TMA compared with cyclophosphamide + thiotepa or busulfan + melphalan.

Several recent studies on TA-TMA point to the development of/or worsening hypertension preceding the development of TA-TMA. It has been postulated that the associated endothelial damage may be due to inflammation-induced alterations in the renin angiotensin system. The pathologic findings include thickened capillary walls and occluded vessel lumens; red blood cell fragments can be seen trapped in the mesangial matrix. Renal arterioles show separation of the endothelial cell layer and vascular occlusion with endothelial debris. These findings have been documented in the lungs, associated with pulmonary hypertension, as well as the small bowel associated with ischemia. Complement protein C4d deposition in arterioles has also been noted suggesting a role for complement activation. These biopsy findings are very similar to those seen in aHUS. Using an experimental in vitro system, marked increases in systemic terminal complement activation were documented in TA-TMA patients.

Transplant-associated TMA often fails to respond to conservative measures, such as drug cessation and PEx, with progression of renal failure, coma, and death. In a single institutional review, prolonged PEx was not associated with improvement in renal function. In small retrospective series, rituximab and defibrotide have been reported to improve outcomes in TA-TMA. Defibrotide is a polyoxymethylene-ribonucleotide used in post-transplant veno-occlusive disease. Defibrotide has been suggested as a potential TA-TMA therapy possibly through its action on platelet aggregation as well as endothelial protection against TNF-α-mediated endothelial cell apoptosis. It induces fibrinolysis and anti-inflammatory activity. Corti et al suggested that defibrotide may be beneficial in approximately 50% of patients post-HSCT.

Given the evidence of complement deposition and the pathologic similarities to aHUS, it is appropriate to consider complement inhibition for the treatment of TA-TMA. In several publications, Jodele et al reported several clinical and laboratory features identifying TA-TMA and response to complement inhibition. The onset of hypertension, a marker of endothelial cell activation and damage, in HSCT patients, occurs prior to the development of the TMA, and similar to aHUS, TA-TMA has been described in both allogenic and autologous transplants. More importantly, in Jodele’s initial study, five of the six patients had underlying complement regulatory protein mutations. Complement factor H-related 1–3 (CFHR 1–3) mutations were reported in five out of six patients (both allo- and auto-HSCT). Antibodies to CFH were identified three of the six patients. This would suggest that the patients with TA-TMA may have an underlying predisposition to develop aHUS or an HUS-like syndrome. African Americans patients were found to have a higher incidence of multiple mutations and worse outcomes. Complement inhibition was effective in resolving the TA-TMA in five out of six patients treated with eculizumab. In the one nonresponsive patient, levels of eculizumab were insufficient and complement inhibition was never achieved. A subsequent publication suggests that more aggressive dosing to achieving complete complement blockade, a CH50 of < 10, or an eculizumab trough level of > 99 μg/mL, may improve the response rate.

**Conclusion**

In summary, cancer-associated TMA, whether due to cancer, CT, or hematopoietic stem cell transplantation, has a dismal outcome. Increased awareness, earlier recognition, and intervention of these disorders will hopefully reduce associated morbidity and mortality. New treatments of TMA in the setting of CT and TA-TMA have realized significant improvements in patient outcomes.

**Addendum**

This review represents a more comprehensive and updated review to one recently published by this author. Some short excerpts of text have been reproduced with the permission of the publisher.
Conflict of Interest
Dr. Weitz reports personal fees, speaker honoraria, from Alexion Pharmaceutical. There were no fees involved in the preparation of this manuscript.

References


Jodele S, Dandoy CE, Myers K, et al. High dose Carboplatin/Etoposide/Melphalan increases the risk of thrombotic microangiopathy and organ damage after autologous stem cell transplantation. Bone Marrow Transplant 2018;53(10):1311–1318


