Thrombotic Microangiopathy Manifesting as Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome in the Cancer Patient

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ABSTRACT The complication of thrombotic thrombocytopenic purpura or hemolytic uremic syndrome (TTP/HUS) can occur in cancer patients. It is characterized by a microangiopathic hemolytic anemia, severe thrombocytopenia, and renal failure. Pulmonary manifestations, especially pulmonary edema, are a common observation. Neurologic changes are also frequently seen. The etiology is unknown at this time. It has been observed in many different types of cancer and is most commonly seen in gastric adenocarcinoma followed by carcinoma of the breast, colon, and small cell lung carcinoma. The hemolysis can be massive and is due to red cell fragmentation, as schistocytes are present in all the cases. Though immune complexes are present in the plasma, the antiglobulin (Coomb’s) test is negative. Chemotherapeutic agents, especially mitomycin C, have been implicated as causative factors. There is a correlation of this complication with the cumulative dose. However, chemotherapy cannot account for all the cases as the syndrome can occur in untreated patients. It can be differentiated from disseminated intravascular coagulation by the absence of a coagulopathy. Management should consist of plasma exchange, use of a Staphylococcus aureus column (Proserba), and control of hypertension. Because of the susceptibility to pulmonary edema, blood volume overloading should be avoided.

Keywords: Cancer, TTP/HUS, mitomycin C, plasmapheresis, microangiopathy

As the association between thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) and cancer is well established,\textsuperscript{1,2} it is fitting to update and review this entity in the present issue of *Seminars in Thrombosis and Hemostasis* devoted to the thrombophilic state of cancer. TTP/HUS should be regarded as a syndrome of severe thrombocytopenia and microangiopathic hemolytic anemia due to formation of widespread microthrombi composed mainly of platelets. Multiple forms of this syndrome are recognized, ranging from those in which the causative factor has been identified, such as in Shiga-toxin-induced TTP/HUS, to the more obscure idiopathic form. Though unfortunately the etiology of most forms of TTP/HUS is still an enigma, a number of contributing factors and much of the pathophysiologic process of their development are now beginning to unfold. In the case of the cancer-associated TTP/HUS, the toxicity of chemotherapeutic agents is implicated, but the role of the tumor cells may also be important. In this article, we will attempt to review the relevant recent literature and discuss the possible pathogenic mechanisms, then review the clinical features and treatment options of TTP/HUS associated with cancer.

Incidence

The true incidence of TTP/HUS in cancer is uncertain, as in many case reports, the distinction with disseminated intravascular coagulation (DIC) is never made. Lohrman et al estimated an incidence of 5 to 6%,\textsuperscript{3} but Brain et al reported that\textsuperscript{4} five of 25 patients with de novo TTP/HUS had cancer, including three with gastric cancer. Among the cancers associated with TTP/HUS, adenocarcinoma predominates,\textsuperscript{3,5-7} accounting for 88% of some series\textsuperscript{7} with gastric adenocarcinoma being the most common type,\textsuperscript{5,7} followed by breast cancer,\textsuperscript{7-11} colorectal cancer,\textsuperscript{12} small cell lung cancer,\textsuperscript{13,14} squamous cancers,\textsuperscript{15} thymoma,\textsuperscript{16,17} and carcinoma of unknown primary origin. Chronic myelogenous leukemia\textsuperscript{18} and Ka-
Clinical Features

Anemia, thrombocytopenia, and renal failure are always present and are the common presenting manifestations. Though the anemia and thrombocytopenia may be confused with the marrow-suppressive effects of therapy or the cancer, it soon becomes apparent that these features are out of proportion to what is usually seen with chemotherapy for adenocarcinoma. In almost all of the cases, the presence of schistocytes is helpful in confirming the diagnosis. The anemia and thrombocytopenia are usually severe, and reticulocytosis is often noted, with elevation of serum LDH levels indicating intravascular hemolysis. The antiglobulin (Coomb’s) test is negative, reflecting the lack of red cell autoantibodies, and the peripheral blood smear usually shows abundant schistocytes. Jaundice (from the hemolysis), and nonfocal neurologic syndromes may occur. The neurolologic manifestations of TTP/HUS associated with cancer are similar to those associated with idiopathic TTP/HUS, and include headache, confusion, hemiplegia or hemiparesis, and coma. Pulmonary manifestations are common and include pulmonary hypertension and dyspnea. Noncardiogenic pulmonary edema is characteristic in this variety of TTP/HUS making it distinct from the other types. This is especially true in the late stages of the disease, when an ARDS-like picture or hemorrhage may develop as a terminal event or it may be related to complications of therapy, such as intravenous immunoglobulin. Another unusual feature is the presence of immune complexes in approximately 90% of the cases. The absence of coagulopathy with normal prothrombin time and normal partial thromboplastin time enables the differentiation from DIC.

Pathophysiology

The clinical manifestations of the TTP/HUS syndrome appear to be the result of an insult to the vascular endothelium, and the pathophysiology has been recently reviewed. In TTP/HUS, hyaline thrombi are present in the small vessels, in capillaries, and arterioles, but not in venules. A detailed analysis of the pathology of the vascular lesion was common in the early literature. There is damage to endothelial cells which either is caused by or contributes to platelet agglutination, and then additional endothelial cell damage, vascular injury with a vicious cycle ending in progressive hemolysis, thrombocytopenia with renal, CNS, pulmonary failure, and death. This process is probably not different in cancer-associated TTP/HUS. Recent studies by Nagaya and his group shed some light on this question. They showed that levels of the cytokines TNFα, IL-1β, and IL-6 were elevated in patients with de novo TTP/HUS and DIC but not in patients with mitomycin C-induced TTP/HUS. Similarly, von Willebrand factor (vWF) antigen and low molecular weight vWF multimers were reduced in DIC and de novo TTP/HUS, but not in the drug-induced syndrome. This despite the observation by others that the histopathology of small vessels in cancer-associated TTP/HUS and de novo TTP/HUS reveals similar findings, and that the red cell changes are indistinguishable in TTP/HUS (de novo or cancer-associated) and a variety of other disorders, including malignant hypertension or renal cortical necrosis. Recently, the role of the microvascular cell apoptosis and the nitric oxide system in the pathophysiology of TTP/HUS have been investigated.

The pulmonary changes that are associated with TTP/HUS may involve intimal proliferation in small pulmonary vessels. Tumor emboli were documented, causing occlusion of the vascular lumen, though if this were the predominant mechanism more patients with tumor emboli should have microangiopathic hemolytic anemia. Fibrin thrombi are also found, though not always in association with tumor emboli. In some patients, the presence of intimal thickening with fibromuscular hyperplasia in the small pulmonary arteries suggests that the process in the lung may be a more chronic process.

RELATIONSHIP TO DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

The pathologic lesions in cancer-associated TTP/HUS are difficult to distinguish from DIC, and fibrinolysis has been observed in an autopsy series. The earliest demonstration of schistocytes in the blood of cancer patients came from Lohrman et al, but, the presence of red blood cell fragmentation in the blood of patients with metastatic cancer may indicate not only TTP/HUS but also DIC. Thus, it is important to distinguish on either laboratory or clinical grounds which pathophysiology is operative. There is a consumption of coagulation factors in DIC but not in TTP/HUS. The laboratory findings of coagulopathy are rarely seen in de novo TTP/HUS but are present in DIC or may be present in cancer-associated TTP/HUS if there is concomitant low-grade DIC. Fibrin deposition occurs in tumor tissues, and there was evidence of fibrin degradation in 75.4% of the 719 cancer patients studied. Thus, DIC and TTP/HUS may coexist in cancer patients and may confuse the diagnosis. There may be vascular injury from chemotherapy or radiation, and tumor cells may invade vessels. Extensive vascular injury, or vasculitis, can result in either DIC or TTP/HUS. It has been suggested that intravascular coagulation is not likely the initiating event in cancer-associated TTP/HUS because the degree of coagulopathy and clotting factor consumption does not correlate with the amount of hemolysis. Further, evidence for DIC is pres-
ent in only about half of the patients with TTP/HUS.\textsuperscript{40} Bull et al reported fine fibrin strands from 0.25 to 2\(\mu\)m in diameter, which sometimes contained tumor cells, red cells, white cells, but not platelets.\textsuperscript{53,54}

Vascular hypertrophy and intimal hyperplasia can be seen in various forms of the TTP/HUS syndromes. These data suggest that the common pathway for vascular injury in these syndromes is not known, and support the idea that a generalized vasculopathy is present in cancer, in patients taking certain drugs, and after exposure to toxins\textsuperscript{55-59} or organisms.\textsuperscript{60,61}

The role of immune complexes in cancer-associated TTP/HUS has been studied,\textsuperscript{41,62} and has led to immune modulation as a form of treatment. These include steroids and immunosuppressive drugs. Recently, the removal of immune complexes by immunoadsorption has been successfully used in patients with cancer chemotherapy-associated TTP/HUS.\textsuperscript{63,64} Snyder et al\textsuperscript{63} reported responses in 25 of 55 cases. Responders did better than nonresponders, with a 62% 1-year survival versus a 22% 1-year survival in nonresponders. Complement components C3 and C4 normalized, and immune complexes were cleared. Side effects included fever, chills, nausea, respiratory symptoms, and blood pressure changes. The mechanism of immune absorption therapy is not known, and though there is likely a clearing of immune complexes, other changes in the humoral and cellular immune systems\textsuperscript{65-67} may occur. The exact role for this treatment modality remains uncertain, and further comparative trials are indicated.

**Cancer Chemotherapy-associated TTP/HUS**

Liu et al reported that renal toxicity caused by the anticancer drug mitomycin C was associated with microangiopathic hemolytic anemia and thrombocytopenia.\textsuperscript{68} TTP/HUS has more recently been associated with many other anticancer drugs, including bleomycin, cisplatin, and gemcitabine.\textsuperscript{69-72} Among those patients that had received mitomycin C, there was a trend to correlation with the cumulative dose.\textsuperscript{73,74} Published reports in the literature showed that the cumulative doses exceed 40 mg/m\textsuperscript{2}.\textsuperscript{73,74} With chemotherapeutic agents other than mitomycin C, there was also an apparent dose relationship to the incidence of this complication. In a series of 581 patients with carcinoma of the breast receiving a high-dose regimen of cyclophosphamide, cisplatin, and carmustine, 2.6% developed TTP/HUS.\textsuperscript{75}

It is often difficult to distinguish between cancer and cancer-chemotherapy-associated TTP/HUS. Murog has reviewed the subject and has found features that separate these entities\textsuperscript{40} though the distinction is far from easy to make. If the assertion that patients in remission likely suffer from chemotherapy-associated TTP/HUS is the discerning feature, it may not prove reliable as it is often difficult to achieve complete remissions from the metastatic adenocarcinomas that are seen in this syndrome.\textsuperscript{1}

The incidence of renal and pulmonary manifestations may not help to distinguish the two, because most patients with metastatic cancer presenting today will have received some form of systemic chemotherapy. We have observed both renal and pulmonary failure in both. It is possible that the higher incidence of renal failure described by Murgo\textsuperscript{40} and observed Snyder et al\textsuperscript{63} is related to the added insult of potentially nephrotoxic drugs such as mitomycin C or cisplatin. We have seen responses with plasma exchange in both entities, whereas heparin therapy should be reserved for those patients who have documented acute DIC.

Elevated plasma vWF levels and arterial thrombosis in patients receiving cisplatin-based regimens have been described.\textsuperscript{69} and a patient with a history of osteosarcoma who received four courses of single-agent cisplatin, then developed TTP/HUS, has been reported.\textsuperscript{75} He was treated with hemodialysis, and the syndrome was resolved. The time interval from the initiation of chemotherapy in this patient was 10 months. The interval from the last dose to the development of the syndrome was 7 months, within the variable range of time of onset after drug exposure as described in the literature.

The antiestrogen tamoxifen contributed to the development of TTP/HUS in a patient with metastatic breast cancer who had previously been treated with a combination of mitomycin C, mitoxantrone, and methotrexate (3M). Autopsy findings were consistent with what would be expected after mitomycin C-associated TTP/HUS.\textsuperscript{76} In a review of their experience with 94 patients who received 3M and tamoxifen, the authors found nine cases with TTP/HUS and suggested that there was an interaction between tamoxifen and one or more of the drugs in this regimen.\textsuperscript{77} Other cancer chemotherapy agents reported to be associated with TTP/HUS include doxorubicin,\textsuperscript{78} methyl CCNU,\textsuperscript{79} bleomycin,\textsuperscript{80-80} and cytotoxic arabinoside, and daunomycin\textsuperscript{80} in a patient with acute leukemia.

There are data that suggest that free radical injury may play a role in the pathogenesis of the endothelial cell injury which is associated with the clinical syndrome. The role of free radicals in this disorder of vascular endothelial cells deserves further study. Recently, Laurence et al reported that plasma from patients with acute TTP/HUS could induce apoptosis in cultured microvascular endothelial cells and that this was associated with the rapid induction of Fas (CD95) expression on these cells.\textsuperscript{81,82}

We believe that the TTP/HUS syndromes are a significant cause of morbidity and mortality in the cancer patient, either because of the underlying disease or its treatment. Therapy with plasma exchange, immunoadsorption columns, or immunosuppressive drugs may be beneficial.\textsuperscript{83} The TTP/HUS caused by other, noncancer-related drugs, should be considered in any patient who presents with clinical findings of anemia, thrombocytopenia, neurologic changes, or renal failure, and prompt therapy with plasma infusion and/or plasma exchange should be instituted.
The increased susceptibility to pulmonary edema in these patients requires meticulous care in limiting the volume of intravenous fluids. In some patients, the presence of hypertension may need special attention. The cause of the hypertension is not clear. Though the presence of a high plasma renin level suggests the use of an ACE inhibitor, this may not always be the case in other patients.73

Finally, new strategies for intervention should be based on a better understanding of vascular biology, and the occurrence in cancer patients may provide clues to the underlying mechanism.

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