Thrombotic Microangiopathy in the Cancer Patient

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Key Words

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Abstract

Thrombotic microangiopathy, manifesting as thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome, is a common complication in cancer patients. It shares the pathogenic microvascular occlusive lesion and many clinical manifestations as the classical TTP, but the spectrum of complications varies widely. Several subsets are seen, including a microangiopathic hemolytic anemia in advanced cancer, chemotherapeutic drug-associated microangiopathy and those with the transplant setting. The prognosis is not as favorable as in classical TTP. Anecdotal reports indicate that responses are seen with plasma exchange and with immunoadsorption.

Introduction

The combined manifestations of hemolysis, thrombocytopenia and impaired renal and neurological functions are often encountered in a cancer patient especially one with extensive metastatic disease. While a state of disseminated intravascular coagulation (DIC), either in an acute or a chronic setting, is most often present, it is sometimes difficult to separate the diagnosis of DIC from that of thrombotic thrombocytopenic purpura (TTP) or that of hemolytic uremic syndrome (HUS). The latter two conditions are characterized by the presence of microvascular thrombotic lesions, composed mainly of aggregated platelets with small amounts of fibrin, in contrast to microvascular fibrin thrombi seen in severe DIC. The underlying pathogenic factor is the presence of endothelial damage whether it is due to chemotherapeutic agents or to the malignant condition itself. There are features of TTP/ HUS in cancer distinct from those seen in the classic idiopathic form of TTP (Moschcowitz syndrome), and from TTP/HUS secondary to infection or to vascular complications of pregnancy. The recognition of these features is essential in the diagnosis and management of this complication in the cancer patient.

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Table 1. Three major subsets of TM in the cancer patient [modified from 12] listed with their respective distinguishing features

Features	MAHA	Drug-associated	Transplantation-associated
State of cancer	Advanced	Any stage	Low tumor burden, if any
Contributing factor	Tumor- derived	Drug toxicity	Drug toxicity and graft rejection
Coagulopathy	Present	Usually absent	Absent
Major organs involved	Lung, kidneys	Kidneys	Kidneys, CNS
Differential diagnosis	DIC	Drug toxicity	GVHD, VOD, DAH, CMV
Intolerance to intravenous fluid	None	Frequent	None
Platelet transfusion	Detrimental	Not contraindicated	Not contraindicated
Immunoadsorption	May be helpful	Not effective	Not effective
Prognosis/status	Tumor-dependent	Fair	Dependent on risk factors; generally poor

MAHA = Microangiopathic hemolytic anemia; GVHD = graft versus host disease; VOD = venous occlusive disease; DAH = diffuse alveolar hemorrhage; CMV = cytomegalic viral infection.

Terminology

Moschcowitz [1, 2] first described in 1924 'an acute pleiochromic anemia' with fever, malaise and upper extremity weakness in a 16-year-old girl who died 13 days later. On postmortem examination, he found widespread hyaline microthrombi in the terminal arterioles and capillaries. Later, Baehr et al. [3] in 1936 recognized that the microthrombi were composed of fibrin and agglutinated platelets and postulated that they were caused by widespread vascular injury. Hence, Singer et al. [4] in 1947 named this condition TTP. Since then, syndromes with clinical and pathological features of classical TTP have been observed as complications secondary to a wide variety of diseases such as infectious hemorrhagic colitis, cancer and vascular complications of pregnancy. Since the term TTP does not describe the hemolytic component of the disease and since purpura is commonly absent, Symmers [5] introduced the term 'thrombotic microangiopathic hemolytic anemia' or abbreviated as 'thrombotic microangiopathy' (TM). In the current literature, the use of this term is helpful when describing conditions of TTP secondary to an underlying disease such as cancer, as it is distinct from the classical TTP as described by Moschcowitz [1, 2]. A milder form of TM with the same vascular pathology but with clinical involvement limited to the kidneys and intestines, commonly seen in children, was named by Gasser et al. [6] as HUS. Since TTP and HUS often overlap in their clinical picture and can be indistinguishable, the term TTP/HUS is often used.

Clinicopathological Features

In the classical TTP, the main features are fever, hemolytic anemia, thrombocytopenia, neurological and renal abnormalities [7–9]. Other manifestations include petechial hemorrhages and ecchymoses, general malaise, weakness and fatigue, nausea and vomiting, pain in the abdomen, joints and muscles, and cardiac arrhythmia. When some or all of these features occur in a cancer patient, particularly one in the advanced stages of the disease, the complication of TTP/HUS must be considered. In the differential diagnosis, the difficulty arises from the fact that many of the findings are nonspecific and commonplace in cancer.

In cancer, manifestations of TTP are usually less pronounced than those seen in the classical TTP, and many patients do not present the full syndrome [10, 11]. This complication has been encountered in a wide variety of tumors, with adenocarcinoma of the stomach, breast and lung being the most common [12, 13]. Several subsets can be identified in cancer-associated TTP, each with their own distinct features: (1) microangiopathic hemolytic anemia in advanced stages of the disease with widespread metastases, (2) chemotherapy (or drug-)associated TTP/HUS, often in patients in clinical remission from their cancer, and (3) those who have TTP/HUS associated with bone marrow transplantation (BMT). Frequently, the clinical features in these groups overlap. In table 1, their distinguishing features are listed.

Table 2. Drugs associated with TTP/HUS

Drugs used in cancer treatment	Other Drugs
Mitomycin C[1]	Clopidogrel [14]
Daunorubicin, Ara-C[1]	Ticlopidine[1]
Bleomycin[1]	Cyclosporin[1]
CDDP[1]	Sulfonomides[1]
Methyl-CCNU[1]	Tacrolimus[1]
Tamoxifen[1]	Sirolimus
Deoxycoformycin[1]	'Crack' cocaine[1]
Gemcitabine [33]	Penicillin[1]
Atorvastatin	Rifampicin[1]
	Penicillamine[1]
	Oral contraceptives[1]
	Arsenic[1]
	Quinine[1]
	Iodine[1]

* Detailed references for these drugs can be found in Gordon and Kwaan [10].

Drug-Associated TTP

The list of drugs that may cause TTP is growing since the recent establishment in the US of several programs reporting adverse drug reactions [14]. In the cancer patient, such drugs may be chemotherapeutic agents or those given for comorbid conditions. Table 2 contains those currently known and may not be complete as newer drugs are being identified. Among the chemotherapeutic agents associated with TTP in cancer patients, mitomycin is the most common. It appears to be dose-related. Since patients are often given several of these agents in combination it is not always certain which specific drug is responsible.

BMT-Associated TTP [15–18]

There is a wide variation in the clinical presentation and prognosis in this group. In a review of the natural history of 172 patients with post-BMT TTP/HUS, a high risk of developing TTP was found in those with allogeneic BMT, treatment with cyclosporine or tacrolimus, onset of TTP/HUS within 120 days of transplantation and neurological manifestations [15]. The mortality was 12% in the absence of these factors. In contrast, it was 85% when two or more of these factors were present. When graft versus host disease is present, increased cytokines may contribute to the endothelial cell damage. In patients treated with tacrolimus, this immunosuppressant has properties that may contribute to the microangiopathy. These include increased endothelin release, causing vasoconstriction leading to increased shear and further exacerbating the

red cell fragmentation. Increased levels of certain cytokines such as IL-8, IL-10, IL-12 were also found and believed to increase endothelial cell adherence. While there are no available data on a prospective clinical trial, the anecdotal reports indicate that either plasma exchange or immunoadsorption altered the outcome in some patients.

Laboratory Findings

The diagnostic feature is the presence of hemolysis, with fragmented red blood cells or schistocytes in the peripheral blood. The degree of anemia is proportional to the severity of hemolysis. Other supporting evidence of hemolysis are the increased unconjugated serum bilirubin (indirect), elevated lactic dehydrogenase, decreased plasma haptoglobin, and increased urobilinogen in urine. If the hemolysis is severe, nucleated red cells may be present in the peripheral blood. Hemolysis is the result of fragmentation of red blood cells and not caused by an immune mechanism. The direct antiglobulin (Coomb's) test is usually negative. There is also thrombocytopenia, which is usually severe with platelet counts in the range of 1.0–3.0 × 10⁹/l. If the patient is not severely debilitated by the underlying cancer, the bone marrow shows erythroid hyperplasia along with an increase in megakaryocytes.

The central lesion is widespread microvascular thrombus composed of aggregated platelets and fibrin. Immunohistochemical stains show that complement and immunoglobulins may be present. Endothelial hyperplasia overgrowing and covering the thrombi are frequently seen together with recanalization of the occluded vessel. There are no cellular infiltrates in the vessel wall, thus excluding the presence of vasculitis. The arterioles and capillaries are the site of these lesions and the venules are rarely involved. In severe cases, the vascular lesions can be found in practically all the tissues and organs in the body. While the microvascular lesion is the same in TM associated with cancer or drugs, the extent of organ involvement may vary. In most cases, renal involvement is dominant.

Many of the clinical and laboratory findings are well correlated with the pathological features. An increase in shear stress to the red cells during their passage through partially recanalized arterioles causes fragmentation and hemolysis. Thrombocytopenia follows excessive platelet consumption as a result of in vivo aggregation and platelet-rich thrombi formation.

Widespread involvement by the occlusive vascular lesion accounts for the multiplicity of symptoms. Clinical

manifestations can be accounted for by functional impairment of the respective organs. Thus, neurological and renal manifestations are due to the presence of microvascular lesions in the brain and kidneys, respectively. Abdominal pain is the result of ischemic changes in the pancreas or in the gastrointestinal tract. Cardiac arrhythmia is due to the presence of vascular lesions in the myocardium.

Pathogenesis

Since the occlusive microvascular platelet-rich thrombus is the core lesion in this disease, investigations into its pathogenesis have been centered on the cause of the platelet aggregation or agglutination. Several lines of investigation have been fruitful. Firstly, much evidence pointing to endothelial damage has been observed. These include findings such as impaired fibrinolytic activity [19], decreased prostacyclin production [20], presence of immune complex in the vessel wall [21], and in vitro findings of endothelial cell apoptosis [22]. Secondly, unusually ultralarge multimers of von Willebrand factor (vWF) are present in circulating blood of TTP patients [23]. These large multimers are broken down to fragments by a recently discovered vWF-cleaving protease. In TTP, the vWF-cleaving proteolytic activity was found to be absent, and is believed to be inhibited by an anti-vWF-cleaving protease IgG [24–26]. Thus, the ultralarge multimers of vWF in the blood would bind platelet membrane adhesive glycoproteins (Gp Ib/IX/V) resulting in further activation of Gp IIb/IIIa. Such findings would explain the well-established therapeutic benefit of plasma exchange, a process that replaces the vWF-cleaving protease missing in patients with TTP. The vWF-cleaving protease has been found to be impaired in the plasma of patients with various forms of TTP. These include classic TTP and TTP associated with ticlopidine and with clopidogrel [14], but not BMT-associated TTP.

On the other hand, in the case of cancer-associated TTP, the picture is less clear. The receptors Gp Ib and IIb/IIIa as well as other integrins are known to be present in a number of cancer cell lines [27, 28]. These glycoproteins enable the tumor cells to bind vWF and fibronectin, vitronectin and other matrix proteins. They may also mediate tumor cell adhesions to platelets. In addition, immune complexes have been found in the plasma of these patients [29, 30]. These are believed to be the host immune response to tumor antigens, but the relevance of these complexes to the TM remains obscure.

Differential Diagnosis

In the cancer patient, fever, abnormal renal function, anemia and thrombocytopenia are common. When these features cannot be accounted for by comorbid conditions, the clinician should consider TTP/HUS as a possible cause. Investigation into the etiology of the anemia is essential. The probability of TTP/HUS is high if the anemia is hemolytic. This will have to be confirmed by laboratory findings such as increased serum LDH, unconjugated bilirubin and the appearance of schistocytes in the peripheral blood. A small number of schistocytes can be due to other causes of red cell fragmentation such as the presence of a cardiac valvular abnormality, an arteriovenous shunt, renal hypertension and DIC. Schistocytes may not be pronounced in mild cases of DIC and their presence signifies a severe DIC. In such cases, gross abnormality in the coagulation factor defects would be apparent. Consideration of these causes will avoid the overdiagnosis of TTP.

Another frequently encountered problem is the differentiation between drug toxicity and TTP. The drugs listed in table 2 have one side effect in common. They can all cause endothelial damage, especially in the kidneys, leading to impaired renal function.

In the transplant patient, the differential diagnoses include graft versus host disease, venoocclusive disease, cytomegalic viral or fungal infections, and diffuse alveolar hemorrhage, as seen in table 1. Particular difficulties in differential diagnosis may be seen with cyclosporine-related complications such as CNS changes and microangiopathy without the full-blown syndrome of TTP/HUS.

Management

The treatment modalities for cancer-associated TTP/HUS are similar to that used in classic TTP [31, 32], with plasma exchange being the single most important element. There are, however, some differences in the cancer patient. Plasma exchange is frequently not effective with response rates of 20–30% in contrast to 80% in classic TTP. In nonresponders, immunoadsorption of the patient's plasma by a staphylococcal protein A column has been used [17, 29, 30]. Immune complexes had been recovered from the column [29, 30]. This suggests an immunological role of the pathogenesis of this disease in the cancer patient although there are no benefits using immunosuppressive therapy. The harmful effects of platelet transfusion are not as evident as in the classic

TTP patients, and thus not contraindicated especially when major bleeding complications are present. Where immunosuppressive agents are used in transplant patients with TTP, a switch to alternative agents is recommended. Supportive treatment may need to be more aggressive depending on the patient's tumor status and red blood cell replacement may be needed more frequently. Cancer patients may not tolerate large volumes of intravenous fluids as pulmonary edema is commonly encountered.

Acknowledgement

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