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Current concepts in the diagnosis and management of thrombotic thrombocytopenic purpura

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Thrombotic thrombocytopenic purpura (TTP) was described first in 1924 when Moschcowitz [1] reported a 16-year-old girl who died suffering from anemia, petechiae, and microscopic hematuria. This early observation and other reports led to the classic description and characterization of this syndrome by Singer [2] in 1947. Since then, understanding of the pathophysiology, etiology, and management of this disease has increased as TTP has become a true medical emergency.

Despite its rarity, recognizing this entity is important, as early institution of appropriate medical intervention has a substantial impact on the outcome of this disease. Its frequency was estimated a decade ago to be only 3.7 cases per year per 1 million people [3,4]. With greater awareness of this disorder and increasing reports of TTP secondary to other illnesses and to drugs, the incidence likely is much higher today. It is more common in women than in men, with a ratio of 3:2, without significant racial difference [5]. Although the range of incidence is wide, from the neonatal period and infancy to as old as 90 years, the peak occurs in the fourth decade, with a median age at diagnosis of 35 years [6,7].

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Thrombocytopenic purpura is a syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction (the pentad), with fewer than 3% of patients surviving before the 1960s [8,9]. The introduction of plasma exchange into the management of this disease has improved the outcome to up to 82% survival [10,11].

Hemolytic uremic syndrome (HUS) [12,13,14] is a closely related disorder first described by Gasser in children with hemolytic anemia, thrombocytopenia, acute renal failure, and cerebral symptoms. Many of the children were found to have preceding gastrointestinal syndromes with bloody diarrhea and were likely suffering from Shiga-toxin enterocolitis [15], described in greater detail subsequently. HUS also has been described in adults since then. There is much overlap between TTP and HUS depending on its severity [16].

Pathology

Thrombocytopenic purpura is a microvascular disease involving the arterioles and capillaries and sparing the venules throughout the body. The vascular lesion consists of platelet microthrombi partially occluding the vessel with overlying proliferative endothelial cells [8]. The incomplete occlusion results in altered hemodynamics with the passage of blood through narrowed channels leading to the damage of erythrocytes in the form of fragmented cells or schistocytes. The microthrombus has a fine granular appearance on light microscopy and is positive for Periodic Acid Schiff (PAS) and Giemsa stains [8] (Fig. 1A). Immunofluorescent and electron microscopy studies reveal that it is composed of fibrin and platelets [17], although complement and immunoglobulins can be found occasionally [8,18]. There is hyperplasia of endothelial cells, resulting in overgrowth over the thrombus so that the thrombus appears to be subendothelial [8]. Although the involved vessel wall shows no cellular infiltration or inflammatory changes, certain characteristics are observed in the endothelial cells. With electron microscopy, these cells are swollen, with cytoplasm containing fibrils that resemble microtubules [17]. Other endothelial cells in the region of the platelet deposits contain numerous cytoplasmic projections, endoplasmic reticulum with rough surfaces, increased mitochondria, enlarged Golgi elements, and numerous lysosomes [17]. The vascular lesion is widespread and spares practically no organ, with the kidneys (Fig. 1B), brain, pancreas, heart, spleen, and adrenal glands being the most severely affected. Microvascular endothelial cells derived from the heart, kidney, and brain have been found to be susceptible to damage by TTP plasma *in vivo*. Lesser degrees of involvement also have been seen in the lung, gastrointestinal tract, gall bladder, skeletal muscles, retina, pituitary gland, ovaries, uterus, and testis [8,19].

Biopsies of the gingival, skin, and bone marrow may yield the diagnostic lesion in 30% to 50% of the cases [5,20–22]. Focal areas of hemorrhage are

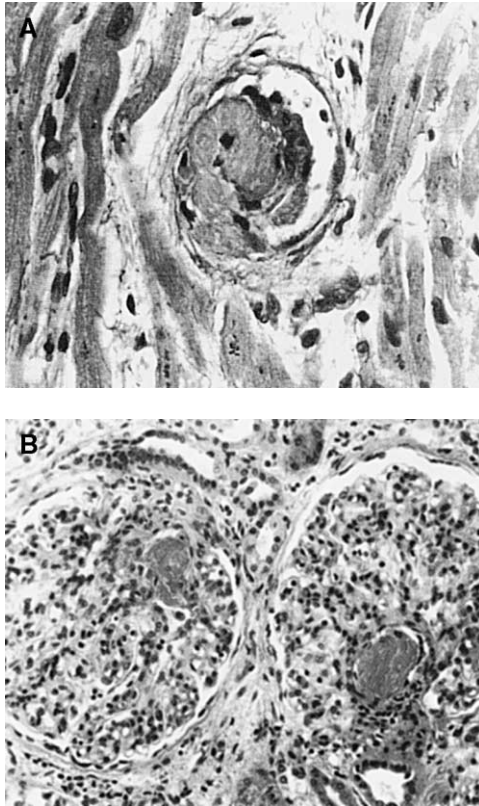


Fig. 1. (A) The characteristic microvascular lesion in TTP in an involved capillary in the myocardium, showing a thrombus partially occluding the lumen with overlying proliferative endothelial cells [8]. (Original magnification $\times 400$. Hematoxylin and eosin stain). (B) A similar lesion involving the glomerular capillaries with microthrombi [8]. (Original magnification $\times 250$. Hematoxylin and eosin stain).

frequently adjacent to an involved vessel, making a petechial spot the best area for a skin biopsy [23]. Although ischemic changes and infarction are more common in the pancreas and kidneys, more extensive hemorrhage usually is seen in the brain, resulting in fatal outcome [24].

Pathophysiology

Endothelial damage

Early investigations suggested that endothelial cell (EC) damage and functional abnormalities such as the loss of fibrinolytic activity [25,26], impaired prostacyclin production [27], and apoptosis [28,29] are present. Microvascular

endothelial cells have been shown to upregulate their Fas receptor, and when exposed to plasma from TTP, patients should undergo apoptosis [28].

Platelet aggregation

Whether it is the abundance of platelet-aggregating proteins, [30–32] or the lack of the aggregation inhibitor (Prostacyclin) [27], it is clear that platelet clumping in the microcirculation of multiple organs contributes to the pathophysiology of this disease. Many studies that used immunohistochemical techniques have shown that an abundance of von Willebrand factor (vWf) is involved in microvascular platelet aggregation in TTP [33–35]. These observations have motivated further studies to better delineate the role of vWf in this disease.

Role of von Willebrand factor

von Willebrand factor is secreted from ECs as an extra large polymer of a polypeptide joined by disulfide bonds [36]. This factor then is cleaved in the circulation at the peptide bond between tyrosine at position 842 and methionine at position 843 by a 200-kd plasma metalloproteinase [36–38]. This cleavage decreases the size of the factor to dimers of 176 kd and 140-kd fragments [37,38]. Unless vWf is unfolded by high levels of shear stress, this protease has little effect on vWf, suggesting that in patients with TTP, the multimers of vWf would be relatively small, because the abnormal shear stress caused by platelet thrombi in the microcirculation should enhance proteolysis of vWf [38,39]. Moake et al showed in 1982 that unusually large multimers of vWf in the plasma of patients with chronic relapsing TTP and proposed that these are contributing to platelet agglutination [40]. These unusually large multimers are larger than the largest multimers of vWf in normal plasma, and they entangle in the subendothelial fibrous components maximizing vWf-mediated adhesion of platelets to the subendothelium [35,41]. This early report concluded that patients with chronic relapsing TTP have a defect in the processing of these unusually large multimers that makes them susceptible to periodic relapses. A major breakthrough occurred when two independent groups reported a lack of vWf-cleaving protease activity in the blood of TTP patients [42,43]. Tsai and Lian suggested that this is because of the presence of antibodies against vWf-cleaving protease [43]. In this study, 39 samples of plasma from 37 patients with acute episodes of TTP had a severe deficiency of vWf-cleaving protease, while no deficiency was detected in 16 samples of plasma from patients with TTP in remission or in 74 samples from normal subjects. Antibodies (IgG) against this protease were detected in 67% of the plasma samples obtained in the acute stage [43]. Furlan et al found severe deficiency of vWf-cleaving protease in patients with chronic relapsing TTP [44] and observed a deficiency of protease activity and an autoantibody against vWf-cleaving protease in the plasma of a patient with recurrent episodes of TTP [45]. These investigators also retrospectively analyzed plasma samples of 53 patients with TTP or HUS [42]. Patients with familial and nonfamilial TTP were found to have protease deficiency,

but none had an inhibitor. Eleven of 13 patients with nonfamilial HUS had normal protease activity levels (two having 26% to 50% of the activity of normal), and patients with familial HUS had normal protease activity. They suggested that with nonfamilial TTP, patients have an acquired deficiency of vWf-cleaving protease caused by an autoimmune mechanism, while in familial TTP, patients have complete protease deficiency. A more recent study of 111 patients with thrombotic microangiopathy (including TTP and HUS) showed that the vWf-cleaving protease activity was deficient in TTP but not HUS and that the deficiency was present in the idiopathic form of TTP and most subsets of TTP [46]. An inhibitor to the vWf-cleaving protease was found in about half of the TTP patients, implying an immunologic basis of the disease. The inhibitory activity was greater in the intermittent form of TTP (90%) than in the sporadic form (40%). These findings may explain the therapeutic benefits of plasma exchange in TTP patients, as this procedure removes the antibody while at the same time replacing the vWf-cleaving protease. The immune process in this disease may explain why some patients respond to immunosuppressive therapy. On the other hand, patients with HUS have normal levels of protease without the presence of an inhibitor; explaining why few patients if any would benefit from plasma exchange therapy in that setting. The distinction between both entities is crucial in clinical practice, as plasma exchange has some morbidity and is costly. Furlan proposed measuring protease activity as a single test to distinguish between these diseases. Despite its importance, this test is not widely available. The ability to differentiate between TTP and HUS can save health care providers time, money, and complications.

Recently, Levy et al performed a genome-wide linkage analysis in four pedigrees of people with congenital TTP and mapped the responsible genetic locus to chromosome 9q34 [47]. The gene was related to ADAMTS family (a disintegrin and metalloproteinase with thrombospondin motif). The analysis revealed that a mutation in that gene is usually responsible for developing the disease, suggesting a molecular mechanism for TTP. Earlier reports demonstrating the purification and sequence analysis of the amino-terminal amino acids of human vWf-cleaving protease confirmed those findings [48,49]. This discovery will have many therapeutic applications and screening potential, allowing early identification of the disease.

In summary, failing to eliminate the large multimers of vWf that are secreted by ECs is key to understanding the pathophysiology of TTP. Those multimers are associated with platelet aggregation as they bind to specific surface platelet receptors. The presence or absence of a vWf-protease inhibitor can explain many manifestations of this disease and suggests that TTP is a different entity than HUS.

Clinical features

Several investigators described the triad of hemolytic anemia, thrombocytopenia, and neurologic complications as initial presentation [50,51]. Others

suggested that the additional features of fever and renal dysfunction form the pathognomonic TTP pentad [5,7,52,53]. Because the early initiation of plasma exchange is a major determinant of a favorable outcome, the presence of only the microangiopathic hemolytic anemia and thrombocytopenia without another clinically apparent cause is considered sufficient for the diagnosis [54,55].

Fever

Although fevers are common, other nonspecific complaints such as general malaise, fatigue, weakness, and flu-like symptoms also occur and may confound the clinical picture [8]. Not infrequently an acute onset of abdominal discomfort or muscular and joint pain also can be present. In some series, the frequency of such a presentation has been as much as 11% to 14% [53]. Although some suggested that this might be related to gastrointestinal ischemic events or to pancreatitis, this has not been verified [8].

Neurologic changes

These changes can manifest as confusion, generalized headaches, altered mental status, focal deficits in the motor or sensory systems, seizures, visual disturbance, and even coma [8]. These symptoms tend to be waxing and waning in nature, possibly because of microhemorrhagic and microocclusive vascular changes in the brain. Visual complaints generally result from retinal choroidal or vitreous hemorrhage and rarely retinal detachment [8,56–58].

Renal changes

Renal involvement is common and is present in as many as 88% of patients [52]. Gross hematuria is present in 15% of affected patients, with most showing associated proteinuria. In severe cases, acute renal failure can be seen [1,53]. These are manifestations of varying defects of microvascular obstruction of the intraglomerular capillaries (see Fig. 1B).

Hematologic changes

Thrombocytopenia, (platelet count $< 20 \times 10^9/L$) is the most common presentation, with subsequent skin changes manifesting as petechial hemorrhages in the lower extremities. Other areas of bleeding, albeit rare, may include the oro-nasal pharynx, retina, central nervous system (CNS), gastrointestinal system, genitourinary tracts, and lung parenchyma [8]. Among these, CNS bleeding is an ominous sign. Despite the severe degree of thrombocytopenia, this disease is usually notable for the lack of bleeding. This is in part because of the thrombotic nature of the microvascular TTP lesion. Most patients present with moderately severe anemia with hemoglobin levels of less than 10 g/dL. Only 3% of patients reported by Ridolfi et al have had normal hemoglobin [53]. A review of the peripheral blood smear usually reveals

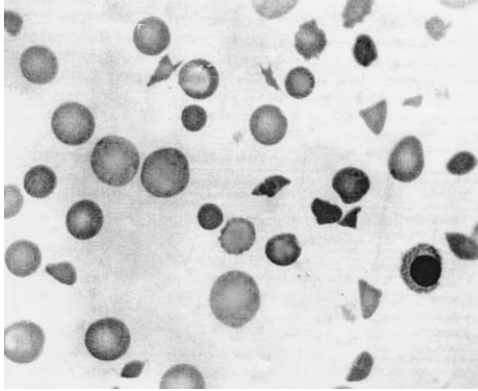


Fig. 2. Schistocytes (fragmented red blood cells) found in the peripheral blood smear of a patient with TTP. (Original magnification $\times 400$. Wright stain).

numerous fragmented erythrocytes (schistocytes) (Fig. 2) of varying sizes and shapes. Nucleated red blood cells and basophilic stippling are often present. Based on the degree of hemolysis, patients can have significant reticulocytosis, elevated unconjugated bilirubin, elevated lactate dehydrogenase (LDH), hemoglobinemia, decreased plasma haptoglobin, and a shortened red cell survival [5,8,52]. LDH is usually used as a day-to-day indicator of the severity of hemolysis, along with hemoglobin value and reticulocyte count.

The hemolysis is related to red cell trauma during their passage through the narrowed microvascular lumen in the involved vessels. There is no immune basis for the hemolysis in the vast majority of cases, and thus, the Coomb's test is negative. A moderate leukocytosis is usually present with left shift, but no morphologic or maturation abnormalities can be detected in white blood cells [160]. Bone marrow examination usually is not required; however, if performed, a reactive process can be demonstrated, reflecting a compensatory response to hemolysis and platelet consumption with hyperplasia of erythroid precursors and megakaryocytes. Occasionally, a megaloblastoid picture is present and can be reversed with folic acid therapy.

Coagulation studies are usually helpful in differentiating TTP from disseminated intravascular coagulation (DIC). In the former, the prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen values are all normal, while in the latter, low fibrinogen and prolonged PT and PTT can be found. This is important, as both entities can have similar morphologic picture when reviewing the peripheral smear. Recently, in children with HUS associated with *Escherichia coli* 0157:H7, changes in the fibrinolytic systems were observed as an increase in the tPA antigen, tPA-PAI-1 complex. This was believed to be the result of a fibrinolytic response to intravascular fibrin formation, as evidenced by increase in D-dimer and prothrombin fragment 1 + 2 [59].

Other manifestations

Cardiac manifestations usually consist of heart failure or arrhythmias. Although extensive myocardial microvascular involvement is evident on autopsy in patients who succumb to the disease, the symptoms in life are mild [60,61]. Electrocardiographic changes show conduction disturbances with various forms of heart block and nonspecific ST-T wave changes, suggesting myocardial damage [8]. A retrospective analysis of cases with known TTP from 1981 to 1998 revealed a subset of patients who could present initially with acute respiratory distress syndrome (ARDS) [62]. Seven out of 56 patients were noted to have ARDS and TTP simultaneously. TTP has been reported as a result of acute pancreatitis [63] and in association with collagen vascular diseases [8,64].

Differential diagnosis

With the advent of plasma exchange therapy, many clinicians tend to err on the side of instituting therapy despite the lack of a firm diagnosis. Biopsies are usually not essential for the diagnosis of TTP and are performed only when excluding other entities such as lupus erythematosus or other collagen vascular diseases. Many diseases can mimic TTP at presentation, such as an overwhelming infectious process and sepsis; pregnancy-associated thrombocytopenia; hemolysis, elevated liver function tests, and low platelets (HELLP) syndrome; autoimmune disorders; and an underlying unrecognized metastatic malignancy. A thorough history and complete physical examination are crucial. Patients with sepsis usually present with high fevers, chills, and hypotension. They occasionally have evidence of end-organ damage and DIC. Coagulation abnormalities are not found in TTP; thus fibrinogen and fibrinogen–degradation product measurements would be helpful. Review of the peripheral smear has become the key element in establishing the diagnosis. Schistocytes are also present in DIC, deformed valves, and in a variety of conditions where blood flow is affected by altered hemodynamics, such as tight aortic stenosis, ruptured cordae tendoneae, malformed or prosthetic valves, arterio-venous fistulas, and even malignant hypertension. In these cases, though, red blood cells are traumatized, leading to hemolysis. The platelets usually are spared, and thrombocytopenia is unusual. Occasionally, TTP can share some of the clinical and pathologic features of systemic lupus erythematosus, antiphospholipid syndrome, and scleroderma [65–68]. Although Evan's syndrome (the concomitant presence of autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura [ITP]) can be mistaken for TTP, performing a direct Coomb's test can aid in distinguishing these syndromes from one another. Coomb's test is usually negative in TTP.

An important consideration is differentiating TTP from another common cause of thrombocytopenia, namely ITP. ITP is an acquired disease of adults and children characterized by isolated thrombocytopenia without additional abnormalities [69]. The autoimmune disorder may be identified by the presence of

platelet antibodies. ITP is usually a diagnosis of exclusion, with the bone marrow showing adequate megakaryocytes. Unlike TTP, there is no evidence of red blood cell fragmentation, renal failure, or neurologic complications. In summary, despite many similarities between TTP and other diseases that cause thrombocytopenia, understanding clinical presentation and correlating laboratory data allow for accurate diagnosis in most instances.

Subsets of thrombocytopenic purpura

Shiga-toxin–associated hemolytic uremic syndrome

Shiga-toxin-related enterocolitis is an important public health problem that has the potential for serious and potentially fatal local and systemic complications [70–75]. Several organisms producing Shiga-toxin have been identified, including *E coli* 0157:H7, *Salmonella* and *Campylobacter*, with *E coli* 0157:H7 being the most common. Risk factors associated with the development of systemic complications have been identified, the most consistent of which are extremes of age (younger than 4 years old or over 65 years of age) and elevated white blood cell count [16,71,160]. Since the first association of TTP-HUS with *E coli* 0157:H7 was described [74], the incidence has risen, with almost 3% to 7% of patients infected eventually progressing to an overt TTP-HUS [70,73]. The major reservoir for *E coli* 0157:H7 is cattle. Because the infectious dose of this organism is low, in the order of a few hundred organisms, an outbreak can result from a single source. Several features are characteristic of this condition. The organism is attached to the colonic epithelium and secretes a powerful Shiga-toxin. Over a period of approximately 8 days, the toxin gains entry into the blood stream by as yet unknown mechanism. This toxin binds to a glycolipid cell surface receptor (Gb3). Under normal conditions, Gb3 is present in insignificant amounts on the endothelial cell surface. When stimulated by inflammatory cytokines, however, this receptor becomes expressed on the endothelial cells, resulting in binding of the Shiga-toxin and cytotoxicity [76]. In addition, Gb3 and the integrin $\alpha_{IIb}\beta_3$ are also present on the platelet surface, and the binding of Shiga-toxin may result in platelet clumping [81]. Clinically, the presentation of Shiga-toxin enterocolitis is a bloody diarrhea, and there is no indication as to which patient will develop TTP-HUS. Thus, an early bacteriologic diagnosis is needed. Secondly, early signs of TTP-HUS should be watched for, and plasma exchange should be instituted promptly. Despite its severity, investigators have shown that patients with Shiga toxins associated TTP-HUS respond to plasma exchange with good outcome. Dundas et al showed that after 16 plasma exchanges, 11 remained alive and responded well to therapy [77]. Treatment with antibiotic has no benefit and in fact has been shown recently to increase the incidence of TTP-HUS, with a relative risk of 17.3 [78]. The use of antimotility agents shown is also contraindicated. Currently, attempts also are being made to block the Shiga-toxin receptor Gb3 by synthetic analogues.

Cancer-associated thrombocytopenic purpura

Since the association between cancer and TTP-HUS was established, the mechanism by which this syndrome develops in the malignant setting has been controversial [52,75,79,80]. Although the true incidence is not defined clearly because of many other comorbidities that complicate the clinical picture, some studies have suggested a 5% to 6% incidence [82]. Among the cancers associated with TTP-HUS, adenocarcinomas predominate, accounting for 88% in some series [83]; gastric adenocarcinoma is the most common [83,84]. Clinical features are similar to the usual signs and symptoms that patients have without an underlying malignancy. The anemia and thrombocytopenia are usually out of proportion, to be explained by the underlying carcinoma or the chemotherapeutic agents given to treat that malignancy [79,80]. The pathophysiology of TTP in the cancer setting resembles the known mechanisms of this disease in the absence of cancer. It is important to note, however, that many chemotherapeutic agents used in treating malignancies are associated with TTP, an issue that would complicate the clinical picture and could make the ability to identify a causative predisposing event fairly difficult. Liu et al reported that renal toxicity caused by the anticancer drug mitomycin C has been associated with microangiopathic hemolytic anemia and thrombocytopenia [85]. Other cancer drugs have been associated with similar changes, including bleomycin, cisplatin, and gemcitabine [67,86–88,153]. In most of these reports, there was a suggestion of a dose-dependent development of TTP. Some investigators tackled the subject of differentiating cancer-related TTP or chemotherapy-induced TTP. Murgo et al found some features that would separate those entities and suggested that patients who develop TTP while in remission would likely have chemotherapy-induced disease [89]. Elevated plasma levels of vWf and arterial thrombosis have been described in patients who received cisplatin [88,90]. Therapy with plasmapheresis and immunosuppressive drugs may be beneficial [11,91]. Despite the presence of immune complexes in the plasma of cancer-associated TTP patients and the benefits of using extracorporeal immunoadsorption columns containing a silica matrix and covalently attached highly purified staphylococcal protein A (PROSORBA column, Johnson & Johnson, Ft Washington, PA); a procedure that specifically removes these immune complexes has not been confirmed in large series [92,93].

Transplant-associated thrombocytopenic purpura

The diagnosis of TTP in the setting of bone marrow transplantation (BMT) can be difficult. Patients could have some degree of renal insufficiency after BMT, and not infrequently they have some neurologic changes in the setting of anemia and fevers. Red blood cell fragmentation also has been noted when reviewing the peripheral smear after BMT [94,95]. Valilis et al showed that the majority of patients who had an allogeneic BMT and received cyclosporin for graft versus host disease (GVHD) prophylaxis had evidence of red blood cell

fragmentation, with more than half showing significant changes [96]. Most BMT patients were on multiple immunosuppressant drugs, and many reports of microangiopathic complications were in patients who received cyclosporin as GVHD prophylaxis [94,97].

It is also crucial to differentiate other comorbidities that can cause similar changes, such as infectious etiologies that involve the liver and other organs, veno-occlusive disease, and sepsis. Because TTP responds well to plasma exchange, most investigators emphasize on instituting this therapeutic intervention early in the course of the disease, especially when faced with a patient suffering from unexplained hemolysis, sudden increase in the need for platelet transfusion, renal insufficiency, or neurological changes after BMT, even if the diagnosis cannot be proved with certainty [98].

Schriber et al [98] reviewed all cases of TTP post-BMT through 1996 that were reported in the English language literature. In that review, patients who had a fatal outcome developed TTP early in the course of BMT (<120 days post-BMT), had an allogeneic BMT, were treated with cyclosporin or FK 506 for GVHD prophylaxis, and had neurologic and renal abnormalities. Although there was slightly higher number of patients receiving total body irradiation (TBI) in the favorable group, this was not statistically significant. The unfavorable group had worse overall survival, with an 85% mortality rate if they had two or three of the risk factors mentioned previously.

Although there has been little information on the etiology of post-BMT TTP, cyclosporin clearly plays an important role in this phenomenon, especially in high-risk patients. Cyclosporin has a direct cytotoxic effect on the ECs and alters the ratio between thromboxane A and prostacyclin [99–101]. Cyclosporin also increases procoagulant activity by inducing thromboplastin release from mononuclear cells and ECs, producing an increase in vWf release [102,103]. All of these effects can explain to a certain degree why some patients develop TTP in the BMT setting. Many reports of patients who received solid organ transplantation and developed TTP have been published [104–107]. The fact that patients are usually on cyclosporin after solid organ transplantation might explain those reported cases. Because the majority of patients who receive BMT or solid organ transplantation do not develop TTP despite being on these immunosuppressive agents, it is obvious that other factors play an equally important role. Researchers have observed that patients who develop low-risk TTP after transplantation, are usually not on cyclosporin [98].

Treatment of transplant-associated TTP can be somewhat different than idiopathic TTP. There are no large series to confirm the benefit of plasma exchange in this setting although it is used commonly. Platelets can be given safely when bleeding complications are feared. Recommendations are based on a single institution's experiences, anecdotal reports, and small series of patients. Discontinuation of the immunosuppressive agents, such as cyclosporin, is warranted, and should be the first line of intervention. Despite the discrepancy in outcome between low-risk TTP and high-risk patients, there are no large series to recommend a different therapeutic approach. Still, most investigators

suggest supportive care initially with close observation and instituting plasma exchange once the degree of hemolysis worsens [98].

Drug-induced thrombocytopenic purpura

Many therapeutic agents have been associated with TTP-like syndrome, including chemotherapy and immunosuppressive drugs used in the transplant setting. It is often challenging to document the offending agent, as most patients are usually on combination therapies. Mitomycin is the most common chemotherapeutic agent associated with TTP, and it appears to be dose-related [79,91]. TTP additionally has been reported with penicillins [108] and oral contraceptives [109,110]. Table 1 lists many of the agents that have been associated with TTP or HUS. Recent evidence has suggested increased incidence of TTP in patients who receive ticlopidine, an antiplatelet agent, with many applications including postangioplasty with stenting, treatment of claudication, and prevention of thrombotic strokes [111–113,156]. In most reports, the incidence of TTP in patients receiving ticlopidine is estimated at 1 in 1600 to 5000 cases. Because clopidogrel has replaced ticlopidine in many clinical scenarios, it became essential to determine the association, if any, between clopidogrel and TTP. Bennett et al reported recently on 11 cases of TTP that developed soon after initiation of clopidogrel [114]. Most cases developed within 14 days after initiation of therapy, and all but one case responded to plasma exchange. As these agents are being applied more frequently in clinical practice, it is imperative to identify these rare occurrences, as instituting early therapy can be life saving.

HIV-related thrombocytopenic purpura

Thrombocytopenia is common among patients with HIV. It is usually immune-mediated and also related to bone marrow suppression or to inadequate thrombopoiesis [115,155]. It is important to identify the subset of patients who develop thrombocytopenia in the microangiopathy setting, as management is distinctly different. This phenomenon was first observed by Boccia in 1984, followed by many other reports discussing the association of HIV with this disorder [70,115–117]. It is important to differentiate between HIV-ITP and HIV-TTP. The former usually responds to steroids and intravenous immuno-

Table 1
Drugs associated with thrombocytopenic purpura or hemolytic uremic syndrome

Chemotherapy agents [85,87,149,150]	Mitomycin c, ARA-C, bleomycin, cisplatin, Daunorobucin
Hormonal agents [109,110]	Tamoxifen, oral contraceptives
Antibiotics [108,152]	Penicillin, rifampin, sulfonamides
Toxins [76,79,159]	<i>Escherichia coli</i> , bee sting
Immunosuppressive agents [125,154]	Cyclosporin, tacrolimus
Others [151,157,158]	Arsenic, iodine, cocaine, quinine

globulins. Also, other usual manifestations associated with TTP such as renal failure, neurologic dysfunction, and fevers are not present with HIV-ITP [74]. If TTP is suspected, treatment should be instituted. Plasma exchange should be started early in the course of the disease. Rarick et al reported on 14 of 18 patients with HIV-TTP who underwent plasma exchange in addition to other therapies. Thirteen achieved complete remission (CR) [51]. It should be noted that in that series, none of the patients who had plasma exchange as monotherapy achieved CR. Splenectomy has been advocated in patients refractory to plasma exchange [118,119]. The statistical association of HIV infection with microangiopathy and the in vitro and in vivo evidence of HIV-mediated EC damage suggest that direct therapy of the underlying viral infection might have a therapeutic benefit. Despite the theoretical advantage of such treatment, no large studies have documented efficacy of this approach [120]. Most studies report a worse prognosis with HIV-TTP, with no patients surviving more than 24 months [116,121]. Despite this grave outcome, Hymes et al have suggested that an aggressive approach with prophylactic antibiotics against *Pneumocystis carinii* and toxoplasmosis, combined with plasma exchange and antiretroviral therapy, might improve the prognosis, with some patients surviving more than 36 months [116].

Pregnancy-associated microangiopathy

Pregnancy is a hypercoagulable state that is associated with many changes in homeostasis [68]. Preeclampsia should be differentiated from TTP. In the former, occasional schistocytes can be seen upon review of the peripheral smear, but hemolysis is rare. Most cases of TTP in the setting of pregnancy occur before 24 weeks of gestation, with more severe presentation of all the elements of the TTP pentad [122]. TTP should also be distinguished from HELLP syndrome. HELLP develops in 5% of patients with preeclampsia [68]. This syndrome develops mainly between the 27th and 36th weeks of gestation, although 10% of cases present earlier, and additional 20% of cases can occur postpartum [123]. To differentiate HELLP from TTP or HUS, it should be recognized that in TTP, neurologic changes are common, and in HUS renal disease is prevalent, while neither are common in HELLP. The diagnosis of HELLP is usually evident when microangiopathic hemolytic anemia and severe thrombocytopenia are superimposed on preeclampsia. Profound liver and renal failure is uncommon, unless patients develop DIC. Clearly, identifying that a patient has HELLP is crucial, as management is different than TTP and involves early delivery, occasionally adding vasodilating agents [68,123].

Thrombocytopenic purpura in the setting of pregnancy can be fatal in the absence of therapy, and terminating pregnancy has little or no effect on the outcome [122]. In some series, 10% of TTP cases occur in women who are pregnant or postpartum [124]. The clinical features are similar and usually occur early in pregnancy as opposed to HELLP, which develops later [125,126]. Clearly, diagnosing TTP in pregnancy can be elusive, and establish-

ing that a patient has this entity relies on identifying subtle changes and a strong clinical suspicion. The development of severe thrombocytopenia in the absence of DIC favors a diagnosis of TTP, while the presence of DIC suggest preeclampsia and HELLP. Treatment is plasmapheresis as in patients with idiopathic TTP [124,126]. Other therapeutic options such as splenectomy or immunosuppressive agents can be difficult to institute in pregnant women. In addition, pregnancy can induce relapse in patients with a history of TTP [124,127]. Anecdotal reports of prophylaxis with antiplatelet agents alone or with steroids have been reported [124].

Autoimmune disorders

There are anecdotal reports of TTP complicating the course of antiphospholipid syndrome [65], lupus erythematosus [64,128], and scleroderma [129]. There may be an autoimmune basis for TTP [18]. Recent findings in TTP patients of antibodies against the vWf-cleaving protease [43,45,46] support this concept. The management of these complications would thus require the consideration of use of immunosuppressive agents in addition to plasma exchange under this theory. Rituximab has some success.

Treatment

The mortality rate from TTP has decreased from 95% to as low as 10% [10,52,130–132] since plasmapheresis treatment was introduced. Since the early report by Rubenstein in 1959 of a dramatic response of TTP to whole blood exchange, several reports have shown remarkable response rate to plasma exchange [50,133,134]. Limited postmortem findings of the vascular lesion have shown that microthrombi were generally smaller and of shorter duration in treated patients compared with untreated fatal cases [24]. Because the delay in starting plasma exchange correlates with treatment failure in some studies, it is essential to start the exchange as soon as technically feasible [54,133,135,136]. If a delay in plasma exchange is unavoidable, therapy should start with plasma infusion, as this alone has been shown to have some benefit [54,137]. Plasma infusion can continue until plasma exchange can be carried out but should not be viewed as an alternative. With the recent identification of vWf-protease deficiency in the pathophysiology of TTP, it has been hypothesized that replacing that deficient factor during plasma exchange explains the excellent response rate [11,36]. In patients who have antibodies against the protease, removal of these antibodies suggests remission is being induced with the procedure [43].

Plasmapheresis usually is accomplished using a device with a wide-bore two-lumen catheter. The femoral site should be the first choice, as patients have moderate-to-severe thrombocytopenia, and hemostasis may be achieved easier in that region with local compression [11]. Plasma exchange is accomplished using blood cell separators where the patient's plasma is removed and replaced by

fresh-frozen plasma (FFP). Plasma exchange regimens for TTP should begin with a single plasma volume exchange (40 mL/kg of body mass) on a daily basis. Daily treatments should continue until the resolution of thrombocytopenia and neurological complications, stabilization of hemoglobin, and normalization of lactate dehydrogenase (LDH) suggesting the cessation of the hemolytic process. It is not uncommon for the renal dysfunction to lag behind and to correct later in the course of the disease [55,136]. If patients do not respond to this initial regimen, it is not unreasonable to increase the frequency of plasma exchange to twice daily. The standard replacement fluid is FFP. The successful use of cryosupernatant in TTP indicates that the putative therapeutic factor is in this fraction of plasma [138,139]. Replacement with albumin or with Plasminite is not effective and is not recommended.

Plasma exchange therapy should continue for several days beyond the point of normalization. Subsequent to this response, plasma exchange should be tapered over a period of approximately 1 to 2 weeks. Relapse of TTP may occur after discontinuation of plasma exchange, most commonly within 1 week to 1 month [3,10]. This procedure is usually tolerated well with minor potential complications at an incidence of 12% to 40%. These are usually related to citrate toxicity, including paresthesia, twitching, muscle cramps, or tetany when hypocalcemia develops [140]. The symptoms related to infusion therapy such as fevers, rigors, bronchospasm, hypotension, chest pain, cardiac arrhythmias, and gastrointestinal symptoms have been reported and usually are resolved when the infusion is completed [11].

Despite severe thrombocytopenia, it is important to recognize that avoiding platelet transfusion is crucial. Many reports indicate that platelet transfusion is followed by rapid clinical deterioration and sometimes death [141]. In post-mortem analysis of patients who died after receiving platelet transfusions in the setting of TTP, extensive platelet aggregation was noted especially in the CNS, suggesting that infused platelets can add to the underlying pathophysiology and results in that unfortunate outcome [11,141].

Desmopressin (DDAVP) acts by releasing vWf from the ECs into the circulating blood. Thus, the use of this agent is contraindicated.

Other agents have been used extensively in TTP, although their absolute benefits have not been shown. Glucocorticoids usually are administered in conjunction with plasma exchange [11,66]. Some authors have suggested that high-dose steroids at 200 mg prednisone daily can have favorable responses, especially in those with mild symptoms and no neurological complaints [10].

Splenectomy has been reported to lead to remission in TTP patients who did not respond to plasma exchange or those who had relapsed. Some authors have shown a response rate of 50% or more [142]. Based on several encouraging reports [55,119,142,143], the current trend is to reserve splenectomy as a salvage approach for those who are refractory to standard plasmapheresis or as an attempt to reduce the incidence of recurrence in patients with chronic relapsing TTP. The theoretical benefit of splenectomy is related to removing a common site for red blood cells and platelet sequestration.

Some clinical trials investigated the role of intravenous immunoglobulin (IVIG) in TTP patients, especially those who did not respond to plasma exchange. The reports were inconclusive, as some showed success while others demonstrated no benefit from this approach [90,144–146]. Despite reports of antiplatelet therapy as a potential beneficial maneuver, the use of such agents is not accepted universally, and they might exacerbate the risk of bleeding [147]. Some investigators attempted administering vincristine empirically at doses of 1 mg to 2 mg intravenously, but it is recommended to reserve this agent for refractory patients [148].

Other supportive measures are also important. For example, red blood cell transfusion often is required. In addition, patients with severe renal failure might require hemodialysis until their underlying problem resolves. It also is advisable to institute anticonvulsant agents in patients who develop seizures.

Summary

Thrombotic thrombocytopenic purpura is a multisystem disease characterized by thrombocytopenia, hemolytic anemia, renal failure, fever, and neurologic abnormalities. Plasma exchange has revolutionized the outcome of this entity from a once fatal disease to a disease that potentially is cured or has prolonged remission. The understanding of the pathophysiology of TTP continues to evolve. Recently, investigators showed that a deficiency in a specific plasma protease responsible for cleaving vWf plays a crucial role in the familial form of TTP. This explains in part why patients usually respond to plasma exchange therapy. The identification of a mutation in a specific gene that belongs to the metalloproteinase family located at chromosome 9q34 could have important therapeutic implications. TTP can be induced by certain drugs, especially immunosuppressants, in the setting of bone marrow and solid organ transplantation. This disease also has been described in association with HIV, pregnancy, cancer, and chemotherapy. TTP remains an ideal example of how knowledge about the etiology of a disease can improve therapeutic interventions.

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