Thrombotic Microangiopathies in the 1980s: Clinical Features, Response to Treatment, and the Impact of the Human Immunodeficiency Virus Epidemic

By Clinton E. Thompson, Lloyd E. Damon, Curt A. Ries, and Charles A. Linker

We reviewed the medical records of 44 adults with 50 consecutive episodes of thrombotic thrombocytopenia purpura (TTP) or hemolytic uremic syndrome (HUS) seen at the University of California, San Francisco affiliated hospitals during the past decade. Patients were treated according to a uniform plan in which initial therapy included daily large volume plasmapheresis using fresh frozen plasma. Patients not responding completely to initial therapy were treated with a salvage regimen including splenectomy, dextran, and corticosteroids. At the time of diagnosis, the lactate dehydrogenase (LDH) was elevated in 98% of cases, with a median value of 1,208 U/L. Other clinical features were present inconsistently, and only 34% of “TTP” episodes involved the classic pentad of hemolytic anemia, thrombocytopenia, neurologic disorders, noninfectious fever, and renal impairment. Primary treatment with plasma exchange produced complete remission in 56% (27 of 48) of the episodes. Previously splenectomized patients uniformly responded to plasma therapy (12 of 12). In patients not responding completely to primary therapy, salvage splenectomy produced complete responses in 81% (13 of 16) of the cases. The pattern of clinical response to therapy was consistent, with initial resolution of neurologic dysfunction (median, 3 days) followed by normalization of LDH levels (5 days) and platelet count (7 days). Normalization of renal function occurred significantly later (15 days). Although short-term responses to plasma therapy in human immunodeficiency virus (HIV)-seropositive patients did not differ from other patients, no HIV-positive patient survived more than 2 years from diagnosis of thrombotic microangiopathy (TMA). We conclude that the diagnosis of TMA requires a high degree of clinical suspicion and that the diagnostic criteria should consist of microangiopathic hemolytic anemia, thrombocytopenia, and an elevated LDH. Initial therapy with plasma exchange leads to disease control in the majority of cases, but an optimal treatment strategy requires the use of alternative methods if initial remission is transient or not achieved. Salvage therapy with splenectomy, steroids, and dextran is highly effective in this setting.

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We reviewed our experience treating TMA in an effort to describe the clinical spectrum of these disorders, as well as to define the efficacy of plasmapheresis as primary therapy and the role of splenectomy as salvage therapy. The natural history of HIV-associated TMA and the outcome of treatment in HIV-positive patients was also reviewed.

MATERIALS AND METHODS

We retrospectively examined the records of adult patients with thrombotic microangiopathies admitted to the University of California at San Francisco (UCSF) affiliated hospitals (Moffitt-Long, San Francisco General, and San Francisco Veterans Administration hospitals) between January 1980 and April 1991. TMs were defined by the presence of thrombocytopenia and a peripheral blood smear showing microangiopathic hemolysis not explained by disseminated intravascular coagulation (DIC). Patients with TMA related to cyclosporin A or mitomycin C were excluded from analysis. Clinical parameters associated with TMA were defined as the following: (1) Fever was defined as an unexplained oral temperature greater than 38.0°C. (2) Neurologic dysfunction was defined as any new abnormality in neuropsychiatric exam. (3) Renal dysfunction was defined as a serum creatinine (Cr) ≥1.5 mg/dL and/or a blood urea nitrogen (BUN) ≥30 mg/dL, or either value 50% greater than previously established baseline values. (4) Thrombocytopenia was defined as a platelet count less than 150,000/μL. TTP was defined as TMA with neurologic dysfunction out of proportion to renal impairment, or with the absence of both neurologic and renal dysfunction. HUS was defined as TMA with significant renal impairment and little or no neurologic dysfunction.

Primary therapy consisted of daily large volume plasma exchange, 60 to 80 mL/kg/procedure, replaced with equal volumes of fresh frozen plasma (FFP), or with half FFP and half liquid plasma. Adjunctive therapies administered with primary plasma exchange at the discretion of the treating physician included intravenous (IV) vincristine (1 to 2 mg weekly; 4 episodes); high-dose corticosteroids (≥1 mg/kg/d; 14 episodes); oral dipyridamole (75 mg, three times daily; 12 episodes) plus aspirin (325 mg/d; 11 episodes); IV Ig (5 to 30 g/d; 4 patients); and oral
azathioprine (1.5 mg/kg/d; 1 episode). Complete remission was defined as ≥ 1 month of normalization of platelet count, resolution of red blood cell (RBC) transfusion requirements, and resolution of acute neurologic events. Generally, patients received two plasma exchanges after achievement of a complete clinical response (CR).

Patients not achieving complete response to initial therapy, or rapidly (≤ 2 weeks) relapsing despite initial response, were treated with the combination of splenectomy, IV dextran-70 (500 mL every 12 hours), and high-dose corticosteroids. Patients not responding quickly (24 to 48 hours) to this regimen were additionally treated with postoperative daily plasma exchange and, occasionally (8 episodes), IV vincristine. Patients referred for care after failing splenectomy were treated with plasma exchange.

Follow-up data were obtained through UCSF clinic records, as well through phone contact with patients or their primary community physicians.

Statistical evaluation of predictors of clinical outcome was assessed via the two-by-two contingency table method (χ² analysis).

RESULTS

We reviewed 50 consecutive separate episodes in 44 patients. Nine of these patients have been reported previously in the medical literature. Seventy percent of the patients (31 of 44) were women and an equal number were Caucasian. The median age was 43 years, with a range of 20 to 78. There were 41 episodes of TTP: 22 were primary disease (15 without prodromal illness, 3 postdiarrheal, and 4 occurring in the peripartum period); 11 episodes occurred in five patients as relapsing disease (occurring from 1 month to 15 years after a previous episode); 7 additional episodes occurred in patients who were seropositive for HIV, and 1 episode was seen in a patient with metastatic parathyroid adenocarcinoma. Nine episodes were classified as HUS: 6 were primary disease (3 without prodromal illness and 3 after diarrheal illness); 3 were secondary disease (2 in patients with scleroderma, and 1 in a patient with metastatic adenocarcinoma of the lung).

Table 1 shows the initial clinical presentation of our patients compared with previously reported series. Seventy-eight percent of TTP episodes presented with the triad of anemia, thrombocytopenia, and neurologic dysfunction, and only 34% with the classic pentad. The most frequent neurologic abnormalities were alteration in mental status (18 episodes), seizures (8 episodes), hemiplegia (6 episodes), and aphasia (6 episodes). Paresthesias (2 episodes) and visual disturbance (1 episode) were also seen. More than one neurologic abnormality was seen in 6 episodes. Seizures were late events, occurring in the setting of advanced disease. In one case, seizures and hemiplegia became manifest after the onset of hematologic response.

Twelve patients with TTP presented with bleeding (3 each with epistaxis, hematuria, gastrointestinal hemorrhage, and menorrhagia); three others subsequently developed life-threatening hemorrhagic events (subarachnoid hemorrhage, postoperative ovarian rupture, and massive hemoptysis). Twelve patients presented with significant abdominal pain, although in no case was there evidence of pancreatitis or other identifiable abdominal pathology.

Laboratory parameters at presentation are shown in Table 2. Serum lactate dehydrogenase (LDH) levels were markedly elevated in all but one case (range, 191 to 4,700 U/L; normal range, 88 to 230 U/L). Plasma Cr levels were elevated in 18 of the TTP episodes (range, 0.7 to 6.4 mg/dL; normal range, 0.5 to 1.4 mg/dL). Cr levels ranged from 2.7 to 11.9 mg/dL in the HUS patients. Only one patient presented with an abnormality in any coagulation parameter (prothrombin time, partial thromboplastin time, fibrinogen, or D-dimers); this patient had a prolonged prothrombin time secondary to chronic active hepatitis. Liver function abnormalities, defined by elevations (greater than or equal to twice normal) in alkaline phosphatase and/or direct bilirubin, were present in 24% (12 of 50) of the episodes.

<table>
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<th>Table 1. Clinical Presentation of TMA Patients</th>
<th>Parameters (% of episodes)</th>
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<td>Study</td>
<td>Fever</td>
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<td>Overall (n = 50)</td>
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<td>Bell et al28</td>
<td>NS</td>
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<td>Rock et al19</td>
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Abbreviation: NS, data not stated.
*Historical triad of anemia, thrombocytopenia, and neurologic dysfunction.
†Classic pentad of anemia, thrombocytopenia, neurologic dysfunction, fever, and renal dysfunction.
‡Data approximated from report.
There were 41 episodes of TTP in 35 patients. One patient died before initiation of treatment. One patient with relapsing TTP (previously treated in this series) in the third trimester of pregnancy was emergently delivered by Cesarian section with complete hemolytic resolution. Thirty-nine episodes in 34 patients were treated with plasma exchange. A CR was achieved in 22 episodes (56%). The number of plasma exchanges required ranged from 3 to 32, with a median number of 9. The response to plasmapheresis was better in previously splenectomized patients. All 11 episodes in asplenic patients achieved CR with plasmapheresis. Three patients had just undergone splenectomy at the time of initial diagnosis of TTP and were transferred to UCSF after failure to respond. Eight patients had been splenectomized in the past, one during staging for Hodgkin's disease, two after abdominal trauma, and five during prior episodes of TTP. In contrast, only 11 of 28 (39%) episodes in nonsplenectomized patients achieved a CR with plasma exchange (P = .002).

Other than splenectomy status, no other clinical features at diagnosis predicted for poor response. Six of seven episodes in HIV-positive patients responded to initial plasmapheresis. All three peripartum patients treated responded to primary plasma exchange. One patient with metastatic parathyroid adenocarcinoma achieved CR with plasma exchange.

Of the 14 patients treated with salvage splenectomy, 7 had had a partial response to initial plasma exchange therapy, but then worsened and failed despite continued plasma exchange; 7 other patients never responded to initial plasma exchange therapy. Twelve of 14 (86%) patients responded completely to the salvage splenectomy program; 2 patients died despite salvage therapy, 1 of postoperative staphylococcal infection (in complete hematologic remission), and 1 (HIV-positive) of unresponsive disease.

Five of 9 patients with HUS treated with primary plasma exchange achieved CR. The number of plasma exchanges required ranged from 2 to 11, with a median number of 7. One patient was previously asplenic (posttraumatic) and responded to primary plasma exchange. Four of the remaining eight patients responded to primary plasmapheresis. Two of four patients who failed plasmapheresis underwent salvage splenectomy. One of these patients had had an initial response to plasma therapy, although she remained chronically dialysis-dependent.

The pattern of response to therapy in the TTP patients is summarized in Fig 1. Neurologic resolution occurred earliest, with a median time to onset of improvement after initiation of therapy 2 days (range, 1 to 7), and median time to neurologic resolution 3 days (range, 1 to 7). Five patients experienced permanent neurologic sequelae despite hematologic CR (2 with hemiplegia, 2 with seizure disorder, and 1 with aphasia, seizure disorder, and hemiplegia). LDH levels were the first laboratory parameter to show improvement, with median time to 50% decrease in LDH 3 days after initiating therapy (range, 1 to 20) and to normalization.
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Platelet count and the serum LDH level are useful markers of TMA. The serum LDH level is greatly elevated in patients with TMA episodes. In the acute setting, high LDH level did not adversely affect outcome, with resolution in 87% (6 of 7) of the episodes, as opposed to 83% (34 of 41) of the episodes in HIV-negative patients. Similarly, there was no difference in short-term survival (6 of 7 v 29 of 36). However, with follow-up (median, 23 months; range 1 to 124 months), striking survival differences have emerged. No HIV-positive patient has survived for 2 years. Causes of death were pulmonary toxoplasmosis (1 month), central nervous system (CNS) lymphoma (6 months), pneumocystis pneumonia (7, 9, and 11 months), and relapsed refractory TTP (20 months; episode not included in acute treatment data). In the HIV-negative group, there has been one late death, a fatal complication of acquired immunodeficiency syndrome (AIDS) acquired during plasma therapy of the initial TTP episode. Long-term survival is 78% (28 of 36) in HIV-negative TMA patients (81% [22 of 27] in HIV-negative TTP patients).

DISCUSSION

The treatment of TMA has remained empiric since Moschowitz's first report in 1924.30 Until the 1960s, fewer than 5% of adult patients with TTP-HUS survived.1 With the introduction of corticosteroids, splenectomy, and anti-platelet agents, survival improved13,14,21,31,32; in the 1970s, with the advent of first whole blood exchange15,16,20 significant advances were made in long-term outcome. Recently, combination therapies including IV vincristine have been shown to be efficacious.17,36 Controversy continues regarding the therapy of choice in these disorders, and the relative roles of corticosteroids, vincristine, antiplatelet agents, and splenectomy remain to be defined.

The diagnosis of a TMA requires a high degree of clinical suspicion. We found that 70% of episodes in TMA patients presented with the triad of thrombocytopenia, hemolytic anemia, and neurologic dysfunction, and only 30% of episodes presented with the clinical pentad. While the first large reviews of TTP suggested that the absence of fever was rare,1 we found fever present at diagnosis in only 61% of cases. Neurologic abnormalities are often subtle at diagnosis and changes in personality or mental status may become evident in retrospect only after response to treatment. More severe neurologic findings usually occur during disease progression. Given the lack of consistent nonhematologic findings (fever, neurologic, or renal), the diagnosis of TMA/TTP should be made by the presence of a microangiopathic hemolytic anemia and thrombocytopenia in the absence of a good alternative diagnosis (such as DIC). Waiting for the onset of neurologic or other organ dysfunction to begin treatment may be hazardous given the potentially catastrophic course of some patients with TTP, and is not advisable.

The serum LDH level is greatly elevated in patients with TMA, and can be helpful in increasing the degree of suspicion for these disorders. The median LDH level in our patients was greater than 1,200 U/L, almost six times the upper limit of normal. This elevation is much greater than that seen in other hemolytic anemias, suggesting a source of LDH other than (or in addition to) RBC hemolysis. The LDH appears to be a valuable clinical tool in recognizing and diagnosing TMA. Serum LDH levels also decrease early in response to therapy, and are a sensitive marker of clinical disease activity. The presence of an extraordinarily high LDH in the presence of microangiopathic hemolysis and thrombocytopenia, in the absence or absence of fever and neurologic or renal abnormalities, should prompt a diagnosis of TMA.

Our patients were treated in a generally uniform manner, and permit an estimation of the efficacy of plasma exchange primary therapy with splenectomy salvage therapy for the TMAs. Fifty-six percent of the episodes achieved CR with plasma exchange alone. This is consistent with other studies in the literature.15,20,23,34 The response to initial plasmapheresis in episodes classified as either TTP or HUS is similar (22 of 39 TTP; 5 of 9 HUS). A recent large series of TTP patients in Canada treated with plasma exchange or plasma infusion showed a similar response rate in those patients receiving plasma exchange.29 Forty-seven percent of TTP patients responded to plasma exchange when analyzed at the end of one cycle of therapy (a cycle was defined as 7 days of treatment or the time to death/rapid deterioration/rapid response if one of these events occurred before 7...
days). However, the response to plasma exchange was better (78%) when response was determined at 6 months.\textsuperscript{29} This suggests that prolonged plasma exchange might benefit some patients we defined as plasma exchange failures. If so, then one must consider the relative risks and benefits of prolonged plasma exchange versus splenectomy in patients not responding well to plasma exchange therapy. When we combine our responses to plasma exchange followed by salvage splenectomy (82%), the outcome in our patients is similar to the Canadian plasma exchange patients (mean, 15.8 exchanges). However, patients having no initial response to plasma exchange, or those clearly deteriorating despite continued daily large-volume plasma exchange, would probably not benefit from continuation of the same therapy and require an alternative approach. The Canadian series also proved the superiority of plasma exchange over plasma infusion as initial therapy for TTP (6-month survival, 78% v 63%; \( P = .036 \)).\textsuperscript{29}

Splenectomy appears to have a beneficial role in the treatment of TMA. Previously splenectomized patients uniformly responded to treatment with plasma exchange (12 of 12 episodes), whereas patients with intact spleens responded less often (11 of 28 TTP episodes; 4 of 8 HUS episodes). Furthermore, splenectomy combined with steroids and dextran proved to be effective as salvage therapy. The addition of splenectomy in patients not responsive to plasma exchange alone produced responses in 81% (13 of 16) of the episodes, including one HUS patient. This finding extends our previous observations on the value of this salvage splenectomy regimen\textsuperscript{12} and indicates that failure to respond completely to initial plasma exchange does not necessarily indicate a dire prognosis. A recent series of TMA patients treated with corticosteroids or corticosteroids plus plasma exchange used salvage splenectomy in six patients failing primary therapy.\textsuperscript{28} Because one patient died perioperatively and the others had hematologic and clinical deterioration soon after splenectomy, these investigators did not recommend splenectomy as salvage therapy. However, the five surviving patients had plasma exchange restarted, as is our practice, and all responded.\textsuperscript{28} This result supports our belief that splenectomy is an effective salvage therapy, but often requires continued plasma exchange support until the effect of splenectomy becomes clinically evident.

TMA are presently eminently treatable with CRs expected in most patients. Overall, the response rate to therapy in our patients was 82%, comparable to recently published series using plasma exchange therapy.\textsuperscript{20} TTP and HUS may be considered for purposes of therapy as related diseases,\textsuperscript{37,38} and should be treated as such in adults.

Although presently the clinical response to therapy cannot be predicted in the individual patient,\textsuperscript{29} we found that the pattern of response to therapy is predictable. Neurologic abnormalities are the most sensitive to therapy, resolving in the first hours to days in patients responding to therapy. The earliest laboratory sign of clinical response is a decrease in the serum LDH, which may improve days before there is an improvement in the platelet count. The slowest clinical abnormality to respond is that of renal abnormalities, which may persist for days to weeks after other abnormalities have normalized.

The recent emergence of the HIV epidemic and numerous case reports of classic HUS and TTP in patients with both symptomatic and asymptomatic HIV infection has suggested a possible relationship between TMA and HIV. This present series represents the largest single series of HIV-positive patients reported in the literature. First reported in 1987,\textsuperscript{1} to date a total of 15 HIV-positive patients have been previously reported in the English literature.\textsuperscript{3,10} The pooled literature and the patients in this series are summarized in Table 3. In the short term, HIV-positive patients with TMA respond equally well to plasma exchange as non–HIV-positive patients, with a response rate in this series of 86% and in the pooled literature of 80%. In both the current patients and pooled literature, the majority of patients were not previously diagnosed with Center for Disease Control (CDC)-defined AIDS-related complex (ARC) or AIDS. While long-term outcomes are unavailable for the previously reported cases, in the present series only one of the six patients achieving CR survived more than 1 year after CR and none survived to 2 years. This suggests that TMA syndromes may occur late in the natural history of HIV-related diseases.

Although the TMAs are likely to be a pathogenically heterogeneous group of diseases, the treatment of these disorders with plasma exchange therapy has significantly improved the prognosis for such patients. Primary therapy with plasma exchange alone can be expected to achieve a CR in at least half of the episodes. Patients who fail to respond or who rapidly relapse are still salvageable and can benefit from alternative therapy. The combination of splenectomy, steroids, and dextran provides effective salvage therapy in the majority of patients, and, overall, a CR should be achieved in greater than 80% of cases. With rapid diagnosis and an aggressive approach to therapy, the mortality rate from these disorders should continue to decline.

\textbf{Table 3. TMA in HIV-Positive Patients}

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<tr>
<td></td>
<td>CR</td>
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<tr>
<td>N</td>
<td>Male</td>
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<td>Pooled literature*</td>
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