REVIEW ARTICLE

blood advances

The remarkable diversity of thrombotic thrombocytopenic purpura: a perspective

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Understanding the autoimmune etiology of acquired thrombotic thrombocytopenic purpura (TTP) has provided precision for the diagnosis and a rationale for immunosuppressive treatment. These advances have also allowed recognition of the remarkable clinical diversities of patients' initial presentations and their long-term outcomes. These diversities are illustrated by the stories of patients from the Oklahoma TTP Registry. The initial presentation of TTP may be the discovery of unexpected severe thrombocytopenia in a patient with minimal or no symptoms. The patient may remain asymptomatic throughout treatment or may die suddenly before treatment can be started. ADAMTS13 activity may be reported as normal in a patient with characteristic clinical features of TTP, or the unexpected report of ADAMTS13 deficiency in a patient with another established disorder may lead to the discovery of TTP. ADAMTS13 activity during clinical remission is unpredictable. ADAMTS13 activity may recover and remain normal, it may remain severely deficient for many years, or it may become normal only many years after recovery. Our treatment of initial episodes and management of patients after recovery and during remission continue to change. The addition of rituximab to the treatment of acute episodes and preemptive rituximab for patients with severe ADAMTS13 deficiency during remission are reported to prevent relapse. Because TTP is uncommon, there are few data to guide these changes. Therefore our patients' stories are profoundly influential. Their stories are the foundation of our experience, and our experience is the guide for our decisions.

Introduction

When I began my career 50 years ago, thrombotic thrombocytopenic purpura (TTP) was a remarkably diverse disorder. It was diagnosed and defined only by a pentad of clinical features (anemia, thrombocytopenia, neurologic abnormalities, kidney function abnormalities, and fever).[1] In some patients, these clinical features may have developed sequentially during several weeks before TTP was recognized. In others, they developed only during the course of a long hospitalization. Eventually, almost all patients died. Then the diagnosis was confirmed by autopsy (Table 1).[1,2] In the late 1970s, effective treatment with whole blood exchange transfusion,[3] plasma infusion,[4] and plasma exchange (PEX)[5] began. Survival increased to 46%, and the frequency of the pentad of clinical features decreased.[6] In 1991, a randomized clinical trial by the Canadian Apheresis Group documented that 78% of patients treated with PEX rather than plasma infusion survived.[7] The only inclusion criteria for this trial were the presence of microangiopathic hemolytic anemia and thrombocytopenia without another apparent cause; thus, they became the diagnostic criteria for TTP. Increased survival then revealed the occurrence of relapse.[8] With the recognition that a severe deficiency of ADAMTS13 associated with anti-ADAMTS13 antibodies was the etiology of acquired TTP,[9,10] ADAMTS13 deficiency became a diagnostic criterion.[11] In the current era, with more precise diagnosis and effective treatment, survival from the initial episode of acquired autoimmune TTP is nearly 90%

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Table 1. Clinical features and death of patients with TTP, 1925-2017

Clinical feature	1925-1964[1]	1964-1980[6]	1982-1989[7]	1995-2017[12]
No. of patients	271	275	102	89
Diagnostic criteria, %				
Thrombocytopenia	96	96	100	100
Hemolytic anemia	96	98	100	100
Neurologic symptoms	92	84	71	64
Kidney injury	88	76	59	25
Fever	98	59	26	10
Survival, %	10	46	78	87

The data in these 4 reports[1,6,7,12] illustrate the trends of clinical features and survival. They are not completely comparable. The earlier observations[1,6] represent data from both the initial presentation and hospital course, which was often prolonged in the era before effective treatment. In the 2 more recent studies,[7,12] thrombocytopenia and microangiopathic hemolytic anemia were required abnormalities for establishing the diagnosis of TTP. In the most recent data, fever was recorded only if it was accompanied by chills.[12]

(Table 1).[12] With more precise diagnosis and effective treatment, I expected that the clinical diversity of TTP would diminish.

Then new diversities were recognized. As the diagnosis of TTP became more precise with the criterion of severe ADAMTS13 deficiency, diversity became more apparent. Documentation of severe ADAMTS13 deficiency identified patients in whom TTP previously would not have been recognized. The apparent absence of severe ADAMTS13 deficiency in patients with characteristic clinical features of TTP caused confusion. As treatment of TTP became more effective, relapses became more common. Relapses occurred many years after the initial episode, which emphasizes the prolonged duration of TTP. Serial measurements of ADAMTS13 during remission revealed that the level of activity was unpredictable. The clinical importance of ADAMTS13 deficiency during remission was uncertain.

I began to work with the Oklahoma Blood Institute (OBI) in 1992, seeing patients for whom PEX was requested for a diagnosis of TTP. In 1995, we began to save serum samples from each patient that were later used for measuring ADAMTS13 activity. This marked the beginning of the cohort of patients who make up the Oklahoma TTP Registry.[13] Through 2017, 89 patients with acquired autoimmune TTP have been enrolled; I saw 85 of these patients during their initial hospitalization. My role has been to provide support for the primary hematologist caring for each patient. My goal for this article is to describe and interpret the diversities of TTP that have occurred within the experience of 1 hematologist in 1 city.

I illustrate the diversity with the stories of selected patients. The initial stories illustrate the diversity of patients' initial presentation, emphasizing the urgency to begin treatment. The subsequent stories illustrate the diversity of long-term outcomes and the complexity of management to anticipate and potentially prevent relapse.

Methods

ADAMTS13 activity has been measured on serum samples collected immediately before beginning PEX for an acute episode of TTP. Collection of serum samples began in November 1995. Since 2004, we have also collected serum samples (approximately once per year) during remission. Measurements of ADAMTS13 activity have been made by both fluorescence resonance energy transfer (FRET; now the typical commercial method) and immunoblotting (IB) methods in the laboratory of Johanna Kremer and Bernhard Lämmle (Bern, Switzerland).[14] Our collaboration began in 2001, before commercial measurements of ADAMTS13 activity were available. We usually send all samples collected during the previous year to Bern in January. Therefore, the time between sample collection and results may be 2 to 14 months. The significance of these delayed results is apparent in the patients' stories, but these ADAMTS13 measurements were intended only for our research, not for patient care decisions. When we began, commercial ADAMTS13 measurements were not available, and the interpretation of ADAMTS13 activity was uncertain. Clinical use of commercial measurements of ADAMTS13 activity for diagnosis has become standard practice in our community, but measurements of ADAMTS13 activity during remission are not yet standard practice.

Diversity of initial presentations

Asymptomatic patient whose thrombocytopenia was discovered by a routine CBC. Patient 1 (Table 2) is a healthy young woman who visited an obstetrician for her first prenatal appointment. The obstetrician's evaluation was normal. A complete blood count (CBC) was obtained, and the results were reported the next day. The results were unexpected: platelet count, 16×10^9/L; hematocrit, 24%. She was told that there had been a laboratory error and that she needed to return for a repeat CBC. She did that, but was not contacted again until 2 days later; the repeat platelet count was 20×10^9/L. She was then told to go to the hospital emergency department immediately where her platelet count was found to be 21×10^9/L. She was admitted to the hospital. TTP was diagnosed the next morning; her platelet count was 20×10^9/L, hematocrit was 25%, and lactate dehydrogenase was 347 U/L (upper limit of normal, 217 U/L). The peripheral blood smear showed multiple schistocytes. PEX treatment was begun. Her ADAMTS13 activity was 7% with a high-titer functional inhibitor of 3.4 Bethesda units (BU). I saw her that day. She had had no symptoms, and her examination was normal. She recovered with PEX, corticosteroids, and rituximab (which was given for an exacerbation that occurred when PEX was stopped after an initial response). Her pregnancy was uncomplicated (although TTP may at times be associated with severe complications including fetal death). Her daughter is healthy.

Her story is unique in my experience because of the complete absence of symptoms and a completely normal physical examination. The lesson is clear: the absence of symptoms and a normal examination do not exclude the diagnosis of TTP. We have had other patients who have had minimal symptoms for which a CBC was performed and in whom an unexpected severe thrombocytopenia was the first sign of TTP.

Minor symptoms and sudden death. Patient 2 (Table 2) had been healthy except for intermittent menorrhagia. After several weeks of abdominal pain and headache, she had 2 days of vomiting with streaks of blood for which she went to her hospital emergency department on a Saturday evening. Her examination was normal. A CBC was obtained because of the blood streaks in her emesis. The results were unexpected: her platelet count was 12×10^9/L and hematocrit was 22%. She was admitted with a diagnosis of immune thrombocytopenic purpura; anemia was attributed to gastrointestinal bleeding and/or menorrhagia. She was transfused with red cells, and corticosteroid therapy was begun. In the hospital, she felt well. Her vomiting resolved and her headache improved, but severe thrombocytopenia persisted. On day 3, a direct antiglobulin test

Table 2. Diversity of initial presentations

Patient No.	Age, y	Race	Sex	Date	Summary	Patient's presentation, clinical course, and outcome
1	20	W	F	2016	Asymptomatic, normal physical examination, thrombocytopenia discovered by a routine CBC	Excellent health. Initial prenatal visit for first pregnancy, gestational age 7 w. CBC: platelets, 16×10^9/L; hematocrit, 24%. Laboratory error was assumed, so the tests were repeated twice during the next 3 d; the patients was then admitted. No symptoms, normal examination, no petechiae or purpura. Cr, 0.9 mg/dL; LDH, 813 U/L; ADAMTS13, 7%; inh, 3.4 BU.
2	37	AA	F	2005	Minor symptoms, sudden death	Excellent health except for intermittent menorrhagia. Headache and abdominal pain for 2-3 w. Vomiting for 2 d with blood streaks. At the hospital emergency department: platelets, 12×10^9/L; hematocrit, 27%; Cr, 1.1 mg/dL; LDH, 722 U/L. Diagnosis: ITP, GI, and/or menstrual bleeding. Treated with corticosteroids. Hospital day 4: DAT, negative; haptoglobin, <15 mg/dL. TTP suspected, PEX begun, and then sudden death. ADAMTS13, <5%, <5%; inh, >2 BU.
3	41	AA	M	1998	Characteristic clinical features of TTP, normal ADAMTS13 activity	Nausea, vomiting, syncope, no fever. Platelets, 7×10^9/L; hematocrit, 28%; Cr, 1.2 mg/dL; LDH, 1730 U/L. Sepsis suspected. Three days later, transient numbness occurred in the left face and left arm, left face weakness, aphasia. Diagnosis: TTP; resolved with PEX. ADAMTS13, 53%, 60%. Four relapses. Fourth relapse, ADAMTS13, <5%, <5%; inh, 1.4 BU.
4	55	W	F	2008	Endocarditis	Chest pain, myocardial infarction. Subsequent hemiplegia, aphasia. Platelets, 33×10^9/L; hematocrit, 33%; Cr, 1.6 mg/dL; LDH, 1141 U/L. Echocardiogram: aortic valve vegetation. Blood cultures: *Enterococcus faecium*. Diagnosis: endocarditis and TTP. PEX begun. ADAMTS13, <5%, <5%; inh, 0 (obtained at admission; results reported 4 mo later). 2009: ADAMTS13, 92%, 100%. 2016: relapse, ADAMTS13, <5%; inh, 1.2 BU.

When 1 result for ADAMTS13 activity is reported, it is with FRET; when 2 results are reported, the first is with FRET, and the second is with IB. Date indicates the year of the patient's initial presentation with TTP. Summary represents key point for including the patient's story in this review.

AA, African American; Cr, serum creatinine; DAT, direct antiglobulin test; F, female; GI, gastrointestinal; inh, functional inhibitor; ITP, immune thrombocytopenic purpura; LDH, lactate dehydrogenase; M, male; W, white.

was negative, haptoglobin was undetectable, and a bone marrow biopsy was normal, although schistocytes were noted on the peripheral blood smear. On day 4, TTP was suspected, and PEX was ordered. When the OBI nurse arrived that afternoon, she waited to begin the PEX while the patient completed her shower. When PEX began, her plasma was bright red. After 30 minutes, her blood pressure suddenly fell to zero but recovered with rapid plasma infusion; PEX was stopped. She then had a cardiac arrest and died 4 hours later. Autopsy demonstrated microvascular thromboses and hemorrhage in her heart, kidneys, adrenal glands, colon, pancreas, thyroid, and other organs. Her pathology is illustrated in a previous publication regarding a hypothetical patient.[15]

Her story illustrates that patients with TTP may suddenly die, even if they did not seem to be critically ill. Two previous patients who had only brief minor symptoms and in whom TTP was suspected because of unexpected severe thrombocytopenia and anemia died soon after arriving at the hospital and before PEX could begin. One patient was a healthy 46-year-old man who had a headache with fatigue that began on a Friday and continued through the weekend. On Monday morning at 10:00 AM, he presented to his primary care physician. His evaluation was normal, but a CBC performed in the office reported a platelet count of 9×10^9/L and hematocrit of 31%. Urinalysis demonstrated 3+ blood and protein. He saw a nephrologist at 2:00 PM and was admitted to the hospital at 5:00 PM. The OBI was called for PEX at 8:00 PM. At 10:00 PM, when the nephrologist arrived to place the central venous catheter, the patient was confused and hypotensive. Twenty minutes later he suffered cardiac arrest and died. No sample for ADAMTS13 activity was obtained. TTP was confirmed by autopsy. The other patient was a healthy 50-year-old woman who presented to her internist at 3:40 PM for 1 day of nausea and vomiting with spontaneous bruising. Her internist noticed the bruises but did not suspect a serious disorder; he ordered a CBC and chemistry profile and sent her home. At 4:30 PM, the results were reported: her platelet count was 6×10^9/L, hematocrit was 30%, creatinine was 2.0 mg/dL, and lactate dehydrogenase was 1793 U/L. He suspected TTP, called me, and then called his patient and told her to go directly to the hospital emergency department. She arrived at the emergency department at 6:00 PM, and she died at 8:35 PM before PEX could begin. ADAMTS13 activity was <5% (no functional inhibitor). TTP was confirmed by autopsy.

Although I did not see these 3 patients, their stories have had a major impact on my judgment. When I saw patient 1 several years later, I was aware that she could die suddenly as a result of TTP. These stories emphasize the danger of TTP and the urgency for diagnosis. Algorithms of clinical and laboratory features can support the diagnosis of TTP.[16-18] Prompt availability of ADAMTS13 activity measurements could expedite the decision to begin PEX. This experience also teaches us that an unknown number of patients may die suddenly before TTP is suspected and the death is not attributed to TTP.

Characteristic clinical features of TTP with normal ADAMTS13 activity. Patient 3 (Table 2) went to a neighborhood clinic because of 3 days of nausea, vomiting, and diarrhea with weakness and an episode of syncope. A CBC was performed, and the results were unexpected: his platelet count was 5×10^9/L and hematocrit was 17%. He was admitted to the hospital, and his examination was normal. Systemic infection was suspected but not confirmed. On day 3, he had a transient ischemic attack with

numbness in his left face and arm, weakness in his left face, and aphasia; TTP was diagnosed. His platelet count recovered to normal after 6 days of PEX (no corticosteroids). I was confident that he had TTP; the transient ischemic attack and response to PEX were typical. During the next 3 years, he had 3 relapses, confirming the diagnosis of TTP. In 2001, we had the first results of ADAMTS13 activity from the serum samples that we had obtained immediately before the initial PEXs from 1998 to 2001. The results were unexpected. At the time of his first episode, his ADAMTS13 activity was normal (53% [FRET]; 60% [IB]). ADAMTS13 activity was not measured at his first relapse. At his second relapse, ADAMTS13 activity was 15% (FRET; inhibitor, 1.4 BU) and 50% (IB; no inhibitor). At his third relapse, ADAMTS13 activity was <5% (FRET; inhibitor, 0.8 BU) and 6% (IB; trace inhibitor).

This patient's story has been previously published.[19] He had 2 additional relapses with ADAMTS13 activity <5%, and functional inhibitors were documented by both FRET and IB. Subsequently, anti-ADAMTS13 antibodies were detected by IB for all of his serum samples, even with his first episode when the reported ADAMTS13 activity was normal. The normal ADAMTS13 activity was attributed to dissociation of ADAMTS13-autoantibody complexes during the in vitro incubation required for the activity assays.[19] These observations do not conflict with the understanding that severe ADAMTS13 deficiency is the definition of TTP and the key element of pathogenesis. They emphasize that measurement of ADAMTS13 activity is complex and that patients may have TTP even when the reported ADAMTS13 activity is not severely deficient.[18,19] Other methods of measuring ADAMTS13 activity and measurements of ADAMTS13 antigen may provide more accurate data. However, this patient's story emphasizes the importance of clinical judgment for the diagnosis of TTP.[20]

Endocarditis. Patient 4 (Table 2) was a healthy woman who came to the hospital emergency department because she had 3 days of dyspnea and right-side pleuritic chest pain. An electrocardiogram documented myocardial infarction. Her platelet count was 33×10^9/L, and hematocrit was 33%. The peripheral blood smear demonstrated many schistocytes. Echocardiogram documented severe aortic insufficiency with vegetation on the aortic valve. On her first day in the hospital, she developed right-side weakness and aphasia; magnetic resonance imaging demonstrated left hemisphere infarction and multifocal cerebellar infarcts. Blood cultures grew *Enterococcus faecium*. Her primary physician diagnosed TTP in addition to bacterial endocarditis because she had 4 of the features in the pentad (Table 2). Therefore, she was treated with 12 days of PEX in addition to antibiotics. She recovered and had uncomplicated aortic valve replacement 3 months later.

I was in New Zealand and did not know about her until after she left the hospital. If I had seen this patient at the time of her admission, I believe that I would have convinced her primary physician that she did not have TTP and that PEX was not appropriate. ADAMTS13 results were reported 4 months later. ADAMTS13 activity was undetectable by both FRET and IB methods, and there was no demonstrable functional inhibitor. I was stunned. I still doubted the diagnosis of TTP. A year later, her ADAMTS13 activity was 92% (FRET) and 100% (IB), excluding a diagnosis of hereditary TTP. Two years later, her ADAMTS13 activity was <5% (FRET) and 50% (IB). She had remained well since her hospitalization. Then she moved away. Eight years later, I was called by a hematologist in Colorado; she had been admitted with relapsed TTP. Her ADAMTS13 activity was <5% with a functional inhibitor of 1.2 BU. I now believe that she had both endocarditis and TTP, although her thrombocytopenia and anemia were not as severe as expected for TTP.[16-18] I believe that if I had convinced her primary physician to not treat her with PEX, she would have died. This patient's story emphasizes the limitations of clinical judgment for the diagnosis of TTP. The primary physician's clinical judgment was right but my clinical judgment was wrong. The lesson for me was that patients with TTP can also have another disorder that could cause the clinical features characteristic of TTP. Wider use and rapid access to ADAMTS13 activity measurements may help identify patients with TTP in whom the diagnosis was not initially suspected by all treating physicians.

Increasing use of ADAMTS activity measurements will inevitably reveal patients who have unexpected TTP. Although it is a common clinical rule that patients have only 1 disorder, some will have 2, or perhaps even more disorders. An alternative explanation for microangiopathic hemolytic anemia and thrombocytopenia does not exclude the possibility of concurrent TTP. These situations may be comparable to the occurrence of an acute episode of TTP apparently triggered by another condition, such as pregnancy.[2,21,22]

Diversity of response to treatments and long-term outcomes

Rapid response to PEX, normal ADAMTS13 activity during remission, and no relapse. Patient 5 (Table 3) went to the hospital emergency department for a severe headache, chest pain, and abdominal pain. She had a 6-year history of migraine headaches. Examination was normal. A CBC was performed, and the results were unexpected: her platelet count was 7×10^9/L and hematocrit was 24%. Her ADAMTS13 activity was <5%, and she had no functional inhibitor. With PEX alone, she recovered in 5 days. She has not relapsed during the 17 years since her TTP episode. Her ADAMTS13 activity has been consistently 94% to 100%. She has had 1 pregnancy with premature delivery.

When we began to measure ADAMTS13 activity during remission in 2004, I assumed that normal ADAMTS13 activity and no relapse, as with this patient, would be the typical course after recovery. However, consistently normal ADAMTS13 activity during remission and no relapses are uncommon. In our previous publication,[23] we reported that all ADAMTS13 measurements during remission were normal (≥60%) in 24 (42%) of 57 patients. However, only 10 of these 24 patients had not been treated with rituximab or had not had a previous relapse. Therefore, the story of patient 5 is uncommon. I hope that her long-term outcome becomes more common with the use of rituximab for treatment of initial episodes of TTP.[24]

Refractory initial and relapse episodes, continuous severe ADAMTS13 deficiency during remission, and no relapse. The initial episode of patient 6 (Table 3) occurred in August 1995, before we began to collect serum samples. Her relapse, 8 months after her initial episode, is the most refractory episode in my experience, requiring treatments for 7 months until remission. For the next 22 years, she has been active and healthy, with the exception of minor symptoms of rheumatoid arthritis for which she has taken methotrexate intermittently. Her ADAMTS13 activity has always been <5% to 15%, often with a strong functional inhibitor. On the basis of her course, as well as similar experiences with other patients, I was reluctant to consider preemptive treatment with rituximab during remission for prevention of relapse[23,25] when it was initially proposed.[26]

Table 3. Diversity of response to treatments and long-term outcomes

Patient No.	Age, y	Race	Sex	Date	Summary	Patient's presentation, clinical course, and outcome
5	19	NA	F	2001	Rapid response to PEX, normal ADAMTS13 activity during remission, no relapse	Headache, chest pain. Platelets, 7×10^9/L; hematocrit, 24%; Cr, 0.9 mg/dL; LDH, 594 U/L. Five PEXs, no corticosteroids or other treatment. ADAMTS13, <5%, <5%; inh, 0. Remission ADAMTS13 (11 times from 2004 to 2016), 94%-100%. No relapse during 17 y.
6	21	H	F	1995	Refractory initial and relapse episodes, continuous severe ADAMTS13 deficiency during remission, no additional relapse	Seizures. Twenty-two PEXs, steroids, vincristine (ADAMTS13 not measured). Relapse, 1996: platelets, 16×10^9/L; hematocrit, 33%; Cr, 0.8 mg/dL; LDH, 612 U/L. ADAMTS13, <5%, <5%; inh, >2 BU. Recovery with 145 PEXs (221 d), steroids, vincristine, aspirin, persantin, and splenectomy. Remission ADAMTS13 (9 times from 2006 to 2016): <5%-15%; 5 times, inh, >2 BU; 4 times, inh, 0-0.7 BU. No additional relapse during 22 y.
7	22	W	F	2000	Refractory initial episode, severe ADAMTS13 deficiency during remission for 9 y, then normal ADAMTS13 activity for 7 y, no relapse	Nausea, vomiting, weakness. Platelets, 5×10^9/L; hematocrit, 21%; Cr, 0.9 mg/dL; LDH, 4296 U/L; ADAMTS13, <5%, <5%; inh, >2 BU. Seventy-four PEXs, corticosteroids, and splenectomy. Remission ADAMTS13 (4 times from 2004 to 2009): <5%-20%; (3 times from 2010 to 2016): 50%-68%. No relapse during 18 y.
8	56	W	F	2000	Refractory initial episode with cardiac arrest, ADAMTS13 activity during remission, 45%-100% for 13 y, then 6%; relapse 3 mo later.	Purpura. Platelets, 7×10^9/L; hematocrit, 23%; Cr, 0.7 mg/dL; LDH, 1135 U/L. ADAMTS13, 12%, <5%; inh, 1.2 BU. Cardiac arrest during twelfth PEX, complete recovery. Remission ADAMTS13 (8 times from 2007 to 2013), 45%-100%; 13 June 2014: ADAMTS13, 6%, 50%. 21 September 2014, relapse: platelets, 15×10^9/L; hematocrit, 21%; Cr, 0.7; LDH, 732. Hypotension during second PEX. Subsequent recovery without additional PEX. Healthy during next 3 y; ADAMTS13, 68%-89%.

Date indicates the year of the patient's initial presentation with TTP. Summary represents key point for including the patient's story in this review.
H, Hispanic; NA, Native American.

Refractory initial episode, severe ADAMTS13 deficiency during remission for 9 years, normal ADAMTS13 activity, and no relapse. The initial episode of patient 7 (Table 3) was refractory and, like that of patient 6, resolved after splenectomy. She has not relapsed, although her remission ADAMTS13 activity was 5% (FRET) and <3% (IB) when it was first measured 4 years after her episode. During the next 5 years (2004-2009), remission ADAMTS13 activity was ≤20%. Then the next year (10 years after her episode), her ADAMTS13 activity was 62% (FRET) and 50% (IB). Six years later, her remission ADAMTS13 activity remained normal (68%, FRET). Her course supported my belief that preemptive treatment with rituximab during remission for prevention of relapse was not appropriate.

Refractory complicated initial episode, ADAMTS13 45% to 100% for 13 years, and 6% the following year with relapse 3 months later. During her initial episode, patient 8 (Table 3) had a cardiac arrest with pulseless electrical activity on her 12th day of PEX, which was attributed to an adverse reaction to plasma. She was successfully resuscitated and recovered completely. Four days later, her platelet count decreased to 10×10^9/L, and PEX was resumed together with high-dose corticosteroids. There were no adverse reactions, and PEX was continued for 6 weeks until a durable remission was achieved. From 2007 to 2013, 6 remission ADAMTS13 activity measurements were 45% to 100% (mean, 76%). In 2011, she had ovarian carcinoma, which was effectively treated with surgical resection and chemotherapy. In 2013, her ADAMTS13 activity was 67% (FRET) and 80% (IB). On 13 June 2014, when her clinical and laboratory evaluations (platelet count, 230×10^9/L hematocrit, 41%) were normal, her ADAMTS13 activities were 6% (FRET; inhibitor, >2 BU) and 50% (IB). On 21 September 2014, she relapsed (platelet count, 15×10^9/L; hematocrit, 21%). With high-dose corticosteroids and rituximab, her first PEX was uncomplicated. However, during her second PEX, she felt faint, her blood pressure decreased to 50/30, her pulse increased to 150, PEX was stopped, and blood pressure recovered with saline infusion. The next day, her platelet count was 104×10^9/L; she achieved a remission with corticosteroids and rituximab, without additional PEX.

We learned of the severe ADAMTS13 deficiency of patient 8 in March 2015, 9 months after the 13 June 2014, sample had been obtained and 6 months after her relapse. This patient's story was a key experience for my appreciation of the potential value of preemptive treatment with rituximab. Prevention of relapse is important for all patients with TTP. Prevention of relapse was more important for this woman, who had life-threatening adverse reactions to plasma. Prevention of relapse is similarly critical for Jehovah's Witness patients, whose treatment cannot include plasma.[27] This experience is one of several patient experiences that began my acceptance of preemptive treatment with rituximab for ADAMTS13 deficiency during remission for prevention of relapse.[28,29]

Conclusions

Table 4 summarizes the conclusions from these patients' stories. The diversity of presentations, from asymptomatic to sudden death, is extreme. Increasing use of ADAMTS13 measurements will identify patients in whom TTP is not suspected. But current methods for measuring ADAMTS13 activity may not report the severe deficiency in patients with TTP.

Although some patients may achieve a durable remission with few PEX treatments, many patients require prolonged treatment with many modalities to achieve remission. These observations have suggested the potential value of routine rituximab for initial treatment, together with PEX and corticosteroids, to decrease the duration of treatment and prevent subsequent relapse.[24,29,30]

Table 4. Conclusions

Observations on initial presentation
Patients with TTP may have no symptoms and a normal physical examination. TTP may first be suspected by unexpected severe thrombocytopenia and anemia on a routine CBC.
Patients with TTP may die suddenly, even when they have had only minor symptoms for 1 or several days.
Reported ADAMTS13 activity ≥10% (and even normal activity of ≥60%) does not exclude the diagnosis of TTP.
Reported ADAMTS13 activity <10% may reveal unsuspected TTP.
TTP may initially occur together with an additional disorder.
Observations on management during remission
ADAMTS13 activity during remission is unpredictable.
Patients may have continuously severe ADAMTS13 deficiency during remission for many years without relapse.
Patients may have continuously severe ADAMTS13 deficiency during remission for many years and then have normal ADAMTS13 activity for many more years without relapse.
Patients may have continuously normal or nearly normal ADAMTS13 activity for many years and then have severe ADAMTS13 deficiency followed by relapse.
Rituximab treatment of severe ADAMTS13 deficiency during remission may prevent relapse; however, the appropriate indication for treatment and the appropriate rituximab regimen are uncertain.

What constitutes appropriate management during remission remains unclear. Some patients may have severe ADAMTS13 deficiency for many years with no apparent adverse effects. It may be that if an additional illness or pregnancy had occurred in these patients, a relapse of TTP might also have occurred. This could be predicted by observing women with hereditary TTP who have their first acute episode at the time of their first pregnancy.[2,21] Neither patient 6 nor patient 7 has been pregnant. Other patients may have severe ADAMTS13 deficiency for many years, and then ADAMTS13 activity spontaneously becomes normal for many years thereafter. These patients demonstrate that rituximab is not required to prevent relapse in all patients with ADAMTS13 deficiency during remission. These patients are comparable to patients with hereditary TTP who may have no acute episodes, even with a lifetime absence of ADAMTS13 activity.[31] However, patient 8 illustrates the potential value for treatment of severe ADAMTS13 deficiency during remission. I believe that preemptive rituximab in June, when severe ADAMTS13 deficiency occurred, may have prevented her relapse in September. I believe that there are other patients in our Registry whose relapses could have been prevented by preemptive rituximab. Relapse can cause death. Among our patients, 2 have died with a relapse,[12] and among those in the French Registry, 2 have died with a relapse.[26] These experiences support the use of rituximab for patients with ADAMTS13 deficiency during remission to prevent relapse,[26,28] but many questions are still unanswered. How often should ADAMTS13 activity be measured? At what level of ADAMTS13 deficiency should treatment with rituximab be considered? What regimen of rituximab should be used? What is appropriate management if rituximab does not increase ADAMTS13 activity? How many patients would need to be treated to prevent a relapse in 1 patient? Acceptance of treating some patients with rituximab who may never relapse is supported by the continually increasing use of rituximab for many hematologic, oncologic, and rheumatologic disorders for the past 20 years with apparent safety.[32,33]

Whether these questions can be answered with data is uncertain. TTP is not only remarkably diverse, it is also uncommon. Our experience is that there are approximately 3 episodes of TTP, including both initial and relapse episodes, per 1 million people per year.[12] Because TTP is uncommon as well as clinically diverse, only a few large randomized clinical trials have been attempted. Among the largest proposed trials, 2 have been successful and 1 failed. The Canadian Apheresis Group, which includes centers throughout Canada, successfully enrolled 102 patients in a randomized clinical trial during the 7 years from 1982 to 1989 that documented the effectiveness of PEX.[7] These data dramatically changed the management of TTP and established the diagnostic criteria that preceded the ADAMTS13 era. In 2009, the Transfusion Medicine/Hemostasis Clinical Trials Network of the National Heart, Lung, and Blood Institute began enrollment in a randomized clinical trial to evaluate the effectiveness of routine initial rituximab treatment in addition to PEX and corticosteroids. Sixteen centers participated. The goal was to enroll 238 patients. This trial was stopped after 1 year after only 3 patients had been enrolled.[34] The phase 2 randomized clinical trial of caplacizumab (2010-2014), sponsored by Ablynx, required 40 months with 56 sites in 13 countries to enroll 75 patients,[35] which emphasizes the enormous effort and cost to engage in such a trial. This experience illustrates the difficulty of performing traditional randomized clinical trials to address questions of TTP management.

In the absence of data, we acknowledge that our management decisions are based on our experience and the experience of others. Patient stories are profoundly influential and are the foundation of our experience.

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