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Ten Patient Stories Illustrating the Extraordinarily Diverse Clinical Features of Patients With Thrombotic Thrombocytopenic Purpura and Severe ADAMTS13 Deficiency

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Patients with thrombotic thrombocytopenic purpura (TTP) and severe ADAMTS13 deficiency are often considered to have typical clinical features. However, our experience is that there is extraordinary diversity of the presenting features and the clinical courses of these patients. This diversity is illustrated by descriptions of 10 patients. The patients illustrate that ADAMTS13 activity may be normal initially but severely deficient in subsequent episodes. Patients with established diagnoses of systemic infection as the cause of their clinical features may have undetectable ADAMTS13 activity. Patients may have a prolonged prodrome of mild symptoms with only microangiopathic hemolytic anemia and thrombocytopenia or they may have the sudden onset of critical illness with multiple organ involvement. Patients may die rapidly or recover rapidly; they may require minimal treatment or extensive and prolonged treatment. Patients may have acute and severe neurologic abnormalities before microangiopathic hemolytic anemia and thrombocytopenia occur. Patients may have concurrent TTP and systemic lupus erythematosus. Patients may have hereditary ADAMTS13 deficiency as the etiology of their TTP rather than acquired autoimmune ADAMTS13 deficiency. These patients' stories illustrate the clinical spectrum of TTP with ADAMTS13 deficiency and emphasize the difficulties of clinical diagnosis. J. Clin. Apheresis 27:302–311, 2012.

Key words: microangiopathic hemolytic anemia; thrombocytopenia; bacterial endocarditis; systemic lupus erythematosus; Upshaw-Schulman syndrome

INTRODUCTION

The variety of clinical features among all patients who are initially diagnosed as having thrombotic thrombocytopenic purpura (TTP) and for whom plasma exchange treatment is requested is well recognized [1]. However, patients whose diagnosis of TTP is supported by documentation of severe ADAMTS13 deficiency (activity $<10\%$) are often described as having ''typical'' TTP [2], which implies more consistent presenting features and clinical courses. This is not our experience. Our experience is that the presenting features and clinical courses of patients with TTP and severe ADAMTS13 deficiency can be extraordinarily diverse.

The goal of this report is to describe the diversity of presenting features and clinical courses of 10 individual patients who have been enrolled in the Oklahoma TTP-HUS (hemolytic uremic syndrome) Registry [3] and who were documented to have severe ADAMTS13 deficiency. The diversity that exists among individual patients is not apparent in our previously described summary data of all patients who had severe ADAMTS13 deficiency [1,3]. Appreciation of this diversity is essential for accurate evaluation of patients who present with microangiopathic hemolytic anemia and thrombocytopenia and in whom the diagnosis of TTP is considered.

METHODS

The Oklahoma TTP-HUS Registry is a population-based inception cohort of consecutive patients with a clinical diagnosis of TTP or HUS identified by a request to the Oklahoma Blood Institute (OBI) for plasma exchange treatment [1,3]. All patients in 58 of Oklahoma's 77 counties, without selection or referral bias, are included in the Registry because [1] the

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Oklahoma Blood Institute is the sole provider of plasma exchange for all hospitals in these counties and [2] plasma exchange is the standard treatment in this region for all adults diagnosed with TTP or HUS, children who are diagnosed with TTP or atypical HUS, and children diagnosed with typical, diarrhea-associated HUS who have severe neurologic complications. No patients are excluded. In the patient presentations, values for LDH are normalized to an upper limit of normal of 200 U/L, to account for different methods among hospital laboratories. The Registry is approved by the Institutional Review Boards of the University of Oklahoma Health Sciences Center and all participating hospitals.

ADAMTS13 activity was measured by Drs. Johanna A. Kremer Hovinga and Bernhard Lämmle (Department of Hematology, Inselspital, Berne, Switzerland) by both quantitative immunoblotting and a fluorogenic assay using FRETS-VWF73 substrate in serum collected immediately before the first plasma exchange since November 13, 1995, when systematic serum collection from all patients enrolled in the Oklahoma Registry was begun [3]. A severe deficiency was defined as ADAMTS13 activity $<10\%$ by either method. Inhibitor activity was determined by measuring residual ADAMTS13 activity in normal plasma, with the FRETS method, after incubation with an equal volume of patient serum [3]. Inhibitor titers were expressed as Bethesda units (BU); titers of <1.0 BU were reported as ''trace positive''; titers of ≥ 1.0 BU were considered to be positive; titers greater than 2 BU were expressed as >2 when residual ADAMTS13 activity was $11-25\%$ and $\gg 2$ when residual ADAMTS13 activity was $\leq 10\%$ [3]. ADAMTS13 antibodies were determined by a commercially available ELISA technique (Technozym®, Techniclone). Results of the ADAMTS13 assays were typically not available until several months after the patient's initial episode.

RESULTS

From November 13, 1995 until March 1, 2012, 336 patients were enrolled for their first episode of clinically diagnosed TTP or HUS; ADAMTS13 activity was measured on 314 (93%) patients. ADAMTS13 activity was $<10\%$ by at least one of the two assay methods in 72 (23%) of the 314 patients. In 6 (8%) of these 72 patients, an alternative diagnosis that explained their clinical features was discovered after PEX treatments had begun: systemic infections, 5 patients; systemic malignancy, 1 patient [3]. In the other 66 patients, TTP was considered to be the definitive diagnosis. Eight patients in whom TTP was considered to be the definitive diagnosis and one patient with a systemic infection were selected to illustrate the variety of presenting features and clinical courses among patients with severe ADAMTS13 deficiency. One additional patient who did not have severe ADAMTS13 deficiency at the time of his initial episodes of TTP was also included (Table I).

TABLE I. Ten Patients Who Illustrate the Variety of Presenting Features and Clinical Courses of Patients With TTP and Severe ADAMTS13 Deficiency

Patient	Presenting features and clinical course
1	Typical acquired, relapsing TTP; initially normal ADAMTS13 activity
2	Typical bacterial endocarditis; severe ADAMTS13 deficiency
3	Minimal symptoms for several weeks; only microangiopathic hemolytic anemia and thrombocytopenia at initial presentation; no neurologic or renal abnormalities; no fever. Rapid death.
4	Sudden syncope, obtunded, fever, severe hypertension, hypoxemia, myocardial infarction. Rapid recovery.
5	Minimal treatment, rapid recovery, no relapse
6	Transient neurologic abnormalities with normal hematocrit and platelet count 1 month prior to recurrent neurologic abnormalities with microangiopathic hemolytic anemia and thrombocytopenia
7	Abdominal pain and bloody diarrhea after eating a suspicious hamburger
8	Concurrent initial diagnoses of TTP and systemic lupus erythematosus
9	A 9-year-old boy with severe thrombocytopenia and anemia
10	An 18-year-old girl with severe thrombocytopenia and anemia

Patient 1: Typical TTP, Normal ADAMTS13 Activity

Patient description

A 41-year-old black/Native American man had 3 days of abdominal discomfort and nausea with no diarrhea; then he had a syncopal episode. He had unexpected severe thrombocytopenia and anemia (platelet count, 7000/μL; hematocrit, 28%); his blood pressure was 130/84; he had no fever; the peripheral blood smear demonstrated schistocytes; a bone marrow biopsy was normal. TTP was diagnosed on his third hospital day when he had a transient episode of expressive aphasia, left facial weakness, and numbness involving his left face and arm. Serum creatinine was 1.2 mg/dL; LDH, 1946 U/L. ADAMTS13 activity was 60% with the immunoblot method, 53% with the FRETS method; no inhibitor activity was detected. He recovered with six plasma exchange (PEX) treatments, without corticosteroids.

Comment

This patient's presentation was perfectly typical of TTP; the normal ADAMTS13 activity was unexpected. During the next 8 years, he had five additional acute episodes of TTP. He died of sepsis following recovery

TABLE II. Serial Measurements of ADAMTS13 Activity and ADAMTS13 Functional Inhibitor in a Patient With Six Episodes of TTP Across 8 Years

	ADAMTS13 activity		ADAMTS13 inhibitor	
Episode	IB	FRETS	IB	FRETS
1	60%	53%	0	0
2	NA	NA	NA	NA
3	50%	15%	0	1.4
4	6%	<5%	Trace	0.8
5	<5%	<5%	1	1.1
6	<5%	<5%	1–2	1.4

Two methods for determining ADAMTS13 activity and the inhibitor titer were used: IB, quantitative immunoblotting; FRETS, fluorogenic assay using FRETS-VWF73 substrate. Inhibitor levels are expressed as Bethesda units. NA, ADAMTS13 data were not obtained at the time of his 2nd episode. Data adapted from Ref. 4.

from his sixth episode. Over the course his subsequent episodes, severe ADAMTS13 deficiency with a demonstrable ADAMTS13 inhibitor occurred (Table II) [4]. Anti-ADAMTS13 autoantibodies were identified by an ELISA technique in all of his acute episodes, including his first episode. Normal *in-vitro* ADAMTS13 activity at the time of his first episode was confirmed in a flow chamber assay of the patient's serum perfused over an endothelial cell monolayer [4,5]. This patient's presentation emphasizes that *in-vitro* assay of ADAMTS13 activity may not always reflect *in-vivo* ADAMTS13 function. We assume that initially this patient had autoantibodies that were sufficient to impair ADAMTS13 *in vivo* but not *in vitro*, and then over the course of multiple episodes of TTP the autoantibody inhibition of ADAMTS13 function became sufficiently strong to also impair *in-vitro* activity [4]. During his initial hospitalization, HIV infection was diagnosed (CD4 count, 260/μL; HIV RNA, 110,000 copies/mL). He was not treated for his HIV infection during his initial hospitalization and he never accepted regular treatment. Although patients with advanced HIV infection may present with clinical features of thrombotic microangiopathy [6], this patient's HIV infection had no apparent clinical consequences. The relationship of HIV infection to his TTP and ADAMTS13 activity is not known [4].

Patient 2: Typical Bacterial Endocarditis, Severe ADAMTS13 Deficiency

Patient description

A 55-year-old white woman was admitted with a 3-day history of dyspnea and chest pain. Initial evaluation demonstrated an ST-segment elevation myocardial infarction with evidence of congestive heart failure. She also had right-sided weakness with expressive aphasia; brain MRI documented multiple left cerebral infarcts. Laboratory data included: platelet count, 33,000/μL; hematocrit, 33%; creatinine, 1.6 mg/dL; LDH, 1085 U/L; the peripheral blood smear demonstrated schistocytes. Echocardiogram demonstrated aortic valve vegetation; blood cultures demonstrated *Staphylococcus epidermidis*. Because she had clinical features of TTP, her physician suspected the diagnosis of TTP in addition to the established diagnosis of bacterial endocarditis; PEX was begun. She recovered with antibiotics and 12 PEX treatments. ADAMTS13 activity was <5% in both assays; no inhibitor was demonstrated. Aortic valve replacement surgery 3 months later was uncomplicated. She has remained well.

Comment

This patient's presentation was perfectly typical of bacterial endocarditis and bacterial endocarditis can mimic TTP [7]. Undetectable ADAMTS13 activity was unexpected; however, there are previous reports of severe ADAMTS13 deficiency associated with sepsis and disseminated intravascular coagulation [8]. The absence of a detectable ADAMTS13 inhibitor suggested the possibility that she had incidentally discovered congenital ADAMTS13 deficiency. However, congenital ADAMTS13 deficiency was excluded when her ADAMTS13 activity was normal (immunoblot, 100%; FRETS, 92%) at a routine follow-up 1 year after her recovery. However, 1 year later her ADAMTS13 activity was again <5% by the FRETS method; activity by the immunoblot was 50%. The reason for this discrepancy between the two different assays for ADAMTS13 activity is not known [3], but awareness that different methods may have different results is important for interpretation of ADAMTS13 activity data. The etiology of her ADAMTS13 deficiency is not known.

Although four other patients with severe ADAMTS13 deficiency had systemic infections and one had systemic malignancy as the assumed etiology of their clinical features, this patient is unique among the 6 patients in whom the clinical features were attributed to a systemic infection or malignancy for having undetectable ADAMTS13 activity by both assay methods. Among the other 5 patients, 3 had ADAMTS13 activities of 13–25% by the FRETS assay and 6–9% by the immunoblot assay while two had ADAMTS13 activities of 8–9% by the FRETS assay and 12–28% by the immunoblot assay.

Patient 3: Minimal Symptoms, Rapid Death

Patient description

A 40-year-old black woman walked into the emergency room complaining of weakness and epigastric pain for several weeks, with some diarrhea and vomiting for several days. She was being followed weekly by her gynecologist for menorrhagia related to uterine fibroids. Physical examination was normal except for

TABLE III. Frequency of Neurologic and Renal Function Abnormalities and Fever Among 72 Patients With TTP and Severe ADAMTS13 Deficiency

Clinical features	Patients
Only microangiopathic hemolytic anemia and thrombocytopenia; no neurologic or renal abnormalities; no fever	10 (14%)
Microangiopathic hemolytic anemia and thrombocytopenia; also neurologic and/or renal abnormalities and/or fever, but not all 5 features	57 (79%)
Complete ''pentad'': microangiopathic hemolytic anemia, thrombocytopenia; neurologic and renal abnormalities, and fever	5 (7%)

All 72 patients had microangiopathic hemolytic anemia and thrombocytopenia as the basis for diagnosis of TTP. In this analysis, neurologic abnormalities included minor symptoms such as confusion and headache; renal abnormalities included a serum creatinine concentration $\geq$1.5 mg/dL [11]. Abnormalities were included if they occurred on the day of diagnosis (defined as the day of the 1st PEX) or within 7 days before or after the day of diagnosis. Among the 5 patients with the complete ''pentad'' of clinical features, one had Group A *Streptococcus* sepsis, one had fulminant hepatitis A, and one had preexisting SLE.

abdominal tenderness. Laboratory data included: platelet count, 10,000/μL; hematocrit, 25%; serum creatinine, 1.1 mg/dL; LDH, 722 U/L; total bilirubin, 2.5 mg/dL; peripheral blood smear was not examined. She was initially diagnosed as having primary immune thrombocytopenia (ITP); anemia was attributed to menorrhagia. She was treated with prednisone and remained asymptomatic throughout her first three hospital days. TTP was initially suspected on her fourth hospital day when creatinine increased and LDH increased further; PEX was started; she died suddenly during the initial PEX treatment. Autopsy demonstrated systemic microvascular thrombi. Most striking was the heart; there was no evidence of overt ischemia or necrosis, but nearly every small vessel was occluded by thrombi. Also her adrenal glands demonstrated extensive microvascular thrombosis and hemorrhage. ADAMTS13 activity was <5% with both methods, with a high titer inhibitor, >2 BU.

Comment

This patient's story has been previously described [9]; it emphasizes that symptoms can be mild and not specific. This patient had no neurologic abnormalities when she initially presented, not even confusion or mild mental status changes; her serum creatinine was initially normal; she had no fever. The diagnosis of TTP requires only the presence of microangiopathic hemolytic anemia and thrombocytopenia [10]. Among our 72 patients with severe ADAMTS13 deficiency, 10 (14%) had only microangiopathic hemolytic anemia and thrombocytopenia; they never had even mild neurologic abnormalities or a serum creatinine $\geq$1.5 mg/dL or fever (Table III) [1,11]. In retrospect, the diagnosis of TTP may have been suspected at the time of admission if the peripheral blood smear had been examined and the presence of microangiopathic hemolytic anemia together with thrombocytopenia appreciated.

Patient 4: Sudden and Severe Symptoms, Rapid Recovery

Patient description

A 24-year-old black man had been in excellent health and was performing his routine twice-weekly vigorous workout at a gym when he suddenly fainted while lifting weights. He was taken by ambulance to the nearest emergency room where he was immediately intubated because of severe hypoxemia; arterial oxygen saturation was 70%. His temperature was 38.6°C (101.5°F); blood pressure was 241/137; platelet count, 49,000/μL; hematocrit, 29%; creatinine, 2.3 mg/dL; LDH, 2,105; the peripheral blood smear demonstrated many schistocytes. Chest X-ray was normal. A brain MRI demonstrated cerebral edema with leptomeningeal thickening, suggesting infectious meningitis. Lumbar puncture demonstrated normal cerebral spinal fluid. EKG documented a non-ST-segment elevation myocardial infarction. Echocardiogram demonstrated left ventricular hypertrophy suggesting preexisting hypertension. Malignant hypertension was considered to be the most likely explanation for his critical illness; TTP and sepsis were also considered; plasma exchange was started. The patient's platelet count increased to 312,000/μL and his LDH decreased to 367 U/L after 3 days; PEX and corticosteroids were stopped. Two days after stopping PEX, he had a minor seizure attributed to continued severe hypertension (blood pressure, 212/110) despite multiple anti-hypertensive medicines. The decreasing platelet count from the maximum of 330,000/μL to 60,000/μL and the increasing LDH to 419 U/L five days after stopping PEX supported the diagnosis of TTP. He again responded to five PEX treatments plus corticosteroids. Creatinine returned to normal. Antihypertensive medications were discontinued 2 weeks later and he has resumed his vigorous activities. ADAMTS13 was <5%, with a very high titer inhibitor, $\gg$2 BU.

Comment

This patient's presentation was unusual for both suddenness and severity. He is one of two patients among our 72 patients with severe ADAMTS13 deficiency who had the complete ''pentad'' of presenting clinical features (microangiopathic hemolytic anemia, thrombocytopenia, neurologic and renal abnormalities, and fever) without an associated condition or other apparent etiology for TTP. Three other patients with severe ADAMTS13 deficiency also had the complete

''pentad'' of presenting clinical features, but their clinical features were subsequently attributed to Group A *Streptococcus* sepsis, fulminant hepatitis A, and preexisting SLE (Table III). Therefore, the expectation that patients with TTP should have the complete ''pentad'' of clinical features must be abandoned.

The initial diagnosis in this patient was infectious meningitis, which was excluded by the normal spinal fluid. Malignant hypertension was then considered to be the most likely diagnosis [12] until exacerbation of TTP occurred. Hypertension resolved when the TTP resolved. The presence of severe hypoxemia with a normal chest x-ray suggested pulmonary emboli which may have been caused by extensive pulmonary microvascular thrombi. Pulmonary vasculature involvement in TTP is thought to be rare [13].

Patient 5: Minimal Treatment, Rapid Recovery, No Relapse

Patient description

A 19-year-old Native American college student was seen in her local hospital emergency room for a severe headache. Five days later the headache returned with severe abdominal and chest pain. Physical examination was normal. Platelet count was 7,000/μL; hematocrit, 18%; creatinine, 0.9 mg/dL; LDH, 1,057. EKG and head CT scan were normal. TTP was diagnosed and plasma exchange begun. Platelet count and LDH were normal after five PEX treatments and treatment was stopped. No corticosteroids or other adjunctive treatments were given. ADAMTS13 was <5% by both methods; trace inhibitor activity was detected by the immunoblot assay; no inhibitor activity was detected by the FRETS assay. She has remained well for 11 years.

Comment

Hereditary TTP may be suspected when the presence of an ADAMTS13 inhibitor was unclear. However, hereditary TTP was excluded when her ADAMTS13 activity recovered to normal; it has been 94–100% on six occasions since her acute episode of TTP. This patient demonstrates that acquired autoimmune TTP with severe ADAMTS13 deficiency can respond completely to a short course of plasma exchange alone, without corticosteroids or rituximab, and may never relapse.

At this time we did not routinely use corticosteroids in addition to PEX [14]. Currently corticosteroids are considered to be standard treatment for patients with suspected severe ADAMTS13 deficiency [1]. Rituximab is also used with increasing frequency [15,16], and it has even been suggested that rituximab may be considered as standard initial therapy to prevent relapses [15]. Although the increasing use of these adjunctive treatments has decreased the average number of PEX treatments to achieve a remission in patients with severe ADAMTS13 deficiency and also has decreased the frequency of PEX-related major complications [17], this patient demonstrates that adjunctive therapy may not always be necessary for achieving a durable remission and for preventing the occurrence of relapse. Her clinical course contrasts with other Registry patients who have had prolonged and complicated clinical courses requiring twice-daily PEX, high-dose corticosteroids, rituximab, vincristine, and cyclophosphamide before remission was achieved [18].

Patient 6: Transient Neurologic Abnormalities With a Normal Platelet Count and Hematocrit 1 Month Preceding Overt TTP

Patient description

A 32-year-old white woman had been previously healthy when she noticed tingling and numbness in her left hand and foot followed by left-sided weakness and ataxia. At her local hospital emergency room, these neurologic abnormalities were documented; platelet count was 237,000/μL; hematocrit, 38%; no examination of the peripheral blood smear was reported; blood chemistries were not tested; head CT scan was normal. The following day a brain MRI documented multiple areas of restricted diffusion consistent with ischemic infarcts. Treatment with clopidogrel was started. Within 3 weeks she had recovered except for residual numbness in her left foot. One month after the initial episode, she developed dysarthria and numbness of her right hand. Brain MRI demonstrated new ischemic signs in the left frontal lobe. Echocardiogram was normal. Hematocrit remained 35%, however, her platelet count had decreased to 28,000/μL; the peripheral blood smear demonstrated schistocytes. LDH was 336 U/L; creatinine, 0.7 mg/dL. The initial impression was an autoimmune disorder predisposing to thrombosis, such as antiphospholipid antibody syndrome or systemic lupus erythematosus (SLE). Corticosteroid treatment was begun. The following day she had episodes of ventricular tachycardia with elevated troponin. With evidence of ischemia in both brain and heart, TTP was diagnosed and PEX was begun. Testing for SLE and antiphospholipid antibody syndrome was negative. ADAMTS13 activity was <5% with both methods with a high titer inhibitor, >2 BU. Serum was not available from her initial emergency room visit 1 month previously.

Comment

We assumed that the initial neurologic events were related to the subsequent diagnosis of TTP. Acute neurologic ischemic abnormalities preceding the development of thrombocytopenia and microangiopathic hemolytic anemia has been reported previously [19–22],

but this has not occurred in any of our other patients. Whether or when the diagnosis of TTP should be considered in patients with acute neurologic ischemic abnormalities and with a normal platelet count and hematocrit is not known. We did not attribute the second neurologic event with documented TTP to clopidogrel since the association of TTP with clopidogrel is uncertain: no patients have been reported who have had recurrent TTP with recurrent clopidogrel exposure; patients with reported clopidogrel-associated TTP have had recurrent TTP without clopidogrel exposure [23]; ADAMTS13 inhibitors present in patients with reported clopidogrel-associated TTP and severe ADAMTS13 deficiency have not been clopidogrel-dependent [23]. She has remained well.

Patient 7: Abdominal Pain and Bloody Diarrhea After Eating a Suspicious Hamburger

Patient description

A 53-year-old black woman was admitted 2 weeks after she and her brother-in-law ate hamburgers from a vending machine. She recalled that they both wondered whether the hamburgers would be safe; then both became ill on the following day with severe diarrhea that was overtly bloody. In both the patient and her brother-in-law, the diarrhea began to resolve over the following week but the patient continued to feel extremely weak. After 18 days, she was admitted to the hospital with a platelet count of 31,000/μL; hematocrit, 27%; creatinine, 1.0 mg/dL; LDH, 1,810 U/L. Because of her history, the initial diagnosis was TTP-HUS caused by Shiga toxin from infection with *E. coli* O157:H7. Stool cultures for *E. coli* O157:H7 and assays for Shiga toxin were negative, but these tests were obtained 18 days after the onset of her bloody diarrhea, when identification of *E. coli* O157:H7 and Shiga toxin is unlikely [24]. She was treated with PEX; recovery required 54 PEX treatments over 87 days. She had multiple exacerbations of thrombocytopenia when the frequency of PEX was decreased until corticosteroid treatment was added. ADAMTS13 activity was 5% by the immunoblot method; <5% by the FRETS method; the inhibitor titer was >1 BU by both assays.

Comment

The preceding symptom of bloody diarrhea in this patient may be described as a ''red herring.'' However, bloody diarrhea can occur in patients with TTP associated with severe ADAMTS13 deficiency because microvascular thrombi can cause ischemic colitis with morphology identical to the hemorrhagic colitis caused by Shiga toxin [9]. Among our 72 patients with severe ADAMTS13 deficiency, bloody diarrhea was a major presenting symptom in two women (including this patient). The absence of renal abnormalities may be a clue that the etiology is not related to Shiga toxin, but adults with a documented *E. coli* O157:H7 etiology of TTP-HUS may have no renal abnormalities [25].

This patient's prolonged course was dramatically different from Patient 5. When this patient presented, we did not routinely use corticosteroids in addition to PEX [14]. She is one of the reasons why our practice changed [1]. When she presented, rituximab was not yet used for treatment of TTP; we would now also use rituximab to avoid prolonged PEX treatment [17].

Patient 8. Concurrent Initial Diagnosis of TTP and SLE

Patient description

A 48-year-old white man had been in his usual health until the past month when he had developed progressive fatigue and dyspnea. He also had erythematous rashes in multiple locations, including a rash on his nose and cheeks. On examination, the malar rash was prominent; there were no neurologic abnormalities. He had no signs of arthritis but he reported that he had had swelling, redness, and tenderness in both hands in his metacarpal-phalangeal joints. He had severe thrombocytopenia and anemia (platelet count, 4000/μL; hematocrit, 17%); the peripheral blood smear demonstrated schistocytes; creatinine was 1.7 mg/dL; LDH, 423 U/L. Serum levels of C3 (21 mg/dL) and C4 (4 mg/dL) were low; ANA was 1:3,240; anti-dsDNA was 1:2,430. Coexisting TTP and SLE were diagnosed. The patient recovered with PEX and corticosteroids. He had a relapse of his TTP 6 months later which responded to PEX, corticosteroids, and rituximab. He is on continuing treatment for SLE with prednisone and azathioprine. ADAMTS13 activity was <5% with both methods; no inhibitor was detected. At the time of his relapse, ADAMTS13 activity was 13% and again no inhibitor was detected.

Comment

The demographics of acquired autoimmune ADAMTS13 deficiency associated with TTP and SLE are similar, both appear predominantly in young black women [3,26,27]. Patients with concurrent TTP and SLE have been previously reported [28]. In our experience, three patients have had a preceding history of SLE; SLE was diagnosed at the time of the initial diagnosis of TTP in this patient and one other patient; in two patients SLE developed following recovery from TTP (Table IV). In these patients it may be difficult to distinguish an acute episode of TTP from a flare of SLE. Even without a demonstrable ADAMTS13 inhibitor, we assume that the etiology of his ADAMTS13 is acquired and autoimmune, consistent with his concurrent diagnosis of SLE. Recovery of ADAMTS13

TABLE IV. Association of SLE With TTP Among 72 Patients With Severe ADAMTS13 Deficiency

Time of SLE diagnosis related to initial diagnosis of TTP	Patients (number)
Before	3[a]
Concurrent	2
After	2[b]

Seven (10%) of the 72 patients who were enrolled in the Oklahoma Registry at the time of their initial diagnosis of TTP, 1995–2012, and who had severe ADAMTS13 deficiency have been diagnosed with SLE. Two additional Registry patients whose initial TTP episodes were in 1987 and 1990, and who did not have ADAMTS13 measured at that time but who have had multiple relapses of TTP, have developed SLE 21 and 25 years after their initial episode of TTP.

[a]SLE was diagnosed 1, 4, and 22 years before the initial episode of TTP. One additional woman had been diagnosed with Sjögren's syndrome 4 months before her initial episode of TTP.

[b]SLE was diagnosed 5 months and 6 years after the initial episode of TTP.

activity during remission would confirm the diagnosis of acquired autoimmune ADAMTS13 deficiency.

Patient 9: A 9-year old Boy With Severe Thrombocytopenia and Anemia

Patient description

A 9-year-old white boy was seen by his pediatrician because of 2 days of intermittent abdominal pain, vomiting with no diarrhea, jaundice, and dark urine. His temperature was 38.3°C (101°F). The remainder of the physical examination, including neurologic examination, was normal. His platelet count was 12,000/μL; hematocrit, 10%; creatinine, 0.7 mg/dL; LDH, 3,433 U/L; the peripheral blood smear demonstrated schistocytes. Urinalysis demonstrated hematuria and proteinuria. He was diagnosed with typical HUS despite the absence of diarrhea, principally because in children this is the most common cause of microangiopathic hemolytic anemia and thrombocytopenia. Because typical HUS in children is managed only with supportive care, without PEX [29], he was managed only with transfusions. Over the next 14 days he received 14 units of red cells to maintain his hematocrit at 17–25% and 13 platelet transfusions to maintain his platelet count at 7,000–14,000/μL. He had no bleeding symptoms. His serum creatinine remained less than 1.0 mg/dL. During these 2 weeks he had several episodes of transient diplopia. When the diagnosis of TTP was finally considered and PEX was begun 14 days after admission, his neurologic examination was normal. Recovery required 34 PEX treatments over 60 days; he was not treated with corticosteroids and he is another reason why our practice changed [1]. ADAMTS13 activity was 25% by the immunoblot assay, 7% by the FRETS assay; an inhibitor was not detected.

Comment

TTP with acquired ADAMTS13 deficiency is rare in children [30]. The next youngest among our 72 patients are two who were 18 years old. Hereditary TTP may have been considered in this boy because he was young and because there was no detectable ADAMTS13 inhibitor. However, 25% ADAMTS13 activity by the immunoblot assay and the absence of an inhibitor may have been caused by his many previous transfusions. The reason for this discrepancy between the two different assays for ADAMTS13 activity is not known [3], but awareness that different methods may have different results is important for interpretation of ADAMTS13 activity data. The requirement for prolonged PEX treatment was also evidence against hereditary TTP. The diagnosis of acquired autoimmune TTP was established when he relapsed one year later and his ADAMTS13 activity was <5% by both assays and an inhibitor of 0.9 BU. In addition, his ADAMTS13 activity 1 year following this relapse, when he was in remission, was 80% by immunoblot and >100% by the FRETS assay.

Patient 10: Hereditary TTP in a Family With Hereditary Elliptocytosis

Patient description

An 18-year-old white girl was admitted to the hospital for the unexpected observation of severe thrombocytopenia (platelet count, 8,000/μL) during evaluation by her primary care physician for a mild cough with some fatigue for 2 days. The patient, her two sisters, her father, and her paternal grandmother all have hereditary elliptocytosis. Physical examination was normal; there were no neurologic symptoms; additional laboratory results included: hematocrit, 28%; creatinine, 0.8 mg/dL; LDH, 644 U/L. The peripheral blood smear demonstrated many dense elliptical red cells and also many other abnormally shaped red cells that could have been considered to be schistocytes. Because of the severe thrombocytopenia, evidence for hemolysis, and the abnormal peripheral blood smear, TTP was suspected; PEX and corticosteroid treatment were begun. The following day she remained asymptomatic; her platelet count had increased to 23,000/μL. Because of the increased platelet count, the absence of symptoms, and also because she had had a reaction to the initial PEX with chest pain and respiratory difficulty, PEX was not performed on the second hospital day. The following day her platelet count increased to 72,000/μL; PEX and corticosteroids were stopped; 2 days later her platelet count was 345,000/μL. ADAMTS13 activity was <5% by the FRETS assay; an inhibitor was not detected.

Additional history revealed that this patient and her two sisters, age 16 and 13, all had severe hemolysis

and hyperbilirubinemia at birth requiring emergency exchange transfusions. This patient's hematocrit and platelet count decreased from 47 to 27% and 146,000/μL to 23,000/μL on her first day of life. Also on her first day of life, she was noticed to have twitching of her left hand and a CT scan documented a small cerebral infarct; she had no neurologic sequelae. She had had no illness since birth prior to this hospitalization.

Comment

Our impression at this time was that the transient thrombocytopenia was not caused by TTP. We speculated that it may have been related to an infectious illness. The report of ADAMTS13 activity <5% without a demonstrable inhibitor was unexpected. Subsequently both of her sisters were also documented to have ADAMTS13 activity <5% without a demonstrable inhibitor. Although severe ADAMTS13 deficiency without a demonstrable inhibitor may suggest congenital ADAMTS13 deficiency, patients with acquired autoimmune ADAMTS13 deficiency may occasionally have no demonstrable inhibitor activity [3]. The familial occurrence of severe ADAMTS13 deficiency almost always indicates congenital ADAMTS13 deficiency, but familial acquired ADAMTS13 deficiency has been reported [31]. Recovery of ADAMTS13 to normal following recovery from an episode of TTP clearly excludes congenital ADAMTS13 deficiency. ADAMTS13 activities of her parents were 56% and 65%, consistent with heterozygosity. Additional FRETS assays with increased sensitivity documented that the ADAMTS13 activity was <1% in the three sisters and that no anti-ADAMTS13 antibodies were detected by an ELISA (Technozym®) assay. In retrospect, hereditary TTP, also known as Upshaw-Schulman syndrome, should have been suspected. However hereditary TTP is very rare. We had not diagnosed a patient with hereditary TTP among 452 previous patients in the Oklahoma TTP-HUS Registry over 23 years. One of the authors (J.N.G.) had previously managed two sisters with hereditary TTP, but that was 38 years ago [32]. The occurrence of severe hemolysis with thrombocytopenia in a newborn infant is a characteristic presentation of hereditary TTP [33]. The occurrence of a neonatal cerebral thrombosis in this patient was also consistent with the diagnosis of hereditary TTP. The absence of any illness in the two older sisters was a diversion from the diagnosis of hereditary TTP, but the presence of two episodes of severe thrombocytopenia, diagnosed as ITP, in the youngest sister when she was age 5 and 12, was also consistent with the diagnosis of hereditary TTP. At this time, all three sisters are healthy with normal physical examinations and normal laboratory data. In the future, pregnancy will be a critical issue as it seems to be inevitably associated with severe manifestations of TTP in the absence of plasma prophylaxis [32–36]. Currently, plasma infusions will be given when thrombocytopenia occurs; prophylactic plasma infusions will not be considered unless frequent episodes of TTP occur [37]. However, the risk for accelerated atherosclerosis [38] as these girls become older adults is a current concern. The lessons learned from this family are presented in Table V. It is important to enroll patients with hereditary TTP in the international Hereditary TTP Registry, to provide maximum ability to learn the long-term outcomes of this disorder.

TABLE V. Evaluation of Patients With Thrombocytopenia and Microangiopathic Hemolytic Anemia for Possible Hereditary TTP

Examples of when to suspect hereditary TTP	Severe hemolytic disease in a newborn infant with thrombocytopenia Episodic ''ITP'' in a child with concurrent anemia TTP in a child (TTP with acquired ADAMTS13 deficiency is rare in children) TTP with persistent undetectable ADAMTS13 activity and undetectable ADAMTS13 inhibitor TTP in a woman with her 1st pregnancy [32–36]
Diagnosis of hereditary TTP	Enroll patient and family in the Hereditary TTP Registry (www.ttpregistry.net; NCT01257269, clinicaltrials.gov) Identification of the *ADAMTS13* mutation (provided by the Hereditary TTP Registry) Possible identification of family members with asymptomatic hereditary TTP

DISCUSSION

These patient's stories speak for themselves. TTP with severe ADAMTS13 deficiency can have extraordinarily diverse presenting features and clinical courses. Recent reports have described multiple patients with atypical presentations of TTP [21,22]. Our experience suggests that atypical presentations are not uncommon. Although only 10 patients were selected for this presentation, many of our other patients with severe ADAMTS13 deficiency had diverse clinical presentations and could also be described as atypical. In fact, if the clinical features of ''typical'' TTP are considered to be severe microangiopathic hemolytic anemia and thrombocytopenia with severe neurologic abnormalities (which we define as transient focal signs in addition to coma, stroke, or seizure [11]) and minimal or no renal function abnormalities, then the minority of our patients with severe ADAMTS13 deficiency are ''typical.''

Of course these patients' stories should not be considered as data; they are only anecdotes. However, stories are a common component of patient care and the stories of individual patients can be powerful tools for teaching [39].

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