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Case Report

A Case Series of Atypical Presentations of Thrombotic Thrombocytopenic Purpura

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Thrombotic thrombocytopenic purpura (TTP) is a heterogeneous disease primarily characterized by thrombocytopenia and microangiopathic hemolytic anemia. Therapeutic plasma exchange has dramatically improved mortality, allowing for emergence of refractory, relapsing, and atypical presentations. In this article, we describe four cases of TTP presenting with minimal schistocytes, mild elevation of lactate dehydrogenase, and symptoms suggestive of macrovascular arterial involvement. With increasing reports of less common presentations of TTP, clinicians should consider this diagnosis in cases of unexplained arterial thrombosis, thrombocytopenia, or hemolytic anemia. Testing for a disintegrin and metalloprotease with thrombospondin Type 1 motif, Member 13 ADAMTS13 activity was extremely useful to help confirm the diagnosis in our series of patients. J. Clin. Apheresis 27:221–226, 2012. ©2012 Wiley Periodicals, Inc.

Key words: atypical thrombotic thrombocytopenic purpura; therapeutic plasma exchange; ADAMTS13; rituximab; microangiopathic hemolytic anemia; macrovascular thrombosis

INTRODUCTION

In 1966, Amorosi and Ultmann [1] described the thrombotic thrombocytopenic purpura (TTP) pentad consisting of fever, thrombocytopenia, microangiopathic hemolytic anemia (MAHA), neurologic abnormalities, and renal failure. In their report of 16 cases, almost 40% of the patients presented with a prolonged prodromal course of hematologic or neurologic symptoms lasting for more than a month. Also, in about 30% of the patients, neurological symptoms included aphasia or hemiparesis; features concerning for acute cerebrovascular accidents (CVA) and less well recognized for TTP in today's era of improved diagnostics and effective treatment.

Without treatment, TTP is almost uniformly fatal with a mortality rate approaching 90%. With the timely institution of therapeutic plasma exchange (TPE) mortality decreases to about 10%–20% [1–4]. In 1991, a pivotal study demonstrated superiority of TPE over simple plasma infusion in the treatment of TTP [3]. In this study, the Canadian Apheresis Group used a less stringent set of inclusion criteria, which included only the dyad of thrombocytopenia and unexplained MAHA. Incorporation of these less stringent diagnostic criteria into our clinical practice combined with the longer survival achieved with plasma exchange has led to an increase in the number of recognized cases of TTP. Today, many cases present atypically as observed in the original and more contemporary reports [1,5–7]. Recently, Sarode [8] reviewed cases of TTP with unusual macrovascular manifestations such as acute coronary syndrome, stroke, and visual disturbances.

A disintegrin and metalloprotease with thrombospondin Type 1 motif, Member 13 (ADAMTS13) levels less than 5% are a hallmark of TTP and may be due to a congenital deficiency or an acquired inhibitor of ADAMTS13 [9]. The prognostic and predictive value of ADAMTS13 plasma activity levels is under investigation in different clinical settings. Few reports exist regarding the use of ADAMTS13 activity levels in the diagnosis and management of TTP with atypical presentations [6,8,10,11].

Immunosuppression with corticosteroids has traditionally been used as a therapeutic adjunct to plasma exchange in the management of TTP [2]. Recent case series indicate that rituximab can induce remission in the majority of patients with classic TTP [12–16]. Of those patients with less typical symptoms of TTP, rituximab has also proved useful in inducing remission in the relapsed setting [8,10].

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This study is a University of Florida IRB-approved retrospective report of four cases of TTP who presented to the university's teaching hospital with minimal microangiopathic changes, variable thrombocytopenia, low ADAMTS13 levels, and clinical sequelae suggestive of macrovascular thromboses. In addition to adding to the existing body of literature on atypical presentations of TTP, our series highlights the importance of testing for ADAMTS13 activity in patients who present with unexplained hemolysis or thrombotic events as well as the potential use of rituximab in this setting. A summary of clinical presentations and laboratory features of these cases is presented in Table I.

Case 1

A 40-year-old Caucasian woman with a remote history of breast cancer status post chemotherapy and radiation therapy was admitted for the management of non-ST elevation myocardial infarction. She underwent coronary artery angiography which revealed a thrombus in the right coronary artery (RCA) but no evidence of advanced atherosclerosis. Her admission laboratory results included a platelet count of 54,000/mm^3, hemoglobin of 11.9 g/dL, and a total bilirubin of 0.6 mg/dL. Review of prior records revealed the presence of chronic thrombocytopenia in the range of 50,000–70,000/mm^3 dating at least 6 months before this admission. A thrombophilia work up was unrevealing. Examination of the bone marrow was negative for malignant involvement. Antinuclear antibody (ANA) was undetectable. She was discharged home but presented 10 days later with an acute CVA involving the right posterior and middle cerebral territories and medial aspects of both inferior cerebellar hemispheres. Findings of magnetic resonance imaging (MRI) were suggestive of an embolic process. MR-angiography (MRA), however, failed to reveal definitive evidence for arterial thrombosis, although nonvisualization of the bilateral posterior inferior communicating arteries (PICA) was noted. In addition, she was noted to have worsening thrombocytopenia with a platelet count of 34,000/mm^3 and stable hemoglobin of 11.7 g/dL, and a creatinine of 1.40 mg/dL. Corrected reticulocyte count was 3.7%, total bilirubin 1.8 mg/dL, direct bilirubin 0.4 mg/dL, lactate dehydrogenase (LDH) 558 U/L (135–225 U/L), and haptoglobin was undetectable, all consistent with hemolysis. Direct antiglobin test as well as heparin platelet factor-4 antibody testing for heparin-induced thrombocytopenia were negative. Examination of the peripheral blood smear did not reveal schistocytes; however, with the potential diagnosis of TTP, steroids and TPE were initiated. Five days into treatment, the platelet count normalized, and her clinical condition improved. ADAMTS13 activity drawn at presentation subsequently returned $<5\%$ with an inhibitor at 6.4 units. She suffered a relapse $\sim$1 year later characterized by nonspecific gastrointestinal and constitutional symptoms and thrombocytopenia (platelet count 49,000/mm^3) but minimal hemolysis (hemoglobin 14.4 g/dL, LDH 399 U/L) and rare schistocytes. She transiently responded to a course of steroids and TPE with normalization of her platelet count. However, on Day 6, her platelet count declined, and rituximab was administered at a dose of 375 mg/m^2 weekly for 4 weeks for refractory TTP. ADAMTS13 activity measured at the time of relapse returned less than 5% with an inhibitor of 1.0 units. The ADAMTS13 activity level increased to $>90\%$ following completion of rituximab therapy. She remained in remission for almost 9 months at which time she was lost to follow-up.

Case 2

A 25-year-old G1P0 Caucasian woman with known pituitary adenoma presented in her 23rd week of pregnancy with 3 months history of intermittent paresthesias involving the left arm and face, slurred speech, blurred vision, and headaches. Imaging studies of the central nervous system were nondiagnostic and thrombophilia evaluation only revealed a low protein S activity, an expected finding during pregnancy. Her ANA was initially mildly positive at 1:40, but the confirmatory test for double-stranded DNA antibody was negative. On presentation, hemoglobin was 11.0 g/dL and platelet count 166,000/mm^3, respectively. She was empirically started on therapeutic low-molecular weight heparin, which was then discontinued in the immediate postpartum period due to pituitary apoplexy. Her hemoglobin was 12.3 g/dL and platelet count was 255,000/mm^3 at this time. A month later, she suffered a stroke in the posterior cerebral artery territory. Her laboratory work-up was unremarkable and hemoglobin and platelet counts were again noted to be normal with the respective values of 12.3 mg/dL and 222,000/mm^3. Seven months later, she presented with another acute stroke in the left occipital lobe and an MRA was unremarkable. Laboratory findings for the first time were remarkable for a platelet count of 27,000/mm^3, hemoglobin 9.4 g/dL, LDH 510 U/L, creatinine 1.2 mg/dL, total bilirubin 1.4 mg/dL, direct bilirubin 0.2 mg/dL, and haptoglobin <9 mg/dL. Review of the peripheral blood smear only showed 1–2 schistocytes per high power field. After 6 days of TPE, her clinical condition rapidly improved, and the LDH and platelet count normalized (196,000/mm^3). The ADAMTS13 activity subsequently returned as $<5\%$, and no inhibitor was identified. The duration of remission was short and she presented within 1 month with worsening thrombocytopenia (platelet nadir of 40,000/mm^3) and vague neurological symptoms. Outpatient infusion of plasma was

TABLE I. Clinical and Laboratory Features, Treatment Received, Outcomes at Presentation and During Relapse Episodes

	Clinical presentation	LDH (U/L)	Schistocytes (/hpf)	Hgb (g/dL)	Plt ($\times 10^3$/mm^3)	Cr (mg/dL)	Treatment	ADAMTS13 activity (>67 %) (Before Tx)	ADAMTS13 inhibitor (<0.4 units) (Before Tx)	ADAMTS13 activity postrituximab (%)	Duration of remission (m)	Atypical features
Case 1												
Initial	MI, stroke	558	Rare	11.7	34	1.4	TPE,CS	<5%	6.4	NA	12	Rare schistocytes,
Relapse 1	Nonspecific symptoms	399	Rare	14.4	49	1.2	TPE,CS,RTX	<5%	1.0	>90% at 0.5 months	9[a]	chronic thrombocytopenia, macrovascular complications predating diagnosis, and normal Hgb at relapse
Case 2												
Initial	Stroke	510	Rare	9.4	27	1.2	TPE	<5%	Undetectable	NA	1	Rare schistocytes,
Relapse 1	Vague neurological symptoms	400	Rare	12	40	1.1	TPE,RTX	<5%	Undetectable	69% at 1 month	12	macrovascular complication predating diagnosis, normal Hgb at relapse
Case 3												
Initial	Seizure	4,764[b]	Present	7.4	27	0.9	TPE,CS	NA	NA	NA		Rare schistocytes,
Relapse 3	CVA	970[b]	Rare	13	130	0.6	TPE,CS	NA	NA	NA		macrovascular
Relapse 4	Seizure	1,576[b]	Present	9.3	86	0.6	TPE,CS, splenectomy	NA	NA	NA	33	complications, mild thrombocytopenia at
Relapse 7	Seizure	844	NA	9.9	73	0.6	TPE,CS,RTX	NA	NA	NA	22	relapse; asymptomatic
Relapse 8	Asymptomatic	610	NA	14.4	62	0.6	TPE,CS,RTX	NA	NA	NA	21	relapse; rituximab
Relapse 9	Asymptomatic	480	Rare	11	61	0.6	TPE,CS,RTX	<5%	1.6	83% at 5 months	15	maintenance
							RTX maintenance	6%	Undetectable	90% at 8 months	20	
Case 4												
Initial	Seizure	1,800	Present	8	14	1.3	TPE,CS,RTX	NA	NA	NA	34	Rare schistocytes,
Relapse 1	Stroke	226	Rare	14	180	1.0	TPE,CS,RTX	<5%	2.8	<5% at 1.5 months	24	macrovascular complications, and normal platelet count at relapse

[a]Lost to follow-up.

[b]LDH range for these values: 313–618 U/L.

LDH: lactate dehydrogenase (135–225 U/L); Hgb: hemoglobin (12–16 g/dL); Plt: Platelets (150–450 $\times 10^3$ /mm^3); Cr: Creatinine (0.4–0.9 mg/dL); ADAMTS13: a disintegrin and metalloprotease with thrombospondin Type 1 motif, Member 13; CS: corticosteroids; m: month after completion of treatment; MI: myocardial infarction; NA: not available; RTX: rituximab; TPE: therapeutic plasma exchange.

unsuccessful, and she required readmission for TPE to which she had a prompt response. She also received four doses of weekly rituximab at a dose of 375 mg/m^2 per dose which resulted in a relapse-free period of more than 1 year with an ADAMTS13 level increasing to 69% after rituximab therapy.

Case 3

A 68-year-old Caucasian woman initially presented 10 years ago with classic signs and symptoms of TTP including altered mental status, schistocytes, platelet count of 27,000/mm^3, hemoglobin 7.4 mg/dL, creatinine 0.9 mg/dL, total bilirubin 3.4 mg/dL, direct bilirubin 0.2 mg/dL, LDH 4764 U/L (313–618 U/L), and an undetectable haptoglobin. There was no serologic evidence of lupus. She was originally treated with TPE and corticosteroids with rapid clinical and hematologic remission. Duration of remission was short, and she was readmitted twice over the following year with MAHA and thrombocytopenia although with minimal symptoms. One year later, she suffered a stroke in the right middle cerebral territory as defined by MRI. No large vessel thrombosis was seen on MRA, but diffuse small vessel disease was noted. Platelet count at presentation was 130,000/mm^3 with no other significant hematologic findings. Treatment with steroids and TPE resulted in prompt recovery of platelet count to $\sim$300,000/mm^3. Two months later, she had another relapse. In addition to TPE, she underwent splenectomy resulting in a relapse-free period of 33 months. After being maintained on a chronic regimen of steroids, she continued to suffer recurrent episodes, which were treated with TPE and titration of steroids. Rituximab at a dose of 375 mg/m^2 weekly for 4 weeks was therefore used as an adjunct to corticosteroids and TPE, and remission was achieved for 22 months. Similar relapse free interval was achieved when she was retreated with the same regimen of rituximab in combination with TPE and steroids 2 years later for another relapse. She presented during her final relapse with asymptomatic thrombocytopenia. She was treated again with TPE, corticosteroids, and rituximab. ADAMTS13 activity at this time was $<$5% with an inhibitor detected at 1.6 units. Five months into remission ADAMTS13 level was 83%, but at 15 months, despite continued clinical remission the ADAMTS13 level declined to 6% (with no inhibitor detected). Rituximab maintenance 375 mg/m^2 every 3 months for 1 year was instituted. She has remained in clinical remission, with normal ADAMTS13 levels for greater than 20 months after the completion of maintenance rituximab and for about 35 months from her last relapse.

Case 4

A 58-year old otherwise healthy Caucasian woman initially presented with headaches, altered mental status, creatinine of 1.3 mg/dL, LDH 1,800 U/L, hemoglobin of 8 g/dL, and a platelet count of 14,000/mm^3. The peripheral blood smear showed 8–10 schistocytes per high power field. She transiently responded to TPE and corticosteroids with the platelet count rising to 106,000/mm^3 in five days. Despite initial improvement, her platelet count began to decline and she required daily TPE for a month. Rituximab at 375 mg/m^2 weekly for 4 weeks was initiated as an adjunct to further daily TPE. Her renal function, hemoglobin, and platelet count normalized at the conclusion of 2 months hospitalization, which was complicated by multiple infections. Due to fluctuations in the platelet count, it was difficult to determine the time to response to treatment with either TPE or rituximab. However, she remained in remission for 34 months until she presented with a stroke involving the right watershed territory of the posterior and middle cerebral arteries. MRA revealed no focal lesions. Complete blood count (CBC) was normal, however creatinine and LDH were slightly elevated at 1.0 mg/dL and 226 U/L, respectively. The following week, her platelet count dropped to 85,000/mm^3 despite marked improvement in her neurologic status. Her hemoglobin and renal function remained normal. TPE, steroids, and weekly rituximab 375 mg/m^2 (for 4 weeks) were started, and the platelet count returned back to normal by Day 4. The ADAMTS13 activity was found to be $<$5% with a detectable inhibitor at 2.8 units at the time of her stroke. Despite attaining clinical and hematologic remission, the ADAMTS13 activity and the inhibitor remained unchanged 6 weeks after the completion of treatment. Nevertheless, she has remained in clinical remission after about 24 months since the completion of last treatment. Rituximab maintenance was offered, but the patient declined.

DISCUSSION

Once considered a fatal disease, TTP is now successfully treated with timely initiation of TPE and immunosuppressive agents. Owing to less stringent criteria for the diagnosis as well as improved survival of the affected individuals, the disease is increasingly presenting with a wide spectrum of symptoms. The ''classic pentad'' is often not observed. In a cohort of 51 patients from the Oklahoma registry, comprised of patients presenting with severe ADAMTS13 deficiency, only three (5%) had all five findings. Two of these patients were subsequently discovered to have systemic infection, and the other had a previous diagnosis of lupus [4]. In addition to the heterogeneity of symptoms, more patients are presenting with relapse, which occasionally does not respond to TPE alone or in combination with corticosteroids. Our paper details cases of TTP in four female patients with minimal features of MAHA, variable thrombocytopenia, and suspected macrovascular involvement. All four patients attained remission following rituximab given during relapse.

Minimal MAHA/Thrombocytopenia

In Case 1, LDH was only mildly elevated, and only few schistocytes were seen on the peripheral blood smear. The diagnosis was retrospectively confirmed by demonstrating very low ADAMTS13 activity level. An interesting observation in this case was the complete normalization of the chronic thrombocytopenia after TPE, which suggests an ongoing subclinical process long before the diagnosis was established. Similarly, despite severe thrombocytopenia at presentation in Case 2, only a few schistocytes were identified on peripheral blood smear. This patient also had longstanding neurological disturbances before diagnosis, also suggesting an ongoing subclinical process. Cases 3 and 4 both illustrate cases of relapsing TTP with very mild thrombocytopenia occurring shortly before and even subsequent to a CVA, indicating that a nearly normal laboratory work up in a symptomatic patient with a history of TTP does not rule out recurrence.

Macrovascular Presentation

The initial presentation in Case 1 consisted of an acute coronary syndrome in the setting of chronic thrombocytopenia and anemia. Due to the chronic nature of thrombocytopenia in this patient who had a prior history of receiving radiation and chemotherapy, the possibility of TTP was not actively sought during the initial hospitalization; TTP was only suspected during the second hospitalization when she presented with acute stroke and worsening thrombocytopenia. In a case report by Ho et al. [17] of a patient with TTP presenting with myocardial infarction, angiography revealed distal occlusion of the left anterior descending artery with no ruptured plaque. This is consistent with our observation in Case 1 with the presence of thrombus in the distal RCA without diffuse atherosclerotic findings.

All the patients in our series presented with stroke confirmed by MRI, and all underwent MRA with variable results. Angiography did not reveal definitive large vessel occlusion in any case, although small vessel disease was noted in Case 3 and nonvisualization of the PICA circulation was appreciated in Case 1. Although radiographic manifestation of stroke in TTP have been reported in several publications [7,8,11,18–20], it is noteworthy to mention that the demonstration of large vessel thrombosis has only been demonstrated in rare case reports [6,21,22].

ADAMTS13 Activity Levels

When measured, ADAMTS13 activity level was found to be universally low during acute episodes in our series. This was associated with presence of variable titers of an inhibitor except in Case 2, where no inhibitor was detected. The lack of response to plasma infusion as well as normalization of ADAMTS13 level after treatment with rituximab ruled out a congenital deficiency of ADAMTS13 in this case. Inability to detect an inhibitor in Case 2 is consistent with findings from the Oklahoma registry, where 17% of patients with ADAMTS13 activity of $<10\%$ did not have demonstrable inhibitors [23]. In a smaller series of 16 patients with ADAMTS13 activity level of $<5\%$, only 44% were found to have detectable inhibitors. [24]. In Case 4, a durable hematologic response was achieved after the first relapse despite a persistent low ADAMTS13 activity level and presence of an inhibitor.

It is noteworthy to mention that very low ADAMTS13 activity levels have been observed in microangiopathic anemias due to other causes such as infection or malignancy [23]. Nevertheless, ADAMTS13 remains a valuable tool in making the initial diagnosis of TTP; the use of the assay, however, to predict or monitor response to treatment remains controversial.

Use of Rituximab

The effectiveness of adjuvant rituximab in addition to TPE in relapsed and refractory TTP has been described in multiple prior and recent publications with remission rates as high as 90% [12–16,25,26]. However, at present, only nonrandomized data have been published, and the appropriate target population, timing of initiation, duration of treatment, and concurrent use with TPE has yet to be established. Given that there may be long periods of remission interrupted by intermittent relapse, as in our series, and given that TPE is used concurrently in the majority of cases, the efficacy of rituximab remains difficult to prove.

In the first prospective study of rituximab in TTP, Fakhouri et al. [27] investigated the efficacy of rituximab for refractory cases as well as its prophylactic use while in remission for relapsing cases. In five cases with multiple relapses who had failed immunosuppression or splenectomy, prophylactic use of rituximab was shown to be beneficial in eradicating the ADAMTS13 inhibitor in the only case with a detectable inhibitor. None of these cases relapsed during the short period of follow-up (11 months). In Case 3 despite attaining clinical and hematologic remission, multiple prior life threatening relapses led us to offer rituximab maintenance on detection of declining ADAMTS13 levels. Rituximab was administered at 375 mg/m^2 every 3 month for 1 year. This further adds to the literature on the use of maintenance rituximab in relapsed TTP, although efficacy remains difficult to determine [28,29].

In conclusion, when approaching patients with symptoms suggestive of macrovascular thrombosis and no apparent risk factors, one should consider the diagnosis of TTP. As demonstrated in our case series, the degree of thrombocytopenia may be mild and features of classic MAHA may not readily be detectable on biochemical profile or review of the blood smear. Early testing for ADAMTS13 may be helpful to confirm the diagnosis at the initial presentation, however caution should be exercised as this assay is not specific for

TTP and severe ADAMTS13 deficiency could also be encountered in microangiopathic anemias due to infections or malignancies [30,31]. Rituximab seemed helpful in our four cases, but due to concomitant use of TPE and given prolonged remissions at other time intervals in the disease course, the efficacy of rituximab remains unproven. Randomized prospective trials in relapsed TTP are encouraged to further clarify the role of rituximab in this setting.

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