

Thrombotic microangiopathy in a patient with systemic lupus erythematosus and systemic sclerosis overlap syndrome: a case report

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Case Report

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Abstract

Background

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare, life-threatening thrombotic microangiopathy (TMA) caused by autoantibody-mediated severe deficiency of ADAMTS13. Its occurrence in the setting of connective tissue disease (CTD) overlap syndromes presents a significant diagnostic challenge given the broad differential of thrombotic microangiopathy in this population.

Case Presentation:

We report a 32-year-old woman with systemic lupus erythematosus and systemic sclerosis overlap syndrome who presented with microangiopathic hemolytic anemia, severe thrombocytopenia, and neurological symptoms. A PLASMIC score was calculated and returned at a high risk for TTP (6). ADAMTS13 activity was confirmed at < 0.03 IU/mL ($< 3\%$ activity) with an inhibitor titer of 9.8 Bethesda units, establishing the diagnosis of iTTP. Systematic exclusion of competing thrombotic microangiopathies including scleroderma renal crisis, catastrophic antiphospholipid syndrome, typical and atypical hemolytic uremic syndrome (HUS), malignant hypertension associated TMA, drug induced TMA, pregnancy associated TMA, and disseminated intravascular coagulation was essential given the distinct and sometimes conflicting therapeutic implications of each diagnosis. Treatment with plasma exchange, corticosteroids, caplacizumab, and rituximab resulted in clinical recovery over a 12-day hospitalization.

Conclusions

This case highlights the diagnostic complexity of thrombotic microangiopathy in CTD overlap syndromes, the importance of ADAMTS13 testing and systematic exclusion of competing diagnoses, and the critical role of empirical plasma exchange guided by the PLASMIC score while confirmation is pending.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening thrombotic microangiopathy (TMA) characterized by microangiopathic hemolytic anemia (MAHA), severe thrombocytopenia, and end-organ ischemia resulting from platelet-rich microthrombi occluding the microvasculature. The worldwide annual incidence of iTTP is 2 to 6 cases per million [1]. In more than 95% of cases, TTP is caused by autoantibodies that inhibit ADAMTS13 activity, a metalloprotease responsible for cleaving ultra-large von Willebrand factor (VWF) multimers; this form is termed immune-mediated TTP (iTTP) [1, 2]. Without prompt recognition and treatment, mortality from untreated iTTP exceeds 90%, making early empirical therapy imperative even before serologic confirmation [1, 2].

The clinical diagnosis of TTP has historically relied on a pentad of findings including MAHA, thrombocytopenia, neurological symptoms, renal impairment, and fever. However, this pentad is present in fewer than 10% of patients with acute TTP, and its absence should never delay treatment [1, 2]. In contemporary practice, the PLASMIC and FRENCH score have emerged as validated clinical prediction tools to risk-stratify patients with suspected TMA for severe ADAMTS13 deficiency while results are pending, allowing clinicians to initiate plasma exchange empirically in high-risk patients [3, 4], especially given the long turnaround time for testing for ADAMTS13 levels and inhibitor.

The diagnostic challenge is magnified considerably when TTP occurs in the setting of connective tissue disease (CTD), particularly systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). The differential diagnosis of TMA in CTD is uniquely broad, encompassing scleroderma renal crisis (SRC), catastrophic antiphospholipid syndrome (CAPS), typical and atypical hemolytic uremic syndrome (HUS), malignant hypertension associated TMA, drug induced TMA, pregnancy associated TMA, and disseminated intravascular coagulation (DIC), each carrying distinct therapeutic implications [5]. Misclassification in this context is not merely academic; treatments that are lifesaving in one condition may be harmful or insufficient in another.

Here we present a case of confirmed iTTP in a patient with SSc-SLE overlap syndrome, highlighting the diagnostic complexity of TMA in CTD overlap, the importance of systematic exclusion of competing diagnoses, and the role of modern combination therapy including caplacizumab and rituximab.

Case Presentation

A 32-year-old woman with a known history of SLE and SSc overlap syndrome presented to the emergency department with a three-day history of severe headache, nausea, and diffuse abdominal pain coinciding with the onset of her menstrual cycle, during which she reported heavy menstrual bleeding. Her rheumatologic history was significant for poor medication compliance, having been off her prescribed medications for at least one year prior to admission, with her last rheumatology follow-up approximately two years prior to presentation. Her home medications included hydroxychloroquine and colchicine, the latter prescribed for prior SLE-associated pericarditis, neither of which she had been taking consistently.

Her SLE diagnosis was supported by prior serologic workup performed approximately five years before admission, demonstrating anti-Smith antibody positivity, strongly positive anti-RNP, and ANA at 1:1280 with nucleolar and speckled pattern. Anti-dsDNA, anti-SSA, anti-SSB, anti-RNA polymerase III, anti-SCL-70, and anticentromere antibodies were all negative at that time. Her SSc diagnosis had been established clinically on initial rheumatologic evaluation based on the presence of salt-and-pepper cutaneous dyspigmentation, sclerodactyly, Raynaud's phenomenon, gastroesophageal reflux disease (GERD), and dysphagia, in the absence of confirmatory SSc-specific antibodies.

On presentation, vital signs were within normal limits, with blood pressure of 118/72 mmHg, heart rate of 88 beats per minute, temperature of 37.0°C, respiratory rate of 16 breaths per minute, and oxygen

saturation of 99% on room air. Physical examination revealed mild diffuse abdominal tenderness without peritoneal signs and a non-focal neurological examination. Initial laboratory evaluation was notable for severe thrombocytopenia with a platelet count of $11 \times 10^9/\text{L}$ and hemoglobin of 6.2 g/dL (mean corpuscular volume [MCV] 92.1 fL).

Lactate dehydrogenase (LDH) was markedly elevated at 2022 U/L, haptoglobin was critically low at less than 8 mg/dL, total bilirubin was elevated at 2.0 mg/dL with an indirect fraction of 1.4 mg/dL, and reticulocyte percentage was elevated at 8.4%, collectively consistent with brisk hemolysis. Direct antiglobulin test (DAT) was negative, excluding autoimmune hemolytic anemia as etiology. Peripheral blood smear demonstrated significant schistocytes, polychromasia, and decreased platelets without platelet clumping, confirming a microangiopathic process. High-sensitivity cardiac troponin was negative at less than 3 ng/L, arguing against cardiac involvement.

Renal function was preserved with creatinine of 0.63 mg/dL, and urinalysis was bland without proteinuria or hematuria. Coagulation studies including prothrombin time (16.7 seconds; international normalized ratio [INR] 1.3), partial thromboplastin time (26.7 seconds), and fibrinogen (364 mg/dL) were not significantly deranged, arguing against DIC. Beta-human chorionic gonadotropin was negative, excluding pregnancy and pregnancy-related TMA, and computed tomography of the head was unremarkable.

Her clinical presentation raised strong suspicion for iTTP, and formal application of the PLASMIC score yielded a value of 6, placing her in the high-risk category for severe ADAMTS13 deficiency [3, 4]. The patient was transferred to the medical intensive care unit and empirical therapeutic plasma exchange and pulse dose steroids were initiated on the day of admission in keeping with current guidelines for high-risk TTP [6, 7].

Concurrent immunologic workup revealed ANA at 1:2560 with speckled pattern, negative anti-dsDNA, and complement levels C3 and C4 within normal limits at 126 mg/dL and 22 mg/dL respectively. Antiphospholipid antibody panel including anti-cardiolipin, anti-beta-2 glycoprotein-1, and phosphatidylserine/prothrombin antibodies were all negative, as was anti-SCL-70. These findings argued against scleroderma renal crisis and catastrophic antiphospholipid syndrome as the primary etiology. Infectious workup demonstrated hepatitis A IgG positivity consistent with prior exposure, absent hepatitis B immunity, and negative hepatitis C and HIV serologies.

ADAMTS13 activity was collected on admission prior to initiation of plasma exchange or any blood product transfusion, resulting on hospital day 6 at $< 0.03 \text{ IU/mL}$ ($< 3\%$ activity; severely deficient; reference range $> 0.67 \text{ IU/mL}$), with a confirmatory ADAMTS13 inhibitor titer of 9.8 Bethesda units, establishing the diagnosis of immune-mediated TTP.

High-dose corticosteroids were initiated concurrently with plasma exchange in the form of intravenous methylprednisolone 500 mg daily for three days (hospital days 1–3), subsequently transitioned to oral prednisone 1 mg/kg daily. The patient received a total of seven plasma exchange sessions between hospital days 1 and 7. One unit of packed red blood cells was transfused on admission given

symptomatic anemia, and hydroxychloroquine was restarted. The patient's severe headache responded to the first plasma exchange session but transiently recurred the following day before resolving permanently after the second session.

Caplacizumab was initiated on hospital day 6, with an initial 11 mg intravenous dose followed by 11 mg subcutaneously once daily, planned for a total of 30 days. Although current guidelines and the pivotal HERCULES trial protocol recommend initiation of caplacizumab at the start of plasma exchange [7, 8], in this case initiation was delayed until ADAMTS13 results confirmed the diagnosis, owing to drug authorization and cost considerations that delayed in-hospital availability.

The patient's clinical and laboratory course is summarized in Table 1. Serial laboratory values demonstrated progressive resolution of the hemolytic process alongside robust platelet recovery. Platelet count recovered from a nadir of $11 \times 10^9/L$, exceeding $150 \times 10^9/L$ on hospital day 6 and remaining above this threshold for two consecutive days, at which point plasma exchange was discontinued after a total of seven sessions. Platelet count continued to rise, reaching $571 \times 10^9/L$ by hospital day 12. LDH declined from 2022 U/L at admission to 209 U/L by hospital day 9, with normalization of haptoglobin to 156 mg/dL and total bilirubin to 0.3 mg/dL over the same interval. Hemoglobin trended upward from 6.2 to 10.4 g/dL over the hospital course.

Peripheral blood smear demonstrated an evolving pattern, with significant schistocytes on admission persisting through hospital day 8 at greater than 10 per high-power field, with progressive improvement to 4–5 per high-power field by hospital day 10 and 2–3 per high-power field by discharge on hospital day 12, despite biochemically resolved hemolysis.

On hospital day 12, the patient was discharged on oral prednisone 50 mg daily, caplacizumab 11 mg subcutaneously daily, and hydroxychloroquine. Rituximab 375 mg/m² weekly for four doses was prescribed at discharge in accordance with current guidelines [6, 7], following receipt of a negative QuantiFERON-tuberculosis result and administration of hepatitis B vaccination. Outpatient follow-up with both hematology and rheumatology was arranged for the following day.

Table 1
Serial Laboratory Values Throughout Hospitalization

Parameter	Day 1	Day 6	Day 7	Day 8	Day 10	Day 12	Normal
Platelets ($\times 10^9/L$)	11	188*	247	288	453	571	150–400
Haemoglobin (g/dL)	6.2	8.6	8.1	9.3	9.3	10.4	12–16
LDH (U/L)	2022	368	257	254	209	241	< 250
Haptoglobin (mg/dL)	< 8	50	85	105	156	183	30–200
Total Bilirubin (mg/dL)	2.0	0.8	0.5	0.3	0.3	0.2	< 1.2
Creatinine (mg/dL)	0.63	0.49	0.52	0.50	0.59	0.63	0.5–1.1
Fibrinogen (mg/dL)	364	–	–	–	–	–	200–400
Schistocytes (/HPF)	> 10	> 10	> 10	> 10	4–5	2–3	< 1
ADAMTS13 Activity (IU/mL)	< 0.03†	–	–	–	< 0.03	–	> 0.67
ADAMTS13 Inhibitor (BU)	9.8†	–	–	–	4.6	–	< 0.4

BU = Bethesda units; HPF = high-power field; LDH = lactate dehydrogenase; – = not collected at this timepoint.

* Platelets exceeded $150 \times 10^9/L$ on day 6 (188) and day 7 (247), meeting the two consecutive day criterion for stopping plasma exchange.

† Collected on admission prior to plasma exchange; resulted on hospital day 6.

Discussion

This case of confirmed iTTP complicating SSc-SLE overlap syndrome illustrates the diagnostic complexity encountered when TTP presents in the setting of CTD overlap. The severely deficient ADAMTS13 activity and high-titer inhibitor confirmed the immune-mediated etiology, while the patient's atypical serologic profile and prolonged medication non-compliance raise important questions about the immunologic triggers of ADAMTS13 autoantibody formation in this unique patient population.

SSc-SLE Overlap Syndrome

Overlap syndrome occurs when a patient simultaneously fulfills classification criteria for two or more distinct connective tissue diseases. SSc is one of the autoimmune rheumatic diseases most frequently involved in overlap, with approximately 20% of SSc patients demonstrating features of at least one additional CTD [9]. SLE is among the recognized overlap partners, with SSc-SLE overlap occurring in approximately 6.8% to 10% of SSc patients [10,11]. Patients with SSc-SLE overlap tend to be younger at diagnosis and more frequently female compared to those with SSc alone [10,11]. From a serologic

standpoint, anti-U1-RNP is strongly associated with SSc-SLE overlap, identified in approximately 30% of patients [11]. Our patient exemplifies this serologic profile, with strongly positive anti-RNP and anti-Smith antibodies and absent SSc-specific antibodies, and her SSc diagnosis was established on clinical grounds based on the presence of sclerodactyly, Raynaud's phenomenon, salt-and-pepper dyspigmentation, GERD, and dysphagia.

The co-occurrence of iTTP and SLE is recognized, though the precise mechanistic relationship remains debated. A large cohort study from the French Thrombotic Microangiopathies Reference Center demonstrated that a substantial proportion of patients with iTTP develop a recognized autoimmune disorder, most commonly SLE, during follow-up after their acute iTTP episode, with the presence of anti-SSA or anti-dsDNA antibodies at the time of iTTP diagnosis identified as significant risk factors [12]. This suggests that anti-ADAMTS13 autoantibody production may share immunologic mechanisms, and possibly genetic susceptibility, with other systemic autoimmune diseases. In a Chinese cohort of SLE patients with TMA, those with acquired ADAMTS13 inhibitor demonstrated a distinct phenotype characterized by more severe thrombocytopenia and central nervous system involvement, with relatively milder renal involvement and rapid response to therapy [13], a pattern that closely matches the clinical presentation of our patient. The presence of SSc as a second autoimmune diathesis may further amplify B-cell dysregulation, potentially predisposing to anti-ADAMTS13 autoantibody formation.

Pathophysiology of iTTP

In iTTP, severe deficiency of ADAMTS13 activity, defined as less than 10% of normal, results from polyclonal IgG autoantibodies that reduce ADAMTS13 through two distinct mechanisms: direct inhibition of enzymatic function and enhanced clearance of the protease from circulation [1,14]. Recent work has demonstrated that antibody-mediated clearance is the predominant mechanism, with anti-ADAMTS13 autoantibodies enhancing ADAMTS13 clearance by 4- to 10-fold in patients with iTTP [14]. ADAMTS13 normally cleaves ultra-large von Willebrand factor multimers secreted by endothelial cells, thereby preventing their interaction with platelets and limiting thrombus formation under normal physiologic conditions [1]. Without adequate ADAMTS13 activity, these ultra-large multimers accumulate, bind platelets via the GPIb-IX-V complex, and promote the formation of platelet microthrombi in the microvasculature [1]. These microthrombi shear circulating red blood cells into schistocytes, causing MAHA, and occlude small vessels producing ischemic organ injury including stroke and myocardial infarction [1]. Importantly, severe ADAMTS13 deficiency is central to the development of iTTP, but some patients may have extended periods of severe deficiency prior to presenting with clinical disease [1]. In our patient, an ADAMTS13 activity of <0.03 IU/mL with an inhibitor titer of 9.8 Bethesda units reflects high-burden autoantibody-mediated ADAMTS13 deficiency, consistent with this mechanism.

Diagnosis

The diagnosis of iTTP begins with recognition of MAHA and thrombocytopenia. Key laboratory findings include thrombocytopenia with a typical platelet count less than $30 \times 10^9/L$, elevated LDH, elevated indirect bilirubin, elevated reticulocyte count, undetectable haptoglobin, and a negative direct antiglobulin

test. Peripheral blood smear demonstrating schistocytes confirms the microangiopathic process [1]. Coagulation studies are typically normal or only mildly prolonged, and their significant derangement should raise suspicion for an alternative diagnosis such as DIC [1]. Fewer than 10% of patients exhibit the full pentad of TTP manifestations at presentation, and its absence should never delay treatment [1,2].

Because ADAMTS13 testing requires reference laboratory processing with reporting times typically exceeding 72 hours, empirical treatment decisions must be made before results are available [1]. The PLASMIC score, a validated 7-point tool, estimates the likelihood of severe ADAMTS13 deficiency using readily available clinical and laboratory data [3,4]. A systematic review and meta-analysis found that a PLASMIC score of 5 or higher had a pooled sensitivity of 99% and specificity of 57% for severe ADAMTS13 deficiency, and prompt hematologic consultation with consideration of empirical plasma exchange should be obtained for patients meeting this threshold [15]. Scores of 6 or 7 denote high risk for severe ADAMTS13 deficiency and probable iTTP [3,4]. In our patient, a PLASMIC score of 6 prompted empirical initiation of plasma exchange on the day of admission, a decision subsequently validated by ADAMTS13 activity <0.03 IU/mL and an inhibitor titer of 9.8 Bethesda units.

Differential Diagnosis of TMA in CTD Overlap

The differential diagnosis of TMA in a patient with CTD overlap is broad and carries direct therapeutic implications, as the management of each entity differs substantially (Table 2) [5]. Scleroderma renal crisis is a life-threatening complication of SSc characterized by acute kidney injury, accelerated hypertension, and MAHA, strongly associated with anti-RNA polymerase III antibodies, which represent the strongest serological risk factor for SRC [16]. The cornerstone of SRC management is prompt blood pressure control with angiotensin-converting enzyme inhibitors, and plasma exchange is not a primary treatment [16]. Our patient had normal blood pressure and preserved renal function, arguing strongly against SRC; she had also tested negative for anti-RNA polymerase III antibodies on prior serologic evaluation.

Catastrophic antiphospholipid syndrome is defined by the rapid onset of simultaneous thrombosis across multiple organ sites resulting in multi-organ dysfunction, with a mortality rate exceeding 50% [17]. Our patient had no clinical evidence of multi-organ thrombosis, and her antiphospholipid antibody panel was entirely negative, making CAPS highly unlikely. Importantly, anticoagulation, a cornerstone of CAPS management, would be harmful in the setting of severe thrombocytopenia from iTTP, underscoring the importance of accurate diagnosis [17].

Typical HUS, mediated by Shiga toxin-producing organisms such as *Escherichia coli* O157:H7, was excluded by the absence of a preceding diarrheal illness. Complement-mediated TMA, also termed atypical hemolytic uremic syndrome, is driven by dysregulation of the alternative complement pathway and characteristically presents with predominant renal involvement and acute kidney injury [18]. Our patient had preserved renal function throughout her admission, with creatinine remaining below 0.65 mg/dL, arguing against the renal-predominant presentation typical of complement-mediated TMA,

though renal-sparing forms have been described. C3/C4 complement levels were within normal limits, further arguing against complement mediated TMA. Treatment involves complement inhibition with agents such as eculizumab, distinct from the plasma exchange-based approach used in iTTP [18].

Disseminated intravascular coagulation was excluded by normal or only mildly prolonged coagulation studies, preserved fibrinogen, and the absence of an obvious precipitating cause such as sepsis, trauma, or malignancy. Pregnancy-associated TMA and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome were excluded by a negative beta-human chorionic gonadotropin assay. Drug-induced TMA was considered unlikely given that her chronic medications (hydroxychloroquine and colchicine) have weak or no recognized association with TMA and she had reportedly been non-compliant for at least one year prior to presentation.

Table 2. Differential Diagnosis of Thrombotic Microangiopathy Considered in This Patient

Differential diagnosis	Key distinguishing features	Typical management	Findings in our patient arguing against the diagnosis
Scleroderma renal crisis	Acute kidney injury with accelerated hypertension; associated with anti-RNA polymerase III antibodies.	Prompt blood pressure control with ACE inhibitors; plasma exchange is not a primary treatment.	Normal blood pressure and preserved renal function; negative anti-RNA polymerase III antibodies on prior serologic evaluation.
Catastrophic antiphospholipid syndrome (CAPS)	Rapid simultaneous thrombosis across multiple organ sites with multi-organ dysfunction.	Anticoagulation (which would be harmful in the setting of severe thrombocytopenia from iTTP).	No clinical evidence of multi-organ thrombosis; entirely negative antiphospholipid antibody panel.
Typical (Shiga toxin-mediated) HUS	Preceding diarrheal illness caused by Shiga toxin-producing organisms such as <i>Escherichia coli</i> O157:H7; predominant acute kidney injury.	Largely supportive care; plasma exchange is not a primary treatment.	No preceding diarrheal illness; preserved renal function.
Complement-mediated TMA (atypical HUS)	Alternative complement pathway dysregulation; characteristically renal-predominant with acute kidney injury.	Complement inhibition (e.g., eculizumab), distinct from the plasma exchange-based approach in iTTP.	Preserved renal function throughout admission (creatinine below 0.65 mg/dL), arguing against a renal-predominant presentation.
Disseminated intravascular coagulation (DIC)	Consumptive coagulopathy with prolonged coagulation times and low fibrinogen; usually a precipitating cause.	Treatment of the underlying cause and supportive blood product support.	Coagulation studies only minimally deranged with preserved fibrinogen (364 mg/dL); no precipitating cause was identified.
Pregnancy-associated TMA / HELLP syndrome	TMA arising in the context of pregnancy or the peripartum period.	Delivery and supportive care.	Negative beta-human chorionic gonadotropin assay, excluding pregnancy.
Drug-induced TMA	TMA from drug-dependent antibodies or dose-related toxicity of an implicated agent.	Discontinuation of the offending agent and supportive care.	Chronic medications (hydroxychloroquine, colchicine) are not recognized causes of TMA, and the patient had been non-compliant for at least one year before presentation.

Across all competing diagnoses, the finding of severely deficient ADAMTS13 activity was the decisive diagnostic feature. iTTP typically presents with more severe thrombocytopenia and relatively preserved renal function compared to complement-mediated TMA, a pattern exemplified in our patient [1]. Systematic exclusion of competing diagnoses combined with ADAMTS13 confirmation established iTTP as the definitive diagnosis and guided appropriate therapy.

Management

The management of iTTP requires prompt initiation of a combination approach incorporating therapeutic plasma exchange, corticosteroids, caplacizumab, and rituximab [1,6,7].

Therapeutic plasma exchange (TPE) remains the cornerstone of acute iTTP management, working through a dual mechanism of removing circulating anti-ADAMTS13 autoantibodies while simultaneously replenishing ADAMTS13 activity via donor plasma. Current guidelines recommend daily plasma exchange until the platelet count exceeds $150 \times 10^9/L$ for at least two consecutive days, with normalization of LDH supporting the decision to discontinue therapy [6,7]. Plasma exchange has been shown to reduce mortality from more than 90% to 10–20% [1,6,7]. Real-world data support the efficacy of a TPE-free strategy combining caplacizumab with early immunosuppression in selected patients [19], and this approach is being prospectively evaluated in the ongoing phase 3 MAYARI trial (NCT05468320) [20], which may further reshape this paradigm. In our patient, seven sessions of plasma exchange were performed, discontinued after platelet count exceeded $150 \times 10^9/L$ over two consecutive days with concurrent normalization of LDH.

Corticosteroids are administered concurrently with plasma exchange to suppress anti-ADAMTS13 autoantibody production. While no specific regimen is mandated by guidelines, oral prednisone at 1 mg/kg daily is commonly used, with intravenous methylprednisolone recommended for patients with severe neurologic features [1,6]. Our patient received intravenous methylprednisolone followed by oral prednisone, consistent with this approach.

Caplacizumab is a humanized nanobody that blocks the interaction between von Willebrand factor and platelets, preventing microvascular thrombus formation independently of ADAMTS13 activity [1]. The pivotal phase 3 HERCULES trial established its efficacy, demonstrating significantly faster platelet count recovery and reduction in iTTP-related death, recurrence, and major thromboembolic events when added to plasma exchange and immunosuppression, with caplacizumab initiated at the start of plasma exchange and continued for 30 days after the final plasma exchange session [8]. Importantly, caplacizumab does not address the underlying autoantibody burden, meaning iTTP may recur if severe ADAMTS13 deficiency persists after drug cessation, making concurrent rituximab essential [1]. In our patient, caplacizumab was initiated on hospital day 6, after ADAMTS13 results confirmed the diagnosis, rather than at the start of plasma exchange as protocolized in HERCULES, owing to drug authorization and cost considerations; this represents a departure from the guideline-endorsed protocol and underscores the real-world barriers to optimal iTTP care in resource-constrained settings.

Rituximab, an anti-CD20 monoclonal antibody, depletes autoreactive B lymphocytes and reduces anti-ADAMTS13 autoantibody production, facilitating durable ADAMTS13 recovery [1]. The 2020 International Society on Thrombosis and Haemostasis (ISTH) guidelines, reaffirmed in the 2025 focused update, conditionally suggest the addition of rituximab to plasma exchange and corticosteroids in patients with acute iTTP, with particular support for its use in patients with comorbid autoimmune disease [6,7]. Prior to initiation, hepatitis B virus screening is mandatory given the risk of reactivation [1]. Our patient received rituximab 375 mg/m² weekly for four planned doses at discharge, following a negative QuantiFERON-tuberculosis result and hepatitis B vaccination.

Monitoring and Relapse Prevention

Following recovery from an acute iTTP episode, long-term monitoring is essential given the risk of relapse, which occurs in approximately 30% to 40% of patients at five-year follow-up [1]. The 2021 International Working Group consensus distinguishes clinical remission, defined as sustained clinical response with cessation of any anti-VWF therapy and ADAMTS13 immunomodulatory treatment for at least 30 days, or attainment of partial or complete ADAMTS13 remission, whichever occurs first, from ADAMTS13 remission, which is further subdivided into partial ADAMTS13 remission (ADAMTS13 activity 20% to less than 50% of normal) and complete ADAMTS13 remission (ADAMTS13 activity at least 50% of normal) [21]. Patients who achieve clinical remission without ADAMTS13 remission remain at increased risk of relapse and require close monitoring [21]. During remission, expert consensus recommends periodic monitoring of complete blood count, LDH, and ADAMTS13 activity, with ADAMTS13 measured monthly during the first year and every 3 to 6 months thereafter [1]. A decline in ADAMTS13 activity below 20% during remission, termed ADAMTS13 relapse, should prompt preemptive rituximab to reduce the risk of clinical relapse [6,21]. Caplacizumab discontinuation while ADAMTS13 activity remains severely deficient has been associated with rebound iTTP, an important consideration in patients discharged with ongoing ADAMTS13 deficiency [1,7]. Our patient was discharged without having achieved ADAMTS13 remission, with persistently undetectable ADAMTS13 activity and a detectable inhibitor, placing her at high risk of relapse. Rituximab was initiated at discharge, caplacizumab continued as a bridge until ADAMTS13 recovery, and close outpatient follow-up was arranged. On most recent outpatient follow-up, approximately one month after the index admission, ADAMTS13 activity had risen to 0.68 IU/mL consistent with complete ADAMTS13 remission, and the inhibitor titer had decreased to 0.6 Bethesda units, indicating a favorable response to immunomodulatory therapy.

Conclusion

We present a rare case of confirmed iTTP, evidenced by severely deficient ADAMTS13 activity and a high-titer inhibitor, complicating SSc-SLE overlap syndrome. The diagnostic evaluation of TMA in CTD overlap demands a systematic approach, as competing diagnoses including scleroderma renal crisis and catastrophic antiphospholipid syndrome carry distinct and sometimes conflicting therapeutic implications. ADAMTS13 activity less than 10% with a detectable inhibitor is the diagnostic cornerstone of iTTP and should be sought in all CTD patients presenting with TMA. The PLASMIC score reliably

identifies patients warranting empirical plasma exchange while ADAMTS13 confirmation is pending. Prompt recognition, multidisciplinary care coordinated across hematology, rheumatology, nephrology, and apheresis services, systematic diagnostic exclusion of competing TMAs, and guideline-concordant combination therapy are essential to achieving favorable outcomes in this rare and diagnostically challenging presentation.

Declarations

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Conflicts of interest/Competing interests: The authors declare that they have no competing interests.

Ethics approval: Ethical approval was not required for this case report in accordance with the policies of the Institutional Review Board of Jefferson Einstein Philadelphia Hospital, as it describes the routine clinical care of a single patient with no experimental intervention. All procedures described were part of routine clinical care and were performed in accordance with the ethical standards of the institution and with the 1964 Declaration of Helsinki and its later amendments.

Consent to participate: Written informed consent to participate was obtained from the patient described in this report.

Written Consent for publication: Written informed consent for publication of this case report and any accompanying clinical data was obtained from the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and material: All data supporting the findings of this case report are included within the article. No datasets were generated or analysed.

Code availability: Not applicable.

Authors' contributions: A.A. and A.T. were both involved in the clinical care of the patient. A.A. conducted the literature review and drafted the manuscript. A.T. supervised the patient's care, and A.T. and J.L. provided mentorship and critically revised the manuscript for important intellectual content. T.B., L.S., and A.H. contributed to the literature review and critical revision of the manuscript. All authors read and approved the final manuscript.

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