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CASE REPORT

Lupus-associated thrombotic thrombocytopenic purpura-like microangiopathy

Daniel Blum, Geoffrey Blake

Daniel Blum, Geoffrey Blake, Department of Hematology, McGill University Health Center, Montreal, Quebec H3G1A4, Canada

Daniel Blum, Department of Internal Medicine (G-050), Jewish General Hospital, Montreal, Quebec H3T1E2, Canada

Author contributions: Blum D performed the chart review of the case being described, searched, reviewed and critically appraised the literature for cases of thrombotic microangiopathy in patients with lupus; Blake G was involved in making the presumptive diagnosis of the TTP-like syndrome in the patient with lupus described in this case report, and in initiating the management of this rare complication of lupus; Blake G also reviewed and amended this case report manuscript prior to its submission.

Institutional review board statement: Not applicable; this report describes the clinical course of a patient under the care of the general medicine team at the Montreal General Hospital.

Informed consent statement: Explicit written informed consent was obtained from the patient described in this case prior to submitting this case report. A copy of the consent form signed by this patient can be provided upon request.

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Correspondence to: Daniel Blum, MDCM, Department of Internal Medicine (G-050), Jewish General Hospital, 3755 Cote Saint Catherine, Montreal, Quebec H3T1E2, Canada. daniel.blum@mail.mcgill.ca
Telephone: +1-514-7582586

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Abstract

Recently reported cases of lupus complicated by a thrombotic thrombocytopenic purpura (TTP)-like syndrome suggest a survival benefit to early treatment with plasma exchange. The following is a report of the eighth such case in the last ten years. A 44-year-old lady known for lupus presented with the nephrotic syndrome and a renal biopsy was consistent with class 4G lupus nephritis. She was given high-dose steroids and cytotoxic therapy, but her induction therapy was complicated by the classic pentad of TTP. She was subsequently treated with another course of high-dose steroids, a different cytotoxic agent, and plasma exchange, with clinical resolution shortly thereafter. Similar to seven recently reported cases of microangiopathy in lupus, this lady's TTP-like syndrome improved dramatically after initiation of plasma exchange, despite not having a severely deficient ADAMTS13. This has implications on both current clinical practice and on the pathogenesis of TTP-like syndromes in lupus.

Key words: Microangiopathic hemolytic anemia; Microangiopathy; Thrombotic thrombocytopenic purpura; Atypical hemolytic-uremic syndrome; Hemolytic uremic syndrome; Systemic lupus erythematosus associated thrombotic thrombocytopenic purpura-like microangiopathic hemolytic anemia; Lupus nephritis; Lupus; Plasma exchange

Core tip: In patients with lupus who develop thrombotic microangiopathy, early initiation of plasma exchange appears to carry a survival benefit - even in those patients whose ADAMTS13 activity levels are not severely deficient. This improved survival has become apparent in the last ten years during which time seven cases of thrombotic microangiopathy complicating lupus and treated with plasma exchange have been reported. The present article describes the eighth such case, reviews the previously described cases and outcomes of microangiopathy in lupus, and hypothesizes as to why plasma exchange appears to be beneficial in this subset of patients with atypical haemolytic uremic syndrome.

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INTRODUCTION

Microangiopathic hemolytic anemia (MAHA) is caused by a number of conditions, several of which are fatal. One such condition is thrombotic thrombocytopenic purpura (TTP), which has been reported to be less responsive to therapy in patients with lupus as compared to the general population[1]. Recent research has revealed a subset of patients with lupus who have a TTP-like syndrome distinct from TTP[2]. We report a case of a patient with lupus and a TTP-like syndrome who received early plasma exchange and survived. A review of this under-recognized clinical entity follows.

CASE REPORT

A 44-year-old lady with a five-year history of systemic lupus erythematosus (SLE) on hydroxychloroquine presented to the Montreal General Hospital with edema, nausea, and vomiting in January 2014. On exam she was noted to have anasarca and hypertension. She was found to have a creatinine of 335 μmol/L and a urea of 54 mmol/L (normal 2-10 mmol/L). Her serum albumin was low and her urine tested positive for protein. Her urine sediment revealed white cell casts, red cells, and oval fat bodies. She was diagnosed with new-onset nephrotic syndrome. Further workup was consistent with a lupus flare with an anti-dsDNA > 800 (negative < 20), and excluded alternative causes such as ANCA-related vasculitides, hepatitis C, and human immunodeficiency virus. She had a renal biopsy which was consistent with lupus nephritis class Ⅳ-G with a predominance of active lesions and 75% cellular crescents; there was no thrombotic microangiopathy.

She was treated with a 3-d pulse of higher dose steroids followed by daily steroid doses equivalent to 1 mg/kg of prednisone. She was started on mycophenolate. Her in-hospital course was marked by persistent vomiting requiring prolonged admission.

Ten days after presentation she was noted to have a falling platelet number and falling hemoglobin. Twelve days after presentation, her hemoglobin fell to a nadir of 39 g/L (from 83 g/L on presentation) (normal 120-150 g/L), requiring transfusion of 2 units of pRBC, and her platelets fell to a nadir of 70 × 10^9/L (from 330 × 10^9/L on presentation) (normal 150-450 × 10^9/L). Her white count was normal. She had no evidence of bleeding, fibrinogen of 5.2 g/L (normal > 1.5 g/L), and normal PT, aPTT. She did not have anti-cardiolipin antibodies. Her reticulocytes were 48. Her Coombs test was weakly positive for IgG. Her LDH was slightly elevated at 246 U/L (normal < 220 U/L), her total bilirubin was 12.5 mmol/L (normal < 20 μmol/L), her haptoglobin was decreased at 0.66 g/L, and several blood smears consistently showed a 10%-15% fragmentation index (normal < 0.5%) in addition to rouleaux formation. There was no bloody diarrhea. Her creatinine was higher than it was at presentation, peaking at 417 mmol/L on the same day as the hemoglobin nadir. Shortly thereafter she became acutely hypoxemic from volume overload refractory to diuretics, and required ultrafiltration. She then became drowsy, and neurological exam was significant for increased reflexes bilaterally.

TTP could not be excluded; therefore she was treated with five days of plasma exchange with fresh frozen plasma (FFP), followed by plasma exchange every second day. She was given a second course of pulse steroids, cyclophosphamide was started, and mycophenolate was stopped. She was also given a dose of intravenous iron sucrose and was started on erythropoietin given the inappropriately normal reticulocyte count.

Following a course of eight plasma exchanges, her platelet count recovered completely to > 200 × 10^9/L, her fragmentation index decreased to below 1%, and her hemoglobin stabilized around 75 g/L. Her cell counts stabilized off of plasma exchange. She remains on prednisone and cyclophosphamide. She now responds to diuresis, and her markers of active inflammation have all reduced. Her anti-dsDNA was 50 in February 2014. Ultimately her ADAMTS13 activity, which was measured prior to initiation of plasma exchange, returned at 49%. This level is only slightly below the lower limit of 56% and therefore both excludes the diagnosis of TTP and is consistent with the diagnosis of an SLE-associated TTP-like MAHA.

DISCUSSION

MAHAs are characterized by intravascular hemolysis. The usual laboratory findings are normocytic anemia, thrombocytopenia, elevated LDH, reduced haptoglobin, and elevated unconjugated bilirubin. The peripheral

Table 1 Differential diagnosis of microangiopathic hemolytic anemia

Disseminated intravascular coagulation
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome
Atypical hemolytic-uremic syndrome
[1]TTP-like MAHA, an aHUS presenting as part of a connective tissue disease
[1]Anti-phospholipid syndrome
Hemolysis with elevated liver enzymes and low platelets of pregnancy
[1]Malignant hypertension
Medications
Malignancy
Mechanical cardiac valves or other foreign bodies in the circulatory system

[1]Indicates conditions at which patients with lupus are at higher risk compared to the general population. TTP: Thrombotic thrombocytopenic purpura; aHUS: Atypical hemolytic-uremic syndrome.

blood smear classically shows schistocytes, or fragmented red cells, which are required to make the diagnosis. The differential diagnosis of MAHA is limited to only a few conditions (Table 1). Patients with lupus are at particular risk for acquiring the anti-phospholipid syndrome, malignant hypertension, and SLE-associated TTP-like MAHA. As its name suggests, SLE-associated TTP-like MAHA is a condition manifested by otherwise unexplained MAHA in a patient meeting the American College of Rheumatology (ACR) criteria for systemic lupus; this condition may be associated with the other classic findings of TTP including acute renal failure, fever, and neurological deterioration, but is not associated with a severe reduction in ADAMTS13 activity, nor is it associated with diarrhea. TTP itself is defined by a MAHA where the activity level of ADAMTS13 is severely deficient. TTP-like MAHAs that occur simultaneously with connective tissue diseases are rare but clinically relevant illnesses that are becoming increasingly recognized as a distinct subgroup of atypical hemolytic uremic syndrome.

Over the last 60 years there have been 127 reported cases of MAHA resembling TTP occurring in patients with SLE. A 2003 review of the English literature from 1968 to 2002 had identified 56 such cases and had suggested that TTP in patients with SLE was associated with a higher mortality than idiopathic TTP, even with optimal treatment[1]. However, the vast majority of the patients in that review were treated prior to the advent of plasma exchange as the optimal therapy for TTP; instead these patients were generally treated with multiple modalities including plasmapheresis without exchange.

In the last ten years, there have been seven additional reported cases of purported TTP occurring in patients meeting the ACR criteria for SLE. Six of these patients were treated with plasma exchange in a timely manner, with or without steroids or cytotoxic therapy, and survived[3,4]. One patient did not receive plasma exchange promptly upon diagnosis and died in hospital[5].

A retrospective study from Japan in 2009 that reviewed a university hospital database for cases of thrombotic microangiopathy occurring in patients with connective tissue disease identified an additional sixty-four patients with thrombotic microangiopathy and SLE. Forty-five of these sixty-four patients received plasma exchange, with or without steroid therapy. Eighteen of the sixty-four died, although the reported data did not clearly address if there was a higher risk of death in patients who were not treated with plasma exchange[2].

Including the case reported here, there are now at least eight cases over the last ten years that suggest that early initiation of plasma exchange, with or without additional therapy, has the potential to be curative for TTP-like MAHA in patients with SLE.

Interestingly, the aforementioned Japanese study found that more than three quarters of the cases of thrombotic microangiopathy occurring in SLE were associated with normal or near normal ADAMTS13 activity. This suggests a different pathogenetic mechanism than that which occurs in idiopathic TTP[2,6], which is classically associated with a severely reduced ADAMTS13 activity. There is no consensus on the mechanism of TTP-like MAHA in lupus patients, but there are several hypotheses that are being investigated. These hypotheses implicate abnormal endothelial activation, elevated d-Dimers, ADAMTS13-resistant von Willebrand Factor, and defects in regulation of the complement system as culprits in causing the illness[6]. We did not measure a d-Dimer in our patient. She did have low C3 and C4 levels, 0.56 and 0.11 respectively, but these are expected given her active lupus. Investigations for mutations in genes encoding complement regulators were not sent. The other hypotheses mentioned could not be tested or confirmed easily in the clinical setting.

Returning to the 2003 review of 56 cases of TTP-like MAHA, an important observation is that plasma exchange appears to be associated with better outcomes than plasmapheresis without FFP infusion in lupus patients with a TTP-like syndrome. This implies that there may be a property of FFP that contributes to the reversal of the underlying pathogenetic process.

COMMENTS

Case characteristics

This 44-year-old lady known for lupus presented with the nephrotic syndrome, was found to have lupus nephritis, and her course of induction therapy was complicated by microangiopathic hemolytic anemia (MAHA), fever, rising creatinine with volume overload, and altered mental status.

Clinical diagnosis

The constellation of finings was suggestive of thrombotic thrombocytopenic purpura (TTP) complicating lupus nephritis.

Differential diagnosis

Atypical hemolytic-uremic syndrome (including a TTP-like syndrome occurring

in the context of a connective tissue disease), disseminated intravascular coagulation, antiphospholipid syndrome.

Laboratory diagnosis

In the context of intravascular hemolysis with schistocytes, rising creatinine, normal coagulation parameters, the absence of antiphospholipids, and an ADAMTS13 level that was not severely deficient, the most likely diagnosis is a TTP-like syndrome occurring in the context of lupus.

Imaging diagnosis

Chest radiography revealed pulmonary edema.

Pathological diagnosis

Histologic examination of the renal biopsy done on presentation revealed class 4G lupus nephritis without evidence of thrombotic microangiopathy; there was no repeat biopsy when she developed the constellation of features described above ten days after her induction therapy. Review of blood films taken after she developed the TTP-like clinical syndrome revealed elevated schistocytes.

Treatment

This lady was initially treated with a pulse of intravenous solumedrol and mycophenolate mofetil (MMF) for induction therapy for class 4 lupus nephritis; when she developed the constellation of features described above ten days later, she was given a second course of pulse IV solumedrol, cyclophosphamide instead of MMF, and plasma exchange.

Related reports

There have been over 50 reported cases of TTP-like syndromes occurring in patients with lupus in the literature, but only 7 such cases have been reported in the last ten years during which time plasma exchange has been the standard of care. Taking the most recent 7 cases as a case series, 6 were treated early with plasma exchange and survived while 1 did not receive plasma exchange early and died. Additionally, retrospective data from Japan has identified a subset of patients with microangiopathy complicating lupus who have near-normal ADAMTS13 levels. The implication is that in these patients, plasma exchange may have a survival benefit even in the absence of a severely deficient ADAMTS13, as suggested by the outcomes of the most recent case series.

Term explanation

MAHA: Characterized by elevated LDH, total bilirubin, decreased haptoglobin, and fragmented cells and schistocytes on blood film; TTP: A thrombotic microangiopathy manifested by fever, acute kidney injury, altered mental status, and intravascular hemolysis. Characterized by a severely deficient ADAMTS13 activity level; Atypical hemolytic-uremic syndrome (HUS): A thrombotic microangiopathy variably associated with acute kidney injury and intravascular hemolysis but with ADAMTS13 activity levels above the severely deficient range. It is often, but not always, associated with gene defects involving inhibitors of the alternative complement cascade; Lupus related TTP-like MAHA: A thrombotic microangiopathy syndrome similar to TTP but with near-normal ADAMTS13 activity; it is a subset of atypical HUS that occurs in patients with lupus and its etiology is unknown.

Experiences and lessons

TTP-like syndromes may complicate the course of active lupus and appear to respond favorably to treatments involving early plasma exchange despite being characterized by near-normal ADAMTS13 activity levels.

Peer-review

This is a very interesting clinical case of a rare complication of patients with LES.

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