Thrombotic Microangiopathy: Always a Challenging Diagnosis

Javier Marco-Hernández MD PhD[1], Sergio Prieto-González MD[2], Miquel Blasco MD[3], Pedro Castro MD PhD[4], Joan Cid MD PhD[5] and Gerard Espinosa MD PhD[2]

Departments of [1]Internal Medicine and [2]Autoimmune Diseases, [3]Nephrology and Kidney Transplant Unit, [4]Medical Intensive Care Unit, and [5]Hemostasis and Hemotherapy Unit, Hospital Clínic, Barcelona, Catalonia, Spain

KEY WORDS: thrombotic microangiopathy (TMA), systemic lupus erythematosus (SLE), antiphospholipid syndrome, atypical hemolytic uremic syndrome, eculizumab

IMAJ 2016; 18: 437–438

Thrombotic microangiopathy (TMA) is a histological lesion suspected in the presence of clinical and pathological features such as intravascular non-immunologic hemolytic anemia, thrombocytopenia, vascular damage, and organ injury. The vascular involvement comprises arteriolar and capillary thrombosis with distinctive abnormalities in the endothelium and vessel wall [1]. Its pathophysiology still remains misunderstood and its etiology covers a wide and disparate group of entities that overlap each other [2]. Classification includes hereditary causes on the one hand, and acquired triggering entities such as neoplastic, infective, and autoimmune disorders on the other [1].

The present case exemplifies the diagnostic challenge of a patient with TMA without a definitive etiology despite a complete diagnostic approach, stressing the need for further work to better understand this serious disorder.

PATIENT DESCRIPTION

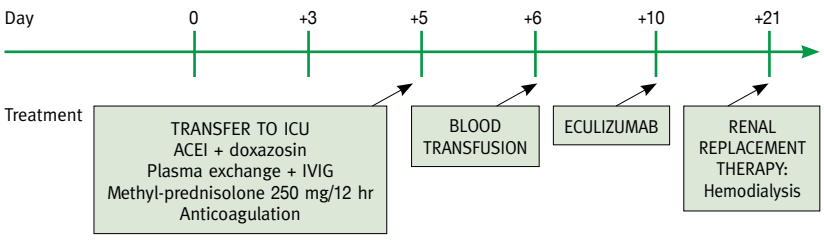
A 56 year old woman presented with a 1 month history of malaise, asthenia, nausea, vomiting and weight loss, which had begun after a mild upper respiratory tract infection treated with azithromycin for 3 days. Her past medical history included systemic lupus erythematosus (SLE) diagnosed after her first pregnancy at the age of 35 years, when she experienced cutaneous and articular manifestations, photosensitivity and Raynaud's phenomenon. Neither abortion nor thrombotic events had been reported. At that time, the immunological tests revealed only antinuclear antibodies (ANA) and a positive direct Coombs test, with no anti-double-stranded DNA (anti-dsDNA) antibodies or hypocomplementemia. At the time of our evaluation, her treatment comprised methylprednisolone 4 mg daily and omeprazole.

Physical examination revealed blood pressure of 140/100 mmHg, with no skin or joint symptoms. The blood test results are summarized in Figure 1. At the time of admission the patient had mild anemia (115 g/L) and slight decrease in estimated glomerular filtration rate (eGFR) (58 ml/min), as well as undetectable haptoglobin levels and elevation of lactate dehydrogenase (LDH). A mild deficit in cyanocobalamin was also detected (194 pg/ml), which was replenished by daily intramuscular injections. Moreover, the urinary sediment showed albuminuria with no hematuria.

Three days later [Figure 1], laboratory tests showed a significant worsening of the anemia (Hb 98 g/L) and renal function (creatinine 1.82 mg/dl, eGFR 30 ml/min), along with thrombocytopenia (100 x10^9/L). A direct Coombs test was negative and no schistocytes were observed in two different blood smears. The immunological study showed ANA (homogeneous pattern) and anti-Ro/anti-La antibodies, with no hypocomplementemia, anti-dsDNA, anti-Sm or antiphospholipid antibodies. The 24 hr proteinuria was 1600 mg with

Figure 1. Laboratory features and treatment

Hemoglobin (g/L)	115	98	68	70	94	81
Platelets (10^9/L)	145	100	100	119	212	159
Creatinine (mg/dl)	1.08	1.82	2.42	2.64	3.15	7.15
eGFR (ml/min)	58	30	20	20	15	5
LDH (U/L)	648	880	–	478	–	695



ACEI = angiotensin-converting enzyme inhibitor, eFGR = estimated glomerular filtration rate, ICU = intensive care unit, LDH = lactate dehydrogenase

inactive sediment. Tumor markers and serologies for hepatitis B, hepatitis C, human immunodeficiency virus (HIV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were negative. A renal biopsy was performed showing the presence of thrombotic microangiopathy lesions in glomeruli and arterioles.

Five days after admission, she presented with neurologic impairment consisting of confusion, amnesia and dysarthria with arterial hypertension (200/100 mmHg), and worsening of the anemia (68 g/L) and renal function (creatinine 2.42 mg/dl, eGFR 20 ml/min). Urgent brain computed tomography scan and magnetic resonance imaging revealed scattered foci of alteration of the signal in subcortical white matter in both cerebral hemispheres. She was transferred to the intensive care unit where plasma exchange (PE), intravenous immunoglobulin (IVIG) (200 mg/kg weight, one dose every two exchanges), IV methylprednisolone (250 mg/12 hours for 3 days), antihypertensive treatment with captopril and doxazosin, and heparin at full anticoagulation dose were started.

A comprehensive study to rule out disorders related to TMA was performed. The activity of disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS-13) was 46%; activity < 10% typically confirms the diagnosis of thrombotic thrombocytopenic purpura (TTP). No ADAMTS-13 antibodies were detected. Stool and urine samples to detect Shiga toxin and a pneumococcal antigen, respectively, were negative. Additional immunological tests showed no anti-Scl70, anti-centromere or anti-RNA polymerase III antibodies. A normal body CT scan and a digestive endoscopy ruled out malignancy, and a Doppler ultrasound showed absence of renal artery stenosis.

Despite the above mentioned treatment, no improvement in laboratory parameters was observed after 5 days under PE+IVIG. The diagnosis of complement-mediated TMA (also called atypical hemolytic-uremic syndrome) was assumed and eculizumab (900 mg/week for 4 weeks and 1200 mg every 14 days for maintenance therapy) was started. After that, hematologic and neurologic remissions were achieved but renal replacement therapy was required. The patient was discharged 45 days after admission, with eculizumab, anticoagulation, glucocorticoid tapering dose and a hemodialysis program.

Three weeks later the patient presented to the emergency room due to heart failure. An echocardiography showed a severe diffuse hypokinesia with a 25% left ventricular ejection fraction. No hemolysis findings or serological markers of SLE disease activity were detected in the blood tests. An endomyocardic biopsy was then performed, showing a lymphocyte inflammatory infiltrate without histological evidence of TMA.

In view of this new event, treatment with eculizumab was withdrawn, and PE, IVIG and glucocorticoid pulses were initiated, along with rituximab (two doses of 1 g every 14 days). This led to an excellent outcome, with a new echocardiography showing a normal left ventricular ejection fraction. After 10 months of follow-up, the patient remains in good condition on treatment with anticoagulation, low dose prednisone, and mycophenolic acid, as well as renal replacement therapy with hemodialysis. She is currently waiting for a kidney transplant.

COMMENT

The present case illustrates how difficult it is to find the underlying cause when a TMA syndrome is detected, especially in a patient with an autoimmune background. Initially, a complement-mediated TMA was assumed after ruling out all the alternate etiologies [3]: TTP, Shiga toxin-mediated hemolytic-uremic syndrome, known infections reported as triggers for TMA syndrome (HIV, CMV, pneumococci), metabolism-mediated TMA (cyanocobalamin deficiency has been reported as responsible for TMA, but its replenishment did not resolve the syndrome), drug-mediated TMA (there are no published cases of patients taking the drugs that our patient took), cancer, malignant hypertension (rapid and easy control of high blood pressure was achieved with oral antihypertensive treatment), and well-defined activity or immunologic markers of autoimmune disorders known to be associated with TMA (SLE, antiphospholipid syndrome or systemic sclerosis) [1,4].

Complement-mediated TMA occurs due to a deficient regulation of complement activation through the alternative complement pathway. It has been reported that about 60% of cases identified as atypical hemolytic-uremic syndrome are due to mutations of genes in the complement system [5]. Genetic and molecular studies attempting to identify alternative complement pathway protein mutations, risk polymorphisms or anti-H factor antibodies were undertaken in our patient when this etiology was suspected, but all were finally shown to be negative. Moreover, the patient developed a new severe manifestation despite the treatment with eculizumab, supporting the novel hypothesis of another underlying condition playing a role.

Taking into account her previous autoimmune background, a different therapeutic approach with rituximab was considered, followed by a promising outcome but still without a well-defined diagnosis. It remains unclear whether kidney transplant would be a suitable intervention in this patient, since we cannot predict the risk of recurrence of the underlying unidentified disease.

Correspondence
Dr. G. Espinosa
Dept. of Autoimmune Diseases, Hospital Clínic, Barcelona, Catalonia, Spain
email: gespino@clinic.cat

References

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014; 371 (7): 654-66.
2. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia* 2015; 35 (5): 421-47.
3. Zuber J, Fakhouri F, Roumenina LT, Loirat C, Frémeaux-Bacchi V. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. *Nat Rev Nephrol* 2012; 8 (11): 643-57.
4. Rodríguez-Pintó I, Espinosa G, Cervera R. Catastrophic APS in the context of other thrombotic microangiopathies. *Curr Rheumatol Rep* 2015; 17 (1): 1-10.
5. Nester CM, Barbour T, de Cordoba SR, et al. Atypical aHUS: state of the art. *Mol Immunol* 2015; 67 (1): 31-42.