Clinical Case Reports International

Case Report
Published: 08 Apr, 2022

Repeated Episodes of Thrombotic Microangiopathy Associated with ADAMTS13 Deficiency in a Patient with Systemic Lupus Erythematosus

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Introduction

Thrombotic microangiopathy is a manifestation in several conditions including typical and atypical hemolytic and uremic syndrome, thrombocytopenic purpura (congenital and idiopathic associated with ADAMTS13 deficiency or non-idiopathic), malignant hypertension, disseminated intravascular hypertension, HELLP syndrome, scleroderma renal crisis.

Hematologic manifestations in Systemic Lupus Erythematosus (SLE) may be similar to those in hemolytic anemia and thrombocytopenia, features shared with thrombotic microangiopathy.

Case Presentation

The patient was diagnosed in 2009, at the age of 26, with dermatomyositis for which she received various treatment regimens: Plaquenil, Imuran for 1 year, then Methotrexate for 2 years. The treatment was interrupted due to the lack of clinical efficacy, the patient developing drug intolerance.

In 2012, following the occurrence of hematological manifestations of moderate leukopenia and thrombocytopenia, the diagnosis of dermatomyositis was refuted, and according to ACR criteria a diagnosis of SLE was made and treatment with cyclosporine was initiated.

After about one year (May 2013), the detection of pathological urine constituents (the glomerular type with normal renal function) and thrombotic microangiopathy (hemolytic anemia and thrombocytopenia) confirms the presence of lupus activity. The biological picture becomes relevant in accordance with the clinical manifestations: Hemoglobin (Hb) - 9.4, Hematocrit (Ht) - 27.3, Platelets (P) - 10,000/mmc; Protein/Creatinine ratio (Pr/Cr) - 1.24; C3-46, ANA dsDNA-111, Ac5 ACL-11.7 and Ac5 Sm-102. Treatment with Methylprednisolone (MPD - 1 g × 3 pulses) was initiated, followed by oral Prednisone (PDN) 0.5 mg/kg bw, followed by Cyclosporine regimen.

In April 2014, the worsening of proteinuria (Pr/Cr ratio =2.84 g/24 h, C3 hypocomplementemia - 64, dsDNA antibodies/anti-double stranded DNA (anti-dsDNA) antibodies- 72.8 IU) in the presence of manifestations of thrombotic microangiopathy (hemolytic anemia: Hb -10.3, Ht - 30.7 and severe thrombocytopenia: 11,000), LDH -1087, and Sledai Score 29 confirm a new lupus flare-up. Histopathological diagnosis of kidney puncture biopsy was membranoproliferative glomerulonephritis (corresponding to WHO class IV lupus nephritis). Cyclosporine treatment was discontinued and treatment with Cyclophosphamide was initiated according to the NIH protocol in combination with MPD 1 g × 3 pulse and continued oral administration of PDN 0.5 mg/kg bw.

In July 2014, the patient had a third episode of thrombotic microangiopathy. The decision was taken to shift from NIH regimen to EURO-LUPUS Trial regimen.

In November 2014, a fourth episode of thrombotic microangiopathy was recorded with biologically relevant data: Hb -13.2, Ht - 42.9, P - 354,000, ANA dsDNA - 135.2. Given the repeated episodes of thrombotic microangiopathy while the patient was on various high-dose immunosuppressive therapeutic regimens, other causes responsible for the relapse of the microangiopathic syndrome had been considered. By exclusion of the causes frequently incriminated in this pathology the determination of ADAMTS13 was determined, the results revealing a deficiency in the activity of this factor. The patient continued treatment with MPD and therapy with Mycophenolate mofetil was initiated. The disease course was favorable with no relapse episodes recorded.

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Received Date: *08 Mar 2022*
Accepted Date: *04 Apr 2022*
Published Date: *08 Apr 2022*

Citation:
Azoicai T, Volovat C, Covic A, Azoicai D, Caruntu ID. Repeated Episodes of Thrombotic Microangiopathy Associated with ADAMTS13 Deficiency in a Patient with Systemic Lupus Erythematosus. Clin Case Rep Int. 2022; 6: 1308.

The definitive diagnosis was SLE and thrombotic microangiopathy due to ADAMTS13 deficiency.

Discussion

Thrombotic Microangiopathy (TMA) is a rare condition (3.7 cases per 1 million patients) characterized pathophysiologically by an injury to the vascular endothelium of small vessels (most often of autoimmune origin) followed by a microvascular thrombosis, consumption thrombocytopenia, and microangiopathic hemolytic anemia, as well as neurological manifestations (through the mechanism of cerebral microthrombosis) eventually leading to ischemia and infarction in the affected organ [1].

Etiologically, TMA is divided into:

- TMA due to genetic defects [2]
- Acquired TMA (Thrombotic Thrombocytopenic Purpura (TTP) due to ADAMTS13 deficiency, shiga-like toxin-mediated or *Streptococcus pneumoniae*-associated hemolytic and uremic syndrome, malignant hypertension, drug-induced TMA - by overdose or intolerance to active substances, complement-mediated TMA) [2-4].

ADAMTS13 is a protease responsible for the cleavage of von Willebrand factor multimers and for their adhesion to the vascular endothelium. In cases of ADAMTS13 deficiency, von Willebrand factor multimers accumulate (through clearance deficiency) causing platelet adhesion with microthrombosis in small vessels [5-7].

TTP due to ADAMTS13 deficiency can be acquired (mediated by antibodies directed against ADAMTS13 activity) or hereditary (Upshaw-Schulman syndrome - homozygous and heterozygous mutation of the gene encoding ADAMTS13 on chromosome 9q34) [8,9]. The classic manifestations are the presence of microangiopathic hemolytic anemia, severe consumption thrombocytopenia, and kidney damage- presence of nitrogen retention, proteinuria and/or hematuria, various neurological manifestations, and fever [10].

The diagnosis is made based on clinical data (skin pallor with scleral subicterus, fever, rash, neurological manifestations - headache, convulsions, obnubilation, coma) and laboratory data (presence of microangiopathic hemolytic anemia, severe thrombocytopenia, nitrogen retention, proteinuria, determination of ADAMTS13 activity can range between <5% and 10% [11,12].

TTP by ADAMTS13 deficiency is a severe form of thrombotic microangiopathy with increased mortality that requires prompt, effective and rapid therapeutic intervention [8,9].

The treatment of choice is plasmapheresis and high-dose corticosteroid therapy (pulse therapy) [12]. Used soon after diagnosis, it can ensure improved survival.

Patients with autoimmune TTP may also benefit from immunosuppressive medication. Immunosuppressant's such as cyclophosphamide, cyclosporine, vincristine, mycophenolate mofetil have been used with inconsistent results [13]. Administration of an anti-CD20 monoclonal antibody (Rituximab) has shown promising results in some studies, but the follow-up period was short (1 year) [13,14].

Eculizumab, a C5-blocking monoclonal antibody recommended as "first-line therapy" for atypical hemolytic and uremic syndrome has been used successfully to treat plasmapheresis-refractory TTP due to ADAMTS13 deficiency [15-22].

Given its autoimmune characteristics, SLE can affect many organs and systems during disease activity [23]. TMA may be a rare form of lupus in the hematopoietic system [23]. The difference between a lupus-related hematological disorder and pure TTP is difficult in some situations (especially when it precedes the diagnosis of SLE).

In SLE patients, TMA is caused by the presence of antiphospholipid syndrome or a mechanism of lupus vasculitis, while the mechanism of pure TTP is different. The association of SLE with pure TTP is extremely rare and inconsistently reported in the literature.

The two clinical entities need to be diagnosed and differentiated rapidly because any delay in initiating the treatment of choice (plasmapheresis) can have a major impact on mortality [24]. ADAMTS13 determination is required in cases of suspected TTP in a patient previously diagnosed with SLE, but not mandatory. Demonstration of ADAMTS13 deficiency in the presence of classical TTP phenomena confirms the diagnosis, but is not essential. The reasoning behind this is that other microangiopathic hemolytic anemia accompanied by thrombocytopenia may have low ADAMTS13 activity but are not diagnosed as TTP (bacterial endocarditis, malignancies, and systemic inflammatory diseases). The sensitivity and specificity of the ADAMTS13 determination is 95% [25].

In a 2015 study of a group of 50 lupus patients who experienced various thrombotic events, low ADAMTS13 activity and increased circulating levels of VW factor monomers (66% ± 27% *vs.* 101% ± 8%, P<0.01 , and 325% ± 151% *vs.* 81% ± 14%, P<0.001) were recorded. Low ADAMTS13 activity and the presence of a PL were recorded in patients with active disease. The authors concluded that ADAMTS13 activity could be a useful predictive biomarker for screening patients with active disease and risk of thrombosis [26].

In our patient, lupus renal involvement, WHO class IV nephritis was confirmed by Renal Puncture Biopsy (RPB).

Conclusion

The peculiarity of this case is represented by the repeated episodes of thrombotic microangiopathy accompanied by moderate nephritic-type relapses identified during SLE activity.

The therapeutic response to immunosuppressant's after various treatment regimens (cyclophosphamide/corticosteroids according to 2 protocols - NIH and EURO-LUPUS, administration of fresh frozen plasma without plasmapheresis) but with frequent TMA relapses, led us to investigate other causes of TMA. Thus, low ADAMTS13 activity corroborated with clinical and laboratory findings, confirmed the diagnosis of TTP.

Another peculiarity of this case was the absence of neurological phenomena during TMA relapses (except for headache), thus raising the suspicion of TTP being delayed.

After a definitive diagnosis was made and the therapeutic regimen was changed (introduction of mycophenolate mofetil) the patient had not experienced any TTP episode (follow-up period 2 years). In the literature there are few reported cases in which patients diagnosed with TTP associated with ADAMTS13 deficiency have benefited from treatment with MMF/steroids/plasmapheresis, with complete remission of TTP and no relapses. This would be a promising therapeutic alternative that requires further study in patients with

TTP refractory to classical treatment, a problem raised by the authors of the article.

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