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Successful treatment of refractory thrombotic thrombocytopenic purpura with cyclosporine; a case report

Maryam Ghazizadeh*

Department of Hematology- Oncology, Faculty of Medicine, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Correspondence to**
Maryam Ghazizadeh, Email: ghazizadeh54@gmail.com, maryamghazizadeh@sbmu.ac.ir

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a rare and fetal disease of the blood coagulation system. The treatment of choice for TTP is plasma exchange. There are some different medical remedies for refractory cases with their own complications. The following case is the report of a refractory TTP, who responded to cyclosporine as a newer way of medical treatment. A 42-year-old woman with systemic lupus erythematosus (SLE) was admitted because of hypermenorrhea, hematuria and purpura. She was involved with acute renal failure, fever and seizure in the course of her admission. Fragmented RBC was detected in the peripheral blood smear. Lactate dehydrogenase (LDH) raised up to 1500 U/L. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) level was reduced and von Willebrand factor-cleaving protease (ADAMTS13) antibodies were elevated significantly. She was undergone plasma exchange in order to manage TTP. Additionally, she received methylprednisolone for the treatment of TTP. Despite initial response to plasma exchange and methylprednisolone, the patient did not improve. She received cyclosporine for the treatment of refractory TTP. Her clinical and laboratory abnormalities improved significantly with cyclosporine and this response was durable. We concluded that cyclosporine can be an effective treatment in refractory TTP and SLE.

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare and fetal disease of the blood coagulation system. TTP occurred because of the presence of the highly reactive high-molecular-weight multimers of von Willebrand factor due to ADAMTS13 deficiency (1).

Also, it may caused by autoantibody directed against von Willebrand factor-cleaving protease (ADAMTS13) that leads to accumulation of the von Willebrand factor multimers, platelet aggregation and thrombosis in the microvascular system (2). The thrombi formation in the microcirculation leads to impairment of kidney and neurologic complications. Platelet consumption in TTP causes thrombocytopenia. TTP is characterized by microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic disorder and renal failure. The main treatment option for TTP is plasma exchange (3). 20-50 percent of patients who respond to plasma exchange experience relapse after initial treatment. The ADAMTS13 activity and antigen is lower in patients with recurrent TTP than other patients. Detection of ADAMTS13 antibodies is more common in patients with recurrent TTP (4). Treatment of refractory TTP includes using cryo-poor plasma instead of fresh frozen plasma (FFP) in plasmapheresis. Other recommended medical therapies in refractory TTP are corticosteroids and rituximab. Other options in patients with poor response to high dose glucocorticoids and rituximab include splenectomy immunosuppressive agents like cyclophosphamide, oral azathioprine, vincristine, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) (5) and autologous stem cell transplantation (6). All of these drugs have significant complications.

We present a patient with refractory TTP

Key point

Thrombotic thrombocytopenic purpura (TTP) is a rare and fetal disease. This is the report of a refractory TTP, who responded to cyclosporine as a new treatment.

and systemic lupus erythematosus (SLE) that responded to cyclosporine – as a new treatment option – without significant complication.

Case Presentation

A 42-year-old Iranian woman with a history of SLE presented with hypermenorrhea, hematuria and purpura for approximately 10 days before admission. She had a history of irregular menstruation for two years. Multiple bruises were detected on her upper and lower extremities. On the day of admission, she found a low-grade fever and acute renal failure. Several days later, a generalized tonic-colonic convulsion and confusion occurred.

Physical examination on admission revealed a low-grade fever (T = 37.8°C) and tachycardia. Her pulse rate was 100 beat/min, and the blood pressure was 100/60 mm Hg. The conjunctive was pale. Multiple ecchymoses were seen on the upper and lower limbs. She had tachycardia and a systolic ejection murmur at upper parasternal border. We detect mild tenderness in the epigastria without splenomegaly. Neurologic examination was normal at admission but later a grand mal seizure occurred. The laboratory studies revealed hemolytic anemia (Hb = 6 g/dL), white blood cell count (WBC = 11 000/mm^3) and thrombocytopenia (platelet count = 10 000/µL). The coagulation tests were normal. Lactate dehydrogenase (LDH) was 1500 U/L (LDH = 1500 U/L). The corrected reticulocyte count was 6.4%. Liver function tests revealed elevated total and indirect bilirubin (total bilirubin = 5 mg/dL indirect bilirubin = 4 g/dL). In the peripheral blood smear polychromasia, anisocytosis, poikilocytosis and schistocytes were seen. However, direct and indirect coombs were negative. Serum level of haptoglobin was decreased. Bone marrow aspiration revealed erythroid hyperplasia. The blood urea nitrogen (BUN) and serum creatinine level were within normal on admission however, in the following days the creatinine level elevated up to 3.5 g/dL. Urine analysis revealed albumin (3+) and RBC 20-30/HFP. Antinuclear antibody (ANA) and double stranded DNA (ds DNA) were positive. Antineutrophil cytoplasmic antibody was negative. Complement component 3 and 4 (C3 and C4) were normal. On admission TTP, flare up of SLE, antiphospholipid syndrome, disseminated intravascular coagulation and Evans syndrome were considered as differential diagnosis. Five days after admission, she had a generalized tonic-clonic convulsion and the platelet count reduced to 6000/µL. Computed tomography scan and magnetic resonance imaging were normal. She underwent plasma exchange with the diagnosis of TTP. This diagnosis was confirmed with the laboratory test. ADAMTS 13 activity was less than one percent and ADAMTS 13 antibody was detected on laboratory test. We prescribed intravenous methylprednisolone (1 g/3 days). With daily plasma exchange the platelet count increased to 30 000/µL and serum creatinine decreased to 1.5 g/dL on the eleventh day. Daily plasma exchange was continued. On the 18th day, the platelet count increased to 90 000/µL and plasma exchange was stopped. One week after stopping plasma exchange the platelet count reduced to 18 000/µL and creatine was elevated to 2.9g/dL. Accordingly, serum LDH increased to1860 U/L. We restarted plasma exchange and methylprednisolone pulse followed by oral prednisolone 1 mg/kg again. We prescribed oral cyclosporine at 2 mg/kg/d. Around 12 days after resuming plasma exchange and cyclosporine, the platelet count increased to 60 000/µL, LDH reduced to 800 U/L, and serum creatinine reduced to 1.8 g/dL. Therefore, the plasma exchange tapered and the dose of cyclosporine increased to 3.5 mg/kg/d. On the 28th day, the platelet count increased to 150 000/µL, her hematuria and proteinuria improved and creatine decreased to 1 mg/dL. Then, the plasma exchange stopped and she was discharged with oral prednisolone (30 mg/d) and oral cyclosporine (4 mg/kg/d). After three months, the prednisolone and cyclosporine dosage were reduced to 10 mg/day and 3 mg/kg/d, respectively. Prednisolone was discontinued after 8 months, and cyclosporine dosage was the same, and the patient achieved sustained remission.

Discussion

TTP is a kind of thrombotic microangiopathy that is defined by thrombocytopenia, hemolytic anemia, microvascular thrombosis, fever, reduced kidney function and neurologic symptom. TTP is caused by deficiency of von Willebrand factor-cleaving protease (ADAMTS13) or antibody directed against ADAMTS13. The prevalence of TTP is three cases per one million per year (7). TTP is an emergency condition that needs immediate therapy. The first description of TTP was reported by Eli Moschowich in 1924 (8,9). The pathology of TTP is hyaline thrombi in several organs. TTP can be a complication of SLE. The prevalence of TTP in patients with SLE is as low as 0.5%. The synchronous occurrence of TTP and SLE is very rare (10). The majority of patients respond to plasma exchange but a minority of patients remain refractory. Refractory TTP is defined as failure to achieve platelet response after 4-7 days of plasma exchange. About 10-42 percent of patient with TTP are refractory to plasma exchange and corticosteroid (11). The prevalence of refractory TTP is more common in patients with severe ADAMTS13 deficiency and antibody directed against ADAMTS13. In patients without severe ADAMTS13 deficiency relapse and refractory TTP is rare (12). In refractory TTP other causes of thrombocytopenia must be ruled out. These patients should be evaluated for sepsis and drug-induced thrombocytopenia. Patients with normal level of ADAMTS13 might not have TTP. If refractory TTP is confirmed by low level of ADAMTS13, twice-daily plasma-exchange is suggested, but the benefit of this treatment is not apparent. In a retrospective study only 3 of 28 patients with refractory TTP responded to twice-daily plasma-exchange (13). Another option in refractory TTP is using cryo-poor plasma that is a production of FFP without

cryoprecipitate and is depleted of high- molecular-weight von Willebrand multimer. However, in multiple trails the benefit of this method was not approved (14). Anti-CD20 monoclonal antibody (rituximab) is recommended in refractory TTP especially those with neurological manifestation (15). A variety of adverse effects have been described with rituximab including; hypersensitivity, anaphylactic reaction, and myelosuppression. Splenectomy is another alternative treatment for refractory TTP; however the usefulness of splenectomy in refractory TTP is controversial (16). Immunosuppressive agents like cyclophosphamide, vincristine, and cyclosporine have been used in refractory TTP. Cyclophosphamide is an alkylating agent with a variety of adverse effects like bone marrow suppression and hemorrhagic cystitis. Vincristine is an antimicrotubular agent that principally induces neurotoxicity, neurotic pain, and loss of deep tendon reflex. Neutropenia is another dose-limiting toxicity of vincristine. Cyclosporine is an immunosuppressive agent that indirectly inhibits calcineurin and suppresses T cell activation. The risk of cytopenia induced by cyclosporine is lower than cyclophosphamide and vincristine. Cyclosporine causes thrombotic microangiopathy. Some articles suggested that cyclosporine induce durable remission in patients with refractory TTP. The mechanism of cyclosporine in the treatment of refractory TTP is not clear, but suppression of T cell by cyclosporine may lead to inhibition of production of ADAMTS13 antibody and treatment of TTP. Our patient initially responded to the plasma exchange and methylprednisolone but in the following days her thrombocytopenia reversed and plasma exchange and glucocorticoid therapy restarted. Despite the increase in platelet count, cyclosporine was administered and its dosage was gradually increased to get a persistent remission. In this way, a durable remission achieved without significant cytopenia. Additionally, the risk of drug-induced cytopenia with cyclosporin is lower than other immunosuppressive agents.

Conclusion

Calcineurin inhibitors like cyclosporin can be an effective treatment in refractory TTP, which produces a durable remission without a significant side effect.

Conflicts of interest

The author has no conflict of interest to declare.

Ethical considerations

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient has provided written informed consent for publication as a case report. Additionally, ethical issues including plagiarism, double publication, and redundancy have been completely observed by the author.

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References

1. Schneppenheim R, Budde U, Oyen F, Angerhaus D, Aumann V, Drewke E, et al. Von Willebrand factor cleaving protease and ADAMTS13 mutations in childhood TTP. Blood. 2003;101:1845-50.
2. Hand JP, Lawlor ER, Yong CK, Davis JH. Successful use of cyclosporine A in the treatment of refractory thrombotic thrombocytopenic purpura. Br J Haematol. 1998;100:597-599. doi: 10.1046/j.1365-2141.1998.00602.x.
3. Tuncer H H, Mayfield CA, Marques MB. Current diagnosis and management of thrombotic thrombocytopenic purpura: utility of von-Willebrand factor cleaving protease (ADAMTS 13). Blood Transfus. 2005;3:32-41.
4. Peyvandi F, Lavorentanos, Palla R, Feys HB, Vanhoorelbeke K, Battaglioli T, Valsecchic, et al. ADAMTS13 and anti ADAMTS13 antibody as marker of recurrence of acquired TTP during remission. Hematologica. 2008;1:93:232-9.
5. Spiekerman k, Worman B, Rumpf KW, Hiddenman W. Combination chemotherapy with CHOP for recurrent TTP. Br J Haematol. 1997;97:544.
6. Passweg JR, Rabusin M, Musso M, Beguin Y, Cesaro S, Ehninger G, et al. Haematopoetic stem cell transplantation for refractory autoimmune cytopenia. Br J Haematol. 2004;125:749-55.
7. Reese JA, Muthurajah DS, Kremer Hovinga JA, Vesely SK, Terrell DR, George JN. Children and adults with thrombotic thrombocytopenic purpura associated with severe, acquired Adamts13 deficiency: comparison of incidence, demographic and clinical features. Pediatr Blood Cancer. 2013;60:1676-82. doi: 10.1002/pbc.24612.
8. Moschcowitz E. Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. Proc N Y Pathol Soc. 1924;24:21–24.
9. Moschcowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries; an undescribed disease. Am J Med. 1952;13:567-9. doi: 10.1016/0002-9343(52)90022-3.
10. George P, Das J. Pawer B, Kakker N. TTP and SLE successful management of a rare presentation. Indian J Crit Care Med. 2008;12(3):128.
11. Farzana A. Sayana Charles S. Abrams. How I treat refractory thrombotic thrombocytopenic purpura. Blood. 2015;125:(25)3860-7.
12. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood. 2008;112:11.
13. Nguygn L.Li X, Duvull D, Terrell DR, Vesely SK, George JN. Twice – daily plasma exchange for patient with refractory TTP: the experience of Oklahoma registry,1989 through 2006. Transfusion. 2008;48:349-57.
14. Michael M, Elliott EJ, Craig JC, Ridley G, Hodson EM. Interventions for hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: a systematic review of randomized controlled trials. Am J Kidney Dis. 2009;53:259-72. doi: 10.1053/j.ajkd.2008.07.038.
15. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ; British Committee for Standards in Haematology. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158:323-35. doi: 10.1111/j.1365-2141.2012.09167.x.
16. Aqui NA, Stein SH, Konkle BA, Abrams CS, Strobl FJ. Role of splenectomy in patients with refractory or relapsed thrombotic thrombocytopenic purpura. J Clin Apher. 2003;18:51-4.