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Case Report

Normalization of Platelet Count after Romiplostim Treatment in a Patient with Thrombotic Thrombocytopenic Purpura: A Case Report

Gholamreza Bahoush[1*] MD, Maryam Vafapour[2] MD, Nahid Rahimzadeh MD[3]

[1] Pediatric Growth and Development Research Center, Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
[2] Firouzabadi Clinical Research Unit, Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
[3] Department of Pediatrics, Rasool-e-Akram General Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
*Corresponding Author: Dr. Gholamreza Bahoush, Pediatric Growth and Development Research Center, Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. Email: bahoush.gh@iums.ac.ir ORCID ID: 0000-0003-1463-9369

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Abstract

Thrombotic Thrombocytopenic purpura (TTP) is the thrombotic microangiopathy (TMA) caused by the severely reduced activity of the von Willebrand factor-cleaving protease ADAMTS13. The deficiency occurs in two main forms, acquired (antibody-mediated) and inherited. Plasma exchange is the mainstay of the disease management; however, Caplacizumab, glucocorticoids, rituximab, and other immunosuppressive drugs may be added to the management protocol, particularly in refractory cases. Thrombopoietic drugs are a known therapy for idiopathic thrombocytopenia purpura (ITP). No studies have been reported so far on the effects of these drugs on the patients with TTP. In this case report, we report the treatment of a 17-year-old female with hereditary TTP and dramatically good response to romiplostim (Nplate) in a one-year follow-up without an increase in the ADAMTS13 level and thrombotic complications.

Keywords: ADAMTS13 deficiency, Romiplostim, Immune Thrombocytopenic Purpura, Thrombotic Thrombocytopenic Purpura

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Introduction

The ADAMTS13 enzyme (A Disintegrin and Metalloproteinase with Thrombospondin Type 1 motif, 13) plays a significant role in regulating the von Willebrand factor (vWF), which is one of the key factors in the process of blood clot formation. This enzyme helps to prevent the formation of abnormal and microscopic clots in small vessels by breaking down Willibrand molecules. Reduced activity or deficiency in ADAMTS13 can lead to a dangerous condition called thrombotic thrombocytopenic purpura (TTP). By forming small clots in small blood vessels, TTP can damage vital organs such as the kidneys and brain (1, 2).

ADAMTS13 deficiency occurs in two main forms: an acquired type, which is caused by the production of antibodies against ADAMTS13, and an inherited type, which is caused by genetic mutations in the gene that codes for this enzyme. Current treatments, especially for the acquired type, include plasma therapy, administration of steroids, and immunotherapy for resistance cases, which help to reduce the activity of harmful antibodies, thereby improving the level of ADAMTS13 activity. Recent studies show that advances in diagnostic methods, including the rapid measurement of ADAMTS13 activity using modern technologies, have aided in the early diagnosis of TTP and increased the success rate of treatment (3, 4).

There are not any reports about the treatment of ADAMTS13 deficiency by drugs that stimulate platelet production such as TPO agonists. Romiplostim, with the trade name ‘Nplate’, is a thrombopoietin (TPO) receptor agonist. By stimulating the thrombopoietin receptors in the bone marrow, this drug increases the production of platelets in patients with immune thrombocytopenia (ITP). Regarding how romiplostim acts, it binds to TPO receptors and increases the activation of the signaling pathways related to platelet production (5). This drug is known as an effective treatment option for ITP patients who are resistant to conventional treatments (6). However, it has been used as an off-label in other important conditions such as acquired aplastic anemia, myelodysplastic syndrome, lymphoproliferative malignancies, chemotherapy induced thrombocytopenia and transplant-associated thrombocytopenia (7).

There are not any reports about the treatment of ADAMTS13 deficiency by TPO agonist drugs. In the patient with hereditary ADAMTS13 deficiency reported in this article, romiplostim was prescribed incidentally, which had an incredibly beneficial effect to normalize the platelet count and control the disease. Therefore, the treatment has been continued until now.

The studied case

The patient is a 17-year-old girl with ADAMTS13 deficiency, whose symptoms began at the age of eleven. At that time, she went to the emergency room with abdominal pain, and initial lab tests were performed with the possibility of acute appendicitis. The tests revealed thrombocytopenia. After platelet transfusion, she underwent appendectomy and was monitored every month with CBC checks. Also, she was treated with low-dose prednisolone with primary diagnosis of ITP during this time.

After a few months, the patient developed menorrhagia, and there emerged severe, treatment-resistant thrombocytopenia. All the related laboratory tests, including Anti-Smith Ab, AntiSSA (Ro) Ab, AntiSSB (La) Ab, Anti-Cardiolipin Ab, ANA, Anti-dsDNA, and Anti-phospholipid Ab, were negative. Following further assessments, she was treated alternatively with high-dose corticosteroids, rituximab, and IVIG without any complete response.

At the age of 14, following a loss of consciousness, kidney failure, significant anemia (which required frequent blood transfusions) and thrombocytopenia, she was hospitalized in PICU with a diagnosis of TTP and was treated with plasma exchange. Then, she underwent maintenance therapy with plasma infusions every two weeks; the thrombocytopenia was resolved, and it remained consistently normal.

During outpatient follow-ups, she was administered weekly or biweekly injections of romiplostim at a rate of five micrograms per kilogram body weight (according to the platelet count monitoring), and plasma therapy was

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stopped due to the remaining normal platelets. Surprisingly, she was asymptomatic without any platelet drop during the next visits. Therefore, the treatment was continued under this research study with the ethics code of IR.IUMS.FMD.REC.1404.336. Since then, the patient has taken an injection of romiplostim every two weeks, her platelets have been maintained in the normal range, and she has not experienced a relapse (Figure 1).

For greater certainty, romiplostim was temporarily stopped. After the platelet count fell below 50,000 per microliter, plasma infusion was started at a rate of 15 milliliters per kilogram body weight every two weeks for three months. During this period, the platelet count returned to normal and was maintained at more than 150,000 per microliter.

This unexpected response suggests that romiplostim may enhance platelet production or stabilize platelet counts even in patients with TTP, despite the primary indication of medication for ITP. The patient continued romiplostim therapy with regular follow-up, demonstrating consistent platelet levels and no relapse. This began to significantly improve her quality of life. ADAMTS13 activity was not increased after the treatment with romiplostim (Table I). In addition, the Whole Exome Sequencing of the patient showed compound heterozygote mutation in the ADAMTS13 gene (Table II).

Table I. The laboratory data of the patient

Laboratory tests	Age: 11	Age: 14	Age: 18
WBC, ($\times 10^3$/mm^3) **PMN (%)** **Lymph (%)**	3.47 60 31	9.3 81 11	**6.46** **45** **40**
Hb, (g/dL)	7	11.5	**12.3**
Platelet count, (1000/microL)	16	96	**542**
PT(Sec)	-	12.9	-
PTT(Sec)	-	34.1	-
INR(Sec)	-	1	-
TT	-	15	**NA**
ADAMTS13 (IU/ml)	-	< 0.007	-
ADAMTS13 Activity (%)	-	< 0.7	**<1**
ADAMTS13 Ab (IU/ml)	-	3 (Neg)	**2**
C3(micro/L)	-	1.44 (in normal range)	**1.53** **(in normal range)**
C4(micro/L)	-	0.38 (in normal range)	**0.34** **(in normal range)**
ANA	-	Neg	-
CH50 (%)	-	135 (in normal range)	**87** **(in normal range)**
Direct comb's	-	Neg	-
Creatinine (mg/dl)	-	**1.43**	**0.8**

WBC, white blood cell; **Hb**, hemoglobin; **PT**, prothrombin time; **PTT**, partial thromboplastin time; **INR**, international normalized ratio; **TT**, thrombin time; **ADAMTS13**, A Distntegrin and Metalloproteinase with a Thrombospondin Type 1 motif, member 13; **C3**, complement factor 3; **C4**, complement factor 4; **ANA**, Antinuclear Antibody; **CH50**, 50% hemolytic complement.

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Table II. Whole exome sequencing of the patient

Gene	Variant coordinates*	Associated disease	Inheritance[a]	Zygosity[b]	ACMG/ClinVar classification[c]
	Chr9-136314972				
	136314977 GTGCCC -:				
	NM_139025.4:(23/29):				**VUS/**
	c.2931_2936delTGCCCG:	Thrombotic	AR	Might be	**Pathogenic**
ADAMTS13	p.Cys977_Arg979delinsTrp	thrombocytopenic		compound	
	rs387906346	purpura,		het	
		hereditary 274150			
	Chr9-136289599 G A:				**Pathogenic/**
	NM_139025.4:(3/28):				**Likely**
	c.330+1G>A rs375415632				**pathogenic**

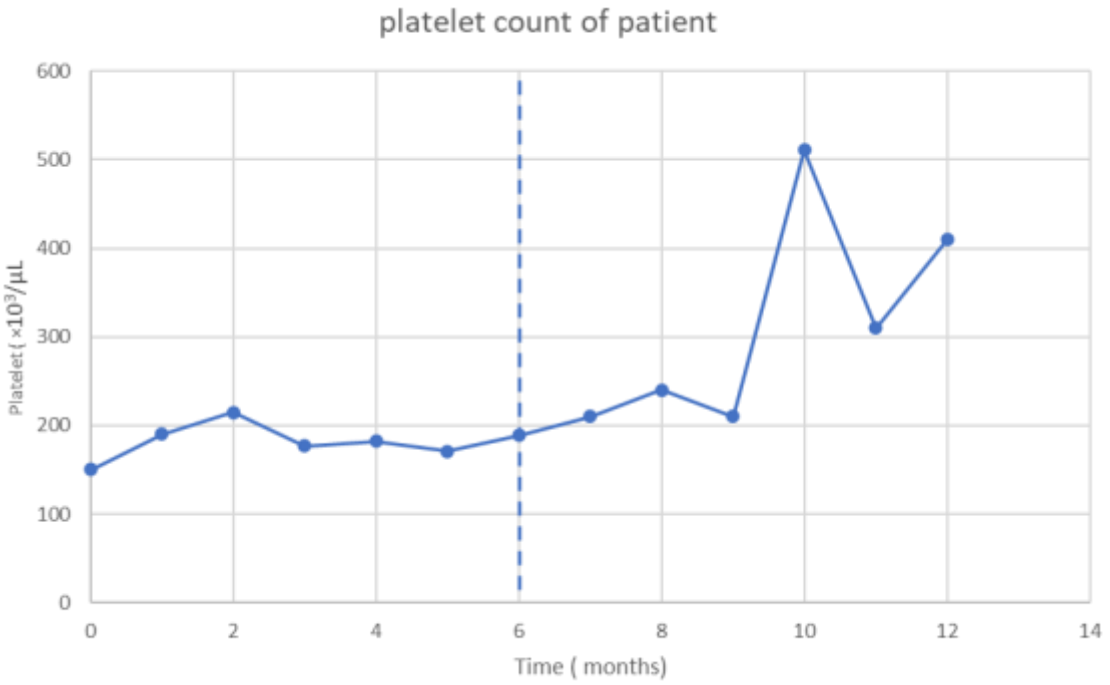

Figure 1. Patient's platelet count. Left of the dashed line: FFP treatment period; Right of the dashed line: Romiplostim treatment period

Discussion

The treatment of immune TTP, according to its pathophysiology, is conducted in a certain process. Plasma exchange is the mainstay of TTP treatment, where the patient's plasma is replaced with healthy plasma to increase ADAMTS13 levels and remove harmful antibodies (8).

Immunosuppressive drugs like steroids and rituximab can be used as adjunctive therapy with plasma therapy in TTP patients. Studies have shown that immunotherapy can be effective for patients who do not respond adequately to plasma therapy (9,10). Caplacizumab is a monoclonal drug that binds to Von Willebrand factor, preventing it from interfering with platelets. Caplacizumab can reduce recovery time and complications.

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Combining Caplacizumab with plasma therapy and steroids helps to control symptoms better and reduce relapses (11).

Recent treatment approaches include ADAMTS13 replacement therapy for hereditary TTP (12). For patients with hTTP, plasma transfusion has been recommended instead of therapeutic plasma exchange (TPE). TPE is not necessary for hTTP because patients do not usually have ADAMTS13 inhibitors that require removal and TPE carries a higher risk of side effects, especially the complications related to the use of a central venous catheter, which is often required (13).

The patient in this study was the first known case of TTP treated with romiplostim. Although romiplostim did not target ADAMTS13 deficiency directly, the patient showed improvement. The mechanism by which romiplostim increased platelet count in this patient is unclear. One hypothesis is that the increase of platelets compensates for the rapid consumption of platelets typical in ADAMTS13 deficiency, reducing the risk of bleeding and other thrombocytopenia-related complications. Additionally, stimulating the TPO receptor may enhance platelet survival, potentially offsetting the effects of the underlying disease (14).

The use of romiplostim in patients presents an interesting opportunity to investigate thrombopoietin receptor agonists for the thrombocytopenia conditions not related to ITP. To date, TPO agonists have been used off-label for other conditions and approved as adjunctive therapy during immunosuppressive therapy for children with acquired aplastic anemia, chemotherapy, and hematopoietic stem cell transplant-induced thrombocytopenia (15).

In our patient, initiating romiplostim increased the platelet count, which was clinically beneficial to improve quality of life by reducing the frequency of relapses and hospitalizations for plasma transfusions. Another notable finding was the clinical improvement after the increase of the platelet count alone without an increase in the ADAMTS13 activity following the use of romiplostim.

Related to the observations in this study, there are several points to consider. Lin et al. reported a case with concurrent immune thrombocytopenic purpura and thrombotic thrombocytopenic purpura and reviewed the literature. The key point in their study and very few similar studies is that the overwhelming majority of the reported cases, unlike the patient in the present research, had immune TTP (16). Given that platelet counts normalized and remained normal during the treatment with both romiplostim and plasma therapy, the hypothesis of the simultaneous existence of ITP and TTP is completely rejected. In addition, TTP was not flared up without any known treatment after romiplostim was started, despite severe ADMTS13 deficiency during the treatment. Apparently, romiplostim may be effective in TTP, perhaps with similar mechanisms effective in the known off-lable therapy.

Another important point is the increased risk of thrombotic events after using romiplostim particularly for patients with TTP. However, no thrombotic complications were observed in the patient while taking the drug. Although the overall incidence of such side effects is low, they should be considered serious when giving the drug, especially in future studies.

Due to the limited data, the present case report is not a license to treat TTP with romiplostim.

Conclusion

In conclusion, it seems that the points discussed in this article can pave the way for new research in the field of pathogenesis and treatment of patients with TTP, regardless of the role of romiplostim in the treatment of our patient.

Availability of Data

All data is available in manuscript.

Ethical Considerations

The treatment was continued under this research study with the ethics code of IR.IUMS.FMD.REC.1404.336

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Authors' Contributions

GB, as the first and corresponding author, was responsible for the patient treatment and the study design. He supervised the study, provided critical revisions, and ensured the accuracy of the histopathological evaluations. MV contributed to the data collection and analysis and drafted the manuscript. NR contributed to the manuscript revision. All the authors had a share in writing the manuscript and approved the final version. The authors did not use AI to write the article.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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