Clinical Case Report

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Acquired idiopathic thrombotic thrombocytopenic purpura successfully treated with intravenous immunoglobulin and glucocorticoid

A case report

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Abstract

Rationale: Plasma exchange is the principal treatment for acquired thrombotic thrombocytopenic purpura (TTP) but is invasive and may have adverse effects. Reports of immunoglobulin therapy for acquired TTP without plasma exchange are rare.

Patient concerns: A 14-year-old girl was admitted because of hemolytic anemia and thrombocytopenia.

Diagnosis: Acquired TTP was diagnosed based on low ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 13) activity and a high ADAMTS13 inhibitor level.

Interventions & Outcomes: Fresh frozen plasma was initially effective. Prednisolone and immunoglobulin resolved the condition with no adverse effects and rendered plasma exchange unnecessary.

Lessons: Compared with biological agents, immunoglobulin is cost-effective, readily available, and has a proven long-term safety record, making it a possible treatment option for acquired thrombotic thrombocytopenic purpura.

Abbreviations: ADAMTS13 = a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 13, HMW-VWFM = high-molecular-weight von Willebrand factor multimers, TTP = thrombotic thrombocytopenic purpura, UL-VWFM = ultra large von Willebrand factor multimers, VWF = von Willebrand factor.

Keywords: ADAMTS13, ADAMTS13 inhibitor, intravenous immunoglobulin, plasmapheresis, thrombotic thrombocytopenic purpura

1. Introduction

Acquired thrombotic thrombocytopenic purpura (TTP) is caused by ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 13) inhibitor.[1,2] Plasma exchange, used to remove the ADAMTS13 inhibitor and replenish ADAMTS13, is the principal treatment for acquired TTP and has reportedly reduced mortality from ~90% to 10% to 20%. The British Society for Haematology guidelines recommend starting plasma exchange immediately after the diagnosis of TTP.[3] Plasma exchange, however, is invasive and may have adverse effects such as bleeding or thrombosis, especially in patients with hemostatic or thrombotic problems such as TTP. For these reasons, TTP treatments not using plasma exchange should be considered.

We report herein a case of acquired idiopathic TTP treated with immunoglobulin, glucocorticoid, and plasma infusion without plasma exchange.

2. Case

A 14-year-old girl was admitted to our hospital with a 1-week history of fever, purpura, hemolytic anemia, and thrombocytopenia. Her past medical history and family history were unremarkable.

A fever, bloody sputum with macrohematuria, and purpura in the lower legs developed 1 week, 5 days, and 2 days before admission, respectively. On the day of admission, the patient complained of dyspnea during a tennis game and visited another hospital where hemolytic anemia and thrombocytopenia were diagnosed. The patient was later transferred to our hospital. A physical examination on admission revealed icteric conjunctiva, purpura of the lower legs, and no neurological abnormalities.

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Ethical approval and patient's consent: Informed consent for the publication of this report was obtained from the patient and her parents. This case report was approved by the Ethical Review Board of National Center for Child Health and Development.

HN and AI conceptualized and designed this report, carried out the initial analyses, reviewed the references, and drafted and revised the manuscript. NI, KN, CS, HN, and MK coordinated data collection, interpreted data, and critically reviewed the manuscript. MH and MM assessed the essential data of the diagnosis and disease process and critically reviewed the manuscript. All authors approved the final manuscript as submitted.

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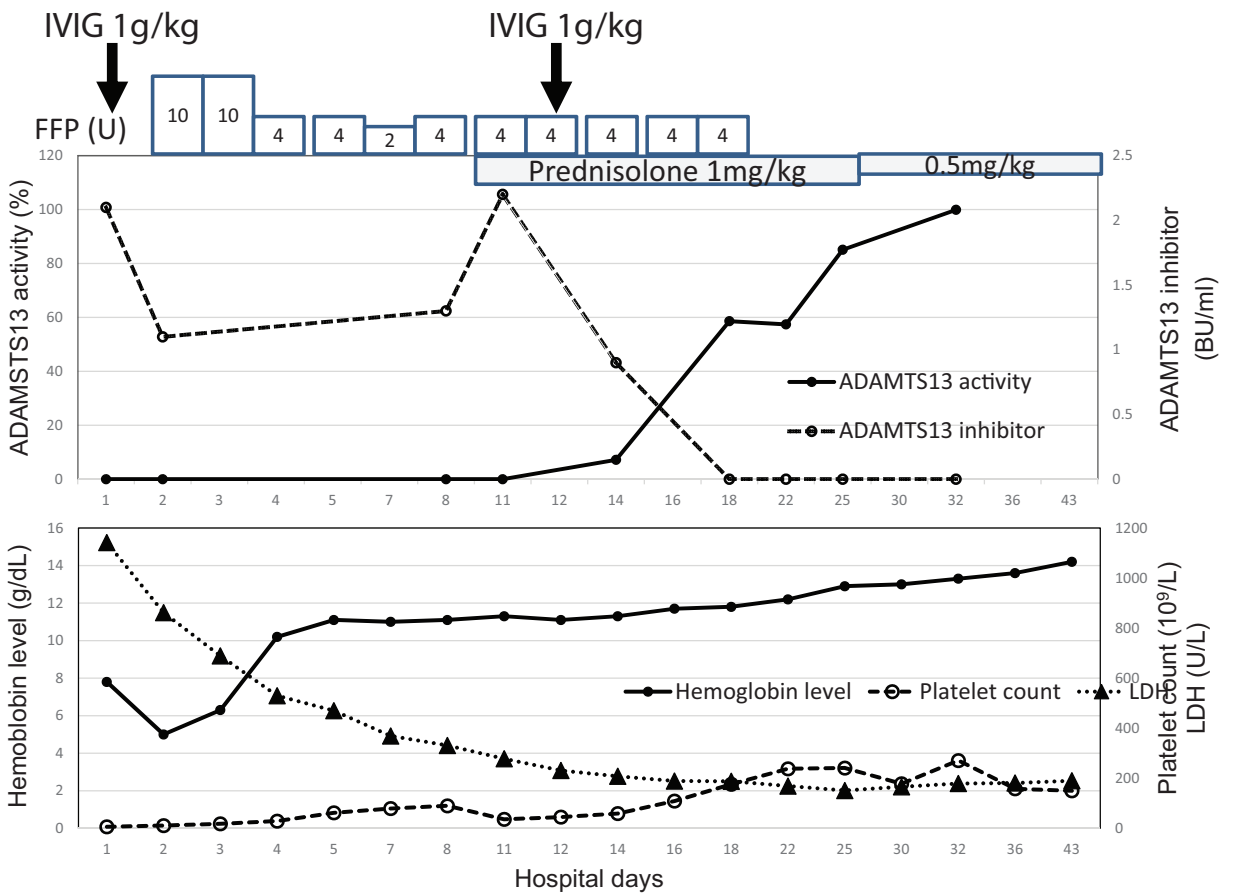


Figure 1. Time series for laboratory data and treatments.

Laboratory findings revealed hemolytic anemia (hemoglobin level: 78 g/L; hematocrit: 22.7%; reticulocyte count: 54×10^9/L; total bilirubin: 66 mg/L; indirect bilirubin: 51 mg/L; aspartate aminotransferase: 50 U/L; lactate dehydrogenase: 1142 U/L; and haptoglobin: undetectable), thrombocytopenia (platelet count: 6.0×10^9/L), and renal damage (urinary protein: 2.3 g/L; serum creatinine: 5.0 mg/L).

Emergency treatment was started immediately after admission with platelet transfusion and intravenous immunoglobulin 1 g/kg for refractory epistaxis. Nonetheless, the hemolytic anemia worsened and the platelets failed to increase. On hospital day 2, fresh frozen plasma (FFP) was started. After a FFP transfusion, the hemolytic anemia improved (Fig. 1), and the patient received repeated transfusions of FFP and additional examinations. On hospital day 4, the fever resolved and the urinary protein disappeared.

Additional laboratory findings demonstrated that ADAMTS13 activity was <0.5% of that of the control and that the ADAMTS13 inhibitor level was 2.1 Bethesda U/mL. There was no suggestion of an underlying malignancy or collagen vascular disease. The verotoxin test was negative. Based on these findings, acquired idiopathic TTP was diagnosed. On hospital day 9, prednisolone 1 mg/kg was started with repeated FFP transfusions. On hospital day 12, because of another decrease in the platelet count and an increase in ADAMTS13 inhibitor, intravenous immunoglobulin was administered again. Starting on hospital day 14, the platelet count and ADAMTS13 activity began to increase while the ADAMTS13 inhibitor level began to decrease, eventually reaching an undetectable level that rendered a FFP transfusion unnecessary (Fig. 1).

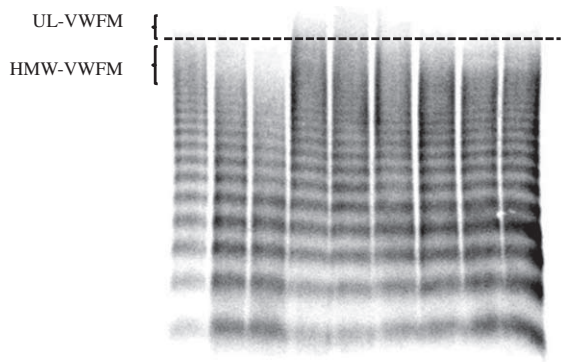
From hospital day 27, prednisolone was tapered. Prednisolone was administered for a total of 4 months. The patient tolerated the treatments well, was discharged on hospital day 45, and eventually recovered without plasma exchange.

Von Willebrand factor (VWF) multimer analysis (Fig. 2) showed a depletion of high-molecular-weight von Willebrand factor multimers (HMW-VWFM) on hospital days 1 and 2 and the presence of ultra large von Willebrand factor multimers (UL-VWFM) on days 8 and 11, when the ADAMTS 13 activity was <0.5%. These data fit the pathophysiology of TTP, in which UL-VWF are not cleaved because of the absence of ADAMTS13 and are consumed in the abnormal thrombotic process.

3. Discussion

We reported a case of acquired idiopathic TTP treated with immunoglobulin, glucocorticoid, and FFP transfusion without plasma exchange. The pathophysiology was confirmed by VWF multimer analysis.

The second dose of immunoglobulin evidently resolved our patient's symptoms. However, reports of immunoglobulin therapy for TTP without plasma exchange are rare. Immunoglobulin therapy for TTP, most of which included plasma exchange, was mainly reported in the early 1990s.[4–11] From 2000, rituximab emerged as an effective treatment option for TTP[12–14], and reports of immunoglobulin therapy markedly



Hospital days	NC	1	2	8	11	14	18	22	32
VWF antigen (%)		146	126	169	165	158	202	231	223
ADAMTS13 activity (%)		<0.5	<0.5	<0.5	<0.5	7.2	58.6	57.4	99.9
ADAMTS13 inhibitor (BU/mL)		2.1	1.1	1.3	2.2	0.9	<0.5	<0.5	<0.5

Figure 2. Changes in multimers by agarose gel electrophoresis and von Willebrand factor (VWF) antigen, activity of ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 13), and ADAMTS13 inhibitor. ADAMTS13 = a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 13, NC = normal control, VWF = von Willebrand factor.

decreased. In 2013, Kawano reported 11 patients with acquired TTP. All 11 patients underwent plasma exchange, 3 received immunoglobulin infusions, and none died. In contrast, of 8 patients who received no immunoglobulin treatment, 5 died.[15] In general, however, reports of immunoglobulin therapy for TTP without plasma exchange are rare.

A phase 2 study and some systematic reviews reported rituximab, an anti-cluster of differentiation-20 antibody, as an effective alternative treatment.[12–14] Rituximab is currently recommended in the British Society for Haematology guidelines as an alternative to immunoglobulin for refractory or recurrent TTP.[3] Most recently, the TITAN study demonstrated the efficacy of caplacizumab, an anti-VWF antibody.[16] However, both rituximab and caplacizumab are expensive, not readily available, and have no evidence of long-term safety. In contrast, immunoglobulin is cost effective, readily available at most hospitals, and has a track record of long-term safety. Therefore, immunoglobulin is worth considering as first-line treatment for TTP.

The reasons for the efficacy of immunoglobulin against acquired TTP remain unknown. Immunoglobulin is used to treat many diseases thought to have an immunological origin, such as Kawasaki disease, idiopathic thrombocytopenic purpura, and Guillain–Barré syndrome. In these diseases, as in TTP, the precise pathological mechanisms are unknown.[17]

In conclusion, immunoglobulin may be a viable treatment option against acquired TTP although further studies are needed to ascertain its exact effects against this disease.

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