

## Case Report

Thrombocytopenia Involving Disseminated Intravascular Coagulation  
Due to Aortic Aneurysm and Immune Thrombocytopenia

Masahiro Sakaguchi<sup>1</sup>, Nana Matsumoto<sup>1</sup>, Shunichi Yasuda<sup>1</sup>, Ayaka Moriyama<sup>1</sup>,  
Takahiko Mine<sup>2</sup>, Yasuhiro Kawase<sup>3</sup>, Masamitsu Shimizu<sup>4</sup>, Ryohei Hamakubo<sup>5</sup>,  
Eriko Morishita<sup>6,7</sup>, Hidesaku Asakura<sup>8</sup> and Norio Yokose<sup>1</sup>

<sup>1</sup>Department of Hematology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan

<sup>2</sup>Department of Radiology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan

<sup>3</sup>Department of Cardiovascular Surgery, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan

<sup>4</sup>Department of Pulmonology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan

<sup>5</sup>Department of Gastroenterology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan

<sup>6</sup>Department of Hematology, Nippon Medical School, Tokyo, Japan

<sup>7</sup>Department of Clinical Laboratory Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Faculty of Health Sciences, Kanazawa University, Kanazawa, Japan

<sup>8</sup>Department of Hematology, Kanazawa University Hospital, Kanazawa, Japan

A 68-year-old man with a history of lung cancer, prostate cancer, inflammatory bowel disease, and aortic aneurysm was referred for evaluation of a sudden decrease in platelet count. Coagulation findings indicated a diagnosis of disseminated intravascular coagulation (DIC) due to aortic aneurysm. Because all DIC-related markers except platelet count improved with DIC therapy, immune thrombocytopenia (ITP) was suspected. His platelet count recovered with rituximab for steroid-resistant ITP. Since thrombocytopenia may have multiple causes, particularly when combined with DIC and ITP, appropriate treatment of each condition is required.

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**Keywords:** disseminated intravascular coagulation (DIC), immune thrombocytopenia (ITP), aortic aneurysm, rituximab, heparin and tranexamic acid

## Introduction

Disseminated intravascular coagulation (DIC) is a serious condition in which multiple microthrombi develop in small blood vessels because of systemic and persistent activation of coagulation in the presence of underlying disease<sup>1</sup>. Leukemia, solid tumors, and infectious diseases are the most common underlying causes of DIC, but many other diseases have been implicated<sup>2</sup>. Aortic aneurysm is also an underlying cause. DIC is treated by selecting therapies for the underlying disease and by preventing activation of coagulation, the main pathogenetic factor.

Immune thrombocytopenia (ITP) is a condition in which platelet count is reduced by immunological mechanisms<sup>3</sup>. Treatment of ITP has evolved. Thrombopoietin receptor agonists (TPO-RA) are now increasingly used when first-line treatment with steroids is ineffective. Splenectomy is no longer the traditional approach. Fostamatinib may be used in addition to rituximab for refractory cases<sup>4</sup>.

A 68-year-old man with a sudden decrease in platelet count was diagnosed with DIC due to aortic aneurysm. Treatment for DIC improved DIC-related markers but did not restore platelet count. We report an instructive case

Correspondence to Masahiro Sakaguchi, [m-sakaguchi@nms.ac.jp](mailto:m-sakaguchi@nms.ac.jp)

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of DIC in a patient whose platelet count was restored by adding a treatment for ITP to DIC treatment.

### Case Report

A 68-year-old man was diagnosed with stage 1A postoperative recurrence of lung adenocarcinoma by a respiratory physician 8 years previously, and afatinib was started. The drug was withdrawn after 5 years, and lung adenocarcinoma did not recur. He was diagnosed with prostate cancer 6 years previously, and his disease was stable (the result of his most recent prostate-specific antigen test was normal) with continued combined androgen blockade. The patient was diagnosed with drug-induced enteritis/ulcerative colitis 3 years previously, and supportive care with mesalazine was continued and stabilized his symptoms. In addition, thoracic aortic aneurysm was detected 6 years previously, and thoracic aortic stent grafting (TEVAR) was performed 6 months previously. During follow-up of these conditions, his platelet count generally remained at approximately 100,000/ $\mu$ L. However, a regular outpatient visit to the Department of Pulmonology revealed a sudden decrease in his platelet count to 31,000/ $\mu$ L, and he was referred to the Department of Hematology.

Investigation of the cause of thrombocytopenia revealed obvious findings of DIC (**Table 1**) and he was urgently admitted. His platelet count on admission had decreased further to 21,000/ $\mu$ L. Physical examination revealed no abnormal vital signs, but there was significant subcutaneous bleeding at the site of blood collection. A CT scan obtained on the day of admission showed no change in the area of stenting for aortic aneurysm and no evidence of infection or hemorrhage. The clinical course of the patient after admission is shown in **Figure 1**.

To prevent activation of coagulation, recombinant thrombomodulin alfa (rTM) was administered for 5 days from the third day of admission, while replacement therapy with fresh-frozen plasma was initiated. This intervention resulted in a rapid decrease in the level of fibrinogen degradation products (FDP) and recovery of fibrinogen to approximately 180 mg/dL. The results of blood testing on admission were thrombin-antithrombin complex (TAT) 44.0 ng/mL, plasmin- $\alpha_2$  plasmin inhibitor complex (PIC) 6.4  $\mu$ g/mL, FDP 63.8  $\mu$ g/mL, D-dimer 20.7  $\mu$ g/mL, and  $\alpha_2$  plasmin inhibitor ( $\alpha_2$ PI) 53%. Enhanced-fibrinolytic-type DIC was diagnosed based on marked activation of fibrinolysis and divergence of FDP and D-dimer<sup>5</sup>. Enhanced-fibrinolytic-type DIC due to aortic aneurysm was considered as the most likely cause of

the decreased platelet count. However, since thrombocytopenia was more severe than usual for enhanced-fibrinolytic-type DIC caused by chronic aortic aneurysm, we suspected factors other than DIC as the cause of thrombocytopenia and, thus, investigated these causes. Lack of response to consecutive platelet transfusions suggested immune system involvement. Furthermore, the sudden decrease in platelet count during a routine outpatient visit suggested ITP. A bone marrow examination was performed on the fourth day. Although the elevated number of megakaryocytes without adherent platelets suggested increased platelet production, there were no other obvious abnormalities. Ga scintigraphy was performed on the 10th day to investigate the possibility of malignant tumor exacerbation or infection; however, no significant findings were observed.

Since thrombocytopenia may have been caused solely by DIC, we decided to treat DIC first. After 5 days of rTM, combination therapy with unfractionated heparin (5,000 units twice daily by subcutaneous injection) and tranexamic acid (250 mg orally, three times daily) was started, in accordance with previous reports<sup>6,7</sup>. This intervention further reduced the level of FDP. Fibrinogen, which had persisted at approximately 100 mg/dL before the start of treatment, quickly recovered to 170–200 mg/dL by the 5th day of rTM administration. Subcutaneous bleeding at the blood collection site gradually disappeared with combined anticoagulation and antifibrinolytic therapy. Therefore, we considered treatment for DIC to be successful. However, thrombocytopenia persisted, which suggested that it was caused by an immunological mechanism in addition to the pathogenesis of DIC. We thus decided to add a treatment for ITP.

Dexamethasone (DEX) 40 mg/day was administered for 4 days starting on day 17 of hospitalization. Although platelet count began to increase, the effect did not persist. On the 32nd day of hospitalization, DEX 40 mg/day for 4 days was again administered, but therapeutic effectiveness was poor. Our patient had multiple underlying diseases, and there were concerns about the risks of secondary treatment. Therefore, treatment with rituximab was selected. From the 35th day of admission, rituximab was administered once a week for 4 consecutive weeks. His platelet count recovered to 26,000/ $\mu$ L on the 53rd day and to 34,000/ $\mu$ L on the 56th day, and he was discharged. At an outpatient visit on the 78th day, his platelet count was 93,000/ $\mu$ L. After discharge, platelet count has generally remained at 50,000/ $\mu$ L, and the patient has since been a regular outpatient for approximately 18

**Table 1** Laboratory findings

|                     | On administration |                                 |                                             | During treatment |                  |
|---------------------|-------------------|---------------------------------|---------------------------------------------|------------------|------------------|
|                     | Present case      | Reference values                |                                             | Present case     | Reference values |
| Blood counts        |                   |                                 | Antinuclear antibody                        |                  |                  |
| WBC, / $\mu$ L      | 3,000             | 3,300–8,600                     | Homogeneous                                 | 1,280×           | $\leq 40\times$  |
| RBC, / $\mu$ L      | $345 \times 10^4$ | $435\text{--}555 \times 10^4$   | Others                                      | $<40\times$      | $\leq 40\times$  |
| Hb, g/dL            | 9.9               | 13.7–16.8                       | Anti-dsDNA IgG Ab, IU/mL                    | 2.3              | $\leq 9.9$       |
| Hct, %              | 29.2              | 40.7–50.1                       | Rheumatoid factor, U/mL                     | 3                | $\leq 15$        |
| Plt, / $\mu$ L      | $2.1 \times 10^4$ | $15.8\text{--}34.8 \times 10^4$ | <i>Helicobacter pylori</i> antibody, U/mL   | 8.7              | $\leq 10.0$      |
| IPF, %              | 4.4               | $\leq 3.0$                      | Direct Coombs                               | Negative         | Negative         |
| Coagulation         |                   |                                 | PA-IgG, ng/ $10^7$ Plt                      | 49.2             | $\leq 27.6$      |
| PT, sec             | 12.4              | 10.0–13.0                       | Lupus anticoagulant (dRVVT)                 | 0.9              | $\leq 1.2$       |
| PT-INR              | 1.09              | 0.90–1.13                       | Lupus anticoagulant (PNP)                   | 0.84             | $\leq 1.16$      |
| APTT, sec           | 41.7              | 26.0–38.0                       | Anti-cardiolipin IgG Ab, U/mL               | 15.3             | $\leq 20.0$      |
| Fbg, mg/dL          | 94.0              | 170–410                         | Anti-cardiolipin IgM Ab, U/mL               | 4.8              | $\leq 20.0$      |
| FDP, $\mu$ g/mL     | 63.8              | $\leq 5.0$                      | Anti- $\beta 2$ Glycoprotein I IgG Ab, U/mL | 7.4              | $\leq 20.0$      |
| D-dimer, $\mu$ g/mL | 20.7              | $\leq 1.0$                      | Anti- $\beta 2$ Glycoprotein I IgM Ab, U/mL | 3.2              | $\leq 20.0$      |
| AT, %               | 92.0              | 75–125                          |                                             |                  |                  |
| TAT, ng/mL          | 44.0              | $\leq 4.0$                      |                                             |                  |                  |
| PIC, $\mu$ g/mL     | 6.4               | $\leq 0.8$                      |                                             |                  |                  |
| $\alpha_2$ PI, %    | 53                | 80–130                          |                                             |                  |                  |
| Biochemistry        |                   |                                 |                                             |                  |                  |
| TP, g/dL            | 7.4               | 6.6–8.1                         |                                             |                  |                  |
| Alb, g/dL           | 3.9               | 4.1–5.1                         |                                             |                  |                  |
| BUN, mg/dL          | 14.0              | 8–20                            |                                             |                  |                  |
| Cr, mg/dL           | 1.02              | 0.65–1.07                       |                                             |                  |                  |
| UA, mg/dL           | 5.8               | 3.0–7.0                         |                                             |                  |                  |
| Na, mmol/L          | 143               | 138–145                         |                                             |                  |                  |
| K, mmol/L           | 4.1               | 3.6–4.8                         |                                             |                  |                  |
| Cl, mmol/L          | 108               | 101–108                         |                                             |                  |                  |
| Ca, mg/dL           | 9.1               | 8.8–10.1                        |                                             |                  |                  |
| T-Bil, mg/dL        | 0.80              | 0.4–1.5                         |                                             |                  |                  |
| AST, U/L            | 23                | 13–30                           |                                             |                  |                  |
| ALT, U/L            | 10                | 10–42                           |                                             |                  |                  |
| LD, U/L             | 241               | 124–222                         |                                             |                  |                  |
| CK, U/L             | 88                | 59–248                          |                                             |                  |                  |
| BS, mg/dL           | 105               | 70–109                          |                                             |                  |                  |
| CRP, mg/dL          | 0.47              | $<0.14$                         |                                             |                  |                  |
| HbA1c, %            | 5.4               | 4.9–6.0                         |                                             |                  |                  |

WBC: White Blood Cell, RBC: Red Blood Cell, Hb: Hemoglobin, Hct: Hematocrit, Plt: Platelet, IPF: Immature Platelet Fraction, TP: Total Protein, Alb: Albumin, BUN: Blood Urea Nitrogen, Cr: Creatinine, UA: Uric Acid, T-Bil: Total Bilirubin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LD: Lactate Dehydrogenase, CK: Creatine Kinase, BS: Blood Sugar, CRP: C-reactive Protein, PT: Prothrombin Time, INR: International Normalized Ratio, APTT: Activated Partial Thromboplastin Time, Fbg: Fibrinogen, AT: Antithrombin, PIC: Plasmin-alpha2-plasmin Inhibitor Complex, TAT: Thrombin-antithrombin Complex,  $\alpha_2$ PI:  $\alpha_2$  Plasmin Inhibitor, dRVVT: Dilute Russell's Viper Venom Time, PNP: Platelet Neutralization Procedure.

months. Combination therapy comprising subcutaneous injection of unfractionated heparin and oral tranexamic acid is ongoing.

### Discussion

Aortic aneurysms may be complicated by DIC<sup>8</sup>. Patients with larger-diameter aneurysms are more likely to have coagulation abnormalities; the complication rate is ap-

proximately 4%<sup>9,10</sup>. In enhanced-fibrinolytic-type DIC associated with aortic aneurysm, thrombocytopenia is generally mild and PT and APTT may be normal<sup>11</sup>. Therefore, for patients with aortic aneurysm, if these laboratory tests are within normal limits and the patient does not exhibit any bleeding tendency in daily life, bleeding symptoms may become apparent after tooth extraction or trauma without being recognized as chronic DIC<sup>12</sup>. Aortic

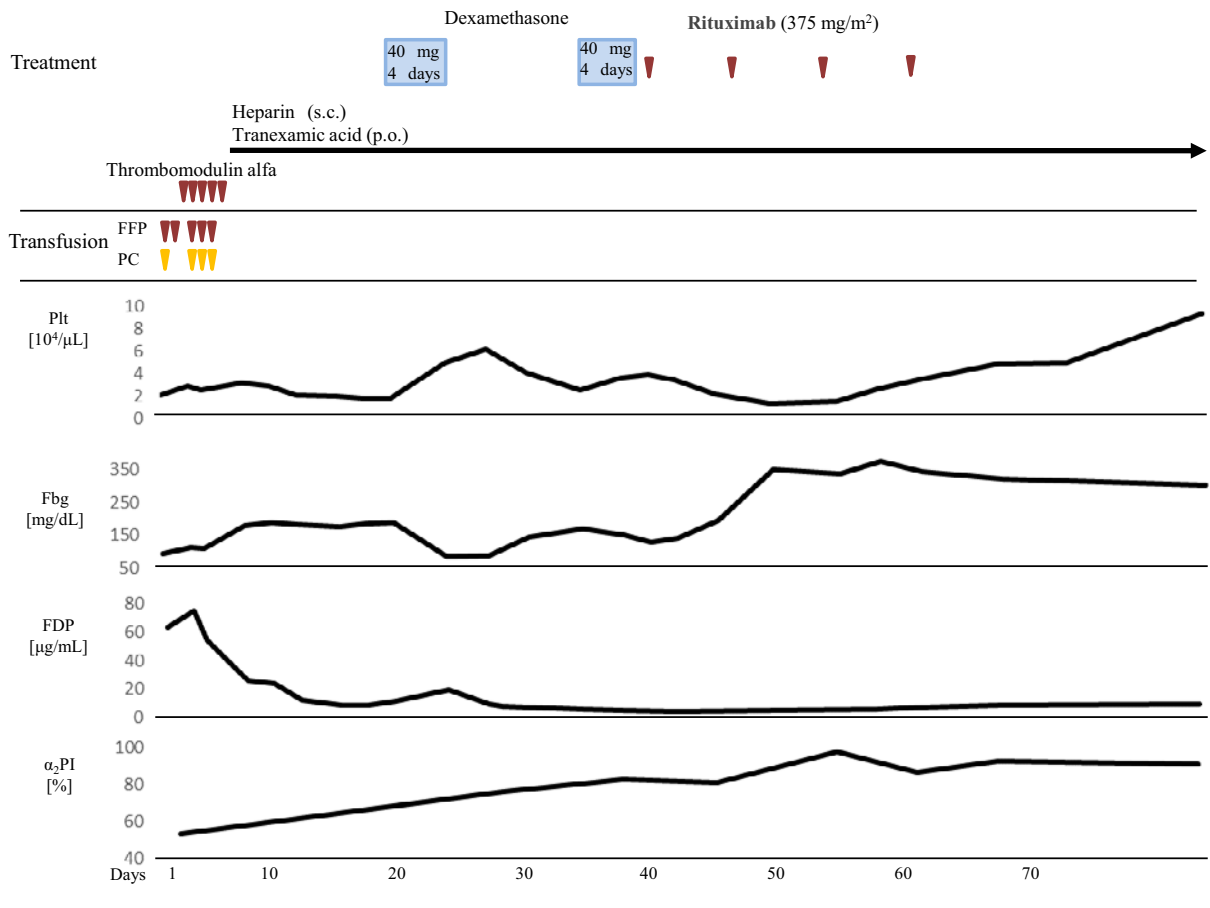


**Figure 1** Course of treatment and coagulation system markers

FFP, Fresh-Frozen Plasma; PC, Platelet Concentrate; Plt, Platelet; Fbg, Fibrinogen; FDP, Fibrin and fibrinogen Degradation Products; α<sub>2</sub>PI, α<sub>2</sub> Plasmin Inhibitor.

aneurysm also needs to be considered in the differential diagnosis when unexplained thrombocytopenia is noted, because patients with undiagnosed aortic aneurysm may be misdiagnosed as having ITP<sup>13</sup>.

In enhanced-fibrinolytic-type DIC, FDP and D-dimer levels are abnormally high, TAT and PIC are elevated, and α<sub>2</sub>PI and plasminogen levels are diminished, even though thrombocytopenia is mild and PT and APTT are within normal ranges<sup>5</sup>. However, TAT, PIC, and α<sub>2</sub>PI results are often not immediately available in hospitals, which complicates rapid diagnosis. In clinical practice, an elevated FDP/D-dimer ratio is considered useful for diagnosing enhanced-fibrinolytic-type DIC<sup>5</sup>. FDP/D-dimer ratio increases because of degradation of fibrin and fibrinogen caused by marked activation of fibrinolysis. In our patient, we quickly identified and treated enhanced-fibrinolytic-type DIC by focusing on the elevated FDP/D-dimer ratio. Furthermore, the patient had severe thrombocytopenia, which led us to suspect another overlapping condition. A blood test just before admission showed a 1,280-fold increase in antinuclear antibodies

(homogeneous type) (Table 1), suggesting that ITP was also complicated by autoimmunity. However, there were no physical findings suggestive of collagen disease, including SLE, and the diagnostic criteria for SLE were not met. Thus, SLE and other collagen diseases were deemed unlikely. In the present case, we selected steroids alone as the first-line treatment. However, it would have been safer if IVIG had also been administered.

Diagnosis of ITP is always challenging because it is diagnosed by exclusion, as in our patient. Furthermore, thrombocytopenia may be caused by multiple conditions, as in this case<sup>14-16</sup>. This is the first reported case of DIC stabilized by continued combination therapy with subcutaneous injection of unfractionated heparin and oral tranexamic acid, and of steroid-resistant ITP treated with rituximab.

Anticoagulation for DIC improves outcomes<sup>17-19</sup>. However, anticoagulation can promote bleeding in DIC, because of the marked activation of fibrinolysis. Therefore, there is currently no established treatment for enhanced-fibrinolytic-type DIC associated with vascular disease.

Antifibrinolytic therapy for DIC is considered to be contraindicated because it suppresses the defense response to dissolve microthrombi by activating fibrinolysis<sup>20</sup>. Antifibrinolytic agents, such as tranexamic acid, used in conjunction with anticoagulation therapy were shown to be effective for enhanced-fibrinolytic-type DIC associated with thoracoabdominal aortic aneurysms<sup>21–25</sup>. Therefore, the combination of anticoagulation and antifibrinolytic therapies has been proposed in Japan for enhanced-fibrinolytic-type DIC, when major hemorrhage is a concern<sup>5</sup>.

rTM<sup>26,27</sup>, low-molecular-weight heparin<sup>14,28,29</sup>, and nafamostat mesylate<sup>30</sup> were reported to be effective as anticoagulant therapy for DIC caused by vascular disease. Twice-daily subcutaneous injections of unfractionated heparin, as in the present case, are a useful treatment and can be continued on an outpatient basis.

The primary treatment for ITP in the absence of *Helicobacter pylori* infection is corticosteroids<sup>31</sup>. If a response is not achieved with first-line treatment, second-line treatment with TPO-RA, rituximab, fostamatinib, and splenectomy is considered<sup>4</sup>. Although the frequency of thrombosis did not increase in TPO-RA clinical trials<sup>32,33</sup>, when it occurs, it usually develops within 1 year of the initiation of TPO-RA medication<sup>34</sup>. Our patient had DIC, a thrombotic condition, and TPO-RA was not selected because it was considered safer to avoid the risk of thrombosis. Because of complications, such as ulcerative colitis, splenectomy was considered to have a high perioperative risk because of the aortic aneurysm, in addition to concerns about the adverse effects of immunological decline. Therefore, splenectomy was not the treatment of choice.

An increase in the platelet count is generally observed at 1–3 months after the start of rituximab treatment<sup>35–37</sup>. In the present case, a platelet increase was achieved after approximately 1 month of rituximab treatment, which was typical of the therapeutic course. On the other hand, the median duration of effect in cases for which rituximab was effective is 1 year, and relapse is common<sup>38–40</sup>. Furthermore, 20–30% of patients maintain a platelet count  $\geq 50,000/\mu\text{L}$  for more than 5 years after receiving rituximab<sup>38–40</sup>. Re-administration of rituximab upon recurrence of thrombocytopenia resulted in a similar response as initial treatment in 75% of cases<sup>41</sup>. Therefore, platelet count may decrease again in our patient, and treatment with other drugs, such as TPO-RA, or re-administration of rituximab may be necessary, in light of the risk of adverse events.

Thrombocytopenia may develop in association with

multiple diseases, as in the present case. This was an instructive case in which a focus on the examination findings made it possible to quickly identify the existing condition and start treatment. DIC is a cause of thrombocytopenia; therefore, if platelet count does not increase despite a response to treatment, other complications that cause thrombocytopenia should be considered.

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