Case Report

Heparin-Related Thrombocytopenia Triggered by Severe Status of Systemic Lupus Erythematosus and Bacterial Infection

Satoshi Suzuki,1,2 Shihoko Nakajima,1 Taiki Ando,3 Keisuke Oda,1 Manabu Sugita,4 Kunimi Maeda,5 Yutaka Nakiri,1 and Yoshinari Takasaki3

1Department of Internal Medicine and Rheumatology, Juntendo University Nerima Hospital, Tokyo 177-8521, Japan
2Department of Internal Medicine Research, Sasaki Institute, Sasaki Foundation, Tokyo 101-0062, Japan
3Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo 113-8431, Japan
4Department of Emergency and Critical Care Medicine, Juntendo University Nerima Hospital, Tokyo 177-8521, Japan
5Department of Internal Medicine and Nephrology, Juntendo University Nerima Hospital, Tokyo 177-8521, Japan

Correspondence should be addressed to Satoshi Suzuki; satsuzu@juntendo.ac.jp

Received 21 May 2016; Accepted 17 August 2016

Academic Editor: Tsai-Ching Hsu

Copyright © 2016 Satoshi Suzuki et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

A patient with severe lupus nephritis developed thrombocytopenia during treatment with high-dose steroids. In addition to viral- or disease-induced cytopenia, the pathology was believed to arise from diverse contributing factors, such as thrombotic microangiopathy and heparin-related thrombocytopenia (HIT). By combining plasma exchange therapy and intravenous cyclophosphamide, we successfully controlled the SLE activity and improved the thrombocytopenia. An antecedent bacterial infection or SLE activity is believed to have contributed to the concurrent HIT.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that can involve all bodily organs, including the lungs, kidneys, and skin. Diagnosis of SLE in Japan is primarily based on the diagnostic criteria of the American College of Rheumatology (ACR) as revised in 1997 [1]. However, there are cases that do not satisfy the diagnostic criteria yet involve symptoms or autoantibodies typical of SLE. Conversely, there are other autoimmune diseases, such as Sjögren’s syndrome, that present with a pathology that would end up being misdiagnosed as SLE when judged purely on the diagnostic criteria [2]. Recently, the Systemic Lupus Collaborating Clinics (SLICC) have proposed new criteria for classifying SLE [3], but neither their sensitivity nor their specificity greatly exceed those of the ACR diagnostic criteria. There are also individual differences in how symptoms manifest, varying from mild pathology limited to skin rashes and arthritis to severe pathology involving major organs. Accordingly, treatment needs to be tailored to suit individual symptoms. SLE is a refractory autoimmune disease that challenges a rheumatologist’s competence in both diagnosis and treatment.

Representative forms of severe pathology with organ involvement include central nervous system lupus and glomerulonephritis (lupus nephritis), but patients so often exhibit severe thrombocytopenia that has also been included in the diagnostic criteria.

2. Case Report

A 52-year-old man with an unremarkable past medical history had anemia noted in a 2014 health check and, by the end of the year, lower limb edema was observed but was left untreated. In March 2015, he was admitted to a nearby clinic with a diagnosis of nephrotic syndrome. Renal dysfunction was observed when the nephrotic syndrome was diagnosed, and blood purification therapy was being considered, for which he was transferred to our hospital. Since progressive renal dysfunction had been observed, methylprednisolone (mPSL) pulse therapy (mPSL 1000 mg/day for 3 days) was initiated on the day of hospital transfer. This was followed by treatment with 100 mg/day (1 mg/kg) of prednisolone (PSL), beginning on hospital day 4. Testing conducted in parallel showed anti-nuclear antibody titers of $\times$320 (Homo
×320, Spe×320), anti-ds DNA antibody (ELISA) 300 IU/mL, anti-cardiolipin antibodies (IgG-aCL) at 16 U/mL, leukocytes at 1000/L, platelets at 100,000/L, and urine protein levels of 2.6 g/gCre, and he was diagnosed with SLE. With such significant systemic edema, difficulty with hemostasis was anticipated, and the patient was unable to lie prone, making it impossible to obtain a renal biopsy to differentiate the type of lupus nephritis. High disease activity persisted, and plasma exchange therapy (double filtration plasmapheresis) was initiated on hospital day 9. On hospital day 11, dialysis (hemodialysis, HD) was initiated. A fever was observed on hospital day 21, and *Staphylococcus aureus* (methicillin-sensitive *Staphylococcus aureus*, MSSA) was detected from a blood culture. At first, vancomycin was selected as an antibiotic, but after sensitivity was confirmed, the antibiotics were deescalated to cefazolin. On hospital day 23, decreases in oxygen saturation and blood pressure were observed, and the patient was admitted to the intensive care unit (ICU) with congestive heart failure. His circulation was supported medically and the antibiotics were continued. The patient’s testing did not support a diagnosis of acute coronary syndrome nor poor drainage during HD; myocardial damage from cytokine storm was believed to be the cause of his heart failure. High-level SLE activity persisted, and the patient was deemed to have a steroid-resistant pathology. We considered introducing cyclophosphamide (CPA) or mycophenolate mofetil (MMF). Laboratory test findings are shown in Table 1. Clinical course is shown in Figure 1.

Platelet count had been gradually decreasing since hospital day 10, and no improvement was observed despite changes in and discontinuation of the drugs used. A search for the cause of his thrombocytopenia identified CMV antigenemia (C7-HRP: 3/50,000 infected cells). He was also positive for CMV-DNA, and the possibility of thrombocytopenia associated with CMV viremia was considered. ADAMTS13 activity, which was submitted at the same time, also exhibited a mild decrease at 53%, and concurrent thrombotic microangiopathy (TMA) was considered, in light of the findings of fever,
Table 1: Laboratory test findings.

| Test              | Result                                      |
|-------------------|---------------------------------------------|
| Blood cell count  | WBC 1000/μL                                 |
|                   | Neu 505/μL                                  |
|                   | Lym 100/μL                                  |
|                   | Eosi 0/μL                                   |
|                   | RBC 280/7/μL                                |
|                   | Hb 6.9 g/dL                                 |
|                   | Hct 24.3%                                   |
|                   | Plt 10000/μL                                |
| Coagulation       | PT IH% (PT-INR 0.95)                        |
|                   | APTT 30.5 sec                               |
|                   | FDP 25.2 μg/mL                              |
| Biochemistry      | T-Bil 0.3 mg/dL                             |
|                   | D-Bil 0.1 mg/dL                             |
|                   | AST 22 IU/L                                 |
|                   | ALT 11 IU/L                                 |
|                   | γ-GTP 21 IU/L                               |
|                   | BUN 62 mg/dL                                |
|                   | Cre 2.46 mg/dL                              |
|                   | eGFR 23.31                                  |
|                   | UA 10.4 mg/dL                               |
|                   | Na 134 mEq/L                                |
|                   | K 5.0 mEq/L                                 |
|                   | Cl 105 mEq/L                                |
|                   | TP 5.0 g/dL                                 |
|                   | Alb 1.9 g/dL                                |
|                   | CRP 1.87 mg/dL                              |
|                   | ANA ×320                                    |
|                   | Homogeneous ×320                            |
|                   | Speckled ×320                               |
|                   | Anti-DNA antibody 300 IU/mL                 |
|                   | Anti-RNP antibody (−)                       |
|                   | Anti-SS-A antibody (−)                      |
|                   | Anti-cardiolipin antibody (IgG) 16 IU/mL    |
|                   | CH50 12/mL                                  |
|                   | C3 24 mg/dL                                 |
|                   | C4 5 mg/dL                                  |
|                   | IgG 1554 mg/dL                              |
|                   | IgA 148 mg/dL                               |
|                   | IgM 290 mg/dL                               |
| Serology          | pH 5.0                                      |
|                   | Protein (+)                                 |
|                   | Ketone body (−)                             |
|                   | Occult blood (+)                            |
| Urinalysis        | RBC 10–19 HPF                               |
|                   | WBC 20–29 HPF                               |
|                   | Hycaln cast (2+)                            |
|                   | Epithelial cast (1+)                        |
|                   | Granular cast (1+)                          |
|                   | Waxy cast (1+)                              |
| Urinary sediment  | WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, Plt: platelet, PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrinogen and fibrin degradation products, BIL: bilirubin, AST: aspartate transaminase, ALT: alanine transaminase, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, TP: total protein, CRP: C-reactive protein, ANA: anti-nuclear antibody, LAC: lupus anticoagulant, CH50: total complement activity, Ig: immunoglobulin, and HPF: high power field.
occurs frequently in highly active SLE with renal complications [6]. SFPP is an effective treatment for TMA and lowers the mortality rate, said to be 85–100% in the absence of treatment, down to 10–30% [7–9]. However, there are cases where SFPP is ineffective at treating or stopping recurrence, and in such cases, rituximab is reportedly effective [10, 11]. HIT is a pathology where, for some reason, pathogenic HIT antibodies are produced out of the autoantibodies (anti-heparin/PF4 antibodies) against platelet factor 4 (PF4) and the heparin complex [12]. HIT antibodies activate the vascular endothelium and induce thrombosis from excessive thrombin production [12]. To diagnose HIT, it is useful to measure HIT antibodies directly, a test which is covered by insurance even in Japan, but it is necessary to have a comprehensive approach by combining the 4T’s score using the extent of thrombocytopenia, history of heparin use, and the presence or absence of thrombosis [13]. Anti-coagulation therapy is required for thrombosis prophylaxis, but heparin exacerbates the thrombocytopenia, in which case argatroban, which is a thrombin inhibitor, is used. Approximately 19% of SLE patients have antibodies against PF4 (anti-PF4 antibodies) [14]. Anti-PF4 antibodies are believed to be synonymous with anti-heparin/PF4 antibodies in that they react to the heparin/PF4 complex (are heparin-dependent). However, heparin-independent anti-PF4 antibodies, which are believed to react only to PF4, have been discovered recently. The appearance of heparin-dependent anti-PF4 antibodies is associated with thrombocytopenia, while the appearance of heparin-independent anti-PF4 antibodies is related to SLE disease activity [14]. The patient presented tested positive for HIT antibodies, and therefore it was believed that autoantibodies against the heparin/PF4 complex (heparin-dependent anti-PF4 antibodies) were being produced, even though disease activity remained extremely high. Anti-heparin/PF4 antibodies are reportedly produced due to a cross-reaction between the complex of PF4 and bacteria (in particular, Staphylococcus aureus and Escherichia coli) [15]. This patient developed MSSA bacteremia, and it was possible that he experienced an abnormal immune response to the complex of bacteria and PF4 and produced anti-heparin/PF4 antibodies due to enhanced SLE activity. The pathology presented with the production of diverse autoantibodies, including anti-DNA, IgG-aCL, and HIT antibodies, and he was believed to have an abnormal enhancement of B-cell function. A malignant lymphoma test (7-amino-actinomycin-D, 7AAD) performed on peripheral blood ruled out B-cell lymphoproliferative disease. Finally, he responded to cyclophosphamide, which is a DNA synthesis inhibitor; in such cases, we feel that a treatment strategy targeting B-cells, such as rituximab or belimumab, may be effective and useful in terms of the risk of adverse reactions.

4. Conclusion
The causes of thrombocytopenia complicating SLE with high disease activity include those associated with the underlying disease, but numerous reports show that TMA, HPS, and similar conditions are also possible. In the present case, HIT antibodies appeared, and the patient is believed to have had concurrent heparin-related thrombocytopenia. In patients who are receiving high-dose steroids and have a high risk of thrombosis, there are some cases where heparin is used prophylactically, but we feel it is necessary to pay attention to the onset of heparin-related thrombocytopenia when the patient is being treated for autoimmune disease with high disease activity or when relatively severe bacterial infection is concurrent.

Competing Interests
The authors declare that they have no conflict of interests.

References
[1] E. M. Tan, A. S. Cohen, J. F. Fries et al., “The 1982 revised criteria for the classification of systemic lupus erythematous,” Arthritis and Rheumatism, vol. 25, no. 11, pp. 1271–1277, 1982.
[2] S. Noah, “Sjögren syndrome and systemic lupus erythematous are distinct conditions,” Dermatology Online Journal, vol. 12, no. 1, article 4, 2006.
[3] M. Petri, A.-M. Orbai, G. S. Alarcón et al., “Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematous,” Arthritis and Rheumatism, vol. 64, no. 8, pp. 2677–2686, 2012.
[4] A. Aamer, S. A. A. Abdurahman, K. Najma et al., “Haematological abnormalities in systemic lupus erythematous,” Acta Rheumatologica Portuguesa, vol. 39, pp. 236–241, 2014.
[5] K. Newman, M. B. Owlia, I. El-Hemaidi, and M. Akhtari, “Management of immune cytopenias in patients with systemic lupus erythematous—old and new,” Autoimmunity Reviews, vol. 12, no. 7, pp. 784–791, 2013.
[6] P. Letchumanan, H.-J. Ng, L.-H. Lee, and J. Thumboo, “A comparison of thombotic thrombocytopenic purpura in an inception cohort of patients with and without systemic lupus erythematous,” Rheumatology, vol. 48, no. 4, pp. 399–403, 2009.
[7] F. Peyvandi, R. Palla, and L. A. Lotta, “Pathogenesis and treatment of acquired idiopathic thombotic thrombocytopenic purpura,” Haematologica, vol. 95, no. 9, pp. 1444–1447, 2010.
[8] J. N. George, “How I treat patients with thrombotic thombocytopenic purpura: 2010,” Blood, vol. 116, no. 20, pp. 4060–4069, 2010.
[9] G. B. Raimundo, M. S. Eva, M. S. Maria et al., “Systemic lupus erythmatous and thombotic thombocytopenia purpura: a refractory case without lupus activity,” Clinical Rheumatology, vol. 9, no. 6, pp. 373–375, 2013.
[10] D. Caramazza, G. Quintini, I. Abbene et al., “Relapsing or refractory idiopathic thombotic thombocytopenic purpura-hemolytic uremic syndrome: the role of rituximab,” Transfusion, vol. 50, no. 12, pp. 2753–2760, 2010.
[11] K. Kamiya, K. Kurasawa, S. Arai et al., “Rituximab was effective on refractory thombotic thombocytopenic purpura but induced a flare of hemophagocytic syndrome in a patient with systemic lupus erythematous,” Modern Rheumatology, vol. 20, no. 1, pp. 81–85, 2010.
[12] H. Yamamoto and S. Miyata, “Ischémic stroke and heparin-induced thombocytopenia,” Clinical Neurology, vol. 51, no. 5, pp. 316–320, 2011.
[13] G. K. Lo, D. Juhl, T. E. Werkentin, C. S. Sigouin, P. Eichler, and A. Greinacher, “Evaluation of pretest clinical score (4 T’s) for the diagnosis of heparin-induced thombocytopenia in two clinical
settings,” *Journal of Thrombosis and Haemostasis*, vol. 4, no. 4, pp. 759–765, 2006.

[14] T. Satoh, Y. Tanaka, Y. Okazaki, J. Kaburaki, Y. Ikeda, and M. Kuwana, “Heparin-dependent and -independent anti-platelet factor 4 autoantibodies in patients with systemic lupus erythematosus,” *Rheumatology*, vol. 51, no. 9, pp. 1721–1728, 2012.

[15] K. Krauel, C. Pötschke, C. Weber et al., “Platelet factor 4 binds to bacteria-inducing antibodies cross-reacting with the major antigen in heparin-induced thrombocytopenia,” *Blood*, vol. 117, no. 4, pp. 1370–1378, 2011.