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CASE REPORT

Yoko Tabushi · Toru Fukazawa · Kaori Abe
Kazuhiko Kaneda · Mika Hirashima · Kim Young-Joon
Shuuhei Takai · Hiroshi Tsuda · Hiroshi Hashimoto

A case of aplastic anemia in a patient with systemic lupus erythematosus

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Abstract A case of aplastic anemia with a 16-year history of systemic lupus erythematosus (SLE) is described. The diagnosis of aplastic anemia was established by bone marrow biopsy. Aplastic anemia is an extremely rare complication of SLE. The pathogenesis of aplastic anemia associated with SLE remains to be clarified.

Key words Aplastic anaemia · Cytokine · Systemic lupus erytematosus (SLE)

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder that includes abnormalities of T cells, as well as hyperreactive B cells that produce autoantibodies. Activated T cells and multiple autoantibodies are postulated to play an important role in the clinical manifestations of SLE. Hematological abnormalities, including anemia, leukocytopenia, and thrombocytopenia, are common complications of SLE.[1] The most common causes of hematological abnormalities are the peripheral destruction of blood cells by autoantibodies, cytotoxic drugs, and various coagulopathies associated with anticardiolipin antibodies. However, SLE-related bone marrow aplasia is extremely rare and its etiological mechanism is undefined. Previously, it has been postulated that autoimmune disorders such as T cell dysregulation, serum inhibition of hematopoietic elements, and peripheral autoantibody production are involved in SLE-associated aplastic anaemia.[2–4] In some cases, treatment with either plasmapheresis or high-dose cyclophosphamide in combination with corticosteroids has been successful in inducing remission. In this case, abnormalities of cytokines and excerbation of SLE were not recognized, suggesting that the immunological mechanism appears not to be involved. However, there might be another mechanism involved in the pathogenesis of SLE with aplastic anemia.

Y. Tabushi · T. Fukazawa (✉) · K. Abe · K. Kaneda · M. Hirashima · Y.-J. Kim · S. Takai · H. Tsuda · H. Hashimoto
Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
Tel. +81-3-3813-3111; Fax +81-3-5800-4893
e-mail: fukazawa@med.juntendo.ac.jp

Y. Tabushi
Department of First Internal Medicine, Osaka Medical College, Takatsuki, Japan

Case report

In 1987, a 42-year-old woman was admitted to the University of Showa Hospital suffering from general fatigue and polyarthritis. Laboratory examinations disclosed pancytopenia and proteinurea. A renal biopsy revealed her nephrological state as lupus nephritis type V. A diagnosis of SLE was established and predonisone (PSL) 30 mg/day treatment was started. By the following year, the dosage of PSL was decreased to 5 mg/day, but the patient did not return to the hospital. In 1988, she was referred to Juntendo Hospital for progressive edema. Laboratory findings at the initial visit showed hypocompletmentemia, elevated anti-DNA antibody, and proteinurea of 10 g per 24 h. She was evaluated as having an exacerbation of the SLE and treated with corticosteroid pulse therapy followed by 5 mg betamethasone per os. At that time, plasmapheresis and a regimen of azathioprine (AZP), 50 mg/day, was started. After 4 months of therapy, she was discharged from the hospital. In 1992, she was rehospitalized for 6 months due to recurrent edema. Proteinurea had increased to 10–20 g per 24 h. She was treated again with corticosteroid pulse therapy, followed by 50 mg PSL per os. After the corticosteroid pulse therapy, intravenous cyclophosphamide pulse therapy (IVCY) was administered three times. AZP was changed to mizoribine, 150 mg/day, but later, mizoribine was stopped and AZP was resumed because of persistent proteinurea. In 1995, the PSL dosage had been reduced to

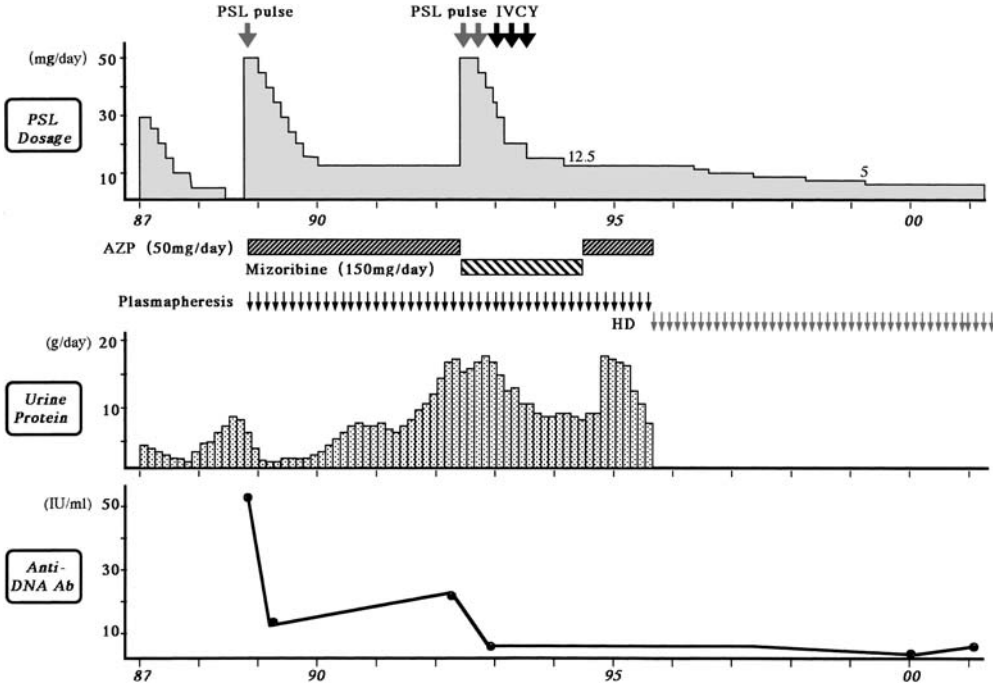

Fig. 1. Clinical course and laboratory findings. The patient was asymptomatic, and this improved state was maintained for a period of 5 years until 2001. *PSL*, predonisone; *IVCY*, intravenous cyclophosphamide; *AZP*, azathioprine; *HD*, hemodialysis

12.5 mg/day and dialysis was indicated because of persistent proteinurea. The patient then became asymptomatic, and this improved state was successfully maintained with PSL at 5 mg/day until 2001 (Fig. 1).

On July 10, 2001, the patient was rehospitalized for recurrent fever associated with cellulitis of the right hand (Fig. 2). Laboratory findings on admission showed the following values: leukocyte count 8.64×10^9/l (normal range {nl} 4.0–10.0×10^9/l), with 84% neutrocytes, 11.5% lymphocytes, 3.3% monocytes); red cell count $305 \times 10^4/mm^3$; hemoglobin 9.9 g/dl (nl 11.2–15.2 g/dl); platelet count 4.0×10^4/μl (nl $14.0–37.9 \times 10^4$/l); reticulocyte count 6.8‰; erythrocyte sedimentation rate 90 mm/h; C-reactive protein 7.0 IU/l (nl < 0.3 IU/l); creatinine 5.73 mg/dl (nl 0.5–0.85 mg/dl); lactic dehydrogenase (LDH) 703 IU/l (nl 280–510 IU/l); albumin (ALB) 3.2 g/dl (nl 3.5–5.3 g/dl); blood urea nitrogen (BUN) 37 mg/dl (nl 9–21 mg/dl); Fe 16 g/dl (nl 80–170 g/dl); ferritin 220 ng/dl (nl 15–150 ng/dl); haptoglobin 73 mg/dl (nl 41–273 mg/dl); PAIgG 64 ng/10^7 cells (nl 9.0–25.0). Immune complex (c1q) was negative. Antinuclear antibody was positive with a titer of 1:40 (homogeneous and speckled pattern). Anti-DNA antibodies, anti-Sm antibodies, and direct and indirect Coombs' test were negative. Anticardiolipin antibody IgM and anti-β 2GP I antibody were negative. Lupus anticoagulant was positive. C3, C4, and CH50 were 117 mg/dl, 39 mg/dl, and 56.1 mg/dl, respectively.

The serum tests for cytomegalovirus, parvovirus B19, and hepatitis B,C were negative. At this time, although the patient's serum LDH was moderately elevated, there were no other findings of hemolysis, since the serum levels of bilirubin and haptogrobin were within normal limits. Treatment with imipenem/cilastatin sodium and clindamycin was started, and the patient's condition improved and her fever subsided within 6 days after the start of antibiotic therapy. At this point, the patient was asymptomatic, with a leukocyte count of 2.5×10^9/l, with 25% neutrocytes, 73% lymphocytes, and 2.0% monocytes, a red cell count of $205 \times 10^4/mm^3$, hemoglobin 6.0 g/dl, a platelet count of 7.2×10^4/μl, and a reticulocyte count of 1.2‰. A review of the patient's medication revealed that she had been receiving mexiletine hydrochloride, metoprolol tartrate, low-dose aspirin, and famotidine. These drugs were discontinued or changed owing to the possibility that they might cause bone marrow suppression (see Fig. 2). In addition, vancomycin hydrochloride and famotidine were negative in drug-specific lymphocyte transformation tests (LTTs). The patient had also required numerous transfusions of packed RBCs and platelets (PLTs) owing to the progression of pancytopenia.

On the 19th day of therapy, a bone marrow aspirate and biopsy revealed marked hypocellularity without proliferation of blasts, dysplastic changes of trilineage, and fibrosis, which are indications of severe aplastic anemia (Fig. 3). The karyotype of bone marrow cells was normal type 46 XX in 16 cells analyzed. Combination therapy with granulocyte colony-stimulating factors (G-CSF) and cyclosporin (CyA), together with antithymocyte globulin (ATG) for her aplastic anemia condition, was tried. The patient remained afebrile until the 19th day of therapy, when her temperature rose to 39°C due to right eyeliditis. Her complete blood cell count was reevaluated at this time, revealing a leukocyte count of 0.7×10^9/l, hemoglobin 7.0 g/dl, platelet count 42×10^9/l, and reticulocyte count <1.0‰. No excerbation of SLE was recognized in her serum examination. On the 24th day of therapy, CyA at 300 mg/day p.o. was administrated, resulting in an improvement of the eyeliditis. However, there was no improvement in the complete blood cell count. Thereafter, she had recurrent fever.

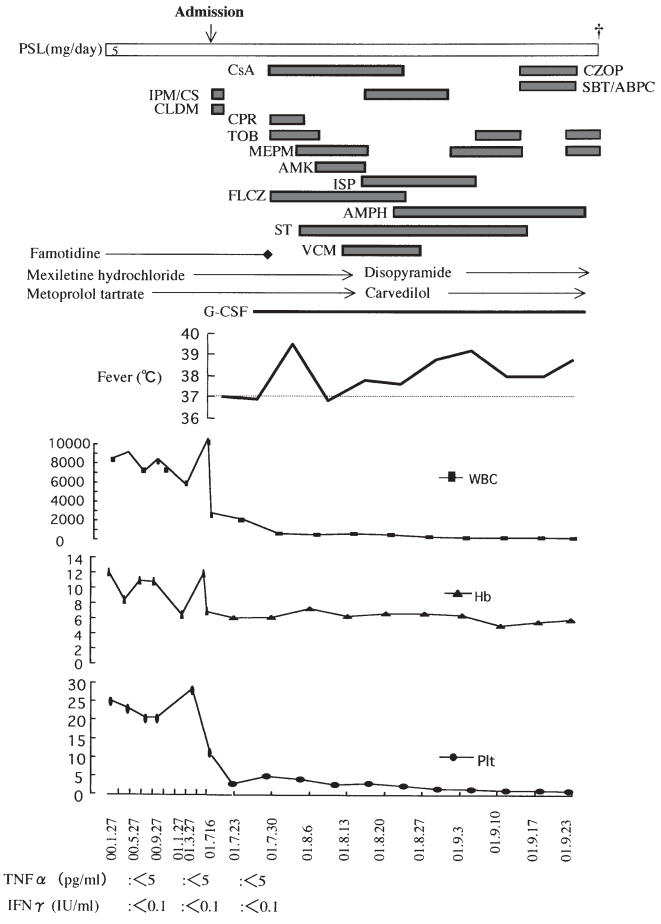

Fig. 2. Hematological findings in peripheral blood during the course of hospitalization. *CsA*, cyclosporin; *IPM/CS*, imipenem/cilastatin sodium; *ISP*, isepamicin sulfate; *CLDM*, clindamycin; *CPR*, cefpirome sulfate; *TOB*, tobramycin; *MEPM*, meropenem trihydrate; *AMK*, amikacin sulfate; *FLCZ*, fluconazole; *AMPH*, amphotericin B; *ST*, sulfamethoxazole-trimethoprim; *VCM*, vancomycin hydrochloride; *CZOP*, cefozopran hydrochloride; *SBT/ABPC*, ampicillin sodium/sulbactam sodium

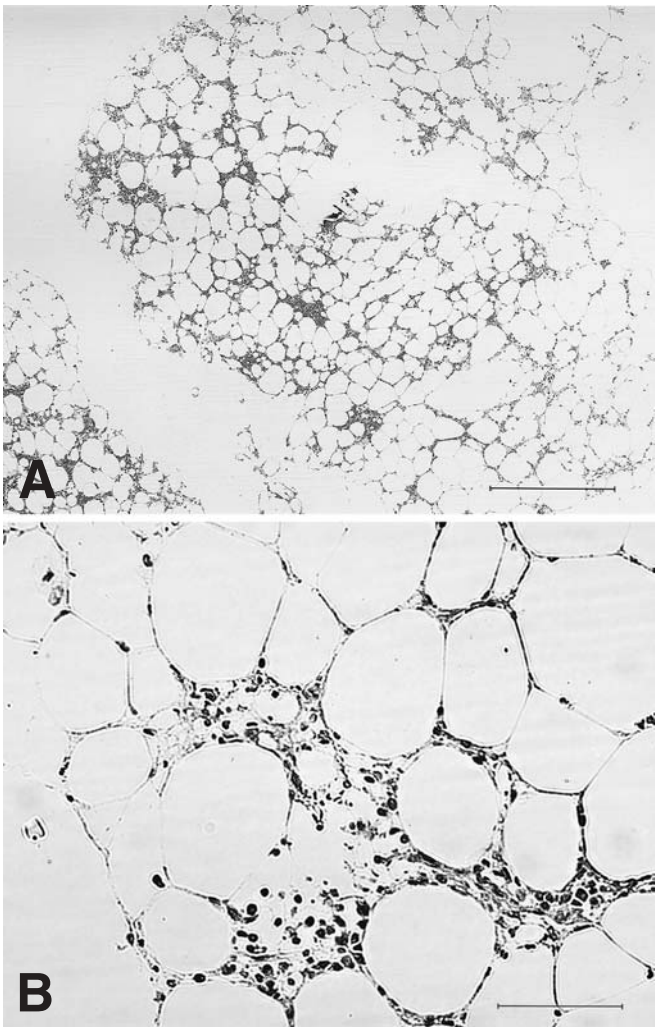

Fig. 3. Bone marrow biopsy demonstrating severe aplasia (hematoxylin & eosin). *Bar*: **A** 500 μm; **B** 100 μm

Multiple cultures, including blood, urine, and stool, obtained at the time of the recurrence of fever were examined, and her blood cultures were positive for *Staphylococcus aureus* and her stool cultures were positive for *Pseudomonas aeruginosa*. The levels of (1→3)-β-D-glucan was also increased. Therefore, on the 49th day of therapy, the administration of CyA was terminated and ATG was not used owing to this infection. Although multiple antibiotics, including vancomycin hydrochloride, sulfamethoxazole-trimethoprim, amphotericin B, and fluconazole, were added to her regimen, her condition deteriorated and on 78th of hospitalization, she died.

Discussion

Aplastic anemia is extremely rare as a complication of SLE. To date, only seven studies have reported SLE with aplastic anemia according to our reference search. Its etiological mechanism is undefined, although it has been speculated that hypoproduction in the bone marrow (BM) due to drug reaction,[5] virus infection, autoimmunity,[1,6,7] or dysregulation of T cells with cytokine abnormalities such as IFN-γ and TNF-α is involved.[8,9]

Drug-induced hypoproduction in the BM is difficult to prove, and it is very difficult to identify the specific drug in drug-induced severe aplastic anemia in a multiple-drug-treated patient with drug-specific lymphocyte transformation tests (LTTs), since previous studies with LTT involving patients with drug allergies have revealed only a 60% sensitivity in the LTT.[10]

In this case, we had administered the same medication for 5 years before the development of aplastic anemia. In addition, the LTT of vancomycin hydrochloride and famotidine were negative, and the cytotoxic cyclophosphamide, azathioprine, and mizoribine had already been discontinued 6 years before development of pancytopenia. Low-dose aspirin and famotidine were immediately discontinued on admission, and mexiletine hydrochloride and

metoprolol tartrate were changed to disopyramide and carvedilol. Drug-induced aplastic anemia was therefore ruled out since cessation of these medications did not delay the further progression of bone marrow failure. As described above, no apparent signs of active infection or serological evidence of viral infection were detected in this case. Autoimmunity played an important role in the development of aplastic anemia in this case, since immunosuppressive therapy had previously resulted in a clinical improvement. Current studies suggest that complement-dependent or noncomplement-dependent antibody and T cell dysregulation may mediate bone marrow aplasia in patients with SLE. Baily et al.[1] detected noncomplement-dependent antibody that inhibited in vitro bone marrow colony formation from granulocyte–macrophage progenitor cells (cfu–gm) and blast-forming units–erythroid (bfu–e) in serum of a patient with SLE and aplastic anemia. Fitchen et al.[11] reported that complement-dependent immunoglobulin G inhibited both granulocytic and erythroid colony formation in a patient with SLE and aplastic anemia. Sumimoto et al.[4] suggested the possibility that abnormal T cells may have dysregulated hematopoiesis thorough an abnormal cytokine network.

In this case, although the patient's general condition was poor at admission, her serum cytokines such as TNF-α and IFN-γ, known to be a common cause of aplastic anemia, were not markedly elevated and no exacerbation of SLE was recognized during her clinical course (see Fig. 2). These laboratory data indicated that no immunological mechanism appears to be involved in this case.

To our knowledge, this is an extremely rare case in which no specific cause could be determined for aplastic anemia associated with SLE. Further studies are needed to clarify the mechanism involved between SLE and aplastic anemia.

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References

1. Bailey FA, Lilly M, Bertori LF, Ball GV. An antibody that inhibits in vitro bone marrow proliferation in a patient with systemic lupus erythematosus and aplastic anemia. Arthritis Rheum 1989;32:901–5.
2. Chute JP, Hoffmeister K, Cotelingam J, Davis TA, Frame JN, Jamieson T. Aplastic anemia as the sole presentation of systemic lupus erythematosus. Am J Hematol 1996;51:237–9.
3. Roffe BC, Cahill MR, Samanta A, Bricknell S, Durrant STS. Aplastic anemia in systemic lupus erythematosus. A cellular immune mechanism? Br J Rheumatol 1991;30:301–4.
4. Sumimoto S, Kawai M, Kasajima Y, Hamamoto T. Aplastic anemia associated with systemic lupus erythematosus. Am J Hematol 1991;38:329–31.
5. Saal JG, Daniel PT, Berg PA. Indoprofen-induced aplastic anemia in active connective tissue disease detected by drug-specific lymphocyte transformation. Klin Wochenschr 1986;64:481–5.
6. Brooks BJ, Broxmeyer HE, Bryan CF, Leech SH. Serum inhibitor in systemic lupus erythematosus associated with aplastic anemia. Arch Intern Med 1984;144:1474–8.
7. Liu H, Ozaki K, Matsuzaki Y, Abe M, Kosaka M, Saito S. Suppression of haematopoiesis by IgG autoantibodies from patients with systemic lupus erythematosus (SLE). Clin Exp Immunol 1995; 100:480–5.
8. Stricher RB, Shuman MA. Aplastic anemia complicating systemic lupus erythematosus: response to androgen in two patients. Am J Hematol 1984;17:193.
9. Miura A, Endo K, Sugawara T, Kameoka J, Watanabe N, Yoshinaga K, et al. T cell-mediated inhibition of erythropoiesis in aplastic anemia: the possible role of IFN-γ and TNF-α. Br J Haematol 1991;78:442–9.
10. Berg PA, Brattig N, Diao GJ. Nachweis von Artzneimittelallergien mit ttilif des Lymphocytenstimulationtests. Klinikarzt 1983;12:792.
11. Fitchen JJ, Cline MJ, Saxon A, Golde DW. Serum inhibitors of hematopoiesis in a patient with aplastic anemia and systemic lupus erythematosus. Recovery after exchange plasmapheresis. Am J Med 1979;66:53.