Clin Rheumatol (2003) 22: 355–358
DOI 10.1007/s10067-003-0742-1

CASE REPORT

K. Hamasaki · T. Mimura · H. Kanda · K. Kubo
K. Setoguchi · T. Satoh · Y. Misaki · K. Yamamoto

Systemic lupus erythematosus and thrombotic thrombocytopenic purpura: a case report and literature review

Received: 15 October 2002 / Accepted: 7 March 2003

Abstract We describe a patient with systemic lupus erythematosus (SLE) who developed severe and acute thrombotic thrombocytopenic purpura (TTP). Detection of the fragmentation of peripheral red blood cells (RBC) helped the early diagnosis of TTP and the patient was rescued by extensive plasma exchange started promptly after the diagnosis. Because manifestations of TTP are similar to those in SLE, it is sometimes difficult to make an accurate diagnosis of TTP in SLE patients. We emphasise here the significance of the early diagnosis of TTP by the observation of fragmented RBC and the intensive therapy, including plasma exchange, for this very severe condition.

Keywords Plasma exchange · SLE · Plasmapheresis · Thrombotic microangiopathy, TTP

Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening disorder characterised by a pentad of signs, i.e. fever, microangiopathic haemolytic anaemia, thrombocytopenia, fluctuating neurological signs and renal involvement [1]. The characteristic feature of TTP is the fragmentation of peripheral red blood cells (RBC). Infection, drugs and pregnancy are known to trigger TTP, but its aetiology remains unclear. Because TTP is also associated with systemic lupus erythematosus (SLE), which may present similar clinical features, and because the effective treatments for these two diseases are different, differential diagnosis between them is important. We encountered a male patient with a long history of SLE who rapidly developed TTP.

K. Hamasaki · T. Mimura · H. Kanda · K. Kubo
K. Setoguchi · T. Satoh · Y. Misaki · K. Yamamoto
University of Tokyo, Tokyo, Japan

T. Mimura (✉)
Department of Rheumatology and Applied Immunology,
Saitama Medical School, 38 Morohongo,
Moroyama-machi, Iruma, Saitama 350-0495, Japan
e-mail: toshim@saitama-med.ac.jp
Tel.: +81-49-276-1462
Fax: +81-49-295-4849

Case report

A 39-year-old Japanese man was admitted to our hospital in December 1998 because of rapidly progressive thrombocytopenia, disturbed consciousness and fever. In his early 20s, he presented with Raynaud's phenomenon and serological examination revealed antinuclear antibody (ANA) and anti-RNP antibody positivity. Later, he experienced polyarthralgia and proteinuria and lymphocytopenia were detected at a local hospital. Twelve years ago a diagnosis of SLE was made and he received 40 mg of prednisolone (PSL) as an initial dose at the same hospital. His symptoms were stable with 10 mg PSL as a maintenance dose until a week ago. Five days before admission, general fatigue and haemoptysis suddenly appeared, and rapidly progressive thrombocytopenia was detected at that time, i.e. his platelet count dropped from $30.8 \times 10^4/\mu l$ to $1.8 \times 10^4/\mu l$. Because progressive proteinuria also appeared, acute exacerbation of SLE was suspected and PSL was increased to 30 mg at the hospital. Because high fever and disorientation developed in spite of the therapy, he was urgently admitted to our hospital. On examination, his blood pressure was 76/0 mmHg, and he was anaemic and somnolent. Laboratory examination revealed his blood haemoglobin concentration to be 7.1 g/dl, haematocrit 21.2 %, and platelet count 41 000/μl. Serum total protein was 4.4 g/dl, albumin 2.3 g/dl and lactate dehydrogenase (LDH) was elevated to 989 IU/l. His blood urea nitrogen (BUN) was 30.1 mg/dl, serum creatinine 2.0 mg/dl and C-reactive protein was 3.8 mg/dl. Prothrombin time was 83.9 %, activated partial prothrombin time was 35.1 s, fibrinogen 664 mg/dl and fibrin degradation product was 6.3 μg/ml. Serological examination revealed positive antinuclear antibody (ANA; 1:320), complement level was normal and anti-DNA antibody, Coombs' test, anticardiolipin–β_2-glycoprotein I complex antibody were negative. Massive proteinuria, haematuria and urinary casts were present. Electroencephalography (EEG) showed diffuse slow waves. Peripheral blood smear showed approximately 5% of fragmented RBC. A diagnosis of TTP was made and plasma exchange and methylprednisolone pulse therapy started immediately. In spite of the treatment, systemic convulsion and temporary cardiopulmonary arrest occurred on the following day. He was transiently under mechanical ventilation and transferred to the intensive care unit (ICU). Plasma

Table 1 Summary of reported cases complicated with SLE and TTP

#	Initial Disgnosis	Age	Sex	SLE	Prognosis	CS	PE	Other	Author	Year
1	SLE	16	F	Active	Died	−	−		Alpert 11	1968
2	SLE	39	F	active	died	+	−		Dekker 12	1974
3	SLE	17	M	active	survived	+	+		Dekker	1974
4	SLE	17	F	active	survived	+	+		Oen 13	1980
5	SLE	35	F	Inactive	died	+	−		Cecere 14	1981
6	TTP	12	F		survived	−	−		Gatenby 15	1981
7	SLE	27	F	active	survived	+	+		Finkelstein 16	1982
8	SLE	38	F	Inactive	survived	+	+		Becker 17	1985
9	SLE	31	F	Inactive	survived	+	−		Dixit 18	1985
10	SLE	50	F	Inactive	survived	+	+		Gelfand 19	1985
11	SLE	21	F	active	survived	+	+	AZ	Gelfand	1985
12	SLE	40	F	active	survived	+	+	AZ, CY	Fox 20	1986
13	SLE	42	F	active	died	+	+		Fox	1986
14	SLE	47	F	Inactive	survived	+	−		Itoh 21	1990
15	SLE	31	F	Inactive	died	+	+		Itoh	1990
16	TTP	10	F	active	survived	−	+		Jonsson 22	1990
17	SLE	19	F	active	survived	−	+	CY	Hess 23	1992
18	SLE	32	F	active	survived	−	+	CY	Hess	1992
19	TTP	30	F		survived	−	+		Simeon-Aznar 24	1992
20	SLE	41	F	Inactive	survived	+	+	VCR, IVIG	Stricker 4	1992
21	SLE	22	F	active	died	−	+	CY	Braun 25	1993
22	SLE	20	F	Unknown	died	−	−		Porta 26	1993
23	SLE	26	F	Unknown	survived	−	+		Porta	1993
24	SLE	52	F	unknown	died	−	+	IVIG	Porta	1993
25	SLE	26	F	Unknown	died	−	+	IVIG	Porta	1993
26	TTP	30	F		survived	−	+		Bray 27	1994
27	SLE	71	F	active	survived	−	+	CY, IVIG	Jain 28	1994
28	SLE	48	F	active	survived	−	+	CY, VCR, IVIG	Jain	1994
29	SLE	30	F	active	died	−	+	VCR	Jain	1994
30	SLE	56	F	Inactive	survived	+	−	CY	Jain	1994
31	SLE	28	M	Inactive	died	−	+	CY	Jain	1994
32	SLE	66	F	Inactive	survived	−	+	VCR	Jain	1994
33	SLE	38	F	active	died	−	+	CY, VCR	Nesher 29	1994
34	SLE	35	F	active	survived	−	+		Nesher	1994
35	Simultaneous	27	F	active	survived	−	+		Nesher	1994
36	Simultaneous	39	F	active	survived	−	+	CY, VCR	Nesher	1994
37	TTP	23	F		Survived	−	+		DiPietro 30	1996
38	Simultaneous	25	M	active	survived	+	+	VCR	Kaloterakis 6	1996
39	Simultaneous	24	M	active	survived	−	+	CY	Lim 31	1996
40	TTP	17	M		survived	−	+		Myung 32	1996
41	Simultaneous	14	F	active	died	+	+		Caramaschi 5	1998
42	Simultaneous	35	F	active	survived	+	+		Caramaschi	1998
43	SLE	52	F	active	survived	+	+		Caramaschi	1998
44	SLE	41	F	Inactive	died	+	+		Jorfen 7	1998
45	SLE	32	F	Inactive	died	+	+	CY	Jorfen	1998
46	Simultaneous	46	F	active	died	−	+	CY	Musio 1	1998
47	SLE	16	F	inactive	survived	+	+	CY	Perez-Sanchez 8	1999
48	Simultaneous	17	M	active	survived	+	+	CY	Perez-Sanchez	1999
49	SLE	38	F	active	died	+	+	VCR, IVIG	Musa 9	2000
50	TTP	23	F		survived	+	+		Musa	2000
51	Simultaneous	33	F	active	died	+	+	CY	Nanke 10	2000
52	Simultaneous	12	F	active	survived	+	−	IVIG	Gungor 33	2001
53	Simultaneous	15	F	active	suvivied	+	+	CY	Sakarcan 34	2001
54	Simultaneous	34	F	active	died	+	+	VCR, IVIG, CY	Vaidya 35	2001
55	SLE	39	F	active	survived	+	+	VCR, CY	Vaidya	2001
56	SLE	39	M	active	survived	+	+		Present case	2002

CS; corticosteroid, PE; plasmapheresis or plasma-exchange, AZ; azathiopurine, CY; cyclophosphamide, VCR; vincristine, IVIG; intravenous immunoglobulin G infusion

exchange was continued for 4 more consecutive days. Steroid pulse therapy for 2 more days was followed by oral PSL 50 mg/day. With these intensive therapies his consciousness level became normal, the fragmented RBC diminished, and the anaemia and thrombocytopenia were markedly improved. TTP was not revived thereafter, but the massive proteinuria persisted. As renal biopsy revealed diffuse proliferative lupus nephritis (WHO class IV + V), monthly intravenous cyclophosphamide therapy was begun. Proteinuria was reduced and a partial response was obtained for more than 3 years.

Table 2 Relationship between the mortality rate and the initial diagnosis

Initial diagnosis	Patients	Died	Mortality (%)
TTP	7	0	0*
Simultaneous	12	4	33.3
SLE	37	15	40.5*
Total	56	19	33.9

Discussion

TTP has been sporadically reported in patients with SLE, although the relationship between these two conditions has not been well defined. SLE and TTP share similar clinical symptoms, such as anaemia, thrombocytopenia, central nervous symptoms, renal insufficiency and fever; however, effective treatments for them are different. Plasma exchange is now considered the most effective for TTP [2], whereas its effectiveness in SLE is controversial [3]. Therefore, the differential diagnosis is very important, although their similarities in clinical manifestations sometimes make it very difficult. One of the most significant observations for the diagnosis of TTP is fragmentation of red blood cells, which is hardly seen in SLE. The recognition of fragmented RBC, or schistocytes, in our patient led us to the diagnosis of TTP.

We thoroughly reviewed the English-language literature on the coexistence of SLE and TTP. Cumulatively, we found 56 cases, including our patient [4–35] (Table 1). Of these 56 cases, seven were male and 49 were female. The overall mortality rate was 33.9% (19 of 56 patients died). The mortality rate of TTP patients with SLE treated with plasmapheresis or plasma exchange was 31.9%, whereas that in patients without plasmapheresis or plasma exchange was 44.4%. Although plasma exchange dramatically improved the prognosis of TTP, e.g. survival rate of 91% [36], the mortality of the patients with TTP complicated by SLE was still relatively high. The onset of SLE preceded TTP in more than half of the cases (37/56; 66.1%). In seven cases the diagnosis of TTP was made before that of SLE, and in 12 cases SLE and TTP occurred simultaneously (Table 2). It is noteworthy that all seven patients in whom TTP preceded SLE survived, and four of the 12 in whom SLE and TTP occurred simultaneously died (33.3%). On the other hand, 15 out of 37 patients in whom SLE preceded TTP died (40.5%). Of interest was that the mortality rate was significantly higher in the patients who had SLE preceding TTP than in those with TTP before SLE ($P < 0.05$). It is possible that the symptoms of TTP were misdiagnosed as those of SLE when SLE pre-existed. Out of the 37 patients with SLE preceding TTP, SLE was active in 20 cases and inactive in 13 when TTP occurred. In four cases the activity of SLE was not described. Seven out of the 20 patients with active SLE described above died (35.0%), and five of the 13 with inactive SLE died (38.5%). It should be noted that TTP with a poor prognosis occurred in SLE patients even when SLE was inactive.

Recently, marked progress has been made on the pathogenesis of TTP. The existence of abnormal, unusually large multimers of von Willebrand factor (vWF) in the plasma of patients with TTP was reported [37]. In 1998, Furlan et al. reported that the activity of vWF-cleaving protease is low in the plasma of TTP patients [38]. Another interesting paper has demonstrated that the activity of vWF-cleaving protease is disturbed by the autoantibody to this protease in TTP [39]. These reports suggested that TTP, or at least a part of TTP, might be an autoimmune disease. In this sense, the coexistence of SLE and TTP might be pathogenically significant. On the other hand, it has recently been reported that reduced activity of vWF-cleaving protease is associated with thrombocytopenic disorders, not only to TTP [40]. More data are necessary in this matter. Finally, the activity of vWF-cleaving protease or autoantibody to the protease was not measured in our case during this episode.

In conclusion, because TTP is a rare but life-threatening complication of SLE, early suspicion of TTP and examination of RBC fragmentation in this condition are important. Early diagnosis of TTP, prompt and intensive plasmapheresis or plasma exchange, and probably additional immunosuppressive therapy for active SLE, may improve the prognosis.

References

1. Musio F, Bohen EM, Yuan CM, Welch PG (1998) Review of thrombotic thrombocytopenic purpura in the setting of systemic lupus erythematosus. Semin Arthritis Rheum 28: 1–19
2. Rock GA, Shumak KH, Buskard NA et al. (1991) Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med 325: 393–397
3. Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM (1992) A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. N Engl J Med 326: 1373–1379
4. Stricker RB, Davis JA, Gershow J, Yamamoto KS, Kiprov DD (1992) Thrombotic thrombocytopenic purpura complicating systemic lupus erythematosus. Case report and literature review from the plasmapheresis era. J Rheumatol 19: 1469–1473
5. Caramaschi P, Riccetti MM, Pasini AF, Savarin T, Biasi D, Todeschini G (1998) Systemic lupus erythematosus and thrombotic thrombocytopenic purpura. Report of three cases and review of the literature. Lupus 7: 37–41
6. Kaloterakis A, Vaiopoulos G, Filiotoy A et al. (1996) Concurrent development of thrombotic thrombocytopenic purpura and systemic lupus erythematosus in a male patient. Clin Exp Rheumatol: 14: 581–582
7. Jorfen M et al. (1998) Fulminant thrombotic thrombocytopenic purpura in systemic lupus erythematosus. Scand J Rheumatol 27: 76–77
8. Perez-Sanchez I, Anguita J, Pintado T (1999) Use of cyclophosphamide in the treatment of thrombotic thrombocytopenic purpura complicating systemic lupus erythematosus: report of two cases. Ann Hematol 78: 285–287
9. Musa MO et al. (2000) Fulminant thrombotic thrombocytopenic purpura in two patients with systemic lupus erythematosus and phospholipid antibodies. Eur J Haematol 64: 433–443

10. Nanke Y, Akama H, Yamanaka H, Hara M, Kamatani N (2000) Progressive appearance of overlap syndrome together with autoantibodies in a patient with fatal thrombotic microangiopathy. Am J Med Sci 320: 348–351
11. Alpert LI (1968) Thrombotic thrombocytopenic purpura and systemic lupus erythematosus. J Mount Sinai Hosp NY 35: 165–173
12. Dekker A, O'Brien ME, Cammarata RJ (1974) The association of thrombotic thrombocytopenic purpura with systemic lupus erythematosus. Am J Med Sci 267: 243–249
13. Oen K, Petty RE, Scoroeder ML, Briggs EJ, Bishop AJ (1980) Thrombotic thrombocytopenic purpura in a girl with systemic lupus erythematosus. J Rheumatol 7: 727–729
14. Cecere FA, Yoshimoya S, Pope RM (1981) Fatal thrombotic thrombocytopenic purpura in a patient with systemic lupus erythematosus. Arthritis Rheum 24: 550–553
15. Gatenby PA, Smith H, Kirwan P, Leuer CS (1981) Systemic lupus erythematosus and thrombotic thrombocytopenic purpura. A case report and review of literature. J Rheumatol 8: 504–550
16. Finkelstein R, Markel A, Carter A, Brook JG (1982) Plasma infusions in thrombotic thrombocytopenic purpura complicating systemic lupus erythematosus: successful outcome. Postgrad Med J 58: 577–579
17. Becker RC, Giuliani M, Weick JK (1985) Thrombotic thrombocytopenic purpura in a patient with systemic lupus erythematosus. Cleveland Clin Q 52: 409–415
18. Dixit R, Krieg AM, Atkinson JP (1985) Thrombotic thrombocytopenic purpura developing during pregnancy in a C2-deficient patient with a history of systemic lupus erythematosus. Arthritis Rheum 28: 341–344
19. Gelfand J, Truong L, Stern L, Pirani CL, Appel GB (1985) Thrombotic thrombocytopenic purpura syndrome in systemic lupus erythematosus: treatment with plasma infusion. Am J Kidney Dis 6: 154–160
20. Fox DA, Faix JD, Coblyn J, Fraser P, Smith B, Weinblatt ME (1986) Thrombotic thrombocytopenic purpura and systemic lupus erythematosus. Ann Rheum Dis 45: 319–322
21. Itoh Y, Sekine H, Hosono O et al. (1990) Thrombotic thrombocytopenic purpura in two patients with systemic lupus erythematosus: clinical significance of anti-platelet antibodies. Clin Immunol Immunopathol 57: 125–136
22. Jonsson OG, Fink CW (1990) Systemic lupus erythematosus presenting as thrombotic thrombocytopenic purpura. J Rheumatol 17: 973–974
23. Hess DC, Sethi K, Awad E (1992) Thrombotic thrombocytopenic purpura in systemic lupus erythematosus and antiphospholipid antibodies: effective treatment with plasma exchange and immunosuppression. J Rheumatol 19: 1474–1478
24. Simeon Aznar CP, Cuenca-Luque R, Fonollosa-Pla V, Bosch-Gil JA (1992) Thrombotic thrombocytopenic purpura preceding systemic lupus erythematosus. Ann Rheum Dis 51: 396–398
25. Braun J, Sieper J, Schwarz A et al. (1993) Widespread vasculopathy with hemolytic uremic syndrome, perimyocarditis and cystic pancreatitis in a young woman with mixed connective tissue disease. Rheumatol Int 13: 31–36
26. Porta C, Bobbio-Pallavicini E, Centurioni R, Caporali R, Montecucco CM (1993) Thrombotic thrombocytopenic purpura in systemic lupus erythematosus. J Rheumatol 20: 1625–1626
27. Bray VJ, West SG, Kristo DA (1994) Simultaneous presentation of thrombotic thrombocytopenic purpura and systemic lupus erythematosus. South Med J 87: 827–830
28. Jain R, Chartash E, Susin M, Furie R (1994) Systemic lupus erythematosus complicated by thrombotic microangiopathy. Semin Arthritis Rheum 24: 173–182
29. Nesher G, Hanna VE, Moore TL, Hersh M, Osborn TG (1994) Thrombotic microangiopathic hemolytic anemia in systemic lupus erythematosus. Semin Arthritis Rheum 24: 165–172
30. Di Pietro G, Menicucci A, Venturini S, Avanti G (1996) A case of thrombotic thrombocytopenic purpura preceding onset of systemic lupus erythematosus. J Clin Apheresis 11: 51–52
31. Lim GT, Kim SS, Park SH et al. (1992) Thrombotic thrombocytopenic purpura-like syndrome associated with systemic lupus erythematosus. J Korean Med Sci 7: 66–70
32. Myung SJ, Yoo B, Lee KH et al. (1996) A case of systemic lupus erythematosus developing two years after remission of thrombotic thrombocytopenic purpura. Korean J Intern Med 11: 178–182
33. Gungor T, Furlan M, Lammle B, Kuhn F, Seger RA (2001) Acquired deficiency of von Willebrand factor-cleaving protease in a patient suffering from acute systemic lupus erythematosus. (letter) Rheumatology 40: 940–942
34. Sakarcan A, Stallworth J (2001) Systemic lupus erythematosus and thrombotic thrombocytopenic purpura: a case and review. Pediatr Nephrol 16: 672–674
35. Vaidya S, Abul-ezz S, Lipsmeyer E (2001) Thrombotic thrombocytopenic purpura and systemic lupus erythematosus. Scand J Rheumatol. 30: 308–310
36. Bell WR, Braine HG, Ness PM, Kickler TS (1991) Improved survival in thrombotic thrombocytopenic purpura–hemolytic uremic syndrome. Clinical experience in 108 patients. N Engl J Med 325: 398–403
37. Moake JL, Rudy CK, Troll JH et al. (1982) Unusually large plasma factor VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. N Engl J Med 307: 1432–1435
38. Furlan M, Robles R, Galbusera M et al. (1998) von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic–uremic syndrome. N Engl J Med 339: 1578–1584
39. Tsai HM, Lian EC (1998) Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 340: 1585–1594
40. Moore JC, Hayward CPM, Warkentin TE, Kelton G (2001) Decreased von Willebrand factor protease activity associated with thrombocytopenic disorders. Blood 98: 1842–1846