The Frequency of Thrombotic Thrombocytopenic Purpura in Patients with Systemic Lupus Erythematosus Undergoing Kidney Biopsy

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ABSTRACT. ***Objective.*** To characterize the frequency of thrombotic thrombocytopenic purpura (TTP) among patients with systemic lupus erythematosus (SLE) undergoing kidney biopsy.
Methods. A retrospective review of all renal biopsies of patients with SLE at Rush-Presbyterian-St. Luke's Medical Center was performed for the years 1989 to 2001.
Results. Four cases of clinical and histopathological TTP were identified among the 257 patients with SLE who underwent renal biopsy during the 12 year study period.
Conclusion. TTP appears to occur at higher than expected frequency among SLE patients undergoing biopsy for unexplained renal failure. (J Rheumatol 2003;30:1227–30)

Key Indexing Terms:
THROMBOTIC THROMBOCYTOPENIC PURPURA
SYSTEMIC LUPUS ERYTHEMATOSUS VON WILLEBRAND CLEAVING PROTEASE

Thrombotic thrombocytopenic purpura (TTP), originally described by Moschcowitz in 1924, is a rare syndrome characterized by a pentad of acute renal impairment, thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, and fever[1-3]. The incidence of TTP in the United States' general population has been estimated to be 3.7 cases/million[4]. Untreated TTP is often rapidly fatal, whereas current plasmapheresis-based therapy may be lifesaving[3,4]. Although the coexistence of SLE and TTP has been considered uncommon, there have been multiple case reports of TTP associated with systemic lupus erythematosus (SLE)[5-9], and a recent autopsy series concluded that TTP may be common in late-stage SLE[7]. We evaluated the frequency of unanticipated TTP among SLE patients undergoing renal biopsy.

MATERIALS AND METHODS

All renal biopsies performed on patients with a diagnosis of SLE at Rush-Presbyterian-St. Luke's Medical Center between the years 1989 and 2001 (n = 257) were reviewed for pathological evidence of renal thrombotic microangiopathy. Case histories of those patients with renal thrombotic microangiopathy were then further examined for clinical evidence of TTP. TTP was defined by the presence of Coomb's negative microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute renal impairment not explained by other conditions[2,3]; fever and neurologic impairment were considered to be supportive evidence.

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RESULTS

Detailed review of 257 consecutive renal biopsies in SLE patients identified 7 cases of renal thrombotic microangiopathy, 4 of whom had been hospitalized for clinical TTP (Table 1). Details of the TTP cases are provided below.

Case 1. A 23-year-old woman with SLE was admitted for worsening peripheral edema. Initial evaluation revealed creatinine 2.6 mg/dl (baseline 1.1 mg/dl), blood urea nitrogen (BUN) 58 mg/dl, hemoglobin 5.6 g/dl with schistocytes, platelets 53,000/mm^3, serum lactate dehydrogenase

Table 1. Renal biopsy results.

Pathological Diagnosis	Cases (n = 257)
WHO I (normal)	2
II (mesangial GN)	33
III (focal and proliferative GN)	47
IV (diffuse GN)	49
V (membranous)	87
III & Diabetic glomerulosclerosis	1
V & interstitial nephritis	1
Acute tubular necrosis	2
Global glomerulosclerosis	15
Focal segmental glomerulosclerosis	9
Membranous GN & interstial nephritis	1
Chronic interstitial nephritis	2
Thrombotic microangiopathy (TMA)	4
WHO IV & TMA	1
WHO V & TMA	2
Segmental glomerular sclerosis & TMA	1

GN: glomerulonephritis

(LDH) 2142 IU/l, white blood cell count (WBC) 10,800/mm^3, haptoglobin 6 mg/dl (normal > 31), negative direct Coombs test, antinuclear antibodies (ANA) 1:320, dsDNA 48 IU, and low complements (Table 2). TTP was diagnosed on hospital day 3 based on renal impairment, Coombs negative MAHA, and thrombocytopenia. She clinically improved with methylprednisolone 500 mg IV qd for 3 days and daily plasmapheresis for 10 days. Renal biopsy performed on day 3 subsequently showed widespread thrombotic microangiopathy and World Health Organization (WHO) class IV diffuse glomerulonephritis. Von Willebrand cleaving protease activity was found to be moderately decreased and antiphospholipid antibodies(aPL) were absent.

Case 2. A 54-year-old woman with SLE presented with headache, emesis, hypertension, and tonic-clonic seizures. Initial evaluation revealed hemoglobin 11.9 mg/dl with schistocytes, platelets 76,000/mm^3, BUN 85 mg/dl, creatinine 7.5 mg/dl, LDH 1522 IU/l, absence of aPL, and normal head computerized tomography (Table 2). She was hemodialyzed and received pulse methylprednisolone 1 g daily for 3 days. On day 2, the hemoglobin and platelet count deteriorated to 8.8 mg/dl and 64,000/mm^3, respectively. On day 4 TTP was diagnosed based on the presence of thrombocytopenia, MAHA, neurologic dysfunction, and acute renal impairment, and daily plasmapheresis was initiated. A renal biopsy performed on day 3 subsequently revealed thrombotic microangiopathy. WHO classification was not assigned due to the absence of immune complex-induced glomerulonephritis.

Case 3. A 44-year-old woman with a history of SLE complicated by chronic anemia, serositis, Raynaud's phenomenon, rash, ANA 1:1280, and polyarthritis was admitted with dyspnea, fatigue, and fever. Laboratory evaluation included BUN 10 mg/dl, creatinine 0.9 mg/dl, platelets 15,000/mm^3, hemoglobin 5.6 mg/dl with schistocytes, LDH 1887 IU/l, negative Coombs test, and the absence of aPL (Table 2). Urinalysis revealed 5 RBC/hpf, 15 WBC/hpf; 24-h urine collection had 6.8 g protein. After transfusion of platelets and packed RBC, and treatment with methlyprednisolone 1 g daily for 3 days she was discharged on prednisone 60 mg/day. Twelve days later she was readmitted with a BUN 148 mg/dl, creatinine 8.2 mg/dl, platelets 82,000/mm^3, hemoglobin 7.3 mg/dl with schistocytes, LDH 4381 u/l, and normal coagulation tests. Twenty-one days after the initial admission, a 7 day course of daily plasmapheresis was begun for TTP. Renal biopsy done the next day revealed thrombotic microangiopathy superimposed upon membranous nephritis (WHO V).

Case 4. A 44-year-old woman was admitted with progressive dyspnea on exertion, scleral icterus, and hemolytic anemia. Laboratory evaluation revealed: BUN 17 mg/dl, creatinine 2.4 mg/dl, WBC 3.28/mm^3, hemoglobin 6.7 g/dl, platelets 32,000/mm^3 with schistocytes, reticulocytes

Table 2. Demographic and laboratory values. All 4 patients were women.

	Case 1	Case 2	Case 3	Case 4
Age yrs	23	54	44	44
Race	Caucasian	AA	AA	AA*
Initial platelet count (mm^3)	53,000	76,000	15,000	32,000
Discharge platelet count (mm^3)	117,000	230,000	230,000	168,000
Initial hemoglobin (g/dl)	5.6	11.9	5.6	6.7
Discharge hemoglobin (g/dl)	8.8	9.5	9.1	10.3
LDH (200–650 U/l)	2142	1522	1887	1283
Schistocytes	Present	Present	Present	Present
Coombs test	Negative	Negative	Negative	Negative
Initial creatinine (mg/dl)	2.4	7.5	0.9	2.4
Discharge creatinine (mg/dl)	1.7	6.4	8	4.3
Total bilirubin (0.2–1.3 mg/dl)	2.1	1.2	1.1	
Indirect bilirubin (mg/dl)	1	1		
PT (11.4–12.9s)	14.3	12.2	13	12.6
INR	1.03	0.97	1.2	1.11
PTT (23–33s)	21	27	26	23
ANA titer	320	1280	1280	1280
dsDNA (IU)	48			0
RNP (0–20 EU)	0.23		0.9	> 200
Smith (0–20 EU)	0.18		1.5	19.7
C3 level (77–179 mg/dl)	35	79	110	56
C4 level (16–58 mg/dl)	9	22	28	6
Antiphospholipid antibodies**	Negative	Negative	Negative	Negative
vWF cleaving protease activity	Decreased			
Delay in plasmapheresis (days)	3	4	21	1

* AA: African American. ** cardiolipin antibody, lupus anticoagulant. vWF: von Willebrand factor.

Table 3. Distinguishing TTP and active SLE.

Characteristics	TTP	SLE
Thrombocytopenia	Non-immune	Immune thrombocytopenic purpura
	Platelets consumed in thrombi	IgG to platelets
Hemolytic Anemia	Microangiopathic	Immune
LDH	Elevated	Elevated
Peripheral smear	Schistocytes from vascular trauma	Spherocytes from anti-RBC Ab & spleen
Bilirubin	High	High
Coombs test	Negative	Positive
Neurologic dysfunction	Delirium, evanescent focal neurologic deficits	Cerebritis, seizures, myelitis, CVA
Fever	Yes	Yes
Acute renal impairment	Yes	Yes
Renal biopsy	Thrombotic microangiopathy	Nephritis, thrombotic microangiopathy
Urinalysis	Proteinuria	Proteinuria, casts
Coagulation profile	Normal PT, PTT	Normal PT, PTT (PTT elevated in APS)
Complements	Normal	Normal or depressed
Therapy	Plasmapheresis	Corticosteroids, cyclophosphamide

CVA: cerebrovascular accident; APS: antiphospholipid antibody syndrome.

4.89%, LDH 1283 IU/l, haptoglobin 36, total bilirubin 1.5 mg/dl, and normal coagulation tests (Table 2). Urinalysis revealed 20 WBC/hpf, 8 RBC/hpf, > 300 mg/dl protein, and 12 granular casts. TTP was diagnosed on day 2 based on MAHA, thrombocytopenia, and renal impairment, and an 8 day course of plasmapheresis was initiated. Rheumatology evaluation revealed a history of synovitis, ANA titer of 1:1280, RNP/Smith 200 IU, Smith 19.7 IU, and the absence of aPL, and a diagnosis of SLE was made. Renal biopsy performed on day 4 revealed thrombotic microangiopathy without evidence of glomerulonephritis.

DISCUSSION

Although in retrospect the diagnosis of TTP in these 4 SLE patients was unambiguous, the diagnosis was delayed in each case. Hemolytic anemia, thrombocytopenia, renal impairment, fever, and neurologic dysfunction are characteristic of each disease process[5] (Table 3). Thus it is possible to mistakenly attribute signs of the TTP pentad to active SLE unless a high degree of suspicion is maintained. In both conditions, hemolytic anemia is characterized by elevated LDH, elevated indirect bilirubin, and decreased haptoglobin; however, the hemolytic anemia of TTP is microangiopathic (characterized by schistocytes) and is Coomb's negative, whereas in SLE it is autoimmune and thus characterized by spherocytes and is Coomb's positive[5]. Similarly, whereas the thrombocytopenia of TTP results from consumption of platelets in platelet-fibrin thrombi deposited throughout the vasculature, in SLE it is usually immune mediated comparable to immune thrombocytopenia purpura[5].

Recent evidence has suggested deficiencies in von Willebrand cleaving protease results in uncleaved von Willebrand factor multimers. These multimers are capable of agglutinating circulating platelets and presumably contributing to the pathogenesis of the thrombotic microangiopathy in TTP[10-13]. Furlan, *et al* has reported these multimers in association with a circulating IgG inhibitor to von Willebrand cleaving protease[13,14]. Of interest, we assayed for this enzyme in the first case of this series and found its activity to be severely decreased.

Four cases of TTP were identified among the 257 patients with SLE who underwent renal biopsy; it should be noted that our selection criteria may have missed additional TTP cases that were not biopsied or who died of TTP prior to biopsy. This series suggests that TTP may occur at higher than expected frequency in patients with SLE undergoing biopsy for unexplained kidney dysfunction. The recognition of the coexistence of TTP and SLE is essential in order to promptly initiate life saving therapy with plasmapheresis.

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