Letters to the Editor

Analyses of ADAMTS13 activity and its inhibitor in patients with thrombotic thrombocytopenic purpura secondary to connective tissue diseases: Observations in a single hospital

Sirs,

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder characterized by generalized platelet thrombi in arterioles and capillaries (1, 2). A severe decrease of a disintegrin and metalloprotease with thrombospondin type I motif 13 (ADAMTS13) activity and positive ADAMTS13 inhibitor have been considered to be characteristic features of classical TTP (3, 4). TTP has been described as a rare but severe complication associated with connective tissue diseases (CTDs) (5). In this study, we examined whether patients with TTP secondary to CTDs have a decreased ADAMTS13 activity and ADAMTS13 inhibitor.

Among the number of 1056 patients with CTDs hospitalized in Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital from 1978 to 2004, 12 patients were diagnosed as having TTP with four or five of the pentad of TTP (Table I). The incidences of TTP secondary to CTDs were estimated as follows: 12 of 1056 patients (1.14%) as a whole, 3 of 53 (5.66%) in systemic sclerosis, 2 of 66 (3.03%) in vasculitic syndrome, 5 of 222 (2.25%) in systemic lupus erythematosus, 1 of 65 (1.54%) in myositis, and 2 of 132 (1.52%) in primary Sjögren's syndrome. All the patients were female, and none of them was pregnant. Ten patients had active CTDs. Anti-phospholipid antibody was detected in none of the nine patients examined. None of them received cyclosporine, antimalarial, ticlopidine, and clopidogrel before the development of TTP. In one patient, TTP developed at the diagnosis of CTD, and in 11 patients 0.2 to 16 years (median 1 year) after the diagnosis of CTDs. The mortality rates were 58% overall, and 88% and 0% in patients with and without neurological disorders, respectively.

Among the eight patients whose ADAMTS13 activity was measured (6, 7), three had a moderately decreased (3 to 25%), two a mildly decreased (25 to 50%), and three a normal activity (more than 50%); the ADAMTS13 inhibitor was detected at a low titer in only one patients. In five of the eight patients tested, unusually-large von Willebrand factor (VWF) multimers were clearly detected, and plasma VWF antigen levels were markedly high, ranging from 440% to 1400%.

In the present study, none of our patients had a severely decreased ADAMTS13 activity, indicating that the pathogenesis of TTP secondary to CTDs is not necessarily the same as that of classical TTP. Mannucci *et al.* (8) reported that patients with systemic lupus erythematosus and systemic sclerosis had low but detectable levels of ADAMTS13 without inhibitor, although they had no sign or symptom of TTP. On the other hand, Matsumoto *et al*. (9) reported that 10 of 43 patients with TTP secondary to CTDs had a severely decreased ADMATS13 activity and its inhibitor was detected in 13 of 27 patients tested. From these findings, it appears that a severely decreased ADAMTS13 activity caused by its inhibitor is involved in some patients with TTP secondary to CTDs, but a mildly to moderately decreased ADAMTS13 level can be a finding in CTD patients with or without TTP.

Particularly interesting was the result that unusually-large VWF multimers were detected in five of eight patients tested. In cases of CTDs, the damage of the endothe-

Table 1. Clinical features and measurement of ADAMTS13 activity, its inhibitor, ULVWFM, and VWF Ag in patients with TTP secondary to CTDs

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				Underlying CTDs							
Patient No.	Sex/age (years)	Disease	Activity	Positive autoantibody*	Treatment	TTP treatment	Outcome	ADAMTS13 activity (%)	Inhibitor (BU/mL)	ULVWFM	VWF Ag (%)
1	F / 28	SLE	None	ANA, DNA	PSL 5 mg/day	PE, mPSL 64mg/day dipyridamole, aspirin	Recovered	NA	NA	NA	NA
2	F / 55	SSc, PM	+	ANA, DNA, Scl-70, RF	PSL 1.4 mg/kg, d-PC	PE, dipyridamole, aspirin	Died	NA	NA	NA	NA
3	F / 67	SjS	NA	ANA, RF	None	PI	Died	NA	NA	NA	NA
4	F / 50	MPA	+	MPO-ANCA, PR3-ANCA	PSL 1.2 mg/kg, CPA	PI	Recovered	NA	NA	NA	NA
5	F / 74	SjS	+	ANA, RF, MPO-ANCA, PR3-ANCA	None	PI, PSL 0.8mg/kg	Died	70	< 0.5	None	440
6	F / 83	SSc	+	ANA	None	PE, dipyridamole, VCR PSL 1.2mg/kg	Died	20	< 0.5	+	500
7	F / 68	GS, MPA	+	RF, MPO-ANCA, GBM	PSL 1.2 mg/kg, CPA	PE	Died	48	< 0.5	None	720
8	F / 42	SLE, SjS	+	ANA- ds-DNA	PSL 0.8 mg/kg	PE	Recovered	17	< 0.5	+	560
9	F / 25	SLE, SjS	+	ANA, ds-DNA, RNP	PSL 1.2 mg/kg	PE	Died	26	< 0.5	+	1400
10	F / 48	SLE	+	ANA, RNP, Sm, SS-A, SS-B	PSL 1.2 mg/kg	PI	Recovered	66	< 0.5	+	560
11	F / 33	SLE	+	ANA, ds-DNA, SS-A	PSL 1.2 mg/kg	PE, PI	Recovered	51	< 0.5	+	680
12	F / 72	SSc	+	ANA, Scl-70, SS-A	PSL 0.6 mg/kg	ACE inhibitor	Died	10	0.5	None	1000

ADAMTS: a disintegrin and metalloprotease with thrombospondin type I motif; TTP: thrombotic thrombocytopenic purpura; CTDs: connective tissue diseases; ULVWFM: unusually-large von Willebrand factor multimers; VWF Ag: von Willebrand factor antigen; F: female; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; PM: polymyositis; SjS: Sjögren's syndrome; MPA: microscopic polyangiitis; GS: Goodpasture's syndrome; NA: not available; ANA: anti-nuclear antibody; RF: rheumatoid factor; MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibody; PR3: proteinase-3; GBM: glomerular basement membrane; PSL: prednisolone; d-PC: d-penicillamine; CPA: cyclophosphamide; PE: plasma exchange; mPSL: methylprednisolone; PI: plasma infusion; VCR: vincristine; ACE: angiotensin converting enzyme

*ANA was measured by immunofluorescent antibody technique, RF by nephelometry, and other autoantibodies by enzyme-linked immunoassay.

lium of capillaries caused by angiitis, the deposition of immune complexes, or certain drugs may result in a defective utilization of ADAMTS13 and the subsequent accumulation of unusually-large VWF multimers in the circulation. Since a markedly high level of plasma VWF antigen observed in our study appears to reflect a proportional increase in plasma unusually-large VWF multimers, it is conceivable that a decreased enzyme-to-substrate (ADAMTS13/unusually-large VWF multimers) ratio results in an accumulation of undigested unusually-large VWF multimers, leading to TTP.

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Fever with rash following zolendronic acid administration

Dear Sirs,
The amino-biphosphonate zolendronic acid is primarily used for the treatment of bone metastases and/or humoral hypercalcemia of malignancy, as well as in the management of Paget's disease (1). Allergic reactions with skin involvement (mainly pruritus, and hives), fever, and transient hematological changes (mainly leukocytosis with relevant lymphocytopenia) have been described within 3 days after biphosphonate infusion (2). We describe a patient presenting with protracted fever and a rash 10 days after zolendronic acid administration.
A 64-year-old woman was admitted due to fever and a skin rash. She suffered from neglected rheumatoid arthritis and received methotrexate, prednisone, folic acid, oral calcium and vitamin-D supplements. A dual energy x-ray absorptiometry showed a t-score of -3.5. Ten days prior to admission, and while afebrile, she was given zolendronic acid for osteoporosis according to a clinical protocol. Six hours later, the patient experienced fever (39ºC) with chills. The fever persisted, and 10 days later she developed a pruritic maculopapular rash in the lower extremities.
The patient was a housekeeper, non-smoker, did not drink alcohol, and recalled no allergic reactions. On admission, her temperature was 38.5°C. Physical examination revealed a confluent maculopapular rash in the medial aspects of both thighs (Fig. 1), and joint deformities of wrists, hands, ankles and knees.
Blood serology, blood and urine cultures and appropriate imaging techniques failed to disclose any infectious causes. Major laboratory findings were: increased C-reactive protein levels (CRP, 61mg/L) and erythrocyte sentimentation rate (48mm/h), while the white blood cell and eosinophil count were normal. The patient was treated with intravenous prednisone 25 mg/day and oral loratadine 10 mg/day. Two days later the rash subsided and the patient was afebrile.
A review of the available literature regarding serious skin reactions associated with biphosphonate administration discloses discontinuation of biphosphonate treatment due to fever and a cutaneous rash (3), generalized macupopapular rash with lesions in the buccal and genital mucosa and keratitis (4), superficial gyrate erythema, erythema multiforme and cutaneous rashes (5-7), as well as severe reactions, such as toxic epidermal necrolysis and pancytopenia (8, 9).
It is the first time that zolendronic acid is implicated in a protracted febrile reaction with skin rash. Although the drug was originally given for the treatment of osteoporosis, it is appreciated that the background of rheumatoid arthritis (putatively via cytokine release) may have played a role in the development of this adverse reaction.

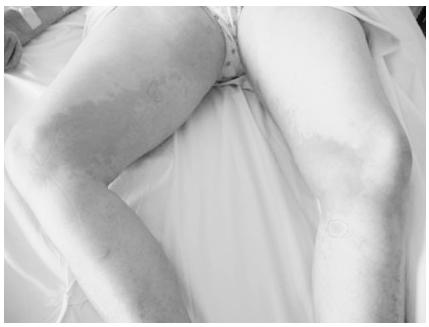

Fig. 1. Rash following zolendronic acid administration.

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