Original Article

Renal Thrombotic Microangiopathies Induced by Severe Hypertension

Bo ZHANG[1)], Changying XING[1)], Xiangbao YU[1)], Bin SUN[1)], Xiufen ZHAO[1)], and Jun QIAN[1)]

Renal thrombotic microangiopathy (TMA) is an uncommon vascular complication of severe hypertension. Until now, its clinical-pathological characteristics and renal survival have been unclear. Twenty-one patients with biopsy-proven renal TMA and with severe or malignant hypertension were retrospectively studied. All the patients exhibited severe hypertension, with systolic blood pressure at 200–280 mmHg and diastolic pressure at 110–180 mmHg. No patients had hemorrhagic manifestations. Elevated lactate dehydrogenase and thrombocytopenia were found in 6 and 5 patients, respectively. Significant proteinuria (>3 g/day) was present in 2 patients and microscopic hematuria in 18 patients. All patients presented with renal insufficiency (creatinine 3.1±2.1 mg/dL). The level of von Willebrand factor:antigen (vWF:Ag) in patients was not significantly higher than that in the healthy subjects, while the ADAMTS13 (a disintegrin and metalloprotease, with thrombospondin-1–like domains) activity was not significantly lower than that in the healthy subjects. Renal histology showed a TMA involving preglomerular arterioles and/or interlobular arteries characterized by fibrin deposits and vascular wall sclerosis. Fibrin glomerular microthrombi were not observed in these patients. Four patients required hemodialysis upon admission for severe acute renal failure. On follow-up, 3 patients had recovered normal renal function and 14 had mild renal insufficiency (creatinine 1.8±0.3 mg/dL), while 4 patients still required persistent hemodialysis. In conclusion, compared with patients having hemolytic uremic syndrome/thrombocytopenic purpura, our patients showed a low incidence of thrombocytopenia and better renal outcome. (*Hypertens Res* 2008; 31: 479–483)

***Key Words*: microangiopathy, kidney, hypertension**

Introduction

Thrombotic microangiopathies (TMA) are characterized by microangiopathic hemolytic anemia, thrombocytopenia, and functional impairment of various organ systems (*1*). The clinical presentation of TMA is thought to indicate either hemolytic uremic syndrome (HUS) or thrombocytopenic purpura (TTP). However, the etiology of TMA may be different from that of HUS or TTP. Malignancy, systemic vasculitis, sepsis, HELLP syndrome (Hemolytic anemia, Elevated Liver enzymes, and Low Platelet count), mitomycin, cyclosporine, tacrolimus, combinations of chemotherapeutic agents, and severe hypertension could also be associated with TMA (*1*, *2*). The pathological findings of TMA include fibrinoid necrosis, obstruction of vessel lumina, thickening of vessel walls, and endothelial cell injury. Malignant hypertension is often presented with progressive renal failure, heart failure, and encephalopathy. It is often associated with microangiopathic hemolytic anemia (*3*, *4*). The pathological changes from kidney damage in malignant hypertension are sometimes similar to renal lesions in HUS/TTP, leading to difficulty in the differential diagnosis for other TMA etiologies. Also, without knowledge of a patient's history, it may be difficult to distinguish HUS from severe hypertension (*5*).

In this report, we present our experience regarding the clin-

From the [1)]Department of Nephrology, First Affiliated Hospital of Nanjing Medical University, Nanjing, P.R. China.

Address for Reprints: Bo Zhang, M.D., Ph.D., Department of Nephrology, First Affiliated Hospital of Nanjing Medical University, Guangzhou Road 300#, Nanjing 210029, P.R. China. E-mail: zhangbo2003@medmail.com.cn

Received August 22, 2007; Accepted in revised form October 5, 2007.

ical-pathological characteristics and short-term follow-up of 21 patients, who presented with severe or malignant hypertension accompanied by biopsy-proven renal TMA lesions.

Methods

We retrospectively analyzed 21 patients (17 male and 4 female) with a median age of 33 years (range 23 to 59) enrolled between July 2003 and October 2006. The systolic blood pressure (BP) of all the patients was more than 200 mmHg, and the diastolic BP was more than 110 mmHg. The medical records were reviewed for the type of treatment administered, the clinical course, and the results of renal histology. No gastrointestinal diseases, infections, vasculitis, cyclosporine treatment, or pregnancy were identified in this group. All other diseases causing thrombocytopenia, in particular idiopathic thrombocytopenic purpura and disseminated intravascular coagulation, were excluded. Ten normal healthy controls were also included.

All patients underwent the following laboratory investigations before treatment: a complete blood count; biochemical tests such as those for serum aminotransferases, bilirubin, lactate dehydrogenase (LDH), blood urea nitrogen, and serum creatinine; direct Coombs test, antinuclear antibodies, coagulation studies, a urine test, and blood and stool cultures. Antinuclear antibody (ANA) was analyzed by indirect immunofluorescence using HEp-2 cells. Anti–double-stranded (ds) DNA, anti-neutrophil cytoplasmic antibody (ANCA), and anti-cardiolipin antibody (ACA, immunoglobulin G subtype) were analyzed by enzyme-linked immunosorbent assay using standard laboratory methods (Source of the assay kit).

Plasma von Willebrand factor (vWF) antigen (vWF:Ag) was measured by enzyme-linked immunosorbent assay as previously described (*6*). vWF-cleaving protease (ADAMTS13 [a disintegrin and metalloprotease, with thrombospondin-1–like domains]) activity was measured as previously described by Rick *et al*. (*7*). Briefly, ELISA plates were pre-coated with 200 μL/well of collagen type III at 5 μg/mL in collagen-coating buffer. Pre-coated plates were kept overnight at 4°C prior to use. Patient or normal plasma samples, 0.05 mL each, were placed in Slide-A-Lyzer mini-dialysis units (molecular weight: 10,000, Pierce Chemical, Rockford, USA) and immersed in reaction buffer (0.005 mol/L Tris, 0.1% Tween 20, pH 8.3 in 1.5 mol/L urea) for 3 h at 37°C. The baseline blood samples were kept at 37°C for 3 h. At the end of the 3 h incubation period, the dialyzed samples and the baseline samples were diluted 1/20 in dilution buffer. These diluted plasma samples (125 μL/well) were added in triplicate to the wells and incubated on a rocker for 1 h. The plates were then washed as above, and horseradish peroxidase–labeled anti-human vWF antibody was added (Dako, Glostrup, Denmark) at a dilution of 1/1,000. The antibody was incubated for 1 h at room temperature with rocking and then developed with *O*-phenylenediamine according to the manufacturer's directions. Plates were read immediately on a plate reader at 490 nm. Data were analyzed as the fraction of collagen binding activity remaining after dialysis compared to the collagen binding in the individual's baseline sample.

Table 1. Clinical Characteristic of Patients on Admission

	% (*n*)
Anemia	85.8 (18)
Hemoglobin ≥10 g/dL	42.9 (9)
Hemoglobin <10 g/dL	42.9 (9)
Elevated LDH	28.6 (6)
Abnormal bilirubin level	0.0 (0)
Thrombocytopenia	23.8 (5)
Hematuria	100.0 (21)
Gross hematuria	14.3 (3)
Microscopic hematuria	85.7 (18)
Proteinuria	100.0 (21)
Urine protein ≥3 g/24 h	9.5 (2)
Urine protein <3 g/24 h and ≥1 g/24 h	33.3 (7)
Urine protein <1 g/24 h	57.2 (12)
Renal insufficiency	100.0 (21)
Ccr <15 mL/min	19.0 (4)
Left ventricular failure	19.0 (4)
Renal replacement therapy	19.0 (4)

LDH, lactate dehydrogenase; Ccr, creatinine clearance.

Renal biopsies were performed in all of these patients with well-controlled blood pressure and recovered to levels defined as normal in coagulation studies. The time of renal biopsy after admission to the hospital ranged from 3 to 10 days. Renal specimens were fixed with 10% neutral buffered formalin and embedded in paraffin using routine procedures. Sections 2 μm in thickness were examined histologically with hematoxylin/eosin (HE), periodic acid-Schiff (PAS), silver methenamine, and Masson's trichrome staining. For immunohistology, sections were stained using antisera monospecific to IgG, IgA, IgM, C3, C4, and C1q. Renal histology of all patients showed narrowing of the lumina of the vasa afferentia caused by a thickened intima of onion-skin–like appearance and intravascular microthrombi in preglomerular lesions, while in glomerular lesions there was shrinkage of the glomerular basement membrane caused by ischemia without intraglomerular microthrombi. These findings were characteristic of one morphological form of HUS-TTP and also resembled renal lesions of primary malignant nephrosclerosis.

Data are expressed as the median and the range in parentheses. Differences among groups were assessed by one-way ANOVA with least significant difference (LSD) analysis using SPSS 10.0. A p value <0.05 was considered statistically significant. A p value <0.01 was considered strongly statistically significant.

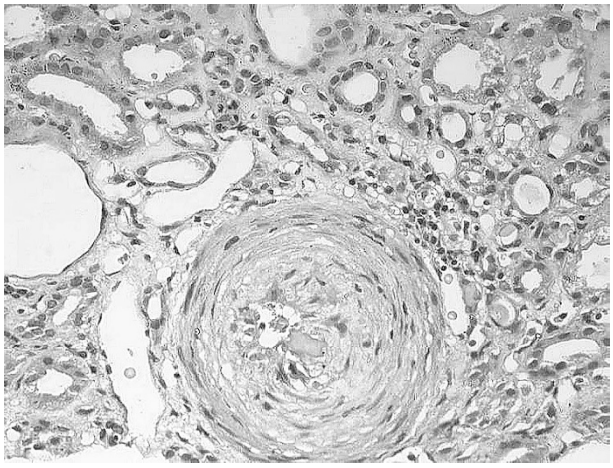

Fig. 1. *Interlobular artery occluded by fibrin-like thrombosis with endothelial thickening. PAS magnification: ×400.*

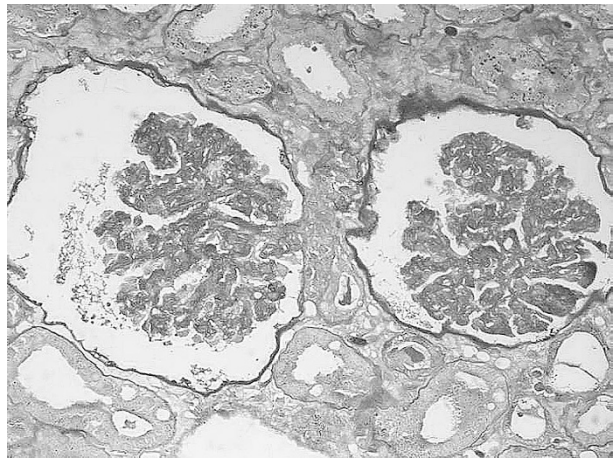

Fig. 2. *Glomerular ischemia: wrinkling of the glomerular capillary wall. PAS magnification: ×400.*

Results

Seventeen patients were presented to the hospital for headache and the other 4 patients with symptoms of acute left ventricular failure. On admission, all the patients exhibited severe hypertension, with systolic BP ranging from 200 to 280 mmHg and diastolic from 110 to 180 mmHg. No patient had hemorrhagic manifestations in skin such as petechia, purpura, or echymoses. No mental status changes or other neurological manifestations were observed in these patients. No patients had a history of chronic renal disease. Four patients had a history of hypertension ranging from 1 to 3 years but did not take any medication regularly. The clinical characteristics of these patients are summarized in Table 1.

Peripheral blood smear showed the presence of rare schistocytes in 3 patients. Ophthalmologic exam showed microangiopathy consistent with hypertension in 3 patients. No flame hemorrhages or papilledema was noted in all the 21 patients. Electrocardiogram and echocardiogram revealed left ventricular hypertrophy in all of the patients. Renal artery ultrasound and renography were performed to exclude renal artery stenosis. Arteriography was not performed. Immunologic profiles of these patients were negative for ANA, ANCA, and ACA. Anemia was observed in 18 patients, with hemoglobin ranging from 7.5 to 11 g/dL. Six patients presented with elevated LDH, ranging from 285 to 425 U/L (normal range 110–250 U/L). Thrombocytopenia was found in 5 patients, with platelet counts ranging from 76,000 to 92,000 μL^{-1}. Renal impairments, including hematuria and proteinuria, are listed in Table 1. Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level, and coagulation factors were normal. A differential diagnosis of disseminated intravascular coagulation was made if laboratory findings did not suggest the consumption of clotting factors with a prothrombin time of 15 s or longer. Significant proteinuria (>3 g/day) was present in 2 patients and microscopic hematuria in 18 patients. None of the patients had nephrotic syndrome. The kidney sizes of these patients were within normal range. All the patients showed impaired renal function with serum creatinine level up to 7.1 mg/dL (mean 3.1±2.1 mg/dL). Decreased creatinine clearance (Ccr), calculated by the usual formula, was found in all patients. The levels of vWF:Ag in these patients (85.5±35.2%) were not significantly higher than in healthy subjects (76.2±28.6%) ($p=0.093$), while the levels of plasma ADAMTS13 in these patients (74.9±16.2%) were not significantly lower than in healthy subjects (84.2±7.8%) ($p=0.089$).

Renal histology showed changes in TMA involving preglomerular arterioles and/or interlobular arteries characterized by fibrin deposits and vascular wall sclerosis. Fibrin deposits occluded the lumen of preglomerular arterioles and were also noted in the arteriolar wall. A high-power view of one artery showed smooth muscle cells of the arterial wall replaced by proteinaceous material, which is the typical change in TMA following arterial wall necrosis. Focal cortical necrosis was not observed. Glomerular ischemia was observed, characterized by flocculus retraction and/or wrinkling of the glomerular capillary wall (Figs. 1, 2). Characteristics of proliferate glomerulonephritis were not present. Fibrin glomerular microthrombi were not observed in these patients. Progressive focal tubular atrophy, tubular basement membrane thickening, and interstitial fibrosis were found in these patients. Findings with immunofluorescence staining were unremarkable, although focal mesangial deposits of C3 or IgM in a nonspecific fashion were seen in some patients.

Four patients required hemodialysis upon admission for severe acute renal failure. No patients received plasmapheresis (PE) treatment or immunosuppressive agents. Symptomatic treatment was aimed at controlling BP and recovering

renal function, as well as correcting fluid and electrolyte disturbance. All patients received at least two antihypertensive agents, including diuretics, calcium antagonists, angiotansin converting enzyme inhibitors, β-adrenoceptor antagonists, and vasodilators. Three patients received intravenous sodium nitroprusside and four patients received intravenous nitroglycerin, while the other patients were given oral drug therapy. Two patients each received 1 U of red blood cell suspension. Two patients who showed severe interstitial fibrosis received erythropoietin therapy. After the aggressive management of BP, the hemoglobin levels of all the patients gradually rose. The follow-up period ranged from 4 to 12 months. Three patients had recovered normal renal function without active urine sediments and proteinuria; 4 patients still required hemodialysis with persistent proteinuria and hematuria for severe vascular lesions and interstitial fibrosis. The other 14 patients showed mild renal insufficiency (mean serum creatinine 1.8±0.3 mg/dL) and low-grade proteinuria (mean urine protein 0.6±0.4 g/day). We found no correlation between severity of hypertension and symptoms of thrombocytopenia. Renal pathological examination revealed that interstitial lesions such as fibrosis and tubular lesions were related to the renal outcome. We also found that renal prognosis was negatively associated with the serum creatinine on admission and with the degree of the involved preglomerular arterioles and/or interlobular arteries.

Discussion

Thrombotic microangiopathies are microvascular occlusive disorders characterized by systemic or intrarenal aggregation of platelets, thrombocytopenia, and mechanical injury to erythrocytes. Although the exact mechanism of TMA has not been fully elucidated, endothelial cell damage may have a pivotal role. It is postulated that endothelial dysfunction has a central role in the pathogenesis of malignant hypertension. Severe and malignant hypertension may accompany TMA. In malignant hypertension with renal impairment, one typical finding is intrarenal TMA (*3*). In one series of 56 patients with malignant hypertension, microangiopathic hemolytic anemia was present in 23 patients (*8*). Espinosa *et al*. (*9*) reported that 13% of patients with systemic TMA showed malignant hypertension. On the other hand, the frequency of intrarenal TMA with malignant hypertension has not been well described (*10*, *11*).

In this study, we analyzed 21 patients who showed intrarenal TMA with severe hypertension to further evaluate the possible pathogenesis of this disease entity. We observed that the clinical and biological symptoms suggestive of renal TMA were not consistent. Thrombocytopenia was absent in 16 cases, and no patients presented with clinical symptoms of HUS/TTP. The low prevalence of hemolytic microangiopathic anemia could be due to the fact that the patients were selected from their renal pathological findings. Bridoux *et al*. (*12*) and other authors described the same low prevalence in systemic lupus erythematosus (SLE) patients with renal TMA (*13*). Kadiri (*8*) reported 56 patients with malignant accelerated hypertension, including 24 patients with both renal and cardiac failure, and 23 patients with microangiopathic hemolytic anemia. Ono *et al*. (*14*) illustrated that the vascular lesions characteristic of malignant hypertension were fibrinoid necrosis of the walls of small arteries and arterioles leading to microangiopathic hemolytic anemia, which was not found in our patients. This may partly explain the low prevalence of microangiopathic hemolytic anemia in these patients. Morel-Maroger *et al*. (*15*) disclosed that microangiopathic hemolytic anemia may occur in apparently healthy people, or may complicate the course of chronic essential hypertension. The patients with a good outcome and those with a poor outcome did not differ in the severity of glomerular lesions but did differ in the severity of arterial intimal thickening.

Although lacking in proliferating characteristics, overt proteinuria was present in the majority of our patients. Interestingly, hematuria was present in all the patients, especially in 3 patients presenting with gross hematuria without any other hemorrhagic signs. Compared with other studies, short-term prognosis was favorable in our group. In a report on 43 patients with HUS, Schieppati *et al*. (*16*) found that severe renal involvement at the onset of the disease (as expressed by elevated serum creatinine) was associated with a long-term unfavorable prognosis. On the other hand, Hollenbeck *et al*. (*11*) concluded that neither serum creatinine nor BP was an independent predictor of prognosis except for the treatment with PE. Conlon *et al*. (*17*) concluded that patient age, sex, presenting platelet count, white blood cell count, hemoglobin level, and the presence of neurological disease were not significantly associated with death or the need for dialysis, while the histopathological features of renal TMA were found in all 5 cases autopsied. In our study, none of the patients received PE treatment. Treatment of TMA in the setting of malignant hypertension consisted of rapid control of hypertension with or without renin-angiotensin-aldosterone system antagonists. Theoretically, there should be no place for PE in the management of TMA in malignant hypertension. It is difficult to distinguish malignant hypertension from TTP/HUS. Early renal biopsies may be helpful in predicting prognosis in this disease entity. Considering the possible complications of PE treatment, we should carefully decide whether it was appropriate to give the patient this invasive therapy.

In plasma, a vWF-cleaving metalloprotease, referred to as ADAMTS13, normally prevents unusually large multimers of vWF from entering circulation (or persistence). In most patients with familial or acquired types of thrombotic thrombocytopenic purpura, plasma ADAMTS13 activity is less than 5% of normal. On the other hand, ADAMTS13 plays little or no role in the pathogenesis of TMA, and there is no deficiency of ADAMTS13 in typical diarrhea-associated HUS (*18*). In most patients with a diagnosis of TTP, ADAMTS13 activity, measured on a pretreatment citrated plasma sample, is 0–5% of normal (*1*). In contrast, plasma ADAMTS13 activ-

ity is not as severely reduced (or is normal) in most patients considered clinically to have the hemolytic-uremic syndrome or other thrombotic microangiopathies. Reduced levels of ADAMTS13 activity can be seen in a variety of clinical settings including renal failure, systemic lupus erythematosus, cirrhosis, inflammatory states, and pregnancy (*19*, *20*). In cases of severe hypertension associated with TMA, a diagnosis of TTP should not be made until the effect of aggressive control of the hypertension can be assessed. If the ADAMTS13 activity is not low, we should consider whether or not a patient with microangiopathic hemolytic anemia should initiate PE treatment. In our opinion, renal function is a good prognostic factor in this group.

In conclusion, the term "TMA" defines a pathologic alteration of the microvasculature, with detachment or swelling of the endothelium, amorphous material in the subendothelial space, and luminal platelet aggregation leading to a compromise in the microcirculation. The two most prominent diseases associated with thrombotic microangiopathy are TTP and HUS, and the laboratory features of both almost uniformly include thrombocytopenia and hemolytic anemia. Our patients showed a low incidence of thrombocytopenia and favorable renal prognosis. Although malignant hypertension can produce a clinical picture of TTP or HUS, the renal pathology of our patients revealed that the degree of the involved preglomerular arterioles and interlobular arteries was a key factor in this special disease entity. Aggressive management of BP could improve the clinical features and renal prognosis.

References

1. Moake JL: Thrombotic microangiopathies. *N Engl J Med* 2002; **347**: 589–600.
2. Liapis H: Thrombotic microangiopathy involving the kidney: a histopathologic perspective. *Hippokratia* 2003; **7**: 152–158.
3. Vaughan CJ, Delanty N: Hypertensive emergencies. *Lancet* 2000; **356**: 411–417.
4. Khanna A, McCullough PA: Malignant hypertension presenting as hemolysis, thrombocytopenia, and renal failure. *Rev Cardiovasc Med* 2003; **4**: 255–259.
5. Egan JA, Bandarenko N, Hay SN, *et al*: Differentiating thrombotic microangiopathies induced by severe hypertension from anemia and thrombocytopenia seen in thrombotic thrombocytopenia purpura. *J Clin Apher* 2004; **19**: 125–129.
6. Galbusera M, Benigni A, Paris S, *et al*: Unrecognized pattern of von Willebrand factor abnormalities in hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. *J Am Soc Nephrol* 1999; **10**: 1234–1241.
7. Rick ME, Molls S, Taylor MA: Clinical use of rapid collagen binding assay for von Willebrand factor cleaving protease in patients with thrombotic thrombocytopenic purpura. *Thromb Haemost* 2002; **88**: 598–604.
8. Kadiri S, Olutade BO: The clinical presentation of malignant hypertension in Nigerians. *J Hum Hypertens* 1991; **5**: 339–343.
9. Espinosa G, Bucciarelli S, Cervera R, *et al*: Thrombotic microangiopathic haemolytic anemia and antiphospholipid antibodies. *Ann Rheum Dis* 2004; **63**: 730–736.
10. Gurkan E, Baslamisli, Guvenc B, *et al*: Thrombotic thrombocytopenic purpura in southern Turkey: a single-center experience of 29 cases. *Clin Lab Haematol* 2005; **27**: 121–125.
11. Hollenbeck M, Kutkuhn B, Aul C, *et al*: Haemolytic-uraemic syndrome and thrombotic-thrombocytopenic purpura in adults: clinical findings and prognostic factors for death and end-stage renal disease. *Nephrol Dial Transplant* 1998; **13**: 76–81.
12. Bridoux F, Vrtovsnik F, Noel C, *et al*: Renal thrombotic microangiopathy in systemic lupus erythematosus: clinical correlations and long-term renal survival. *Nephrol Dial Transplant* 1998; **13**: 298–304.
13. Farrugia E, Torres VE, Gastineau D, *et al*: Lupus anticoagulant in systemic lupus erythematosus: a clinical and renal pathological study. *Am J Kidney Dis* 1992; **20**: 463–471.
14. Ono H, Ono Y: Nephrosclerosis and hypertension. *Med Clin North Am* 1997; **81**: 1273–1288.
15. Morel-Maroger L, Kanfer A, Solez K, *et al*: Prognostic importance of vascular lesions in acute renal failure with microangiopathic hemolytic anemia (hemolytic-uremic syndrome). Clinicopathologic study in 20 adults. *Kidney Int* 1979; **15**: 548–558.
16. Schieppati A, Ruggenenti P, Cornejo RP, *et al*: Renal function at hospital admission as a prognostic factor in adult hemolytic uremic syndrome. The Italian Registry of Haemolytic Uremic Syndrome. *J Am Soc Nephrol* 1992; **2**: 1640–1644.
17. Conlon PJ, Howell DN, Macik G, Kovalik EC, Smith SR: The renal manifestation and outcome of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in adults. *Nephrol Dial Transplant* 1995; **10**: 1189–1193.
18. Tsai HM, Chandler WL, Sarode R, *et al*: von Willebrand factor and von Willebrand factor–cleaving metalloprotease activity in *Escherichia coli* O157: H7–associated hemolytic uremic syndrome. *Pediatr Res* 2001; **49**: 653–659.
19. Moore JC, Hayward CPM, Warkentin TE, *et al*: Decreased von Willebrand factor protease activity associated with thrombocytopenic disorders. *Blood* 2001; **98**: 1842–1846.
20. Mannucci PM, Canciani MT, Forza I, Lussana F, Lattuada A, Rossi E: Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. *Blood* 2001; **98**: 2730–2735.