The Oncologist®

Thrombotic Thrombocytopenic Purpura Associated with Bone Marrow Metastasis and Secondary Myelofibrosis in Cancer

JAE C. CHANG,[a] TAHIR NAQVI[b]

[a]University of California, Irvine College of Medicine and Division of Hematology/Oncology at UCI Medical Center, Orange, California, USA; [b]Department of Medicine, Wright State University School of Medicine, Dayton, Ohio, USA, and Hematology and Oncology Section, Good Samaritan Hospital, Dayton, Ohio, USA

Key Words. *Thrombotic thrombocytopenic purpura · Bone marrow metastasis · Secondary myelofibrosis · Microangiopathic hemolytic anemia · Thrombotic microangiopathy*

ABSTRACT

To examine the relationship between cancer and development of thrombotic microangiopathy (TM), the medical records of patients with known TM were examined in one institution from January 1981 to December 2002. Nine out of 93 patients with the established diagnosis of TM had active cancer. All nine of those patients had thrombotic thrombocytopenic purpura (TTP). Among those patients, two patients received chemotherapy prior to the development of TTP. Six of the seven patients who received no chemotherapy had extensive bone marrow metastasis and secondary myelofibrosis. There were two patients each with breast cancer, lung cancer, and stomach cancer. Severe anemia and thrombocytopenia with leukoerythroblastosis were prominent clinical features in all six patients. Four patients had neurological (mental) changes and three developed fever, but none had significant renal dysfunction. Upon establishing the diagnosis of TTP, four patients were treated with exchange plasmapheresis (EP) and two patients were treated with chemotherapy because there were no neurological changes. Three patients achieved complete remission of TTP, one with EP alone and two with chemotherapy. The one patient who achieved remission with EP alone was later treated with chemotherapy and survived for 2 1/2 years. The other three patients treated with EP alone died within 2 months after the diagnosis of TTP. Since TTP occurred in association with bone marrow metastasis and myelofibrosis in six patients among seven chemotherapy-untreated cancer patients, this marrow change was considered to be the possible cause of the development of TTP. It is recommended that all cancer patients with unexplained anemia and thrombocytopenia be evaluated for the coexistence of bone marrow metastasis and TTP. ***The Oncologist*** *2003;8:375-380*

INTRODUCTION

In the past two decades, in addition to idiopathic thrombotic thrombocytopenic purpura (TTP), more cases of secondary TTP have been identified, perhaps due to an enthusiasm for cure potential with an availability of exchange plasmapheresis (EP) [1]. In addition, the term thrombotic microangiopathy (TM) has been introduced to include hemolytic uremic syndrome, hemolysis with elevated liver enzyme levels and a low platelet count (HELLP) syndrome, and dyadic TTP in addition to classical TTP. Secondary TM has been known to be associated with collagen vascular diseases [2-5], use of certain drugs [6-9], transplants [10-13], surgeries [14-17], infections [18, 19], pregnancy [20, 21], and cancer [22-24]. In cancer patients, at least two causes for TM have been identified. One is the complication from chemotherapy [6, 25-31], and the other is the manifestation of the cancer itself without any relationship to chemotherapy. No specific pathologic feature,

Correspondence: Jae C. Chang, M.D., Division of Hematology/Oncology, Chao Family Comprehensive Cancer Center, University of California at Irvine Medical Center, 101 The City Drive, Orange, California 92868, USA. Telephone: 714-456-5153; Fax 714-456-2242; e-mail: jaec@uci.edu *Received February 6, 2003; accepted for publication April 30, 2003.*

however, has been implicated for TM in the patient with cancer. In this article, we describe that TTP in cancer patients is associated with bone marrow metastasis and secondary myelofibrosis. The possible pathophysiologic mechanism of bone marrow metastasis contributing to TTP is discussed.

Patients and Methods

All identifiable cases of TM seen at the Good Samaritan Hospital in Dayton, Ohio, from January 1981 to December 1994 were documented and recorded retrospectively in the personal computer system. Cases of TM from January 1995 to December 2002 were prospectively recorded. These studies included all patients with TTP, hemolytic uremic syndrome, and HELLP syndrome. The medical records and peripheral blood and bone marrow biopsy slides of the patients among these that were diagnosed with TM simultaneously with active cancer were reviewed. The essential diagnostic criteria for TM were unexplained thrombocytopenia and microangiopathic hemolytic anemia (MAHA) [14]. The diagnosis of MAHA was based on schistocytosis, reticulocytosis, and elevated lactic acid dehydrogenase (LDH) level or decreased haptoglobin level. In some patients, additional clinical features, such as neurologic changes, renal dysfunction, and fever, were present. The identifiable causes of thrombocytopenia were excluded with the evaluation of clinical history, review of medical records, and laboratory findings, including previous history of thrombocytopenia, drug administration, blood transfusion, and evidence of infection.

Pertinent laboratory studies were also performed and their results were reviewed. Consumption coagulopathy was ruled out by a normal fibrinogen level, prothrombin time, and activated partial thromboplastin time and a negative result of fibrin split products when this diagnosis was a possibility. Heparin-induced thrombocytopenia was excluded according to criteria described previously [32] and with a lack of heparin-induced platelet aggregation, a normal ^{14}C serotonin release assay [33], or the absence of platelet factor 4 and heparin-associated antibodies [34] when these tests became available. Thrombocytopenia caused by infection, such as sepsis or pneumonia, or by blood transfusion was ruled out by appropriate examinations, including blood cultures, roentgenographic and imaging studies, and clinical information.

The diagnosis of cancer was established on the basis of clinical, laboratory, and pathologic examinations. In all active cancer patients presenting with anemia and thrombocytopenia, bone marrow studies, both aspiration and biopsy, were reviewed when available. The bone marrow samples were studied for the extent of the metastasis and secondary myelofibrosis, since these were the consistent abnormalities.

Hematologic data reviewed were the hemoglobin, hematocrit, platelet count, reticulocyte count, LDH level, and haptoglobin level. Reports of peripheral blood films were also reviewed and blood smears were examined. The degree of schistocytosis was estimated as follows [14]: the score of 0 was given for a finding of <1% of schistocytes among red blood cells; 1+ was given for 1%-2%; 2+ was given for 2%-5%; 3+ was given for 5%-10%; and 4+ was used for findings of >10%.

The treatments, both EP and chemotherapy regimens, of TM associated with cancer and their final outcomes were recorded.

Results

There were 93 patients with the diagnosis of TM between 1981 and 2002 in our institution. The primary diagnosis of TTP was present in 77 patients, hemolytic uremic syndrome was diagnosed in eight, and HELLP syndrome was the primary diagnosis in another eight. Among these patients, nine patients with TM had active cancer, and all of those had TTP (Table 1). Six patients had the classical triad of TTP, but three patients had only dyadic TTP with thrombocytopenia and MAHA. The neurologic manifestation was mostly mental changes, such as confusion, disorientation, lethargy, and visual disturbance. Four patients had breast cancer, two had lung cancer, two had stomach cancer, and one had unknown primary cancer. The histological types of cancer were adenocarcinoma in seven patients, small-cell anaplastic carcinoma in one patient, and positive cytology of non-small cell type from an unknown primary in pericardial fluid in one patient. Two patients with breast cancer were receiving chemotherapy when TTP developed: patient 2 with mitomycin C and vinblastine for metastatic disease and patient 9 with doxorubicin and cyclophosphamide in the neoadjuvant setting. Patient 9 was unusual in that TTP occurred following the insertion of a life-port after the second cycle of doxorubicin and cyclophosphamide. This patient had no evidence of cancer beyond the breast. Seven other patients had not taken any chemotherapy within 3 months prior to the diagnoses of TTP, although two patients with breast cancer were on hormonal therapy: patient 1 with megestrol acetate until 8 weeks prior to the diagnosis of TTP and patient 4 with tamoxifen.

Among the seven patients who had TTP in the absence of chemotherapy during the three preceding months, six had bone marrow metastasis with secondary myelofibrosis. None of those patients was known to have idiopathic myelofibrosis prior to the diagnosis of TTP and splenomegaly was not present. One patient who had pericardial effusion with positive cytology from an unknown primary showed neither

Table 1. Clinical data in all patients with cancer

Patient	Age years/sex	Primary cancer site	Pathologic type	Chemotherapy/endocrine therapy before diagnosis of TTP	TTP Criteria[a]
1	66/female	breast	adenocarcinoma	none/megestrol acetate	TANF
2	66/female	breast	adenocarcinoma	mitomycin C + vinblastine	TA
3	59/female	stomach	adenocarcinoma	none	TANF
4	58/female	breast	adenocarcinoma	none/tamoxifen	TANF
5	77/male	lung	small-cell carcinoma	none	TA
6	64/female	lung	adenocarcinoma	none	TAN
7	65/female	stomach	adenocarcinoma	none	TA
8	66/female	unknown	cytology positive for non-small cell type	none	TAN
9	42/female	breast	adenocarcinoma	doxorubicin + cyclophosphamide	TAN

[a]T = thrombocytopenia; A = MAHA; N = neurologic changes; F = fever.

hematologic abnormalities nor evidence of bone marrow metastasis. Tables 2-4 show the hematologic data, treatment modalities, and outcomes of the six patients who had active cancer with bone marrow metastasis. All patients had clear evidence of MAHA and unexplained thrombocytopenia when evaluated by hematologists. The degree of anemia was severe, and levels of hemoglobin fluctuated because of multiple blood transfusions. Platelet counts ranged from 7-96 $\times 10^3/\mu$l. Peripheral blood slides showed mild-to-moderate schistocytosis as reported in the examinations by technologists and hematologists. Schistocytosis, reticulocytosis, and elevated levels of LDH with decreased haptoglobin levels confirmed the diagnosis of MAHA in all six patients. All had a varying degree of leukoerythroblastosis in the peripheral blood and extensive metastasis to the bone marrow when bone marrow biopsy specimens were examined (Table 3). Additionally, secondary myelofibrosis was present in all six patients. According to the isotopic bone scan, bone metastasis, however, was present only in three patients.

As soon as the diagnosis of TTP was established, four patients were started on EP and two patients were treated with chemotherapy, one with etoposide and carboplatin (EC) and the other with paclitaxel (T) since those patients had only dyadic TTP without neurologic manifestation (Table 4). Only one patient treated with EP achieved complete remission (CR) of the TTP. This was followed by combination chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) with a good partial response, and that patient survived 31 months. Three patients gained no benefit from EP due to advanced cancer as well as advanced TTP, and they died within 2 months. Two patients who were treated with chemotherapy achieved CR of their TTP, although their cancers showed only partial remission. One survived 10 months and the other survived 11 months after their diagnoses of TTP.

Discussion

In the past two decades, with the availability of EP as an effective treatment, more cases of TTP, including atypical and secondary cases, have been recognized and treated

Table 2. Hematologic data from patients with bone marrow metastasis

Patient	Hemoglobin (g/dl)	Hematocrit	Platelets ($\times 10^3/\mu$l)	Reticulocytes (%)	Blood smear (schistocytes)	LDH (U/l)	Haptoglobin (mg/dl)
1	7.7	0.238	96	22.9	3+	388	<5
3	6.1	0.188	20	4.7	1+	1,211	<5
4	7.9	0.227	7	3.4	2+	770	<5
5	8.8	0.256	73	1.6	2+	2,916	12
6	10.4	0.306	50	7.3	2+	408	<5
7	8.0	0.245	86	2.1	2+	417	<5

Control values were: hemoglobin = 14-18 g/dl (male), 12-16 g/dl (female); hematocrit = 0.40-0.50 (male), 0.38-0.50 (female); platelets = 140-440 $\times 10^3/\mu$l; reticulocytes = 0.5%-1.5%; schistocytes = 0 if <1%; 1+ if 1%-2%; 2+ if 2%-5%; 3+ if 5%-10%; 4+ if >10%; LDH = 90-180 U/l; haptoglobin = 20-150 mg/dl

Table 3. Blood and bone marrow findings from patients with active cancer and bone marrow metastasis

Patient	Blood film (nRBC[a])	Blood film (Immature granulocytes[b])	Bone marrow (Extent of metastatic cancer)	Bone marrow (Extent of myelofibrosis)
1	2	5	diffuse and extensive	focal and severe
3	7	19	diffuse and extensive	focal and mild
4	8	35	diffuse and extensive	diffuse and severe
5	3	22	diffuse and extensive	minimal
6	1	7	focal	focal and severe
7	4	14	diffuse and extensive	diffuse and severe

[a]The number of nucleated red blood cells per 100 nucleated blood cells.

[b]The number of nonsegmented granulocytes per 100 white blood cells.

Table 4. Treatment, outcome, and survival of patients with active cancer and bone marrow metastasis

Patient	Treatment modality	Outcome of TTP	Survival from diagnosis of TTP (months)
1	EP (8) + chemotherapy (CAP)	CR	31
3	EP (10)	died	1
4	EP (1)	died	<1
5	Chemotherapy (EC)	CR	10
6	EP (6)	died	<1
7	Chemotherapy (T)	CR	11

The numbers in the parentheses denote the total number of EP (exchange plasmapheresis).

with better outcomes in clinical practice [35-37]. In patients with cancer, various cancer chemotherapeutic agents have been implicated; mitomycin C [6, 25-26] has been most commonly associated with both TTP and hemolytic uremic syndrome, and other agents, including cisplatin [27], deoxycoformycin [28], the regimen of cisplatin, bleomycin, and a vinca alkaloid [29], the combination of daunorubicin and cytosine arabinoside [30], and combination regimens containing cisplatin [31], have also been implicated. In addition, cancer itself has been suspected to cause TTP [22-24], but neither a clear link between cancer and the development of TTP nor a risk factor for TTP in cancer patients has been identified.

We attempted to address this issue by reviewing all the known cases of TTP in patients with active cancer in our institution for a period of more than 20 years. In our series, only two cases were associated with chemotherapy: one with the combination of mitomycin C and vinblastine for metastatic breast cancer and the other after the insertion of a life-port following neoadjuvant chemotherapy of a second cycle of doxorubicin and cyclophosphamide. In the second patient, acute TTP was temporally related to the insertion of a life-port that was placed for the purpose of chemotherapy and was considered not to be a complication of chemotherapy, since the patient had no evidence of TTP after the first cycle. The relationship between acute TTP and the vascular procedure is not certain in this patient. However, it is known that vascular procedures can initiate acute TTP [14]. In six active cancer patients in this study, TTP occurred in association with extensive bone marrow metastasis and secondary myelofibrosis. The primary sites of cancer origin were the breast, lung, stomach, and an unknown primary, and pathologic type was adenocarcinoma in all but two patients. In view of this observation, bone marrow metastasis of cancer with myelofibrosis is suspected to be the main feature associated with the development of TTP. In the literature, reported cases of TTP and hemolytic uremic syndrome in cancer have been associated with severe anemia and advanced cancer [38, 39]. It is quite conceivable that those patients could indeed have had unrecognized bone marrow metastasis with myelofibrosis.

The pathogenesis of TTP is still not well understood. Recent studies, however, have shed some light on the understanding of its pathophysiologic process. Relatively consistent findings have been the deficiency of a von Willebrand factor (vWF)-cleaving protease (ADAMTS 13) due to an inhibitor(s) or congenital deficiency [40-42] and the detection of unusually large (uL)vWF multimers in some patients with TTP [43]. It is also known that the protease cleaves uLvWF multimers to smaller ones, and

uLvWF multimers, if not cleaved, promote the activation and aggregation of platelets [44]. In a disease or injury involving the endothelial cell, uLvWF multimers may be released into the circulation, and these multimers, if the vWF-cleaving protease is not available, promote the activation and aggregation of platelets in the arteriolar capillaries, resulting in thrombocytopenia and MAHA

As seen in the metastasis of cancer to other organs, metastasis within the bone marrow may also be associated with increased angiogenesis for the growth of cancer. It is speculated that, in addition to abnormal angiogenesis in the marrow, aggressive growth of tumors and secondary myelofibrosis may injure endothelial cells of the vessels in the marrow by direct encroachment. These changes, it is speculated, could cause the release of uLvWF multimers, and with a possible decrease in the availability of the uLvWF-cleaving protease through undetermined mechanisms, such as decreased production or immune reaction, in advanced cancer may contribute to the aggregation of platelets. Since TTP has been seen mostly in adenocarcinoma, this pathology could be another contributing factor, perhaps related to the production of mucin, which may exert a direct detrimental effect on the pathologic endothelial cell to change endothelial function.

TTP associated with cancer might have responded poorly to EP due to delayed diagnosis of TTP and advanced cancer. Since our two patients who were treated with chemotherapy alone and the one treated with EP without chemotherapy showed complete remission of TTP, both EP and chemotherapy seem to be effective treatments in some patients with TTP and cancer.

Conclusions

TTP can be associated with cancer, but only in a very small fraction of cancer patients. Nonetheless, it is important to recognize the diagnosis early, since hematologic abnormalities in cancer may be the presentation of the combination of bone marrow metastasis and TTP and unnecessary diagnostic procedures, including extensive laboratory and imaging studies to determine the cause of thrombocytopenia and mental changes, may be spared if TTP can be recognized in a timely fashion. The prognosis of TTP in cancer patients is poor, but early diagnosis, as seen in patient 1 in this study, and effective chemotherapy, as seen in patients 5 and 7, may alter the course of the disease. It is recommended that all cancer patients presenting with unexplained anemia and thrombocytopenia be evaluated not only for bone marrow metastasis, but also for coexistence with secondary TTP.

References

1 Moake JL, Chow TW. Thrombotic thrombocytopenic purpura: understanding a disease no longer rare. Am J Med Sci 1998;316:105-119.

2 Dekker A, O'Brien ME, Cammarata RJ. The association of thrombotic thrombocytopenic purpura with systemic lupus erythematosus: a report of two cases with successful treatment of one. Am J Med Sci 1974;267:243-249.

3 Ruggenenti P, Remuzzi G. Thrombotic thrombocytopenic purpura and related disorders. Hematol Oncol Clin North Am 1990;4:219-241.

4 Shipstone A, Chang JC, Gross HM et al. Coexisting morbidities as a determinant in the outcome of treatment of thrombotic thrombocytopenic purpura (TTP). Blood 1994;84(suppl 1):699a.

5 Ridolfi RL, Bell WR. Thrombotic thrombocytopenic purpura: report of 25 cases and review of the literature. Medicine (Baltimore) 1981;60:413-428.

6 Giroux L, Bettez P, Giroux L. Mitomycin-C nephrotoxicity: a clinico-pathologic study of 17 cases. Am J Kidney Dis 1985;6:28-39.

7 Maguire RB, Stroncek DF, Campbell AC. Recurrent pancytopenia, coagulopathy, and renal failure associated with multiple quinine-dependent antibodies. Ann Intern Med 1993;119:215-217.

8 Shulman H, Striker G, Deeg HJ et al. Nephrotoxicity of cyclosporin A after allogeneic marrow transplantation: glomerular thromboses and tubular injury. N Engl J Med 1981;305:1392-1395.

9 Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K et al. Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. Ann Intern Med 1998;128:541-544.

10 Hochstetler LA, Flanigan MJ, Lager DJ. Transplant-associated thrombotic microangiopathy: the role of IgG administration as initial therapy. Am J Kidney Dis 1994;23:444-450.

11 Valbonesi M, Valente U, Pellicci R et al. Thrombotic microangiopathy of the miscellaneous secondary type responding to plasma exchange in a liver transplant recipient. Int J Artif Organs 1988;11:131-133.

12 Hebert D, Sibley RK, Mauer SM. Recurrence of hemolytic uremic syndrome in renal transplant recipients. Kidney Int Suppl 1986;19:S51-S58.

13 Dzik WH, Georgi BA, Khettry U et al. Cyclosporine-associated thrombotic thrombocytopenic purpura following liver transplantation: successful treatment with plasma exchange. Transplantation 1987;44:570-572.

14 Chang JC, Shipstone A, Llenado-Lee MA. Postoperative thrombotic thrombocytopenic purpura following cardiovascular surgeries. Am J Hematol 1996;53:11-17.

15 Pavlovsky M, Weinstein R. Thrombotic thrombocytopenic purpura following coronary artery bypass graft surgery: prospective observations of an emerging syndrome. J Clin Apheresis 1997;12:159-164.

16 Chang JC, El-Tarabily M, Gupta S. Acute thrombotic thrombocytopenic purpura following abdominal surgeries: a report of three cases. J Clin Apheresis 2000;15:176-179.

17 Chang JC, Gross HM, Jang NS. Disseminated intravascular coagulation due to intravenous administration of hetastarch. Am J Med Sci 1990;300:301-303.

18 Meisenberg BR, Robinson WL, Mosley CA et al. Thrombotic thrombocytopenic purpura in human immunodeficiency virus (HIV)-seropositive males. Am J Hematol 1988;27:212-215.

19 Bar Meir E, Amital H, Levy Y et al. Mycoplasma-pneuominae-induced thrombotic thrombocytopenic purpura. Acta Haematol 2000;103:112-115.

20 Esplin MS, Branch DW. Diagnosis and management of thrombotic microangiopathies during pregnancy. Clin Obstet Gynecol 1999;42:360-367.

21 Mastrobattista JM, Ramin SM, Gilstrap LC. Thrombotic thrombocytopenic purpura in pregnancy. Prim Care Update Ob Gyns 2000;7:168-171.

22 Gordon LI, Kwaan HC. Thrombotic microangiopathy manifesting as thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in the cancer patient. Semin Thromb Hemost 1999;25:217-221.

23 Kressel BR, Ryan KP, Duong AT et al. Microangiopathic hemolytic anemia, thrombocytopenia, and renal failure in patients treated for adenocarcinoma. Cancer 1981;48:1738-1745.

24 von Bubnoff N, Sandherr M, Schneller F et al. Thrombotic thrombocytopenic purpura in metastatic carcinoma of the breast. Am J Clin Oncol 2000;23:74-77.

25 Liu K, Mittelman A, Sproul EE et al. Renal toxicity in man treated with mitomycin C. Cancer 1971;28:1314-1320.

26 Nagaya S, Wada H, Oka K et al. Hemostatic abnormalities and increased vascular endothelial cell markers in patients with red cell fragmentation syndrome induced by mitomycin C. Am J Hematol 1995;50:237-243.

27 Canpolat C, Pearson P, Jaffe N. Cisplatin-associated hemolytic uremic syndrome. Cancer 1994;74:3059-3062.

28 Leach JW, Pham T, Diamandidis D et al. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) following treatment with deoxycoformycin in a patient with cutaneous T-cell lymphoma (Sezary syndrome): a case report. Am J Hematol 1999;61:268-270.

29 Jackson AM, Rose BD, Graff LG et al. Thrombotic microangiopathy and renal failure associated with antineoplastic chemotherapy. Ann Intern Med 1984;101:41-44.

30 Byrnes JJ, Baquerizo H, Gonzalez M et al. Thrombotic thrombocytopenic purpura subsequent to acute myelogenous leukemia chemotherapy. Am J Hematol 1986;21:299-304.

31 Porta C, Danova M, Riccardi A et al. Cancer chemotherapy-related thrombotic thrombocytopenic purpura: biological evidence of increased nitric oxide production. Mayo Clin Proc 1999;74:570-574.

32 Chang JC. White clot syndrome: a serious complication of heparin therapy. Postgrad Med 1990;87:293, 296, 298.

33 Sheridan D, Carter C, Kelton JG. A diagnostic test for heparin-induced thrombocytopenia. Blood 1986;67:27-30.

34 Amiral J, Wolf M, Fischer A et al. Pathogenicity of IgA and/or IgM antibodies to heparin-PF4 complexes in patients with heparin-induced thrombocytopenia. Br J Haematol 1996;92:954-959.

35 Lara PN Jr, Coe TL, Zhou H et al. Improved survival with plasma exchange in patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Am J Med 1999;107:573-579.

36 Lichtin AE, Schreiber AD, Hurwitz S et al. Efficacy of intensive plasmapheresis in thrombotic thrombocytopenic purpura. Arch Intern Med 1987;147:2122-2126.

37 Rock GA. Management of thrombotic thrombocytopenic purpura. Br J Haematol 2000;109:496-507.

38 Gordon LI, Kwaan HC. Cancer- and drug-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Semin Hematol 1997;34:140-147.

39 Antman KH, Skarin AT, Mayer RJ et al. Microangiopathic hemolytic anemia and cancer: a review. Medicine (Baltimore) 1979;58:377-384.

40 Furlan M, Robles R, Galbusera M et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med 1998;339:1578-1584.

41 Tsai H-M, Lian EC-Y. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 1998;339:1585-1594.

42 Zheng X, Chung D, Takayama TK et al. Structure of von Willebrand factor-cleaving protease (ADAMTS13), a metalloprotease involved in thrombotic thrombocytopenic purpura. J Biol Chem 2001;276:41059-41063.

43 Moake JL, McPherson PD. Abnormalities of von Willebrand factor multimers in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. Am J Med 1989;87(3N):9N-15N.

44 Moake JL, Turner NA, Stathopoulos NA et al. Involvement of large plasma von Willebrand factor (vWF) multimers and unusually large vWF forms derived from endothelial cells in shear stress-induced platelet aggregation. J Clin Invest 1986;78:1456-1461.