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ORIGINAL ARTICLE

High coagulation factor VIII and von Willebrand factor in patients with lymphoma and leukemia

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Abstract The risk of venous thromboembolism is increased in patients with lymphoma and leukemia; however, little is known about the potential underlying hereditary or acquired thrombophilia. We prospectively analyzed procoagulant markers and gene mutations in patients with lymphoma ($n = 35$) and leukemia ($n = 10$) at diagnosis and over the course of treatment. Global coagulation tests were normal in all patients, as were antithrombin and protein S. Activated protein C resistance caused by the factor V Leiden mutation was found in four patients, one patient had the G20210A mutation of the prothrombin gene, and one patient had protein C deficiency. The most striking findings were sustained very high levels of factor VIII (>150 %) in 30 patients (68 %), which correlated with high von Willebrand factor. An acute phase response in these patients was ruled out by absence of fever and normal IL-6 and -α. Elevated factor VIII is an independent thrombophilic risk factor and may play an etiologic role in thromboembolic complications in patients with malignant lymphoma. Since high von Willebrand factor is most likely caused by endothelial cell injury, an additional, unknown pathophysiological association with malignant lymphoma and acute leukemia is possible.

Keywords Lymphoma · Leukemia · Thrombophilia · Factor VIII · VWF

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Introduction

Cancer is associated with an increased risk for venous thromboembolism [1, 2] and patients with venous thromboembolism carry an excess risk of cancer [3, 4]. Additionally, prognosis of cancer associated with venous thromboembolism is particularly poor [5]. Recent investigations in our institution found thromboembolic events in 8 % of 1038 patients with aggressive and indolent non-Hodgkin's lymphoma and Hodgkin's disease [6] and in 12 % of 455 patients with acute leukemia [7]. Endothelial cell activation by either malignancy or chemotherapy, procoagulatory cytokines as well as platelet activation and hereditary and acquired thrombophilic factors have been implicated in the pathogenesis of thromboembolism in patients with malignant disease [2]. Data on patients with hematologic malignancies such as malignant lymphoma or acute leukemia is very limited to date and rather refers to coagulation activation markers with special focus on DIC than to hereditary or acquired thrombophilia. On the other hand, understanding of laboratory analysis and definition of new procoagulant factors such as high factor VIII activity and gene mutations has greatly increased in the past years. Therefore, we initiated this prospective study on congenital and acquired prothrombotic disorders in patients with malignant hematologic diseases.

Patients, materials and methods

45 consecutive patients with acute leukemia and malignant lymphoma regardless of age and without prior venous thromboembolism treated at Magdeburg university Hospital in 2004 and 2005 were included in this study after confirmation of diagnosis. Patients with paraproteinemia

Table 1 Coagulation parameters: median and range

	Normal	Median	Range
Antithrombin (%)	>80	91	56–121
Protein C (%)	>70	94	22–150
Protein S (%)	>70	100	45–210
Free protein S (%)	>70	80	30–144
Factor XII (%)	>70	87.5	30–158
ACL (u/l)	<40	20.00	9–328
Fibrinogen (g/dl)	1.5–4.0	4.1	2.03–7.63
F1 + 2 (nmol/l)	<1.40	1.61	0.70–14.4
D-dimers (g/dl)	<0.4	0.86	0.2–4.95
VIII:C (%)	70–130	150	65–400
VWF:Ag (%)	70–130	321	117–718
VWF:CB	70–130	199	108–280

(multiple myeloma or immunocytoma) or promyelocytic leukemia, disease entities with supposedly distinct hemostatic abnormalities were excluded.

Citrated blood was collected at routine checkups before, and within 7 days after chemotherapy and at 2 additional time points, 3 weeks–3 months later before additional chemotherapy courses. Oral patient's consent was obtained before blood was taken as recommended by the local ethics committee. Global coagulation tests such as activated partial thrombin time (aPTT), prothrombin time, thrombin time, fibrinogen, antithrombin as well as D-dimers were performed immediately. Citrated blood was centrifuged at 1500*g* for 10 min and either used for analysis of global coagulation tests or centrifuged for another 20 min at 2500*g* and then stored at −80 °C until further use. In 6 patients with indolent lymphoma no therapy was started and baseline laboratory data was obtained only. In 30 patients laboratory testing was done at at least 3 distinct time points.

Reagents used for analysis of coagulation parameters are listed below. All tests were performed following the manufacturer`s instructions: Prothrombin time (Dade® Innovin®), prothrombin fragment 1 + 2 (F1 + 2) (Enzygnost micro assay) both from Dade Behring (Marburg, Germany); PTT (STA APTT KAOLIN, STA®), thrombin Time (STA THROMBIN, STA®), antithrombin III (STA Antithrombin III), D-dimer (STA Liatest® D-DI) and von Willebrand factor (VWF) (STA Liatest®), all from DIAGNOSTICA STAGO (Asnieres, France) for Roche (Mannheim, Germany); Fibrinogen Reagent, protein S (EIDFIX® Protein S) and protein C (Technocrom Protein C) all from Technoclone (Vienna, Austria); activated protein C resistance (COATEST® APC™ Resistance and COATEST® APC™ Resistance V) from Chromogenix (Milano, Italy); von Willebrand factor collagen binding activity (IMMUNOZYM VWF:CBA, Baxter AG, Vienna, Austria). Coagulometric testing of factors VIII and XII was done with factor deficient plasma from Technoclone (Vienna, Austria) and the Platelin® LS PTT reagent (Biomerieux, Durham, NC, USA). Anticardiolipin antibodies (ACL) were measured with an enzyme immunoassay for the detection of IgG, IgM and IgA antibodies by IMTEC (Immundiagnostika, Berlin, Germany). Screening for lupus anticoagulants was done with the Mix Con LA PTT reagent and the LAC Screen and LAC Confirm test, all from Instrumentation Laboratory (Milano, Italy). PCRs for detection of the factor V Leiden and the prothrombin gene mutation were done with the Factor V Gene Mutation Assay™ and the Prothrombin Gene Mutation Assay™ both from Vienna Lab (Vienna, Austria). PCRs were performed at baseline and D-dimer as well as VWF:Ag and VWF:CB testing was done in the first 24 patients only. IL-6 and TNF-α levels were determined with commercially available ELISA (IL-6 and TNF-α enzyme immunoassay, Coulter Beckham, Marseille, France).

Statistical analysis

Results of laboratory testing were collected in an electronic data base. Statistical analyses were done with SPSS 15.0. Correlation analysis was done using the Spearman correlation rank test. Influence of gender on factor VIII and VWF levels and comparison of patients with normal controls were determined with the non-parametric Mann–Whitney *U* test and comparison of VIII:C, VWF:Ag and VWF:CB at baseline and ≥1 year later was done using the Wilcoxon matched pair signed rank test. Test results were considered positive, if $P \leq 0.050$ and/or the correlation coefficient ≥0.500.

Results

45 consecutive patients with acute leukemia and malignant lymphoma, mean age 61 years, were included in this study after confirmation of diagnosis. 20 patients had aggressive NHL, 8 had indolent NHL, 6 had Hodgkin's disease, 1 had primary CNS lymphoma and 10 had acute leukemia, 27 patients were male (60 %) and 18 were female (40 %). Chemotherapy protocols used in this patient group included CHO(E)P ± rituximab, BEACOPP, cytarabine plus anthracycline and DexaBEAM.

Because of the unexpected findings of very high factor VIII activity (VIII:C), von Willebrand factor antigen (VWF:Ag) and von Willebrand factor collagen binding activity (VWF:CB) levels testing of these 3 parameters was repeated if possible at ≥1 year follow-up. 27 of the initial 45 patients were available for VIII:C testing after 1 year as were 13 of the initial 24 patients in whom VWF testing had been done.

12 healthy hospital staff members served as a normal control group for VIII:C, von VWF:Ag and von VWF:CB testing in addition to the control plasma provided by the manufacturer.

Heterozygous factor V Leiden was found in 4 patients (9 %) and the prothrombin gene mutation in 1 patient (2 %) and all patients with the former had activated protein C resistance on coagulometric testing. One patient had protein C deficiency (protein C = 22 %) and one patient with mantle cell lymphoma had elevated anticardiolipin antibodies possibly related to the lymphoma—titers that decreased from 328 to 96 u/ml during the further therapeutic course—without detection of a lupus anticoagulant and no history of thromboembolic events. Protein S, free Protein S, antithrombin and factor XII were normal in all 45 patients during the entire study period.

Frequently increased parameters included fibrinogen (51 % of analysis, median 4.1 g/dl), D-dimers (83 % of analysis, median 0.86 g/dl) and F1 + 2 (64 % of analysis, median 1.61 nmol/l), findings that are consistent with activated coagulation. The most striking findings were increased activity of coagulation factor VIII (VIII:C) and VWF and VWF:CB: 31 of 45 patients (69 %) had high VIII:C (≥150 %) at at least 1 time point with sustained elevations (≥2 time points) in 23 (51 %). VIII:C was very high (≥180 %) in 22 patients (49 %). VWF and VWF: CB were constantly high in all 24 tested patients and most patients (87 %) had strikingly high levels (≥200 %) (Table 1).

High VIII:C correlated with VWF (Fig. 1) and VWF:CB, but not with F1 + 2, fibrinogen or D-dimer or IL-6 and TNF-α levels. No positive correlation of IL-6 or TNF-α with F1 + 2 was detected, but fibrinogen was increased if IL-6 was high (Table 2) and IL-6 and D-dimers showed somewhat of a correlation (0.488) both findings explained by local fibrin formation and lysis as common events during inflammatory response.

Overall VIII:C ($P = 0.002$), but not VWF ($P = 0.151$) was significantly higher in females, most likely due to physiologically increased VIII:C in women due to hormonal influence [8, 9] (Fig. 2): in 89 % of the female patients VIII:C was ≥150 %, whereas only 55.5 % of the male patients had VIII:C ≥150 %. Mean VIII:C ($P = 0.004$), and VWF:CB ($P = 0.007$) were significantly higher at diagnosis than approximately 1 year thereafter, whereas mean VWF:Ag showed no significant difference ($P = 0.137$) at both time points (Fig. 3). Mean VIII:C, VWF and VWF:CB were significantly higher in lymphoma and leukemia patients than in healthy controls ($P < 0.001$) (Fig. 4a–c). 11 patients with APC resistance without the factor V Leiden mutation had high (≥150 %), whereas only 2 had normal VIII:C.

Table 2 Correlation analysis of selected parameters day 1 of study

	VIII:C	VWF:Ag	VWF:CBA	IL-6	TNF-α
VIII:C	**1.000**	**0.842**	**0.855**	0.035	0.007
VWF	**0.842**	**1.000**	**0.924**	0.287	0.245
VWF:CBA	**0.855**	**0.924**	**1.000**	0.183	0.124
IL-6	0.350	0.287	0.183	**1.000**	0.030
TNF-α	0.007	0.245	0.124	0.030	**1.000**
D-Dimer	0.022	0.081	0.152	0.488	−0.112
Fibrinogen	0.385	0.100	0.100	**0.533**	−0.117
F1 + 2	−0.200	−0.184	−0.197	0.135	0.038

Two-sided correlation coefficient according to the Spearman correlation rank test:: ≥0.5 = positive correlation (in bold letters) <0.5 = no correlation

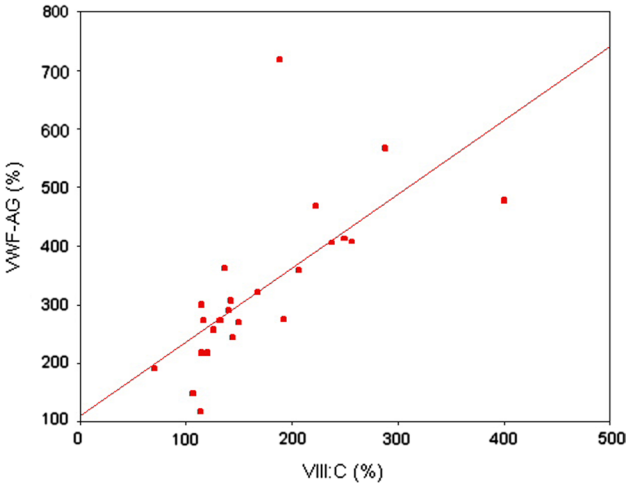

Fig. 1 Correlation of VIII:c and VWF:Ag

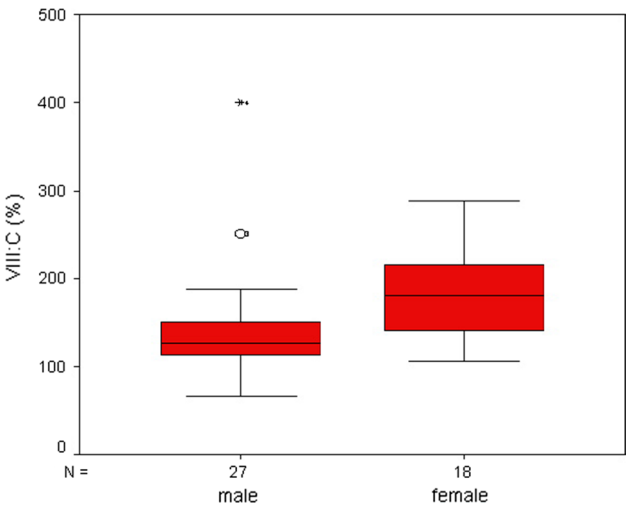

Fig. 2 Median VIII:c: comparison of male and female patients

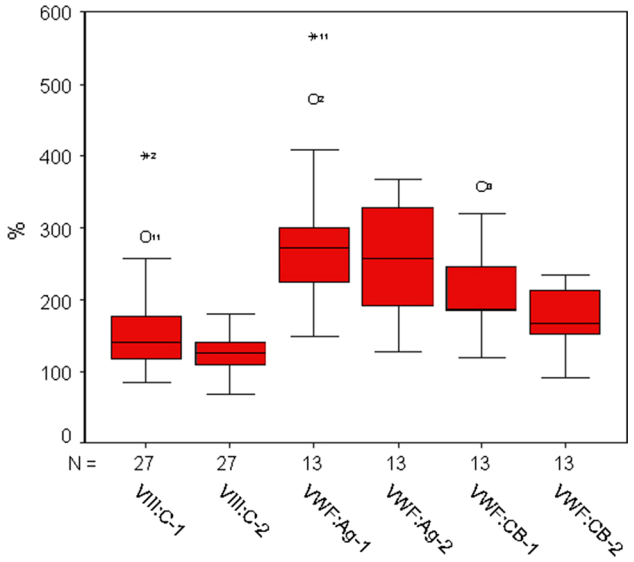

Fig. 3 Comparison of VIII:C, VWF:Ag and VWF:CB at diagnosis (−1) and ≥1 year later (−2)

Discussion

Increased fibrinogen, D-dimer and F1 + 2 levels are consistent with subclinically activated coagulation as has been observed in patients with malignancies before [10–13]. However, we failed to show an impact of chemotherapy or decrease of tumor burden on these parameters during the further clinical course and we found no impact on protein C, protein S or antithrombin, findings that concur with previously published smaller studies cited above.

The aim of our study was to investigate a broader array of procoagulant factors in patients with lymphoma and leukemia including congenital thrombophilia such as the F V Leiden and the prothrombin gene mutation. Prevalence of inherited prothrombotic conditions was not higher than expected in the normal population [14–17] and neither antithrombin nor protein S deficiency was found. Highly increased ACL in the absence of a lupus anticoagulant in one patient with lymphoma were most likely associated with the B cell malignancy and accordingly titers decreased during successful therapy. The latter findings, however, contrast with a previously published study that showed increased ACL titers in 27 % of patients with NHL [18].

The most striking findings in our study were very high sustained increases of VIII:C, VWF:Ag and VWF:CB in the majority of tested patients, that were sustained even at follow-up ≥1 year later but at a somewhat lower level and VIII:C, VWF:Ag and VWF:CB were significantly higher in patients than in normal controls. Factor VIII is a 300-kDa molecule that is synthesized mainly in the liver [19, 20]. To escape from inactivation by activated protein C or other proteases in the circulation factor VIII forms a tight non-covalent complex with VWF. Since VWF regulates factor VIII plasma levels, changes in VWF plasma levels are usually coupled with a concordant change in VIII:C [21, 22].

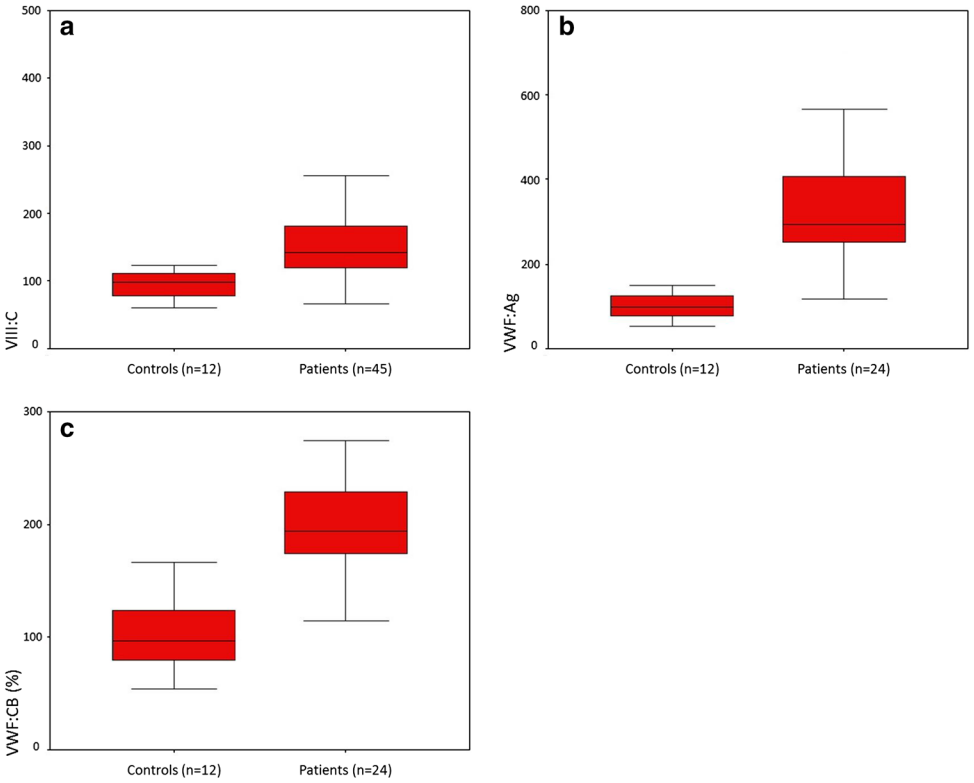

Fig. 4 Comparison of VIII:c (**a**), VWF:Ag (**b**) and VWF:CB (**c**) in patients and normal controls (mean and standard deviation)

Considering regulation of secretion and degradation of factor VIII there are 3 possible explanations for high VIII:C in patients with malignant hematologic disease:

1. Abnormalities of the factor VIII and VWF gene in patients with leukemia and lymphoma: genetic abnormalities are very unlikely since the factor VIII and VWF genes are located on different chromosomes (X chromosome and chromosome 12, respectively) and no associated polymorphisms in the VWF and factor VIII genes in thrombosis patients with high VIII:C were found in an earlier investigation [23, 24]. Additionally, Bowen et al. failed to identify a gain-of-function mutation in the factor VIII binding domain of VWF that could explain elevated VIII:C levels [25].

2. Increased synthesis of factor VIII and VWF either due to synthesis by malignant cells or an acute phase reaction in leukemia and lymphoma patients: There is no evidence of factor VIII and VWF synthesis in leukemia and lymphoma cells and factor VIII levels continued to be elevated even in complete remission of the malignancy. An acute phase reaction seems very unlikely, since TNF-α and IL-6, initiators of acute phase reactions were normal in all patients with high VIII:C and these findings concur with earlier observations [26, 27].

3. Decreased clearance of factor VIII eventually also leads to increased plasma VIII:C. Increased VWF, abnormal affinity of VWF for factor VIII impeding its degradation by proteolytic enzymes as well as decreased hepatic clearance of factor VIII could be the underlying cause. Since we found both, VWF:Ag as well as VWF:CB to be very high in patients with hematologic malignancies and highly correlating with VIII:C, a causal relationship seems probable. This is backed by the findings of Schambeck et al. who showed that more factor VIII molecules per VWF multimer are bound in thrombosis patients with high VIII:C [28] and another group found that in patients with deep-vein thrombosis high VIII:C correlated with VWF, but not with other endothelial cell derived coagulation and/or fibrinolysis markers [29].

Interestingly high VIII:C was associated with APC resistance also in patients without the F V Leiden mutation when tested without F V-deficient plasma. This observation has already been made previously [30] and can be explained by the failure of APC to inactivate an abnormally increased amount of F VIII. High VIII:C (≥150 %) is a known independent thrombophilic risk factor [31–34] and a recently published study also found high VWF (>141 %) to be a common and independent risk factor for venous thromboembolism [35]. However, in our prospectively analyzed cohort of 45 patients with hematologic malignancies only 2 patients developed venous thromboembolism: one patient had thrombosis of the inferior cava vein due to tumor compression and the other patient had heterozygous protein C resistance as an additional thrombophilic risk factor.

Very high levels of VWF and VIII:C have been observed in patients with multiple myeloma recently and were most likely associated with activity status [36].

An increasing amount of evidence has been gathered in the past 15 years suggesting that angiogenesis and endothelial cell activation play a major role in pathogenesis and progression of solid tumors and hematologic malignancies and has been previously reviewed by several groups [37–39]. Bone marrow blood vessel density as well as increased concentrations of angiogenic factors such as VEGF had been found in patients with a variety of malignancies. Hussong et al. found evidence of increased angiogenesis in 20 patients with AML in comparison to normal controls by looking at bone marrow blood vessel density and VWF staining [40], whereas a Norwegian group analyzed bone marrow blood vessel density as well as a broader array of angiogenic factors in 93 patients with a variety of hematologic malignancies such as AML, CLL, multiple myeloma and NHL and found increased microvessel density as well as increased levels of IL-6 and VEGF concluding that bone marrow angiogenesis plays a role in pathogenesis and progression of these diseases [41]. In a previously published study of 72 patients with Waldenström macroglobulinemia (WM) surprisingly very high VWF:Ag was found in 59 % of patients with no correlation with plasma levels of VEGF, but an association with shorter survival [42]. Originally this study had rather aimed to look at acquired von Willebrand disease in WM, so the results came very unexpectedly, similarly to our findings.

Although evidence is limited to date these studies suggest that high VWF is caused by angiogenesis and thus may rather be implicated in disease pathogenesis and progression than in thrombogenesis. However, although recent work supports our findings in patients with leukemia and lymphoma, we cannot make definite conclusions about either the etiologic or prognostic significance due to the heterogeneity of diseases in our patients and the paucity of data so far. Yet our study underlines the importance of further investigations looking into the role of FVIII:C and VWF:Ag in a larger patient cohort.

We conclude that physiological inhibitors of coagulation remain intact in patients with hematologic malignancies and inherited prothrombotic states are not present more often than would be expected in the normal population. FVIII:C and VWF are substantially increased in patients with malignant lymphoma and leukemia, findings that warrant further investigation.

References

1. Baron J, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer. The Lancet. 1998;351:1077–80.
2. Deitcher R. Cancer and thrombosis: mechanism and treatment. J Thromb Thrombolysis. 2003;16:1–31.
3. Sorensen H, Mellemkjaer L, Flemming H, Olsen J, Nielson G. The risk of a cancer after primary deep venous thrombosis or pulmonary embolism. N Engl J Med. 1998;338:1169–73.
4. Murchison J, Wylie L, Stockton D. Excess risk of cancer in patients with primary venous thromboembolism: a national, population-based cohort study. Br J Cancer. 2004;91:92–5. doi:10.1038/sj.bjc.6601964.
5. Sorensen H, Mellemkjaer L, Olsen J, Baron J. Prognosis of cancers associated with venous thromboembolism. N Engl J Med. 2000;343:1846–50.
6. Mohren M, Markmann I, Jentsch-Ullrich K, Koenigsmann M, Lutze G, Franke A. Increased risk of thromboembolism in patients with malignant lymphoma: a single centre analysis. Brit J Cancer. 2005;92:1349–51.
7. Mohren M, Markmann I, Jentsch-Ullrich K, Koenigsmann M, Lutze G, Franke A. Increased risk of venous thromboembolism in patients with acute leukaemia. Br J Cancer. 2006;94:200–2.
8. Miller C, Dilley A, Drews A, Richardson L, Evatt B. Changes in von Willebrand factor and factor VIII levels during the menstrual cycle. Thromb Haemost. 2002;87:1082–3.
9. Sanchez-Luceros A, Meschengieser S, Marchese C, Votta R, Woods C, Nadal M, et al. Factor VIII and von Willebrand factor changes during normal pregnancy and puerperium. Blood Coagul Fibrinolysis. 2003;14:647–51.
10. Catani L, Gugliotta L, Mattioli Belmonte M, Vianelli N, Gherlinzoni M, Belardinelli A, et al. Hypercoagulability in patients undergoing autologous or allogeneic BMT for hematologic malignancies. Bone Marrow Transplant. 1993;12:253–9.
11. Chojnowski K, Wawrzyniak E, Trelinski J, Niewiarowska J, Ciernie C. Assessment of coagulation disorders in patients with acute leukaemia before and after cytostatic treatment. Leuk Lymphoma. 1999;36:77–84.
12. Bairey O, Gabbay U, Blickstein D, Stark P, Prokocimer M, Epstein O, et al. Levels of proteins C and S do not decline subsequent to first line chemotherapy in lymphoma patients. Hematol Oncol. 1998;15:121–7.
13. Notoya A, Sawada K, Leko M, Tarumi T, Koizumi K, Fukada Y, et al. Subclinical alterations in coagulation and fibrinolysis in patients undergoing autologous peripheral blood stem cell transplantation. Leuk Lymphoma. 1998;28:405–13.
14. van der Meer F, Koster T, Vandenbroucke J, Briet E, Rosendaal F. The Leiden Thrombophilia Study (LETS). Thromb Haemost. 1997;78:631–5.
15. Lindmarker P, Schulman S, Sten-Lindner M, Wiman B, Egberg N, Johnsson H, the DURAC Trial Study Group. The risk of recurrent venous thromboembolism in carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. Thromb Haemost. 1999;81:684–9.
16. Poort S, Rosendaal FR, Reitsma P, Bertina R. A common genetic variation In the 3′-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996;88:3698–703.
17. Lane D, Mannucci P, Bauer K, Bertina R, Bochkov N, Boulyjenkov V, et al. Inherited thrombophilia: part 1. Thromb Haemost. 1996;76:651–62.
18. Genvresse I, Luftner D, Spath-Schwalbe E, Buttgereit F. Prevalence and clinical significance of anticardiolipin and anti-beta-glycoprotein-I antibodies in patients with non-Hodgkin`s lymphoma. Eur J Haematol. 2002;68:84–90.
19. Tuddenham E. Factor VIII-Novel insights into form and function. Br J Haematol. 2002;119:323–31.
20. Bhopale G, Nanda R. Blood coagulation factor VIII: an overview. J Biosc. 2003;28:783–9.
21. Federici A. The factor VIII/von Willebrand factor complex: basic and clinical issues. Haematologica. 2003;88(9):3–12.
22. Kaufmann R, Pipe S. Regulation of F VIII expression and activity by von Willebrand factor. Thromb Haemost. 1999;82:201–8.
23. Kamphuisen P, Eikenboom J, Rosendaal F, Koster T, Blann A, Vos H, et al. High factor VIII antigen levels increase the risk of venous thrombosis but are not associated with polymorphisms in the von Willebrand factor and factor VIII gene. Br J Haematol. 2001;115:156–8.
24. Mansvelt E, Laffan M, McVey J, Tuddenham E. Analysis of the F8 gene in individuals with high plasma factor VIII:c levels and associated venous thrombosis. Thromb Haemost. 1998;80:561–6.
25. Bowen D, Maclean R, Pellard S, Collins P. High concentrations of coagulation factor VIII and thrombosis: is the factor VIII binding domain of von Willebrand factor implicated? Br J Haematol. 2001;113:655–7.
26. O`Donnel J, Mumford A, Manning R, Laffan M. Elevation of FVIII:c in venous thromboembolism is persistent and independent of the acute phase response. Thromb Haemostasis. 2000;83:10–3.
27. Kamphuisen P, Eikenboom J, Vos H, Pablo R, Sturk A, Bertina R, et al. Increased levels of factor VIII and fibrinogen in patients with venous thrombosis are not caused by acute phase reactants. Thromb Haemost. 1999;81:680–3.
28. Schambeck S, Grossmann R, Zonnur S, Berger M, Teuchert K, Spahn A, et al. High factor VIII levels in venous thromboembolism: role of unbound FVIII. Thrombosis Haemost. 2004;92:42–6.
29. Bombeli T, Jutzi M, De Conno E, Seifert B, Fehr J. In patients with deep-vein thrombosis elevated levels of factor VIII correlate only with von Willebrand factor but not other endothelial cell derived coagulation and fibrinolysis proteins. Blood Coagul Fibrinolysis. 2002;13:577–81.
30. Mathonnet F, Mazancourt P, Denninger M, Morot M, Benattat N, Giudicelli Y. Role of factor VIII on activated protein C resistance ratio in inflammatory disease. Br J Haematol. 1996;95:423–5.
31. Kyrle P, Minar E, Hirschl M, Bialonczyk C, Stain M, Schneider B, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. N Engl J Med. 2000;343:457–62.
32. Kraaijenhagen R, Anker P, Koopman M, Reitsma P, Prins M, van den Ende A, et al. High plasma concentration of factor VIII:c is a major risk factor for venous thromboembolism. Thromb Haemost. 2000;83:5–9.
33. Legnani C, Benilde C, Michela C, Mirella F, Guazzaloca G, Palareti G. High plasma levels of factor VIII and risk of recurrence of venous thrombo-embolism. Br J Haematol. 2003;124:504–10.
34. Libourel E, Balje-Volkers C, Harmulyak K, Prins M, Middeldorp S, Büller H, et al. High factor VIII plasma levels as a risk factor for venous thrombosis: no evidence of inheritance from a family cohort study. Haematologica. 2004;89:118–20.
35. Tsai A, Cushman M, Rosamond W, Heckbert S, Tracy R, Folsom A. Coagulation factors, inflammation markers and venous thromboembolism: the longitudinal investigation of thrombosis etiology. Am J Med. 2002;113:636–42.
36. Minnema M, Fijnheer R, De Groot P, Lokhorst H. Extremely high levels of von Willebrand factor antigen and of procoagulant factor VIII found in multiple myeloma patients is associated with activity status but not with thalidomide treatment. J Thromb Haemost. 2003;1:445–9.

37. Medinger M, Fischer N, Tzankov A. Vascular endothelial growth factor-related pathways in hemato-lymphoid malignancies. J Oncol. 2010;. doi:10.1155/2010/729725.
38. Ruan J, Hajjar K, Rafii S, Leonard JP. Angiogenesis and antiangiogenic therapy in non-Hodgkin`s lymphoma. Ann Oncol. 2009;20:413–24.
39. Ribatti D, Nico B, Ranieri G, Specchia G, Vacca A. The role of angiogenesis in human non-Hodgkin lymphomas. Neoplasia. 2013;15:231–8.
40. Hussong JW, Rodgers G, Shami P. Evidence of increased angiogenesis in patients with acute myeloid leukemia. Blood. 2000;95:309–13.
41. Negaard HFS, Iversen N, Bowitz-Lothe IM, Sandset PM, Steinsvik B, Ostenstaad B, et al. Increased bone marrow microvascular density in haematological malignancies is associated with differential regulation of angiogenic factors. Leukemia. 2009;23:162–9.
42. Hivert B, Caron C, Petit S, Charpy C, Fankam-Siaka C, Zawadzki C. Clinical and prognostic implications of low or high level von Willebrand factor in patients with Waldenström macroglobulinemia. Blood. 2012;120:3214–21.