Journal of Translational Medicine BioMed Central

Research

Open Access

Congenital and acquired thrombotic risk factors in lymphoma patients bearing upper extremities deep venous thrombosis: a preliminary report

Pierpaolo Di Micco*[1], Alferio Niglio[1], Amalia De Renzo[2], Anna Lucania[2], Rosanna Di Fiore[3], Olga Scudiero[3] and Giuseppe Castaldo[3,4]

Address: [1]Divisione di Medicina Interna, Seconda Università di Napoli, Naples, Italy, [2]Divisione di Ematologia, Università di Napoli "Federico II", Naples, Italy, [3]Dipartimento di Biochimica e Biotecnologie Mediche e CEINGE-Bioteconologie avanzate, Università di Napoli "Federico II", Naples, Italy and [4]Facoltà di Scienze, Università del Molise, Aesernia, Italy

Email: Pierpaolo Di Micco* - pdimicco@libero.it; Alferio Niglio - alferio.niglio@unina2.it; Amalia De Renzo - aderenzo@unina.it; Anna Lucania - aderenzo@unina.it; Rosanna Di Fiore - difiore@dbbm.unina.it; Olga Scudiero - scudiero@dbbm.unina.it; Giuseppe Castaldo - castaldo@dbbm.unina.it

* Corresponding author

Published: 22 March 2004

Journal of Translational Medicine 2004, **2**:7

Received: 03 January 2004
Accepted: 22 March 2004

This article is available from: http://www.translational-medicine.com/content/2/1/7

Abstract

Background: Congenital thrombotic risk factors, oncological diseases and its therapies have been related to an increased occurrence of upper extremities deep venous thrombosis (UEDVT).

Patients and methods: We studied seven patients bearing lymphoma (one Hodgkin's and six non-Hodgkin's) who developed UEDVT, one at diagnosis and six during chemotherapy (two of these six cases had implantation of a central venous catheter and four received Growth Colony Stimulating Factors in addition to chemotherapy). Patients were screened for: factor V G1691A (Leiden), prothrombin G20210A, methylene tetrahydrofolate reductase (MTHFR) C677T mutations and antithrombin III, proteins C and S plasma activity.

Results: All patients were wild-type homozygotes for G20210A. One was heterozygote for factor V G1691A, the other 6 were wild-type homozygotes. Three of the 7 patients were homozygotes and 2 heterozygotes for the MTHFR mutation; the remaining 2 were wild-type homozygotes. Clotting inhibitor levels were normal in all patients.

Conclusions: UEDVT in patients bearing haematological malignancies can occur irrespective of congenital thrombophilic alterations. However, in a subgroup of patients UEDVT could also depend on congenital thrombophilic alterations. A screening for inherited thrombophilia can identify high risk patients that could be specifically treated to prevent thrombotic complications.

Introduction

Upper extremities deep venous thrombosis (UEDVT) is much less frequent than lower extremities deep venous thrombosis (LEDVT) [1,2]. However, UEDVT is frequent in patients affected by malignancies and bearing central venous catheters [3]. Given the association between

haematological malignancies and acquired thrombophilia [4], UEDVT and LEDVT could be a complication of neoplasia [4,5]. It is known that UEDVT can be triggered by onco-haematological care, i.e., surgery, bed rest, implantation of a central venous catheter, chemotherapy, and administration of growth colony stimulating factors [5]. Inherited thrombotic risk factors could also be present in several cases, but data on inherited thrombophilic predisposition in patients that develop UEDVT are scarce. Ruggeri et al. reported a low prevalence of anticoagulant protein deficiency in patients with UEDVT [6], and Martinelli et al. found a hypercoagulable state and hyperhomocysteinemia nearly in 15% of patients with UEDVT [7]. Prandoni et al. [8] reported a prevalence of 10–26% of inherited thrombophilic alterations in patients bearing UEDVT. In an attempt to shed light on the association between UEDVT, haematological malignancy and congenital thrombophilia, we studied three markers of thrombophilia predisposition, i.e., Factor V G1691A Leiden (FVL), the prothrombin G20210A gene mutation ($PTHRA_{20210}G$) and the methylene tetrahydrofolate reductase (MTHFR) C677T gene mutation, as well as the plasma activity of anticoagulant proteins antithrombin III (ATIII), protein C (PC) and protein S (PS) in 7 patients affected by haematological neoplasia and UEDVT, consecutively admitted to our observation.

Patients and methods

Patients

In the last year we observed 10 cases of newly diagnosed UEDVT. We studied 7 selected patients (6 females and 1 male, mean age 37 ± 8 years) bearing UEDVT as complication of an underlying lymphoproliferative disease; the other 3 referred patients affected by UEDVT were excluded because 2 (1 male and 1 female) carrier of a thoracic outlet syndrome while the third subject, an elderly woman, was affected by peritoneal metastasis and non-valvular atrial fibrillation. Of the seven selected patients, one female was affected by Hodgkin's disease, and six other patients by non Hodgkin's lymphoma. One patient showed UEDVT as the presenting sign of non Hodgkin's lymphoma, whereas six others developed UEDVT during chemotherapy. Two of these six patients had a central venous catheter (CVC) implant, four others received growth colony stimulating factor (G-CSF) during chemotherapy; only one patients had both CVC and G-CSF during chemotreatment. Six patients had mediastinal involvement (two bulky), and one had extranodal non Hodgkin's lymphoma. UEDVT was diagnosed in all patients by ultrasound imaging with 7–10 Mhz probe (ATL 1500 HDI, Philips).

Methods

A whole blood sample (5 mL) was collected in EDTA by venipuncture. DNA was extracted using the "Nucleon BACC2" kit (Amersham, Germany). Patients were screened for the following mutations: Factor V gene G1691A (Leiden), G20210A in the prothrombin gene and C677T in the MTHFR gene using PCR amplification with specific primers, and the Light Cycler apparatus (Roche, Italy). Plasma activity of antithrombin III and protein C was evaluated with commercial kits (Boehringer, Germany) as was plasma protein S activity (Biopool, Sweden).

Results and discussion

Results of molecular analysis are reported in Table 1. All 7 patients were wild-type homozygotes for the prothrombin G20210A mutation. One of the 7 was heterozygote for Factor V G1691A (Leiden), the other six being wild type homozygotes. Three of the 7 patients were homozygotes for the MTHFR mutation, two were heterozygotes, a condition not associated to higher risk of thrombophilia [7], and two were wild-type homozygotes. The plasma activity of AT III, PC and PS was within the reference intervals (data not shown).

Table 1: Type of neoplasia and thrombophilia risk factor mutations in seven patients bearing upper extremities deep venous thrombosis

Patient	Sex	Age (years)	Diagnosis of neoplasia	Factor V Leiden (G1691A)	$PTHRA_{20210}G$	MTHFR C677T
1	F	40	Extranodal NHL	WT/WT	WT/WT	WT/WT
2	F	53	NHL	WT/WT	WT/WT	MUT/MUT
3	M	27	NHL	WT/WT	WT/WT	WT/WT
4	F	38	NHL	MUT/WT	WT/WT	MUT/WT
5	F	28	NHL bulky	WT/WT	WT/WT	MUT/MUT
6	M	33	NHL bulky	WT/WT	WT/WT	MUT/MUT
7	F	30	HD	WT/WT	WT/WT	MUT/WT

NHL: non Hodgkin's lymphoma; HD: Hodgkin Disease; WT: wild type allele; MUT: mutated allele

The observations concerning the frequency of UEDVT increased since the first studies conducted in the 1980s [9,10] particularly in neoplastic patients as a consequence of such triggering factors as central venous catheter plant, chemotherapy, growth colony stimulating factors and others [3,4,11]. These data agree with our experience in the last year. Although in this period we examined nearly 90 oncological patients suspected to have a DVT (UEDVT, LEDVT or both), DVT was confirmed by ultrasound imaging in 30% of these (i.e. 27 patients). Moreover, nearly 67% of diagnosed DVT were LEDVT, while the remaining 33% were UEDVT, so confirming the increased incidence of UEDVT in oncological patients. Furthermore, in this report we may also testify an increased UEDVT risk in oncohaematological patients vs oncological patients because 7/8 of observed patients showed a lymphoproliferative disease in this particular population. Inherited alteration of clotting inhibitors (AT III, PC and PS) or genetic polymorphisms associated to a higher risk of thrombotic events have been reported in a percentage of patients with UEDVT ranging between 10 and 26% [6]. Yet our data, although on a preliminary population, indicate that more than 50% of neoplastic patients bearing UEDVT have altered markers of thrombophilia. Three patients, in fact, were homozygotes for the MTHFR mutation (42.8% versus 20% reported in the general population) and one was heterozygote for the Leiden mutation (14.7% versus 5.0% reported in the general population) [12]. On the contrary, none of our patients carried altered plasma levels of clotting inhibitors, confirming the observation of Ruggeri on the low prevalence of anticoagulant protein deficiency in patients with UEDVT [6].

However, our patients did not have a history of thrombotic events up to our observation. The fact that they developed UEDVT during chemotherapy for lymphoproliferative disorders suggest that the genetic alteration could act a predisposing factor, and that oncological disease and its therapy triggered the UEDVT. On the other hand, 3 patients without mutations in the genes examined developed UEDVT confirming that also in absence of inherited predisposition UEDVT can occur in oncological patients [2,8], so confirming the relevant role as thrombotic risk factors of malignancies and their care. However, we cannot exclude the possibility that they may carry other gene mutations predisposing to thrombophilic alterations [12].

Six of the seven patients in our study developed UEDVT during chemotherapy, four of which also received G-CSF and two had received central venous catheter implant to simplify administration of chemotherapy, thus confirming that these factors are strictly related to thrombotic complications in neoplastic patients [3,8]. Interestingly, in 6 patients the haematological malignancy showed mediastinal involvement, in two cases as bulky disease, which can cause vascular compression. Thus, also mediastinal involvement during haematological malignancy could be a risk factor for UEDVT, possibly mimicking a condition similar to thoracic outlet syndrome [3].

It must be underlined that UEDVT has been recently associated to higher morbidity and mortality for pulmonary embolism than LEDVT [13]. Furthermore, post-thrombotic sequelae may follow UEDVT [14]. On the other hand, specific therapies to prevent UEDVT in neoplastic patients are available [15].

Conclusions

Venous thromboembolism is a multifactorial disease in which inherited and acquired risk factors are involved. UEDVT are less common than LEDVT, but recently other UEDVT thrombotic risk factors have been identified such as inherited thrombophilia and plant of central venous catheters so improving knowledge on UEDVT pathophysiology. Although on a preliminary population our data show the contemporaneousness of inherited and acquired thrombotic risk factors in UEDVT patients bearing lymphoma. In particular, four of seven patients showed genetic polimorphisms with a trend toward thrombophilia and six of seven studied patients showed UEDVT during chemotherapy so underlying this gene-enviromental association. Thus, given the high occurrence of thrombophilic alterations observed in our population of UEDVT patients, we suggest to test also molecular markers of inherited thrombophilia in onco-haematological patients before chemotherapy in order to consider a primary thromboprophylaxis for UEDVT, in particular if other enviromental oncological factors occur, such as plant of CVC, G-CSF administration and mediastinal involvement.

List of abbreviations

UEDVT: upper extremities deep venous thrombosis

LEDVT: lower extremities deep venous thrombosis

MTHFR: methylene tetrahydrofolate reductase

FVL: factor V Leiden

PTHRA: prothrombin G20210A gene mutation

Acknowledgements

Grants from Ministero della Salute (L.502/92, annualità 2001), MIUR (FIRB 2001), Regione Campania (L.41/94, annualità 2000) and Università del Molise are gratefully acknowledged. We are indebted to Jean Ann Gilder for editing the text. We thank Prof. F. Salvatore for criticism and suggestions.

References

1. Balbarini A, Rugolotto M, Buttitta F, Mariotti R, Strata G, Mariani M: **Deep venous thrombosis: epidemiologic, diagnostic and therapeutic aspects.** *Cardiologia* 1998, **43:**605-615.
2. Girolami A, Prandoni P, Zanon E, Bagatella P, Girolami B: **Venous thromboses of upper limbs are more frequently associated with occult cancer as compared with those of lower limbs.** *Blood Coagul Fibrinolysis* 1999, **10:**455-457.
3. Niglio A, Torella R, Izzo T, Viggiano G, Di Micco P: **Inquadramento clinico diagnostico delle trombosi venose profonde degli arti superiori.** *Haematologica* 2003, **88(Suppl 7):**S17-S18.
4. Falanga A: **Tumor cell prothrombotic properties.** *Haemostasis* 2001, **31(Suppl 1):**1-4.
5. Ottinger H, Belka C, Kazole G, Engelhard M, Meusers P, Paar D, Metz KA *et al.*: **Deep venous thrombosis and pulmonary artery embolism in high grade non-Hodgkin's lymphoma: incidence, causes and prognostic relevance.** *Eur J Haematol* 1995, **54:**186-194.
6. Ruggeri M, Castaman G, Tosetto A, Rodeghiero F: **Low prevalence of thrombophilic coagulation defects in patients with deep vein thrombosis of upper limb.** *Blood Coagul Fibrinolysis* 1997, **8:**191-194.
7. Martinelli I, Cattaneo M, Panzeri D, Taioli E, Mannucci PM: **Risk factors for deep venous thrombosis of upper extremities.** *Ann Intern Med* 1997, **126:**707-711.
8. Prandoni P, Bernardi E: **Upper extremity deep vein thrombosis.** *Curr Opin Pulm Med* 1999, **5:**222-226.
9. Prescott MS, Tikoff G: **Deep venous thrombosis of upper extremity: a reappraisal.** *Circulation* 1979, **59:**350-355.
10. Monreal M, Davant E: **Thrombotic complications of central venous catheters in cancer patients.** *Acta Haematol* 2001, **106:**69-72.
11. Di Micco P, Niglio A, Chirico G, Russo F, Izzo T, Castaldo G, D'Uva M *et al.*: **Significant reduction of free S protein in women receiving chemoendocrine adjuvant therapy for breast cancer based on intravenous CMF administration and oral tamoxifen.** *Exp Oncol* 2002, **24:**301-304.
12. Souto JC: **Search for new thrombosis related genes through intermediate phenotypes. Genetic and household effects.** *Pathophysiol Haemost Thromb* 2002, **32:**338-340.
13. Hingorani A, Ascher E, Hanson J, Scheinman M, Yorkovich W, Lorenson E, De Pippo P, Salles-Cunha S: **Upper extremity versus lower extremity deep venous thrombosis.** *Am J Surg* 1997, **174:**214-217.
14. Prandoni P, Polistena P, Bernardi E, Cogo A, Casara D, Verlato F, Angelini F *et al.*: **Upper-extremity deep vein thrombosis. Risk factors, diagnosis and complications.** *Arch Intern Med* 1997, **157:**57-62.
15. Lensing AW, Prandoni P, Prins NH, Buller HR: **Deep-vein thrombosis.** *Lancet* 1999, **353:**479-485.