An Important Factor In Etiology Of Deep Venous Thrombosis: Malignancy

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Citation

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Abstract

Purpose: To determine the frequency of subsequent malignancy in patients with deep venous thrombosis and to evaluate them in accordance with literature data.

Material and Method: We studied 212 consecutive patients with confirmed deep venous thrombosis of the lower extremity between January 2001 and March 2003 at our department. We analysed records from malignancy detected patients and results were discussed.

Findings: Twenty-one patients had a malignancy (9.9%). Mean age was 57.7 (35-72) and male to female ratio was 10/11. The most frequently detected malignancies were gynecologic (33.3 %) and pulmonary neoplasias (28.5 %). Gastrointestinal (GI) (14.3 %) and urologic (14.3 %) malignancies were less commonly observed. Gynecologic malignancies were localized to the uterus (n=4), ovaries (n=2) and vulva (n=1). Pulmonary malignancies were small cell cancer (n=4) and epidermoid cancer (n=2). GI neoplasias were all localized to the colon. Of 3 urologic malignancies, 2 were hypernephroma and 1 was a prostate cancer. Venous thromboses were localized most commonly to the femoral vein (85.7%). Hemoglobin, thrombocyte and albumin levels were found to be significantly lower in the malignancy group compared to other group ($p< 0.05$). Protein C, protein S and antithrombin 3 levels did not differ among groups, however carcinoembryonic antigen levels were significantly higher in malignancy group ($p< 0.05$) .

Results: Deep venous thrombosis is associated with a significantly higher frequency of malignancy. The results suggest that detailed screening especially for gynecologic and pulmonary malignancies is necessary in patients with no known risk factor for hypercoagulability.

INTRODUCTION

Despite improvement in diagnosis and treatment methods, deep venous thrombosis is still an important morbidity and mortality factor in cancer patients. Age, sex, immobilization, surgery, oral contraceptives, pregnancy and cancer are well known risk factors associated with deep venous thrombosis [1]. Although risk factors are well known and despite application of effective prophylaxis, deep venous thrombosis incidence is 1/1000 in normal population, however this rises up to 10 % in cancer patients. This ratio may increase up to 3-6 folds in pancreas, breast, genitourinary, gastric, colon and lung cancer [1,2,3]. For this reason, it is beneficial to remember that deep venous thrombosis may develop in malignancy patients. Yet, deep venous thrombosis may appear as the first sign of malignancy. In the epidemiologic studies, it is suggested that cancer incidence increases in patients with idiopathic venous thrombosis and may be recognized by 10 % in two years follow up of those patients correlated with the tumor type [4,5].

Figure 1

Table 1: Localization of malignancies

The aim of this study was to determine the frequency of subsequent malignancy in patients with deep venous thrombosis and to evaluate them in accordance with literature data.

MATERIALS AND METHODS

We studied 268 consecutive patients with acute pain and swelling complaints of the lower extremities between January 2001 and March 2003 at our department. Of these

patients, 56 did not had a confirmed deep venous thrombosis by Doppler ultrasonography and were therefore excluded. Previously diagnosed patients who are on routine controls were not included in the study. In all patients deep venous thrombosis was diagnosed by detailed history, careful physical examination and colour doppler ultrasonography. Deep venous thrombosis detected patients were hospitalized and their medical therapy was initiated with low molecular weight heparin for 5-10 days followed by warfarin for 3 to 6 months.

The following routine tests were performed on all patients: whole blood count, erythrocyte sedimentation rate and biochemistry. Carcinoembryonic antigen (CEA), protein C, protein S and antithrombin-III levels were investigated in only 53 patients.

In patients with no known deep venous thrombosis risk factor, a detailed history focused on malignancy was taken; abdominal ultrasonography, gynecologic and urologic consultations were done.

Protein C and protein S levels were analysed by coagulometric method (STA-Staclot protein C kit, STA-Staclot protein S kit, USA). Antithrombin-III levels were measured by nepholometric method and CEA levels were analysed by enzyme immunometric assay technique. Normal levels are for protein C, 70-130 %; for protein S, 65-140 %; for antithrombin-III, 21.9-30.2 mg/dl; and for CEA, 0-2.5 ng/ml.

Statistical Analysis: Datas obtained were analysed by the SPSS (version 9.0; SPSS Inc., Chicago, IL, USA) program. Results were given as mean and the standard deviation of the mean. Distribution of the non-categoric data was analysed by Mann-Whitney U- test. $p < 0.05$ was accepted as statistically significant.

RESULTS

Mean age of acute deep venous thrombosis patients was 53.7 (12-89), with a male to female ratio of 121/91.

For the 21 patients who were diagnosed with a malignancy, the mean age was 57.7 (35-72) and the male to female ratio 10/11.

The most frequently detected malignancies were gynecologic (33.3 %) and pulmonary neoplasias (28.5 %). GI) (14.3 %) and urologic (14.3 %) malignancies were less commonly observed. Gynecologic malignancies were localized to the uterus (n=4), ovaries (n=2) and vulva (n=1). Pulmonary malignancies were small cell cancer (n=4) and epidermoid cancer (n=2). GI neoplasias were all localized to the colon. Of 3 urologic malignancies, 2 were hypernephroma and 1 was a prostate cancer. Venous thromboses were localized most commonly to the femoral vein (85.7%), and were usually unilateral (Table 2).

Figure 2

Table 2: Localization of venous thromboses

	Localization	Number of patients	%
Femoral vein	Left	9	42.8
	Right	8	38.1
	Bilateral	1	4.8
Vena cava inferior		3	14.3
Total		*21*	*100*

Hemoglobin, thrombocyte and albumin levels were found to be significantly lower in the malignancy group compared to other groups.

Carcinoembryonic antigen (CEA), protein C, protein S and antithrombin-III levels were investigated in 53 patients of whom 7 had a malignancy. Protein C, protein S and antithrombin-III levels did not differ significantly among groups, however carcinoembryonic antigen levels were significantly higher in the malignancy group (Table 3).

Figure 3

Table 3: Alterations in hemoglobin, thrombocyte and albumin levels

		Malignancy	Non-Malignancy	p value
Hemoglobin	(gr/dl)	11.3 ± 0.4	12.7± 0.3	**0.013***
Thrombocyte	(/mm³)	243 000 ± 26 604	316 000 ± 30 780	**0.029***
Albumin	(gr/L)	3.8 ± 0.2	4.3 ± 0.4	**0.040***
Protein C	(%)	87.7 ± 14.0	79.8 ± 12.2	0.420
Protein S	(%)	103.4 ± 14.2	93.1 ± 11.9	0.370
Antithrombin III	(ng/mL)	22.7 ± 4.0	23.9 ± 4.7	0.553
Carcinoembryonic antigen (CEA)	(ng/mL)	44.6 ± 7.4	1.9 ± 1.1	**0.014***

* $p < 0.05$ in Mann Whitney U- test

DISCUSSION

In this study of patients with deep venous thrombosis, malignancy incidence was 9.9 %. Most frequently detected malignancies were gynecologic (33.3%) and pulmonary neoplasias (28.5 %), while gastrointestinal (14.3 %),

urologic (14.3 %), intracranial and breast (4.8%) malignancies were less commonly observed.

Ibrahim et al. showed that malignancy is an important factor in patients developing deep venous thrombosis at intensive care unit with a ratio of 30.8 % [6]. Greenfield et al. detected gastrointestinal system neoplasias most frequently among deep venous thrombosis patients [7]. In our study, gynecologic malignancies, especially uterine neoplasias, were the most common underlying etiologies. Yet, since cancer cells have the ability to synthesize thrombin, it is commonly accepted that deep venous thrombosis is more common in ovarian cancer. Morgan et al. found ovarian cancer as the most frequent among gynecologic malignancies [8]. Another property of gynecologic malignancies is the development of deep venous thrombosis as a result of invasion and compression of the iliac veins.

In our study, routine abdominal ultrasonography and gynecologic examination of female patients with deep venous thrombosis played an important role in detection of gynecologic neoplasias. Although a malignant state was known in 1 of 7 patients at DVT diagnosis, all other patients were diagnosed after the development of deep venous thrombosis. In 4 of those; malignancy was detected after abdominal ultrasonography, in the remaining 2 malignancy was detected after gynecologic examination. Definite pathologic diagnosis of all patients was confirmed by tissue biopsy.

The tendency of thrombosis increases as a result of direct or indirect interaction between the coagulation system of the patient with cancer and the cancer cells. Interrupted fibrinolytic capacity, reduction in plasminogen activators and increase in plasminogen activator-inhibitors are important factors in development of deep venous thrombosis. Deep venous thrombosis risk increases with the growth of cancer cells and the development of metastases since thrombin synthesis is also increased [9,10,11,12,13]. Also deep venous thrombosis incidence increases in cancer patients after surgical interventions [14]. In our clinic, deep venous thrombosis was detected after chemotheraphy in 24 % of cases and after surgery in 14 % of cases. The chemotherapeutic agents and the endothelial injury of the injected drug play an important role in deep venous thrombosis development after chemotherapy [15].

The defects in coagulation system inhibitors such as antithrombin-III, protein C and protein S also result in an increase in thrombosis [14]. In our study, we couldn't find a significant difference between groups for those parameters.

CEA is a protein molecule existing in various cells in the body, whose levels are increase with fetal development and cancer of gastrointestinal, pulmonary, breast, ovarian or thyroid origin [15]. In our study, carcinoembryonic antigen levels were significantly higher in the malignancy group. CEA levels may help diagnosing malignancy in patients with idiopathic deep venous thrombosis. Certainly, this can not be generalized for all malignancies.

The number of thrombocytes is reduced due to hypoproteinemia, malnutrition, circulating immune complexes, tissue factors released from cancer cells and chemotherapeutics [9,13,16]. Alt et al. showed that the number of thrombocytes is reduced in the acute phase of deep venous thrombosis due to consumption of circulating thrombocytes [17]. Inflammatory cytokines (like tumor necrosis factor-a) play an important role in the reduction of albumin levels together with malignancy [1]. In our study, hemoglobin, thrombocyte and albumin levels were found to be significantly lower in the malignancy group compared to the other group aspreviously reported in the medical literature.

Though deep venous thrombosis may be seen in both upper and lower extremities, it is more commonly observed in the lower extremity veins [14]. Inferior vena cava thrombosis usually develops secondary to tumoral invasion. In our study, the most frequent localization for thrombosis was the femoral vein (85.7 %). Thrombosis of the inferior vena cava was detected in 2 patients with hypernephroma and in 1 patient with gastrointestinal malignancy.

Doppler ultrasonography is the most commonly used technique to diagnose deep venous thrombosis and is helpful in the differential diagnosis, since extremity edema and pain may develop due to various reasons such as trauma, heart failure and muscular hematoma.

We used doppler ultrasonography in all patients suspected of deep venous thrombosis on physical examination. Seventy-nine percent of those were definitely diagnosed with deep venous thrombosis.

Acute treatment of deep venous thrombosis includes classical heparin, low molecular weight heparin, fibrinolytic agents and surgery, however the most commonly used method is to treat with classical heparin or low molecular weight heparin for 5 to 10 days, followed by oral anticoagulation for 3 to 6 months in average [18]. In our

clinic, patients with deep venous thrombosis were hospitalized and treated for 5-10 days with classical heparin or low molecular weight heparin then switched to oral anticoagulation for 3-6 months in average.

In conclusion, deep venous thrombosis is associated with a significantly higher frequency of malignancy. The results clearly suggest that detailed screening especially for gynecologic and pulmonary malignancies is necessary in patients with no known risk factor.

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References

1. Johnson MJ, Spoule MW, Paul J. The prevalence and associated variables of deep venous thrombosis in patients with advenced cancer. Clin Oncol 1999;11:105-110
2. Maxwell GL, Myers ER, Clarke-Pearson DL. Cost-effectiveness of deep venous thrombosis prophylaxis in gynecologic oncology surgery. Obstet Gynecol 2000;95:206-214
3. Ravin AJ, Edwards RP, Krohn MA, Kelley JR, Christopherson WA, Roberts JM. The factor V leiden mutation and risk of venous thromboembolism in gynecologic oncology patients. Obstet Gynecol 2002;100:1285-1289
4. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Eng J Med 2000;343:1846-1850
5. Aderka D, Brown A, Zelikovski A, Pinkhas J. idiopathic deep vein thrombosis in an apparently healty patient as a premonitory sign of occult cancer. Cancer 1986;57:1846-1849
6. Ibrahim EH, Iregui M, Prentice D, Sherman G, Kollef MH, Shannon W. Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. Crit Care Med 2002;30:771-774
7. Greenfield LJ, Proctor MC, Saluja A. Clinical results of Greenfield filter use in patients with cancer. Cardiovasc Surg 1997;5:145-149
8. Morgan MA, Iyengar TD, Napiorkowski BE, Rubin SC, Mikuta JJ. The clinical course of deep vein thrombosis in patients with gynecologic cancer. Gynecol Oncol 2002;84:67-71
9. Wojtukiewicz MZ, Rucinska M, Zimnoch L, Jaromin J, Piotrowski Z, Rozanska-Kudeska M, Kisiel W, Kudryk BJ. Expression of prothrombin fragment 1+2 in cancer tissue as an indicator of local activation of blood coagulation. Thromb Res 2000;97:335-342
10. Hoffman MS, DeCesare S, Fiorica JV, Roberts WS, Cavanagh D. Management of gynecologic oncology patients with a preoperative deep vein thrombosis. Gynecol Oncol 1997;64:76-79
11. Biyani CS, Basu S, Botomley DM, Shah TK. Prostatic adenocarcinoma masquerading as lymphoma and presentation with axillary-subclavian vein thrombosis. Urol Oncol 2003;21:3-6
12. Lykke J, Nielsen HJ. The role of tissue factor in colorectal cancer. European Journal of Surgical Oncology 2003;29:417-422
13. von Tempelhoff GF, Niemann F, Schneider DM, Kirkpatrick CJ, Hommel G, Heilmann L. Blood rheology during chemotherapy in patients with ovarian cancer. Thromb Res 1998;90:73-82
14. Meissner MH, Strandness E. Pathophysiology and natural history of acute deep venous thrombosis. In:Rudherford RB(Ed). Vascular Surgery. Fifth edition. Philadelphia. W.B.Saunders Company, 2000:1921-1937
15. Nightingale CE, Norman A, Cunningham D, Young J, Webb A, Filshie J. A prospective analysis of 949 long-term central venous Access catheters for ambulatory chemotherapy in patients with gastrointestinal malignancy. Eur J Cancer 1997;33:398-403
16. Sawabata N, Ohta M, Takeda S, Hirano H, Okumura Y, Asada H, Maeda H. Serum carcinoembryonic antigen level in surgically resected clinical stage I patients with non-small cell lung cancer. Ann Thorac Surg 2002;74:174-179
17. Alt E, Banyai S, Banyai M, Koppensteiner R. Blood rheology in deep venous thrombosis-relation to persistent and transient risk factors. Thromb Res 2002;107:101-107
18. Zacharski LR. Anticoagulations in cancer treatment: malignancy as a solid phase coagulopathy. Cancer Lett 2002;186:1-9

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