Deep vein thrombosis as the first paraneoplastic presentation of undiagnosed cancer

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Abstract:

Introduction: Epidemiological studies reported a mean 4-12% prevalence of unrecognized cancer in patients with unprovoked deep vein thrombosis (DVT). The objective of our study was to assess the relation between unprovoked DVT and first diagnosis of a previously undiagnosed cancer and to investigate if it is justified to routinely screen these patients for malignancy with computed tomography (CT) scan.

Methods: We performed a retrospective analysis of medical records data of 276 patients with unprovoked extremity DVT admitted from 2015 to 2021. All patients underwent basic laboratory exams and a contrast enhanced CT scan of thorax, abdomen and pelvis with the purpose of screening for an occult, underlying tumor.

Results: In 46 patients (16.7%) a tumor was detected with malignancy confirmed in 37 cases (13.4%). In the majority (64.8%) the diagnosed tumor was confined to the primary organ with no or limited lymph node metastasis. In 16.2% the tumor was at advanced, metastatic stage. Lung (24.3%) and kidney (21.6%) were the most frequent primary locations, followed by colorectal (16.2%) and pancreatic (13.5%) cancer.

Conclusion: Patients presenting with unprovoked DVT have a relatively high possibility of an underlying malignancy, indicating that high level of medical awareness is advised. Routine screening of these patients with CT scan may be helpful for the early diagnosis of cancer.

Key words: deep vein thrombosis, cancer, paraneoplastic syndrome, computed tomography, diagnosis

INTRODUCTION

The relationship between venous thromboembolism (VTE) and cancer was first hypothesized by Virchow and reported by Trousseau in 1865.[1] An important amount of recent epidemiological studies has suggested the increased prevalence of VTE in terms of deep vein thrombosis (DVT) with or without pulmonary embolism (PE) in patients with cancer.[2-5] The mechanisms leading to this are associated with the Virchow's triad of blood stasis, endothelial injury and hypercoagulability, especially since cancer is considered as an hypercoagulable state.[1-2] Patients with known malignancy are reported to have a 5-fold increased rate of developing VTE, with an annual incidence of 0.5% compared with 0.1% in the general population.[5-6] Approximately, 4-20% of these patients will develop VTE at some stage of their disease.[5-6]

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What is interesting is the fact that cancer patients tend to develop DVT more often in the initial period following the diagnosis of cancer.[7] Moreover, an amount of patients with unprovoked DVT and without a history of malignancy are diagnosed with cancer during the VTE treatment, usually during the first months after the VTE diagnosis.[7] This lead to the question whether the development of DVT could be useful as an early diagnostic marker of undiagnosed, occult cancer in the general population, thus leading to earlier diagnosis and better treatment options for these patients.[7-8] Epidemiological studies reported a 4-12% prevalence of unrecognized cancer in patients with unprovoked DVT, which is lowered to 2-6% in patients with other known VTE risk factors.[9-14] However, the prevalence of DVT seems to vary greatly between individual studies depending on the sample size, patients' individual characteristics, the inclusion and exclusion criteria and the diagnostic imaging method used for detecting an occult and possibly malignant tumor.[9-14]

Aim of this study is to quantify the correlation between unprovoked DVT and first diagnosis of a previously unknown cancer, to determine the possible confounding variables and to investigate whether it is justified to routinely screen these patients for malignancy.

METHODS

We performed a retrospective analysis of prospectively col-

lected data from DVT patients from a single vascular surgery university tertiary center. The study period covered seven years from 2015 to 2021 and the investigational protocol was approved from our institutional ethics committee. A total of 359 consecutive patients with DVT of the lower or upper extremity were admitted in our department. From analysis were excluded all patients with history of thrombophilia, autoimmune diseases and/or cancer the last 10 years and/or with any other risk factor which could have provoked the thrombosis. Patients lost during follow up were also excluded. Eighty-three patients met these criteria and were excluded and finally 276 patients were enrolled in analysis.

Prior to admission, all patients were examined at the emergency department and were assessed with the Wells DVT score for the probability of DVT. A detailed medical history was obtained with emphasis on the risk factors for VTE, comorbidities and previous history of VTE and/or cancer. Laboratory work-up included a complete blood count and a basic metabolic panel, as well as the basic coagulation tests (PT-INR, aPTT, fibrinogen levels) and D-dimers plasma levels. The diagnosis was made by means of real time B-mode compression venous ultrasonography and patients were admitted to our clinic. A chest X-ray and an electrocardiogram were performed upon admission. On day 1, we performed a detailed colored duplex venous ultrasound (cDUS) of the affected limbs. According to our protocol, an iodine contrast enhanced CT scan of the thorax, abdomen and pelvis after per os administration of gastrografin was performed on day 2, with the intention of discovering an occult PE and/or a subclinical and undiagnosed tumor. Graduated compression stockings were applied and an adjusted therapeutic dosage of low molecular weight heparin (LMWH) was administered daily for the duration of their stay. Post-discharge anticoagulant medication in patients with negative imaging workup included a direct oral anticoagulant (DOAC) in therapeutic dosage, such as rivaroxaban 20mg q.d. or apixaban 5mg b.i.d.. Patients with positive findings in imaging or laboratory work-up indicating a possible malignancy remained in LMWH treatment and were referred for oncological consultation to establish the definite diagnosis and for further treatment. All patients were followed-up both clinically and with cDUS at 3 months, 6 months and 1 year.

Statistical analysis

We reviewed the files of these 276 unprovoked DVT patients and recorded the patients' demographics (age, gender), individual patient risk factors such as smoking, comorbidities and medication with emphasis on antiplatelet or anticoagulant treatment. In cancer patients, the site of cancer, pathology report and TNM staging were reviewed. The data were entered in a computerized database and the statistical analysis was performed by using the IBM SPSS Statistics program - version 22.0 for macOS (IBM, NY, USA). Categorical variables are presented as counts and percentages and were analyzed with the chi-square test. Continuous variables that follow the normal distribution are presented as mean ± standard deviation (STD) and were analyzed with Student t-test, whereas those which do not follow the normal distribution are presented as median and interquartile range (IQR) and were analyzed with Mann-Whitney U-test. The significance level of the various performed statistical tests was defined at p-value < 0.050.

RESULTS

Forty-six patients (16.7%) with unprovoked DVT were found to have a previously undiagnosed solid tumor and further oncological specialist evaluation confirmed malignancy in 13.4% (n=37) of our series. Accordingly, the patients were divided in subgroup A, which included 239 (86.7%) patients free from malignancy, while patients with a malignant neoplasm (n=37, 13.4%) constituted the subgroup B. Table 1 shows the demographics, basic characteristics and clinical presentation data of the study sample, as well as of the two subgroups. Notably, male gender and smoking were significantly more frequent in subgroup B (p=0.030 and p=0.005, respectively).

In the vast majority of patients (n=266, 96.3%), the thrombosis was located at the deep veins of the lower extremities, with no difference between the two subgroups (p=0.256). Iliofemoral DVT was significantly more frequent in subgroup B (75.7% vs. 69.0%, p=0.018). Twenty-five patients (9.1%) experienced DVT under antiplatelet treatment, while six patients (6.2%) under anticoagulant treatment. No difference was discovered between the two subgroups (p=0.069 and p=0.099, respectively). PE was diagnosed in 30 cases overall (10.9%). All PE cases were subclinical, and a malignant tumor co-existed in 5 patients (13.5%) of subgroup B. Analysis showed that PE was found to be marginally correlated with neoplastic disease (13.5% vs. 10.4%, p=0.051).

Table 2 summarizes the blood analysis data of the commonly used factors in the evaluation of patients' coagulation and thrombotic potential. No difference was found between the subgroups regarding the platelet number (p=0.197). Mean fibrinogen levels were significantly higher in subgroup B (457 ± 70 vs 387 ± 64 mg/dl, p=0.037). Similarly, analysis showed that median D-dimers was more than two times greater in subgroup B compared with the relevant value in subgroup A (13.21 - 7.8 vs 6.13 - 6.4, p=0.003).

Table 3 depicts the primary location of the malignant tumors that were discovered through the CT scan in these 37 patients of our study sample. The most common primary sites for the neoplasms were the lungs (n=9, 24.3%) and kidneys (n=8, 21.6%), followed by the gastrointestinal tract (n=7, 18.9%) and pancreas (n=5, 13.5%). Notably, at 1-year follow-up none of the subgroup A patients were diagnosed with a neoplasm. Table 4 shows the TNM staging of these 37 malignant neoplasms at the time of the imaging diagnosis. The majority was diagnosed at an early stage (stages I and II), with the tumor confined to the primary organ (n=15, 40.5%) or with limited lymph node metastasis (n=9, 24.3%). Six patients (16.2%) were found at an advanced stage (stage IV), with distant metastases. It must be emphasized that during the time of imaging diagnosis none of these patients with primary or metastatic neoplasm experienced any symptom indicating or implying a possible underlying malignancy. In all stage I and II cancer patients, surgical resection of the primary tumor was

Table 1. Demographics, basic characteristics and clinical data of the study population

Variables	Patients with unprovoked DVT - n (%)			P-value
	All patients 276 (100%)	Subgroup A 239 (86.6%)	Subgroup B 37 (13.4%)	
Age (years)	65.1 ± 7.2	63.5 ± 7.1	67.9 ± 7.6	.101
Male gender	137 (49.6)	111 (46.4)	26 (70.3)	**.030**
Smoking	180 (65.2)	146 (61.1)	34 (91.9)	.005
Obesity, BMI >30	57 (20.7)	49 (20.5)	8 (21.6)	.123
CAD	30 (10.9)	26 (10.9)	4 (10.8)	.275
COPD	20 (7.2)	17 (7.1)	3 (8.1)	.185
CKD	25 (9.1)	15 (9.2)	3 (8.1)	.176
Antiplatelet [a]	25 (9.1)	21 (8.9)	4 (10.8)	.069
Anticoagulant [b]	6 (2.2)	5 (2.1)	1 (2.7)	.099
Lower limb	266 (96.3)	231 (96.7)	35 (94.6)	.256
Iliofemoral DVT	193 (69.9)	165 (69.0)	28 (75.7)	.018
PE	30 (10.9)	25 (10.4)	5 (13.5)	.051

***Abbreviations**: BMI body mass index, CAD=coronary artery disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, DVT=deep vein thrombosis, PE=pulmonary embolism.*

[a] *Aspirin or clopidogrel*

[b] *Dabigatran, rivaroxaban, apixaban or acenocumarol.*

Categorical variables are presented as n (%). Continuous variables are presented as mean ± SD. Statistically significant difference at p<0.050 level appear bold typed.

Table 2. Laboratory data of the study sample

Variables	Patients with unprovoked DVT - n (%)			P-value
	All patients 276 (100%)	Subgroup A 239 (86.6%)	Subgroup B 37 (13.4%)	
PLT (*10^3/μl)	342 ± 91	332 ± 92	361 ± 100	.197
INR	1.02 ± 0.07	1.03 ± 0.08	1.01 ± 0.09	.234
aPTT (sec)	34.5 ± 2.8	35.6 ± 2.7	32.9 ± 3.3	.138
FBG (mg/dl)	418 ± 68	387 ± 64	457 ± 70	**.037**
D-dimers (mg/L)	6.99 - 8.6	6.13 - 6.4	13.21 - 7.8	.003

***Abbreviations**: aPTT=activated partial thromboplastin time, FBG=fibrinogen, INR=international normalized ratio, PLT=platelets count.*

D-dimers are presented as median - IQR. Other continuous variables are presented as mean ± std. Statistically significant difference at p<0.050 level appear bold typed.

Table 3. Primary location of malignant tumors

Location	Total number n=37 n (%)
Lung	9 (24.3)
Kidney	8 (21.6)
Colorectal	6 (16.2)
Pancreas	5 (13.5)
Uterus	3 (8.1)
Non-Hodgkin Lymphoma	3 (8.1)
Other [a]	3 (8.1)

[a] Other includes stomach, liver and prostate cancer of 1 case each.

Table 4. Stage of cancer at the time of the diagnosis

TNM staging [a]	Total number n=37 n (%)
Stage I	15 (40.5)
Stage II	9 (24.3)
Stage III	7 (18.9)
Stage IV	6 (16.2)

[a] TNM criteria of each individual organ

performed promptly, with adjuvant chemotherapy in 11 of them (29.7%). In stage III patients, neoadjuvant chemotherapy +/- radiation therapy was performed first, followed by locoregional resection of the neoplastic tissues. Finally, in the five stage IV patients, chemotherapy and palliative care was applied. At 1-year follow-up two deaths were reported, both from the stage IV subgroup. No other major morbidity was reported. Notably, at 1-year follow-up none of the subgroup A patients were diagnosed with a neoplasm.

DISCUSSION

The relationship between venous thromboembolism (VTE) and cancer is well established, with DVT to be considered a common complication among cancer patients.[1-4] Patients with neoplasm seem to be in a prothrombotic state due to the development of paraneoplastic syndrome.[4-5] Epidemiological studies confirmed the relatively high incidence of an unrecognized cancer in patients with unprovoked extremity DVT, but there seems to be no consensus in actual prevalence and the extent of screening. The reported incidence varies from 7.2% to 13.1%.[9-14] The reason behind this variability between the individual studies seems to be related with the sample size, the patients' inclusion and exclusion criteria and the modality and extent of diagnostic imaging used for detecting a possibly malignant tumor.

Goals of our study were to determine the prevalence of occult malignant neoplastic disease in patients with unprovoked DVT and to investigate the value of routine CT imaging in early detection of undiagnosed neoplasms. The proper imaging approach of DVT patients should implicate the presence of a silent PE as well of a malignant tumor.[14-15] Contrast enhanced thorax, abdomen and pelvis CT scan with per os gastrografin is a modality with great availability and feasibility in general practice, which combines the ability of high accuracy in detection of both PE and neoplasms and was therefore the selected method of routine imaging in our study.[15] Other imaging modalities such as magnetic resonance or positron emission tomography have equal or even greater diagnostic accuracy but the lack of availability and feasibility in general practice question their applicability as first line diagnostic tools for these patients.[15] The results of our study confirmed the high incidence of cancer (13.94%) in a total of 276 patients with unprovoked extremity DVT. Furthermore, during the 1st years' follow-up none of the 239 cancer-free patients was diagnosed with a new neoplasm.

Individual patient risk factors associated with an underlying cancer etiology are age, sex, race and comorbidities such as obesity, lung disease and renal failure.[9,12] A risk score for more extensive examination for cancer has been proposed, but it not validated.[13] In our study, only male gender and smoking were found to be significantly associated with diagnosis of cancer. Additionally, in 25 cases (9.1%) DVT was developed despite the fact that these patients were under antiplatelet treatment. In these cases, researchers have suggested an occult malignancy as the most likely underlying etiology, which triggers the thrombosis.[16] Our study confirmed a trend towards this direction but failed to prove this hypothesis (p=0.069). Regarding the clinical extent and severity, iliofemoral DVT was significantly more frequent in the cancer subgroup (75.7% vs. 69.0%, p=0.018). Moreover, the results showed that PE was marginally correlated with an underlying neoplastic disease.

Routine blood analysis results didn't seem to differ between the two subgroups. However, fibrinogen and especially D-dimers levels were found to be significantly elevated in patients with an occult malignancy, mirroring the hypercatabolic state of an active cancer. The median value of D-dimers was significantly higher in cancer patients of our series (13.21 - 7.8 vs 6.13 - 6.4, p=0.003) and this highlights the potential use of D-dimers as a marker of patients in risk of neoplastic disease. However, further research is required to achieve general agreement in this field.

Clinical manifestation of cancer in DVT patients is related with primary site, staging and histological type.[17-19] Malignant tumors of pancreas, uterus, lung, stomach, and kidney have been reported to be more frequent among DVT patients.[17-19] In our study kidney and lung cancer accounted for nearly half (45.9%) of our cases. Previous studies formulated the hypothesis that malignant tumors in DVT patients are usually contained to the primary organ site with limited to none lymph node metastasis and that this early detection is associated with better treatment options, better response to treatment and better overall survival rates. [17-20] Our study confirmed that 64.8% of the diagnosed malignant tumors were at stages I and II with no or limited lymph nodes infiltration and were set timely in the proper treatment. Widespread and incurable stage IV disease was found only in 16.2% of cases. Moreover, the only two deaths reported at 1-year follow-up came from the advanced stage IV, and not from the early stages. These results seem to ratify the rationale and need for routine CT cancer screening in patients presenting with unprovoked DVT.

However, the debate on the necessity and the extent of screening for malignancy when unprovoked DVT is diagnosed is ongoing and there is no consensus yet between researchers. A relatively high prevalence of an occult malignancy in patients with DVT does not automatically imply that extensive screening for cancer is indicated since it is unknown whether a substantial proportion of these malignancies can be diagnosed at a relatively early stage and whether earlier detection will ultimately lead to better treatment options and longer life expectancy.[21-23] Meta-analysis showed that extensive cancer screening diagnosed a higher number of malignancies compared with limited screening, but conferred no significant reduction in all-cause mortality or cancer related mortality.[10-11] Moreover, extensive screening is not without drawbacks. Physical and emotional distress, economical costs, false positive findings and hazards resulting from contrast and ionizing media must be taken into consideration.[10-11] The only thing for sure is that physicians dealing with unprovoked DVT should be aware of the possibility of an occult malignancy, especially during the first year of diagnosis.

Our study has the limitation of its retrospective, observational character, thus our results reflect only a particular time frame. A prospective, cohort study with a larger sample size and duration of follow-up is needed to assess the dynamics of cancer development in patients with unprovoked DVT and to provide useful results about the better diagnostic and treatment strategies. Moreover, a cost-effectiveness analysis should be performed evaluating the clinical and economical importance of routine CT-scan screening of all patients with unprovoked DVT in order to detect a possible underlying malignancy.

CONCLUSION

Patients presenting with unprovoked extremity DVT have a relatively high possibility of having an underlying, previously unknown malignancy. Routine screening with CT scan at the time of the DVT diagnosis in a general practice environment may be helpful as an diagnostic marker for the early diagnosis of malignancy. Therefore advanced awareness is advised. Further research is needed to determine whether CT screening should be performed as part of routine in all patients with unprovoked DVT.

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