Prognostic relevance of an asymptomatic venous thromboembolism in patients with cancer

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To cite this article: Dentali F, Ageno W, Pierfranceschi MG, Imberti D, Malato A, Nitti C, Salvi A, Siragusa S, Squizzato A, Vitale J, Agnelli G. Prognostic relevance of an asymptomatic venous thromboembolism in patients with cancer. *J Thromb Haemost* 2011; **9**: 1081–3.

There are increasing numbers of reports of incidentally detected, asymptomatic venous thromboembolisms (VTE) in patients undergoing chest or abdominal computed tomography (CT) for reasons other than a clinical suspicion of either a deep vein thrombosis (DVT) or a pulmonary embolism (PE). The increasing frequency of these incidental findings is probably because of the introduction of multi-detector computed tomography (CT) scanners with high acquisition speeds, increased spatial resolution and resultant improved visualization of abdominal vein and peripheral pulmonary arteries [1,2].

The detection of asymptomatic VTE is becoming a particular clinical problem with CT scans performed for cancer staging [3–5]. In a recent systematic, we estimated a prevalence of asymptomatic PE of 3.2% in patients undergoing a CT scan for staging of the disease [6].

Symptomatic VTE predicts poorer prognosis in patients with cancer [7]. In a recent retrospective study, survival rates of cancer patients with an unsuspected, asymptomatic PE found on a routine cancer staging CT scan were found to be lower than in matched patients without an asymptomatic PE [8]. Thus, an asymptomatic VTE in cancer patients found during staging of the disease may be an important prognostic marker that might influence management strategies.

To explore this clinical issue, we performed a multicenter-retrospective study with the aim of comparing 6-month survival rates in a group of 60 cancer patients with an incidentally detected asymptomatic VTE, in a group of 120 cancer patients with a symptomatic VTE, and in a group of 60 cancer patients in whom a VTE was excluded.

An asymptomatic VTE was defined as the detection of an unsuspected PE or DVT on a CT scan. Scans were usually ordered by the treating oncologist during baseline staging, or to determine treatment effect after a defined duration of therapy. A symptomatic VTE was objectively diagnosed according to commonly accepted criteria [9,10]. In all patients with a PE, either incidentally detected or symptomatic, a compression ultrasound of the lower limbs was performed. In the third group, a clinically suspected VTE had to be objectively excluded by commonly accepted criteria [9,10].

All included patients had been referred to the anticoagulation clinics of the study centers (Varese, Ancona, Piacenza and Palermo, Italy) between January 2007 and September 2008. Classification of patients as asymptomatic or symptomatic was done locally, without central adjudication. Patients with a prior VTE were excluded.

At each participating center, all VTE patients are monitored regularly for morbid outcomes, and information on clinical events is documented and registered in computerized databases. All patients are reviewed regularly in their local Oncology Department.

At each center, medical records of patients were reviewed by a trained physician for patient demographics, type and histology of the primary malignancy, presence and sites of metastases, concomitant chemotherapy, hormonal therapy, radiotherapy, therapy with erythropoietin and use, type and dose of anticoagulant therapy. Data extraction from the medical records was performed using selection criteria and data collection forms that were prepared before the chart reviews. Information on 6-month mortality in the three groups was obtained for all patients.

Baseline characteristics of patients were compared using Student's *t*-test (for continuous variables) and the χ^2- or Fisher's exact test (for dichotomous variables). Six-month mortality was calculated in each group. Differences in mortality rates were first considered taking into account patients with and without thrombosis. Afterwards, the rates were compared among the three groups. Finally, logistic regression analysis was used to examine the influence of individual variables on the likelihood of death at 6 months. Only variables found significant in the univariate analysis were used as covariates in the multivariate analysis.

The present study was approved by local Institutional Review Boards and patient information was codified to ensure anonymity. Baseline characteristics of included patients are

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DOI: 10.1111/j.1538-7836.2011.04259.x

Received 15 December 2010, accepted 23 February 2011

summarized in Table 1. Age and gender were similar in the three groups [P = not significant (NS)], and there were no differences among groups in cancer site and stage (P = NS). PE was significantly more prevalent in the group of patients with an asymptomatic VTE than in the group with symptomatic VTE (85% vs. 20%, $P < 0.001$). All patients with symptomatic or asymptomatic VTE were initially treated with low-molecular-weight heparin (LMWH) or unfractionated heparin. Long-term treatment with LMWH was used in 73.3% of patients with asymptomatic VTE and 78.3% of patients with symptomatic VTE (P = NS), the remaining patients were treated with warfarin. A minority of asymptomatic VTE patients were treated with prophylactic doses of LMWH (6.7%). Total duration of treatment was similar between the two groups of VTE patients. Although no autopsies were performed, mortality was ascribed by the treating oncologists to cancer progression in the large majority of patients in the three groups.

Six-month mortality rates were significantly higher in patients with a VTE (both symptomatic and asymptomatic) as compared with patients without a VTE (46.7% vs. 26.7%; $P = 0.007$). Six-month mortality rates were similar in patients with a symptomatic VTE and in patients with an asymptomatic VTE (47.5% and 45.0%, respectively, $P = 0.75$) and were significantly higher in each of the two groups when compared with patients without a VTE ($P = 0.007$ and $P = 0.036$, respectively).

At multivariate analysis (after considering the VTE presence, the VTE site and the presence of symptoms) VTE (either symptomatic or asymptomatic) remained significantly associated with an increased risk of 6-month mortality (OR 2.72; 95%CI 1.0, 7.43; $P = 0.048$), whereas the presence of symptoms and the VTE site did not ($P = 0.90$ and $P = 0.55$, respectively).

A small group of studies have provided data on the natural history of patients with an incidental PE [1–8,8–13], but only one provided information on mortality rates. In the study by O'Connel *et al.* [8], patients with a PE had an increased risk of death [hazard ratio (HR) 1.79; 95% confidence interval (CI) 1.10, 2.90] and the presence of an incidental PE appeared to confer a poorer survival (5 vs. 14 months; $P = 0.0009$) in comparison to cancer patients without a VTE. The present findings confirm these results and, in addition, show for the first time that the prognosis of patients with cancer and an asymptomatic VTE is similar to that in cancer patients with a symptomatic VTE.

The present study has some limitations. First, the retrospective design limits inferences that can be drawn. Second, a relatively small number of patients were included and thus CIs around the association between VTE and mortality are wide. To decrease the risk of bias in this small sample, we enrolled patients consecutively and information on 6-monthmortality was gathered for all patients. Third, we enrolled all cancer types; different types of cancer may have a different natural history independent of the presence of VTE. However, the proportion of cancer types was not apparently different in the three groups. As a result of the small numbers we were unable to determine the magnitude of the association between an asymptomatic VTE and each cancer type or between an asymptomatic VTE and different cancer therapies. Fourth, we cannot exclude that dissimilarity in the baseline characteristics of these patients with a symptomatic and an asymptomatic VTE may have influenced the results of the present study. However, in multivariate analysis these two groups appeared to behave similarly. Finally, not all 'incidentally detected' events may have been truly 'asymptomatic'. It is possible that signs or symptoms of VTE may have existed in patients and were missed by the clinical team.

Table 1 Baseline characteristics of included patients

	Asympomatic VTE	Symptomatic VTE	No VTE
Number	60	120	60
Male sex, *n* (%)	31 (52)	65 (54)	29 (48)
Mean age (SD)	65.8 (10.9)	69.6 (11.5)	68.6 (10.2)
Advanced stage, *n* (%)	58 (96.6)	112 (93.3)	58 (96.6)
Cancer site	28 gastroenteric	37 gastroenteric	18 gastroenteric
	8 pulmonary	17 pulmonary	14 pulmonary
	6 lymphatic	15 lymphatic	5 lymphatic
	6 breast	16 breast	12 breast
	12 others	35 others	11 others
Venous thrombosis location	37 PE + DVT	20 PE + DVT	–
	9 isolated DVT	96 isolated DVT	
	14 isolated PE	4 isolated PE	
Antithrombotic treatment	44 therapeutic LMWH	94 therapeutic LMWH	
	4 prophylactic LMWH	0 prophylactic LMWH	
	12 LMWH + warfarin	26 LMWH + warfarin	
Cancer treatment	55 chemotherapy	101 chemotherapy	49 chemotherapy
	2 hormonal therapy	7 hormonal therapy	6 hormonal therapy
	15 radiotherapy	30 radiotherapy	12 radiotherapy
	9 erythropoietin	13 erythropoietin	8 erythropoietin
Mortality, *n* (%)	27 (45)	57 (47.5)	16 (26.7)

VTE, venous thromboembolic events; PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin.

In conclusion, our data suggest that the presence of an asymptomatic VTE may have a clinical impact on the prognosis of cancer patients, and that this impact is similar to that seen in patients with a symptomatic VTE. Prospective studies are warranted to confirm our preliminary findings.

Addendum

F. Dentali, W. Ageno and G. Agnelli designed the study and wrote the protocol. F. Dentali analyzed and interpreted the data. M.G. Pierfranceschi, D. Imberti, C. Nitti, A. Salvi, J. Vitale, A. Malato, S. Siragusa and A. Squizzato collected and analyzed the data. F. Dentali performed the statistical analysis. F. Dentali, W. Ageno, D. Imberti, S. Siragusa and G. Agnelli wrote the manuscript.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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Large deletions identified in patients with von Willebrand disease using multiple ligation-dependent probe amplification

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To cite this article: Yadegari H, Driesen J, Hass M, Budde U, Pavlova A, Oldenburg J. Large deletions identified in patients with von Willebrand disease using multiple ligation-dependent probe amplification. *J Thromb Haemost* 2011; **9**: 1083–6.

von Willebrand disease (VWD) is the most common inherited bleeding disorder caused by quantitative or qualitative deficiency of the von Willebrand factor (VWF) protein. VWD is classified into three primary categories [1,2]. Type 1 and type 3 VWD are characterized by mild or severe quantitative deficiencies of VWF, respectively. Type 2 VWD variants (subtypes A, B, M and N) express qualitative deficiency associated with a loss or gain of function of the VWF protein [3]. A large diversity of mutations such as missense, nonsense and splice site mutations, small deletions/insertions and large deletions has been reported in the *VWF* gene database http://www.vwf.group.shef.ac.uk. Large deletions are regarded as being a rare cause of VWD, usually resulting in a complete lack of VWF protein [4]. Twelve large deletions, ranging in size from a single exon to the entire gene, responsible for type 3 VWD are reported up to now. Interestingly, a large deletion covering all VWF A domains has been described for type 2A (http://www.vwf.group.shef.ac.uk).

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DOI: 10.1111/j.1538-7836.2011.04260.x

Received 4 January 2011, accepted 24 February 2011