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Asymptomatic pulmonary embolism in patients with symptomatic deep vein thrombosis of the extremities: Three year results of a prospective study

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ABSTRACT

Objective: Symptomatic pulmonary embolism (PE) has been associated with high morbidity and mortality. However, data on the clinical impact of AsPE on patients with known deep vein thrombosis (DVT) are limited in literature.

Methods: Patients treated in our institution for symptomatic DVT without any symptoms or signs of PE were prospectively included in this study. The diagnosis of DVT was verified using colored Duplex ultrasonography based on international guidelines. All patients underwent a thorax-computed angiography in order to detect cases with AsPE. Basic characteristics of all patients and major outcomes were compared between patients with DVT and no PE and patients with DVT plus AsPE. Mean follow-up was 3 ± 0.32 years.

Results: AsPE was detected overall in 39 patients (32%). The majority (37%) of patients reported long-lasting bed rest/immobility, 15% had a neoplasia, although 32% of patients did not have any typical DVT risk factor. There was no difference regarding age, gender, location of thrombosis or typical risk factors. Basic serum parameters did not differ between the two groups, either. However, more patients with PE showed d-dimer values of <5mg/l compared to patients with DVT only (p=0.017). Deaths from all causes and total days of initial hospitalization did not differ between the two groups. However, AsPE was found to be a risk factor both for new symptomatic PE (RR = 5.675, CI 95% [1.592 – 20.233], p = 0.0074) as well as readmission to hospital (RR = 2.736, CI 95% [1.523 – 4.915], p = 0.0008).

Conclusions: AsPE occurs frequently in patients with symptomatic DVT, although neither typical risk factors nor the location of DVT seem to be associated with its presence. Therefore, early recognition of AsPE as well as close long-term monitoring is necessary to reduce possible recurrence and readmission.

Key words: *Deep vein thrombosis, silent pulmonary embolism, asymptomatic pulmonary embolism, prognosis, management*

Introduction

Asymptomatic or silent pulmonary embolism (AsPE) has been the subject of several publications evaluating the incidence of AsPE and potential clinical, therapeutic or socioeconomic implications [1,2]. However, the results to date have been quite disparate and specific recommendations concerning early detection and management have not been incorporated in international guidelines [1]. Although the incidence of unsuspected PE diagnosis reaches only 2.6% in patients undergoing computed-tomography scanning of the thorax for various reasons [3], incidence of AsPE in patients with symptomatic DVT rises to 32%, ranging from 11% to 59% in various studies [4]. Furthermore,

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results on the effect of AsPE have been controversial as well. Although a number of studies have found no advantage associated with diagnosis [5], others have concluded that patients with DVT and AsPE may show increased morbidity, especially in the early setting [1].

Therefore, the aim of this study was to prospectively determine the true incidence of AsPE in patients with DVT, to evaluate possible associations with specific thrombotic risk factors and to investigate the clinical impact of AsPE presence in such patients.

Methods

All data referring to patients treated for symptomatic DVT of the extremities without any symptoms or signs of pulmonary embolism in a vascular surgery department of an urban tertiary centre were prospectively collected and evaluated. Symptoms or signs of DVT included oedema, tenderness or pain, redness or discoloration, low oxygen saturation and distention of extremity veins. Typical or atypical symptoms or signs of PE were defined as the following: dyspnea, tachypnea, chest pain, cough or hemoptysis, cyanosis or circulatory instability, tachycardia or hypotension and fever. All symptoms or signs were evaluated at the time of clinical examination or reported by the patient itself.

DVT was verified in all patients through a colored Duplex ultrasonographic evaluation. Criteria for DVT verification included: visualization of a hypoechoic structure within the vein, passive distension of the vein or absence of local or distal compressibility and changes in venous flow dynamics [6]. All patients underwent a computed angiography of the thorax in order to exclude any pulmonary embolism. The positive criterion was a filling defect, in place of the contrast, within the pulmonary arterial tree. The extent of the contrast defect could be total or partial and, in the latter case, either as a ring or at an angle to the vessel wall [6].

All patients were divided into two major groups: patients with DVT and AsPE and patients with DVT and no PE. The study was in compliance with the Helsinki Declaration and was approved by the Ethical Committee of the Hospital where it was performed. Informed written consent was obtained from all participants. Basic characteristics of all patients taking part in the study, including gender, age, location of the DVT, risk factors for DVT and initial laboratory measurements, were recorded and compared between the two major groups. Moreover, major outcomes investigated in this study included days of initial hospitalization, duration of total anticoagulant therapy, incidence of new symptomatic PE, infection of lower respiratory system, death (from all causes), major cardiovascular events and readmission to hospital (from causes linked to AsPE). Mean follow-up of all patients was 3 ± 0.32 years.

All patients were treated according to protocol, which consisted of 3-5 days of low molecular weight heparin, adjusted for weight, followed by orally-administered antagonists of vitamin K drugs until an international ratio (INR) ≥2 was achieved, and at that point, the heparin was removed. All patients remained in bed for the first 24 hours with the lower-extremities elevated, and were mobilized on the next day after applying Class II pressure stockings. Patients diagnosed with AsPe received per os therapy for at least 6 months. Patients with DVT and no PE received per os therapy for at least three months, according to international Guidelines [7]. Cases where anticoagulant therapy was contraindicated (patients with increased risk for bleeding) were excluded.

Follow-up consisted of a daily clinical examination until discharge and evaluation of new symptoms or signs. Physical examination was programmed one-three-six months after discharge as well as each year thereafter. Each patient underwent a duplex ultrasound of the lower extremities three and six months after discharge. Additionally, each patient presenting new symptoms or signs indicative for PE was evaluated with clinical examination, new computed angiography and duplex ultrasound of the lower extremities.

Comparisons between groups were performed using the t test for continuous variables and x^2 and Fisher exact tests for categorical variables as appropriate. Statistical significance was defined at a P value of <0.05. Multivariate logistic regression was used to identify independent associations between various risk factors and AsPE prevalance.

Results

Overall, 122 patients with a symptomatic DVT of the extremities were included in this prospective study. No patients showed any typical or atypical symptoms or signs of pulmonary embolism. Out of the 122 pa-

tients, 83 (68%) patients had only a DVT and the remaining 39 (32%) patients were diagnosed with an AsPE. Overall, 48% of patients were of male gender and the other 52% were of the female gender. Regarding the recorded thrombotic risk factors, the majority (37%) of patients reported long-lasting bed rest or immobility, 15% of patients had a history of or were diagnosed with a malignant neoplasia, although 32% of patients did not report any typical DVT risk factor. Regarding the location of DVT, the majority of patients had a proximal DVT of the lower extremities (femoral/popliteal vein).

All data compared between the two groups of patients are listed in Table 1. There was no difference between the two groups regarding mean age, prevalence of male gender, main DVT risk factors and location of DVT. Regarding the laboratory measurements, none of the basic parameters in serum showed any variation between patients with AsPE and patients without AsPE. However, more patients with DVT and no PE had d-dimer values lower than 5mg/l compared to patients with both DVT and AsPE ($p = 0.017$).

Regarding the association of AsPE with major out-

Table 1. Basic characteristics of patients in both groups of interest.

	DVT only (n = 83)	DVT and AsPE (n = 39)	P value
Mean age (years)	62 ± 2.5	64 ± 1.6	NS
Male gender (n)	44	15	NS
Risk Factors			
Neoplasia (n)	12	6	NS
Bed rest/immobility (n)	28	17`	NS
Recent surgery (n)	11	6	NS
Recurrent thrombosis (n)	2	0	NS
Pregnancy (n)	1	0	NS
No risk factor (n)	25	14	NS
Location			
Upper extremity (n)	3	2	NS
Iliac veins (n)	15	12	NS
Femoral/popliteal veins (n)	51	21	NS
Infrapopliteal veins (n)	14	4	NS
Laboratory measurements			
White Blood Cells (n/mm^3)	11,315 ± 2,345	11,826 ± 1,965	NS
Hematocrit (%)	40.2 ± 5.7	38.2 ± 6.4	NS
Platelets (n/mm^3)	320,000 ± 64,000	412,000 ± 58,000	NS
Creatinine (mg/dl)	0.95 ± 0.12	1.03 ± 0.11	NS
Urea (mg/dl)	45 ± 6	49 ± 7	NS
C-reactive protein (mg/dl)	4.8 ± 2.4	5.6 ± 1.5	NS
SGOT (U/L)	28 ± 4	35 ± 3	NS
SGPT (U/L)	24 ± 7	27 ± 5	NS
NT-pro-BNP (pg/ml)	250 ± 75	300 ± 56	NS
Cardiac Troponine I (ng/ml)	0.04 ± 0.01	0.05 ± 0.01	NS
Prothrombin time (sec)	11.4 ± 2.7	10.7 ± 1.7	NS
International ratio (INR)	1.1 ± 2.5	1.0 ± 2.1	NS
aPTT (sec)	26.4 ± 5.4	28.7 ± 4.2	NS
D-Dimers (mg/l)	5.1 ± 1.3	3.9 ± 1.9	NS
D-Dimers < 5mg/l (n)	44	30	0.017

aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; AsPE, asymptomatic pulmonary embolism; NT-pro-BNP, N-terminal pro-brain-type natriuretic peptide.

comes, the results are presented in Table 2. There was no difference between the two groups of patients with respect to days of initial hospitalization, death from all causes as well as major cardiovascular events during the follow-up period. However, patients with both DVT and AsPE received anticoagulant therapy for a longer mean period of time compared to patients with DVT and no PE (10.8 ± 1.6 months versus 5.3 ± 0.5 months; p = 0.003). Moreover, patients with AsPE presented more new symptomatic PE events (p = 0.046) and new infections of the lower respiratory system (p = 0.047) during follow-up. Finally, more patients with AsPE were readmitted to hospital (p = 0.009) based on causes linked to AsPE. (Table 2)

AsPE was found to be a risk factor both for new symptomatic PE (RR = 5.675, CI 95% [1.592 – 20.233], p = 0.0074) as well as readmission to hospital (RR = 2.736, CI 95% [1.523 – 4.915], p = 0.0008).

Discussion

In this prospective study, it was found that a high prevalence of AsPE existed in patients with symptomatic DVT of the extremities. Moreover, basic patient characteristics did not elicit any differences between patients with strictly DVT and patients with DVT plus AsPE, though AsPE was a major risk factor for new symptomatic PEs and readmission to hospital.

Almost one third of the patients studied showed an AsPE and this is in concurrence with other studies, as well [4,8]. Additionally, gender, age, location of DVT or history of a typical thrombotic risk factor did not seem to play any role in the prevalence of AsPE in our cohort. However, several studies have indicated an association between male gender [9] or older age [10] with AsPE in patients with DVT. Furthermore, the absence of typical thrombotic factors has been linked to a higher AsPE prevalence in several studies. Boc et al. [8] and Jimenez et al. [11] have identified unprovoked proximal DVT as major risk factor for occurrence of AsPE. This could justify a genetic thrombophilia assessment in all patients with a suspicious family history. In our study, however, we did not include results of genetic thrombophilia testing as this was conducted in younger patients with unprovoked DVT and no PE.

Location of DVT did not play a significant role in causing AsPE in the study presented here. However, data concerning this matter are controversial in recent literature. In a large study of almost 11,000 patients, below-knee DVT was associated with a higher rate of PE compared to above-knee DVT [12]. Li et al. [9] have concluded that right side and proximal location of the thrombus are major risk factors for AsPE occurrence. The fact that the embolization of proximal thromboses is more frequent than distal DVTs is observed in symptomatic PEs as well [10]. However, ongoing guidelines recommend anticoagulation coverage for both proximal and distal DVTs [13], justifying our results. Finally, all of the patients were mobilized within 24 hours wearing stockings. Early ambulation is not associated with increased risk for DVT progression or death [14], and it is recommended under proper compression in order to reduce pain, swelling and risk for post-thrombotic syndrome [15].

Basic laboratory serum values did not vary between patients with and without AsPE. Several circulating markers have been proposed as alternative (or additional) tools for risk stratification of patients with

Table 2. Major outcomes in both groups of interest.

	DVT only (n = 83)	DVT and AsPE (n = 39)	P value
Days of hospitalization (n)	6.3 ± 1.1	6.8 ± 1.5	NS
Mean duration of therapy (months)	5.3 ± 0.5	10.8 ± 1.6	0.003
New symptomatic PE (n)	3	8	0.046
Infection of lower respiratory system (n)	2	7	0.047
Deaths (of all causes; n)	6	5	NS
Major cardiovascular events (n)	6	4	NS
Readmission to hospital (n)	14	18	0.009

PE, pulmonary embolism; DVT, deep vein thrombosis; AsPE, asymptomatic pulmonary embolism.

acute PE in general. However, no investigation has focused on the evaluation of such markers in patients with AsPE only. N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) has been associated with an increased risk for early death and complications in patients with acute PE [16]. Yet, the lack of any connection in this study could indicate that perhaps AsPEs carry a lower embolic burden, causing lower stress to the right heart chambers and releasing therefore lower levels of NT-pro-BNP. Regarding the role of cardiac troponine I (cTnI) as a predictor in patients with PE, the literature is controversial [17,18]. As well, d-dimers are included in the recommended algorithms for exclusion of venous thromboembolism [7]. The data made available so far has suggested that in patients with a low pretest probability for DVT, d-dimer levels < 0.5 mg/l show high negative predictive value [19]. That being said, there is insufficient data on patients with AsPEs evaluating its predictive role. These results showed that perhaps values under 5mg/l could be indicative of AsPE nonexistence.

Regarding the impact of AsPE on major health outcomes, it was found that AsPE increases both the rates of new symptomatic PE and readmission to hospital within a period of 3 years after the initial diagnosis, although the influence on the total days of initial hospitalization and major cardiovascular events was not significant. This concurs with the findings of García-Fuster et al. [10], who found that hospital stay was extended only by an additional half day in patients with silent PE. However, concerning recurrence, Tzoran et al. [1] studied almost 2,400 patients and concluded that patients with AsPE showed a higher incidence of symptomatic PE events within the first 15 days, but this effect does not appear after 3 months. Finally, Jiménez et al. [11] underline that silent PE causes more recurrence of VTE events compared to isolated DVT (11% vs 0%, P = 0.0045) at one year. This study's results, however, indicate that patients with AsPE need to be under a close observation program for at least 3 years and the duration of therapy should be adjusted for longer than 6 months in order to ameliorate recurrence rates. Follow-up should include regular clinical examinations and duplex ultrasounds, while pulmonary angiography should only be performed when there is suspicion of recurrence.

Finally, there has been major concern regarding the investigation of AsPEs in all patients with symptomatic DVT and the appropriate further management of such patients. Standardized imaging utilizing pulmonary computed angiography, the gold standard to date [20], raises concerns on the additional economic costs and radiation exposure. Especially in elder patients, the use of contrast media could increase the risk for renal function deterioration. However, silent PEs were associated in the present study with higher recurrence and readmission rates under proper therapy duration, justifying the need for early diagnosis. Additionally, ACCP (American College of Chest Physicians) Guidelines [21] recommend the placement of vena cava filters in patients with new embolic events under anticoagulants. Therefore, the early identification of patients with AsPE at the time of presentation could identify such cases that are simple recurrences rather than new events needing only an extension of treatment.

The limitations of this study include: (i) the small number of patients; (ii) the symptomatic cases not detected where patients could not identify possible atypical symptoms, like tachycardia or hypotension, though these were not present at the time of clinical examination; and (iii) not all patients underwent genetic thrombophilia testing that could have recognized a possible genetic risk factor in unprovoked cases.

Overall, silent PE is a frequent complication in patients with symptomatic DVT, but neither typical thrombotic risk factors nor the location of the thrombosis seem to be associated with its presence. Therefore, early recognition of AsPE as well as close long-term monitoring is necessary in order to reduce possible recurrence and readmission.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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