ORIGINAL ARTICLE

Suspected acute pulmonary embolism in patients with and without cancer: alternative diagnoses

Silvia GÓMEZ-ZORRILLA MARTÍN[1], Antoni RIERA-MESTRE[1], David LEIVA PEDRAZA[2], Sara JORDÁN LUCAS[3], Javier JACOB RODRÍGUEZ[3], Ramon PUJOL FARRIOLS[1]

[1]Servicio de Medicina Interna, [2]Servicio de Radiodiagnóstico, [3]Servicio de Urgencias, Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain.

Correspondence:
Silvia Gómez-Zorrilla Martín
Servicio de Medicina Interna
Hospital Universitari
de Bellvitge-IDIBELL
L'Hospitalet de Llobregat,
Barcelona, Spain
E-mail:
sgomez@bellvitgehospital.cat

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Objectives: To determine the alternative diagnoses made in patients with and without cancer who undergo computed tomography (CT) to confirm or rule out a suspected diagnosis of acute pulmonary embolism in a hospital emergency department.
Methods: Retrospective study of all patients who underwent CT with a suspected diagnosis of acute pulmonary embolism in 2006 and 2007.
Results: A total of 265 case records (for 93 patients with cancer and 172 without cancer) were studied. In 98.5% of the patients, clinical suspicion of pulmonary embolism was high, based on the Wells or Geneva Scales, or low-intermediate clinical suspicion and positive D-dimer level. A diagnosis of pulmonary embolism was confirmed in 25.8% of the cancer patients and 39.5% of the noncancer patients. When pulmonary embolism was ruled out, an alternative diagnosis could be reached by CT in 81.2% of the cancer patients and 67.3% of the noncancer patients. The most common alternative diagnosis in cancer patients was tumor progression, which was even more common than the diagnosis of pulmonary embolism. In noncancer patients, the most common alternative diagnoses were acute heart failure, exacerbation of chronic obstructive pulmonary disease (COPD), and pneumonia.
Conclusions: CT facilitates the differential diagnosis of a large percentage of patients suspected of having acute pulmonary embolism. The most common alternative diagnosis is tumor progression in patients with cancer; in noncancer patients the most common alternative diagnoses are exacerbated COPD and acute heart failure. [Emergencias 2013;25:92-98]

Keywords: Acute pulmonary embolism. Computed tomography. Hospital emergency health services.

Introduction

Pulmonary thromboembolism (PTE) is the most serious manifestation of venous thromboembolism (VTE). It is associated with high rates of morbidity and mortality, especially in cancer patients, where VTE is the second leading cause of death after cancer itself[1]. Suspected PTE is a common situation in the emergency department (ED) and requires rapid diagnosis and therapy; mortality in untreated PTE is 30%[2,3]. Early diagnosis in the ED is essential since immediate treatment decreases mortality[4-6].

Given that the signs and symptoms of PTE are non-specific, imaging tests are usually necessary to confirm its presence or absence[4]. Pre-test clinical probability scales (CPS) represent a formal objective method to estimate the probability of developing PTE before diagnostic tests are performed and are especially useful in the ED[7-9]. The prevalence of PTE at 3 months, according to low, moderate or high clinical probability is 5-10%, 20-30% and 60-80%, respectively[10]. These scales have been included in the main consensus guidelines; their main value is their high negative predictive value (NPV) when combined with D-dimer values, and further tests are considered unnecessary if these scales indicate low clinical probability of PTE when D-dimer is negative[4,11-13].

Currently, computed tomography (CT) is the imaging test of choice for clinically suspected PTE[4,6,14]. Along with its high sensitivity and speci-

ficity, one potential advantage of CT with respect to other techniques for the diagnosis of PTE is its ability to provide information allowing possible alternative diagnoses. A normal CT scan allows one to exclude the diagnosis of PTE and facilitates alternative diagnoses to explain the signs and symptoms[13,14]. This is clinically important since 60-70% of patients with suspected PTE do not have the disease[15-17]. Few studies have addressed these alternative diagnoses in the ED[16-19]. The aim of this study was to make known the alternative diagnoses to PTE in cancer and non-cancer patients treated in the ED of a university hospital who underwent CT for suspected PTE.

Method

We performed a retrospective study including ED patients with suspected PTE who underwent a CT scan between January 2006 and December 2007. Patients were selected from our hospital Radiology Department register of urgent CT performed. The setting was Bellvitge Hospital, a tertiary university hospital, which also attends emergencies arising in a 100-bed monographic cancer hospital (Hospital Duran i Reynals, Catalan Institute of Oncology) affiliated to our center. This study was approved by the Clinical Research Ethics Committee of Bellvitge Hospital.

For the purposes of the present study, inclusion criteria were: patients attended in the ED for clinical suspicion of PTE who underwent a CT scan and were followed for at least 3 months. The clinical suspicion of PTE was defined as: sudden onset or worsening of dyspnea, or chest pain without apparent etiology. CT in suspected PTE was performed according to an established protocol for the diagnosis of PTE in our center. This requires calculating the Wells scale value and D-dimer determination for each patient. CT is recommended for all patients with high clinical suspicion (> 6 points). It is also indicated in patients with low (< 2 points) or intermediate clinical suspicion (2-6 points)when D-dimer determination is positive. Since D-dimer was determined using a latex agglutination test with only moderate sensitivity, the diagnosis of PTE can only be excluded with negative D-dimer when clinical probability is low. In patients with intermediate probability and negative D-dimer values, the indication for CT must be individualized.

We compared patients with versus without cancer. Those with cancer were defined as having active diagnosed neoplasia before the index episode of suspected PTE, whether they were receiving curative or palliative treatment or not, or who had finished cancer treatment six months before the index episode. Patients who did not have active neoplasia were considered as non-cancer patients.

We recorded demographic, clinical, laboratory data and risk factors for VTE (history of VTE, surgery or immobility for medical reasons during the month before). Although the diagnostic protocol for PTE in our center includes Wells scale values, these were often not specifically stated in most medical records[7]. For better evaluation of clinical suspicion and to study the usefulness of clinical probability scales in practice, we also added the values of the Geneva scale[8]. Both were calculated retrospectively in all patients.

We recorded blood gas and D-dimer values, determined in the ED, the latter by latex agglutination immunoassay (Instrumentation Laboratory, ILtest). Concentrations of 250 µg/L or less were considered normal.

For the imaging study a 16 Slice CT Scanner was used (GE, BrightSpeed) with 1.25 mm axial slices from the neck to the adrenal glands after peripheral administration of intravenous iodine contrast. Multi-plane reconstructions were subsequently performed with 0.625 mm slices and analyzed by a medical specialist in imaging diagnosis. CT criteria for the diagnosis of acute PTE were complete or partial occlusion of the pulmonary artery, seen as a contrast filling defect on at least two consecutive slices[20].

We recorded all pathological CT findings of the lung parenchyma, mediastinum, pleura, cardiovascular system and skeleton, which allowed defining an alternative diagnosis. For the final determination of alternative diagnoses, we considered whether these were made exclusively on the basis of CT findings or also required clinical data. These data were obtained taking into account the clinical diagnosis made in the ED, at hospital discharge or during follow up.

To ensure the absence of PTE, all patients were followed until 3 months after the CT study. Mortality and any thromboembolic events during this period were recorded. VTE recurrence and mortality were determined by ambulatory monitoring of medical records or by telephone interview with the patient or their family. Recurrence of VTE was defined as clinical suspicion documented by objective examinations (CT or lung scan, or Doppler ultrasound in suspected deep vein thrombosis). Cases of death were investigated to determine whether the cause was attributable to VTE or some other disease.

Data are expressed as absolute numbers and percentages for qualitative variables and as mean ± standard deviation (SD) for quantitative variables. We performed a univariate analysis using chi-square test to compare qualitative variables and Student's t test for quantitative variables. Differences with a P value < 0.05 were considered statistically significant. The data were analyzed using SPSS (version 15.0).

Results

During the study period 1166 thoraco-abdominal CT, 693 abdominal CT and 473 thoracic CT were performed. Of all these urgent CT studies, 440 (37.7%) were performed for suspected pulmonary embolism. Of these, 163 were not initially requested from the ED so were not included in the study. Of the remaining 277, 12 were excluded for lack of follow up data.

The overall mean age was 65.5 years (range 25-96, SD 16.4) and 52.5% were male. A third 35% (93 patients) had known malignancy and were defined as cancer patients, while 65% (172 patients) were non-cancer patients. PTE was diagnosed in 92 patients (34.7%), 24 (25.8%) in the cancer group and 68 (39.5%) in the non-cancer group. In 98.5% of patients, the indication for CT was in accord with our hospital protocol.

Clinical features, EPC, complementary scans and follow up data for the cancer and non-cancer groups are shown in Table 1. D-dimer values were determined in 229 patients, with 8 (3.5%) negative results. Three patients with negative D-dimer were cancer patients. In accordance with the CPS, non-cancer patients with PTE showed higher average values on the Wells scale ($p < 0.001$) and the Geneva scale ($P < 0.01$),while in the cancer group these differences were only significant for the Wells scale ($p < 0.001$).

In non-cancer patients, the percentage of PTE diagnoses despite low Wells scale and Geneva scale probability was 7.4% and 26.5%, respectively. No cancer patients with low Wells scale probability presented PTE, while 25% of these patients with low Geneva scale probability had PTE.

Four (2.3%) of the non-cancer patients with low Wells scale probability and three (1.7%) of these same patients with low Geneva scale probability had negative D-dimer. Despite this, CT scan was performed but showed no PTE in all these cases. All cancer patients with low scale probability had positive D-dimer justifying the performance of a CT scan.

The histological types that most frequently presented PTE were adenocarcinoma (20.8%), hematological tumors (16.6%), squamous cell carcinoma (12.5%) and ductal breast carcinoma (12.5%). The data on the histological types and tumor sites of the cancer patients with PTE are shown in Table 2.

On follow-up at three months, no recurrence of VTE was found in cancer patients with initial PTE, and in the subgroup of patients without PTE there were two new events of PTE. In non-cancer patients no episodes of VTE were detected. Both cancer and in non-cancer patients without PTE showed higher, but not significant, mortality.

Table 3 shows the final alternative diagnoses, according to CT, clinical findings and diagnostic criteria included in discharge reports. CT scans provided alternative diagnosis to PTE in the ED for 81.2% of cancer patients and 67.3% of non-cancer patients. The most frequent alternative diagnoses were cancer progression and decompensation of chronic obstructive pulmonary disease (COPD) in cancer patients and acute heart failure (AHF) and COPD decompensation in non-cancer patients. AHF and COPD decompensation, alone or concomitantly, accounted for 93.3% of the alternative diagnoses for non-cancer patients. Of these, nine patients with no previously known malignancy were diagnosed with cancer, detected on the initial CT in five of them. The types of neoplasia were: lung cancer (four patients) and thymic carcinoma, leukemia, breast cancer, prostate and ovarian cancer (one each).

Discussion

The percentage of PTE diagnosed in our series (34.5%) was similar to that reported previously[16-19,21,22]. Current multislice CT scanners have improved visualization of the pulmonary arteries, both segmental and sub-segmental, with a negative predictive value of > 99%, and this allows ruling out PTE without resorting to lower limb Doppler ultrasound[13,16,19]. In our study, we detected two new events of PTE in the follow up of cancer patients without a diagnosis of pulmonary embolism in the ED. One of them occurred 2 months after initial CT and the other at 6 days without clinical improvement: the latter was assumed to be the only case of false negative CT. These data, along with evidence of no fatal PTE event during follow-up, confirm the value of a negative CT result in the ED, in accordance with other published work[13,16].

Table 1. Comparison between cancer and non-cancer patients with and without pulmonary thromboembolism (PTE)

	Cancer patients (N = 93)		Non-cancer patients (N = 172)	
	PTE N = 24	No PTE N = 69	PTE N = 68	No PTE N = 104
Clinical Features				
Male gender [n (%)]	15 (62.5%)	45 (65.2%)	29 (42.6%)	50 (48.1%)
Age, years (mean ± SD)	64.8 ± 12.8	66.4 ± 12.3	65.5 ± 19.3	65.2 ± 17.8
– Age ≥ 70 years [n (%)]	10 (41.7%)	33 (47.8%)	38 (55.9%)	52 (50%)
Risk factors for VTE				
Metastasis	11 (45.8%)	38 (55.1%)	0 (0%)	0 (0%)
Chemotherapy	12 (50%)	30 (43.5%)	0 (0%)	0 (0%)
Recent surgery (previous month)	3 (12.5%)	2 (2.9%)	9 (13.2%)	5 (4.8%)*
Previous VTE	3 (12.5%)	5 (7.2%)	17 (25%)	4 (3.8%)‡
Immobility (previous month)	4 (16.7%)	12 (17.4%)	12 (17.6 %)	21 (20.2%)
PTE characteristics				
Wells scale score (mean ± SD)	5.2 ± 1.6	3.5 ± 1.9‡	5.1± 2.2	2.3 ± 2.0‡
– Low risk (≤ 1 point) [n (%)]	0 (0%)	17 (24.6%)†	5 (7.4%)	59 (56.7%)‡
– Low-intermediate (≤ 6 points) [n (%)]	19 (79.2%)	61 (88.4%)	54 (79.4%)	95 (91.3%)‡
Geneva scale score (mean ± SD)	6.0 ± 2.2	5.0 ± 2.4	5.9 ± 2.4	4.7 ± 1.9†
– Low risk (≤ 4 points) [n (%)]	6 (25%)	29 (42%)	18 (26.5%)	40 (38.5%)
– Low-intermediate (≤ 8 points) [n (%)]	18 (75%)	57 (82.6%)	57 (83.8%)	90 (86.5%)*
pO_2 (mmHg) (mean ± DE)	61.9 ± 14.94	62.8 ± 14.4	68.8 ± 39.4	67.0 ± 18.3
– pO_2 < 60 [n (%)]	10 (41.7%)	29 (42%)	24 (35.3%)	38 (36.5%)
pCO_2 (mmHg) (mean ± DE)	35.0 ± 9.0	36.2 ± 8.7	35.4 ± 6.7	37.3 ± 8.9
– pCO_2 < 35 [n (%)]	13 (54.2%)	32 (46.4%)	28 (41.2%)	43 (41.3%)
D-dimer (μ/L) (mean ± DE)	2.585 ± 2.242	2.200 ± 4.004	3.588 ± 4.851	1.730 ± 2.915†
– Negative < 250 [n (%)]	1 (4.2%)	2 (2.9%)	0 (0%)	5 (4.8%)
Three-month follow up				
Recurrence of VTE	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)
– Recurrence of PTE (± DVT)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)
– Recurrence of DVT alone	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Overall mortality [n (%)]	8 (33.3%)	37 (53.6%)	5 (7.4%)	14 (13.5%)
– Cancer	3 (12.5%)	35 (50.7%)	0 (0%)	5(4.8%)
– Fatal PTE	5 (20.8%)	0 (0%)	5 (7.4%)	0 (0%)
– Bleeding	0 (0%)	0 (0%)	0 (0%)	0 (0%)
– Other	0 (0%)	2 (2.9%)	0 (0%)	9 (8.7%)

Comparison of patients with PTE vs without PTE: *P < 0.05, †P < 0.01, ‡P < 0.001. SD: standard deviation; VTE: venous thromboembolism, PTE: pulmonary embolism, DVT: deep vein thrombosis.

In addition, CT allows an alternative diagnosis, a very important fact since 60-70% of patients with suspected PTE do not actually have the disease[15-17]. In our study, CT alone allowed making an alternative diagnosis in 81.2% of cancer patients and 67.3% of non-cancer patients. Over a third (35%) of our patients had a known malignancy, which is higher than the 15.7% reported in another ED study[23]. This high rate is probably due to the fact that our center also attends emergency visits from a nearby cancer hospital. Increased physician awareness and clinical suspicion of PTE in cancer patients probably explains a lower rate of PTE diagnosis than in non-cancer patients, 25.8% vs. 39.5% (P < 0.05). The most common histological finding in cancer patients with PTE was adenocarcinoma, a tumor with high thrombotic capacity due to the release of mucin[1,24].

Regarding the use of the probability scales, the Wells scale presented better diagnostic value than the Geneva scale in cancer patients. In this respect it should be mentioned that the Wells scale

Table 2. Histological type of neoplasia in cancer patients

	Cancer patients with PTE (n = 24) n (%)	Cancer patients without PTE (n = 69) n (%)
Lung [n (%)]	5 (20.8%)	23 (33.3%)
ADC	2 (8.3%)	5 (7.2%)
Squamous	2 (8.3%)	11 (16%)
NSCLC	1 (4.2%)	5 (7.2%)
SCLC	0 (0%)	2 (2.9%)
Breast [n (%)]	3 (12.5%)	12 (17.4%)
Hematologic [n (%)]	4 (16.7%)	8 (11.6%)
Urological [n (%)]	4 (16.7%)	6 (8.7%)
Prostate ADC	2 (8.3%)	5 (7.2%)
Renal	2 (8.3%)	1 (1.5%)
Digestive tract [n (%)]	1 (4.2%)	6 (8.7%)
ADC	1 (4.2%)	4 (5.8%)
Squamous	0 (0%)	2 (2.9%)
Squamous ENT [n (%)]	1 (4.2%)	7 (10.1%)
CNS [n (%)]	2 (8.3%)	1 (1.5%)
Others [n (%)]	4 (16.7%)	6 (8.7%)

ADC: adenocarcinoma, NSCLC: non-small cell lung carcinoma; SCLC: small cell lung carcinoma (histology not defined); ENT: ear, nose and throat tract tumors; CNS: central nervous system.

Table 3. Alternative diagnoses in patients without pulmonary thromboembolism (PTE)

	Cancer patients (n = 69) n (%)	Non-cancer patients (n = 104) n (%)
Utility initial CT		
Diagnosis by CT alone	56 (81.2%)	70 (67.3%)
Definitive alternative diagnosis		
Oncological disease	34 (49.3%)	7 (6.7%)
– Lung cancer progression*	19 (27.5%)	4 (3.8%)
– New lung M1	6 (8.7%)	2 (1.9%)
– Pericardial pleural effusion	4 (5.8%)	1 (0.9%)
– Lymphangitic carcinomatosis	3 (4.4%)	0 (0%)
– Bone M1	2 (2.9%)	0 (0%)
AHF (± pulmonary effusion)	10 (14.5%)	46 (44.2%)
COPD exacerbation	13 (18.8%)	34 (32.7%)
COPD and AHF	6 (8.7%)	17 (16.3%)
Pneumonia (± pleural effusion)	7 (10.1%)	16 (15.4%)
Other	5 (7.2%)	7 (6.7%)
Fractured rib/vertebra	1 (1.4%)	2 (1.9%)
Pericarditis	0 (0%)	2 (1.9%)
AMI	2 (2.9%)	1 (0.96%)
Sepsis	1 (1.4%)	1 (0.96%)
Musculoskeletal	1 (1.4%)	1 (0.96%)

*Primary pulmonary neoplasia unknown in non-cancer patients. CT: computed tomography; M1: metastasis; AHF: acute heart failure, COPD: chronic obstructive pulmonary disease. AMI: acute myocardial infarction.

includes neoplasia as one of its variables. However, the Geneva scale includes blood gas values which, in cancer patients, could be altered for other reasons related with the neoplasia (lung metastases, opportunistic infection, radiotherapy or cachexia). In the non-cancer patients, 2.3% according to the Wells scale and 1.7% according to the Geneva scale had low probability of PTE and negative D-dimer: performing a CT in this context is not justified. The retrospective nature of our study may have led to underestimating clinical data to justify CT and possibly overestimated the importance of the blood gasometry result performed with oxygen therapy in some patients.

If D-dimer negativity is obtained using highly sensitive techniques, such as ELISA, then it is safe not to initiate anticoagulation treatment or perform other complementary examinations to rule out PTE when the clinical probability of PTE is low or intermediate. But if only moderately sensitive techniques are available, such as latex agglutination as used in our ED, the diagnosis of PTE can only be excluded when clinical probability is low[4,6,11].

The main alternative diagnosis in most cancer patients was cancer progression (32.3%), which was more found more often than PTE itself (25.8%). This should be taken into account in these patients, where D-dimer is often positive[6,25] because of the disease itself. In cancer patients, one should conduct a comprehensive assessment in the ED of the medical history, the physical examination and the chest X-ray for data that suggest cancer progression as a possible cause of dyspnea.

In non-cancer patients, the most frequent alternative diagnoses were AHF and exacerbation of COPD. Both are also frequent reasons for visits to the ED[26]. Although generally the cause of decompensation of these diseases is recognized, it is sometimes not identified. In addition, studies show that both COPD and AHF patients have increased risk of thromboembolic events than the general population and that VTE prophylaxis in the ED is usually inadequate[27-30].

Our study has its limitations. The main one is the retrospective design of the study. The categorization of clinical risk for PTE using probability scales was performed retrospectively by the investigators. This calculation may include significant biases. Regarding the Wells scale, it is difficult to consider the most likely diagnosis by the clinician. As for the Geneva scale, blood gas values are necessary for its calculation, and in some patients we could not be sure the recorded values were obtained at baseline. However, the low number of patients with low clinical probability and negative D-dimer who underwent CT for suspected PTE supports our results.

In conclusion, in patients with suspected PTE in the ED, the most frequent alternative diagnoses were disease progression in cancer patients and AHF or decompensated COPD in non-cancer patients. CT results allowed an alternative diagnosis in 81.2% of cancer patients and 67.3% of non-cancer patients. Although the recommendations on diagnosing PTE in the ED were correctly implemented, the diagnosis rate was low, especially in cancer patients. Further studies are needed to investigate the use of specific probability scales for these patients.

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Diagnóstico alternativo al tromboembolismo pulmonar en urgencias en pacientes oncológicos y no oncológicos

Gómez-Zorrilla Martín S, Riera-Mestre A, Leiva Pedraza D, Jordán Lucas S, Jacob Rodríguez J, Pujol Farriols R

Objetivo: Conocer los diagnósticos alternativos al tromboembolismo pulmonar (TEP) en los pacientes oncológicos y no oncológicos atendidos en un servicio de urgencias hospitalario (SUH) a los que se les solicitó una tomografía computarizada (TC).
Método: Estudio retrospectivo con inclusión de todos los pacientes a los que se les practicó una TC desde un SUH por sospecha de TEP durante los años 2006 y 2007.
Resultados: Se incluyeron un total de 265 pacientes, 93 oncológicos y 172 no oncológicos. El 98,5% presentaban, o bien una sospecha clínica alta de acuerdo a las escalas de Wells y de Geneva, o bien una sospecha clínica baja o intermedia con una determinación de dímero D positiva. En los pacientes oncológicos y no oncológicos, el porcentaje de diagnosticados de TEP fue del 25,8% y 39,5%, respectivamente. En los pacientes con sospecha de TEP en los que éste no se confirmó, la TC permitió determinar el diagnóstico alternativo en el 81,2% de los pacientes oncológicos y en el 67,3% de los no oncológicos. En los oncológicos el diagnóstico alternativo más frecuente fue la progresión neoplásica, que incluso fue más frecuente que el de TEP. Los diagnósticos alternativos más frecuentes en los no oncológicos, fueron la insuficiencia cardiaca aguda (ICA), la enfermedad pulmonar obstructiva crónica (EPOC) descompensada y la neumonía.
Conclusiones: En los pacientes con sospecha de TEP, la TC permitió determinar el diagnóstico alternativo en un elevado porcentaje de pacientes. Los diagnósticos alternativos más frecuentes fueron la progresión neoplásica en los pacientes oncológicos y la EPOC descompensada y la ICA en los no oncológicos. [Emergencias 2013;25:92-98]

Palabras clave: Tromboembolismo pulmonar. Tomografía computarizada. Servicios de urgencias hospitalarios.