The Role of CT Pulmonary Angiography in the Investigation of Unilateral Pleural Effusions

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Key Words

Pleural effusion · Pulmonary embolism · Pleural malignancy · CT pulmonary angiography

Abstract

Background: Pulmonary embolism (PE) is frequently cited as a common primary cause of unilateral pleural effusion, but in clinical practice appears to be uncommon. **Objectives:** In order to evaluate this observation, CT pulmonary angiography (CTPA) was performed in consecutive patients presenting to a single centre with a new uninvestigated unilateral pleural effusion and no clear cause and was supplemented by delayed-phase thoracic CT, optimized for visualization of the pleura. **Methods:** All patients underwent standard clinical assessment and pleural investigations in line with recent national guidelines and were followed up for a minimum of 1 year or until histological/microbiological diagnosis. **Results:** One hundred and fifty patients were recruited, and of these, 141 had a CTPA. PEs were detected in 9/141 (6.4%) patients, and of these, 8/9 were subsequently diagnosed with pleural malignancy. In only 1 case was PE clinically suspected and in no case was PE the primary cause

of effusion; 9.8% (8/82) of patients who were ultimately diagnosed with pleural malignancy had PE at presentation. **Conclusions:** This study indicates that PE is a frequent concomitant finding in patients with malignant effusions but uncommon as a primary cause of unilateral effusion. In addition, it highlights the known difficulty of clinical diagnosis of PE in the context of malignancy. In view of this, we recommend that CTPA combined with pleural-phase thoracic CT should be considered at presentation when investigating patients with suspected malignant pleural effusion.

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Introduction

Pulmonary emboli are widely cited as a frequent cause of pleural effusion, but this relationship seems to be uncommon in clinical practice. Clinical diagnosis of pulmonary embolism (PE) is challenging and chest X-ray signs and biomarkers such as D-dimer are non-specific, particularly in the presence of a pleural effusion [1–4], but whether a primary cause of effusion or co-existing with other pathology, PE is an important diagnosis to estab-

lish. UK national guidelines suggest that PE needs to be excluded in patients without a clear diagnosis following standard clinical and laboratory investigations [5, 6]. Data to support the assertion that pleural effusions are commonly a cause of effusions come from observational studies of patients presenting with PE, in which effusions are found in up to 50% of cases [7, 8]. However, there have been no prospective series to date, examining the frequency of PEs in patients presenting with an undiagnosed pleural effusion as their primary problem. The true significance of this association in terms of the need to investigate for PEs in patients presenting with pleural effusions is therefore unknown.

The present study examined the incidence of pulmonary emboli in patients presenting to a secondary care pleural disease service with a new unilateral pleural effusion and no obvious cause. Patients underwent a CT scan protocol incorporating a CT pulmonary angiogram (CTPA) and delayed-phase thoracic CT, optimized for visualization of the pleura such that the modern day gold standard diagnostic test for PE was applied early in the investigation pathway.

Method

The study had institutional research ethics committee approval, and written informed consent was obtained for each patient.

Between 2008 and 2010, consecutive patients with a new unilateral pleural effusion referred to a single institute were recruited to the study. Exclusion criteria included clinically obvious pleural infection, unstable renal function or estimated glomerular filtration rate (eGFR) <30 ml/min, <18 years of age, pregnant/lactating women, or a recent staging CT thorax (performed within the previous 10 days).

All patients underwent comprehensive clinical assessment including: plain chest radiograph, routine blood tests and diagnostic pleural aspiration under ultrasound guidance with fluid sent for cytological examination, as well as culture and biochemical tests (lactate dehydrogenase, protein and pH). The criteria of Light et al. [9] were applied for the division of exudates and transudates. All patients underwent a CT scan as per trial protocol at initial presentation. Additional investigations, including thoracoscopy, CT-guided pleural biopsies and interval CT scans were conducted in patients in line with current national and international guidelines.

CT Acquisition

CT images were acquired on one of two scanners: Philips MX8000 4 slice scanner (Philips Healthcare, UK) or Toshiba Aquilion CX 128 slice scanner (Toshiba Medical Systems, Europe). CTPA images were supplemented with a 45-second delayed scan, designed to optimize pleural conspicuity, through the thorax and upper abdomen.

The combined CTPA/pleural-phase CT protocol is fully detailed in supplementary material.

Imaging Assessment

The volume of the effusion and affected hemithorax on plain X-ray was documented. Effusion size on presenting chest X-ray was classified as small ($\leq 1/3$ hemithorax), moderate ($>1/3$ and $\leq 1/2$ hemithorax) and large ($>1/2$ hemithorax), consistent with convention [8].

CT scans were independently reported using a pro forma by 2 radiologists trained in thoracic imaging (M.D. and I.L.) with 17 and 5 years of experience, respectively. The CTPA component was assessed for subjective quality of pulmonary artery opacification: the extent of PE (if present) and the size of effusion (small, moderate or large). Pleural-phase imaging was reported according to our standard practice using the criteria of Leung et al. [10].

Patient Follow-Up and Final Diagnosis

The final diagnosis of each effusion was established independently by two consultant respiratory physicians by comprehensive review of case notes, investigation results and imaging. Patients were followed up until: histological, cytological or microbiological diagnosis; complete resolution of effusion; or for a minimum of 1 year. Diagnostic criteria were established from the principles of the British Thoracic Society Guideline for the investigation of a unilateral pleural effusion 2010 [6].

Statistical Analysis

All analyses were performed using statistical software (Graphpad Prism Version 5.0). Data are presented as proportions, means ($\pm$ SD) or medians (range or interquartile range) as appropriate. Descriptive statistics were used to summarize patient characteristics as well as radiological findings.

Results

One hundred and fifty patients were recruited, but only 141 met the inclusion criteria and underwent the CTPA/pleural-phase CT at presentation (fig. 1).

Patient Characteristics

We included 93 men and 48 women with a median age of 73 years (range 43–96), consisting of 87 out-patients and 54 in-patients.

Pleural Effusions

Effusions were marginally more common on the right (72/141), and by chest X-ray size criteria, 76 were moderate, 44 large and 21 small [5]. Fluid sampling was either not performed or inadequate in 9/141 patients; in the remainder, there were 116 exudates and 16 transudates.

CTPA/Pleural-Phase CT

Concordance between the reporting radiologists was good, with no differences in the detection of pulmonary emboli. Twenty-five of 141 (17.7%) scans revealed bilat-

Fig. 1. Patient recruitment and data acquisition.

eral effusions in contrast to the plain chest X-rays, all of which demonstrated unilateral pleural effusions. Quality of pulmonary artery opacification at CTPA was considered good in 88.7% of cases, adequate in 9.9%, and poor in only 1.4%. Similarly, pleural enhancement on the delayed phase of the scan was good in 96% of cases, adequate in 3.5% and poor in the remainder.

Detection and Characterization of Pulmonary Emboli

Pulmonary emboli were present on 9/141 (6.4%) CTPA scans. PE was clinically suspected at presentation in just 1/9 of these cases. All patients with PE presented with an exudative pleural effusion. PE was not the primary cause for the presenting pleural effusion in any of these 9 cases, but in 2 cases, was considered to be a secondary, contributory cause of effusion. Eight out of 9 patients with PE had a cytologically proven malignant pleural effusion.

In total, a histological or cytological diagnosis of malignant pleural effusion was reached in 82 patients. Eight out of 82 (9.8%) patients of this sub-group had a concomitant PE at baseline assessment.

The characteristics of patients with PE are summarized in table 1.

Patient Co-Morbidities and Risk of Thromboembolic Disease

Four of 141 patients (3%) had a previous history of thromboembolic disease and 16/141 (11%) were fully anti-coagulated. One of 9 patients with a PE was anti-coagulated with warfarin for atrial fibrillation at presentation.

Fifty-two out of 141 (37%) patients had a significant history of cardiac disease, 80/141 (57%) were being treated for hypertension, and 23/141 (16%) were known to be diabetic.

Clinical Diagnosis

Final clinical diagnoses are summarized in table 2. Consultants independently reached the same primary diagnosis in 137/141 (97%) of cases ($\kappa = 0.949$; 95% confidence interval 0.900–0.998). In the remaining 4 cases, a consensus was reached after discussion.

Discussion

This study provides two important insights into the relationship between unilateral pleural effusions and PE: (1) PE is an uncommon isolated finding in this context, and (2) when present, PE is frequently associated with pleural malignancy.

Table 1. Characteristics of patients with pulmonary emboli

						Mode of diagnosis
A	Ipsilateral	Multiple	Sub-segmental	Moderate	1. Malignant (NSCLC) 2. Pleural infection 3. PE	Malignant cytology, sepsis, consolidation/position of PE
B	Bilateral	Multiple	Sub-segmental	Small	1. Pleural infection 2. PE	Sepsis, resolution with antibiotics + anticoagulation
C	Bilateral	Multiple	Segmental	Moderate	Malignant (metastatic cholangiocarcinoma)	Malignant cytology
D	Contralateral	Multiple	Lobar	Moderate	Malignant (NSCLC)	Malignant cytology
E	Contralateral	Multiple	Lobar	Moderate	Malignant (NSCLC)	Malignant cytology
F	Contralateral	Multiple	Lobar	Large	Malignant (NSCLC)	Malignant cytology
G	Contralateral	Multiple	Segmental	Moderate	Malignant (metastatic ovarian carcinoma)	Malignant cytology
H	Contralateral	Single	Segmental	Large	Malignant (metastatic oesophageal carcinoma)	Malignant cytology
I	Contralateral	Multiple	Segmental	Large	Malignant (NSCLC)	Malignant cytology

NSCLC = Non-small cell lung cancer.

Table 2. Final cause of the unilateral pleural effusions

Diagnostic category for cause of pleural effusion	Patients
Metastatic pleural malignancy (histological or cytological diagnosis)	62
Malignant pleural mesothelioma	20
Malignant (radiographic diagnosis with progression – no histology)	6
Cardiac cause	20
Pleural infection	6
Simple parapneumonic effusion	3
Tuberculous pleuritis	2
After coronary artery bypass graft surgery	2
Benign asbestos-related effusion	5
Idiopathic pleuritis	6
Other benign cause	4
Undiagnosed after exhaustive investigation and follow-up	2
Inadequate follow-up achieved for diagnosis against criteria	1
Total	141

To the best of our knowledge, this is the first prospective study to evaluate the incidence of PE using CTPA in patients with unilateral pleural effusions at presentation. Although often quoted as a common cause of unilateral pleural effusions, PE was not a primary cause of pleural effusion in any patient in this series. This contrasts with the medical literature, which often quotes PE as the third

most common cause of unilateral effusions, after malignancy and pleural infection [1]. However, the historical literature relies upon retrospective data in which patients presenting with PE, in itself a common diagnosis, have been noted to have effusions, and thus, is likely to overstate the true relationship [1]. In this series, patients were referred with an undiagnosed pleural effusion either by a general practitioner or from the emergency department.

A clinically significant finding is that almost 10% of patients who subsequently proved to have malignancy had a co-existent PE at presentation. In spite of this, the initial diagnostic impression of the experienced reviewing physicians correlated poorly with the presence of pulmonary emboli; only 1 of 9 patients demonstrated to have PE on CTPA would have been investigated for possible PE at presentation in routine clinical practice. As such, classical clinical correlates of PE appear non-specific in the context of a symptomatic pleural effusion.

Malignancy is a major independent risk factor for venous thromboembolic disease (VTE) [11], but data regarding the precise incidence of symptomatic PE in cancer patients in general is difficult to interpret due to the heterogeneity of the studies. However, in a study by Blom et al. [12] of 3,200 individuals with a range of cancers, the overall risk of VTE was found to be increased 7-fold compared to the general population and, in patients with lung cancer risk, it was 22 times higher. Notably, in this group of patients, the likelihood of VTE was markedly increased in the first 3 months after diagnosis (adjusted odds ratio

53.5; 95% confidence interval 8.6–334.3) [12]. In a separate study involving 13,800 oncology out-patients in a tertiary centre, PE was detected incidentally on chest CT in 2.87% (395/13,783) [13]. Approximately 50% of PEs in this cohort were unsuspected and detected on a staging CT thorax rather than on CTPA. As such, it is important to recognize that the scan protocol influences the likelihood of detecting PE: a standard staging scan of the thorax is usually triggered to acquire images when the thoracic aorta (rather than the pulmonary vasculature) is maximally opacified. Regardless, it is common for the pulmonary vasculature to be adequately opacified on a staging scan to allow detection of pulmonary emboli, if present, but CTPA remains the gold standard for exclusion of PE [14]. This is in contrast to CT optimized for characterization of the pleura, which is acquired after at least a 45-second delay following contrast administration and, as a result, provides poor vascular enhancement. For pleural assessment, it is this tissue phase of imaging which is of interest for the assessment of the disease [15]. Therefore, a two-phase scan incorporating CTPA and pleural-phase imaging, as used in this study, allows both exclusion of PE and pleural assessment.

The importance of detection of PE in patients with pleural malignancy must be emphasized as it represents a treatable cause of breathlessness; identification and management have a role to play in optimizing patients for palliative chemotherapy and improving the quality of a limited life expectancy. Furthermore, early diagnosis is particularly important in this group prior to invasive pleural procedures (e.g., local anaesthetic thoracoscopy or indwelling pleural catheter placement) that carry an inherent risk of temporary respiratory compromise. It was deemed clinically appropriate to treat all patients who had underlying malignancy and pulmonary emboli detected in the trial with life long anticoagulation in accordance with current guidelines.

There are some limitations to this study: our total study population is relatively small compared to epidemiological databases evaluating pleural effusion and PE. However, our data appear to match routine clinical experience and, crucially, comprise a prospective analysis of a potentially overlooked component of the evaluation of pleural effusion. Patients in this series were referred by primary healthcare services, which potentially introduces selection bias; however, the aim was to evaluate patients without an obvious cause for the effusion, and as such, it seems reasonable to expect that this initial 'triage' will have strengthened, rather than weakened, our selection. With any radiological procedure involving ionizing ra-

diation, the dose must be considered; using the two-phase scan protocol, total dose to the patient was around 14 mSv. This compares adequately for the average dose in the UK of 15 mSv for CTPA alone [16]. However, this could be further improved by altering some of the imaging parameters, such as kV, without significantly reducing scan quality. Some units have developed scan protocols with prolonged contrast bolus injections that allow intermediate vessel enhancement and good quality pleural imaging [17] in a single scan acquisition, thereby minimizing radiation. However, pulmonary artery opacification is not as high as with formal CTPA, and thus, PE could be potentially overlooked.

In summary, we have demonstrated that while PEs are an uncommon primary cause for unilateral pleural effusions, they are frequently present at presentation in the context of pleural malignancy. In order to ensure that this important diagnosis is not overlooked, we advocate CT of the thorax including CTPA and pleural-phase imaging for patients presenting with a pleural effusion where malignant pleural disease is clinically suspected.

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Financial Disclosure and Conflicts of Interest

The authors declare that they have no competing interests.

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