A 60-Year-Old Woman with a 6-Week History of Shortness of Breath and Intermittent Chest Pain Due to Chronic Thromboembolic Pulmonary Disease Undetected by Computed Tomography Pulmonary Angiography (CTPA) and Diagnosed by Ventilation-Perfusion Imaging

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Patient: Female, 60-year-old
Final Diagnosis: Chronic thromboembolic pulmonary disease with pulmonary hypertension
Symptoms: Chest pain • dry cough • reduced exercise tolerance • shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Cardiology • Pulmonology

Objective: Unusual clinical course
Background: Chronic thromboembolic pulmonary disease (CTEPD) is the persistent occlusion of pulmonary arteries resulting from 1 or more thrombo-emboli. Its presentation is often non-specific, with exertional dyspnea and fatigue, yet if left undiagnosed risks of chronic thromboembolic pulmonary hypertension and right-sided cardiac failure can ensue. Computed tomography pulmonary angiography (CTPA) and ventilation/perfusion (V/Q) imaging are most commonly utilized for investigating CTEPD. This report is of a 60-year-old woman with a 6-week history of breathlessness and intermittent chest pain due to CTEPD, undetected by CTPA and diagnosed by V/Q imaging.

Case Report: A 60-year-old woman presented with a 6-week history of breathlessness, intermittent chest pain, and reduced mobility. Her past medical history included chronic obstructive pulmonary disease, pulmonary sarcoidosis, and obesity. Screening tests for infective and ischemic cardiac etiologies were unremarkable. A calculated Wells score was 6, making CTEPD the main differential diagnosis, and she was commenced on therapeutic dose anticoagulation. A CTPA performed on day 2 of admission showed no evidence of acute thromboembolic pulmonary disease or CTEPD. Instead, V/Q scintigraphy on day 6 revealed a perfusion mismatch in the right lung apex, consistent with CTEPD. The patient improved clinically and was discharged on long-term apixaban.

Conclusions: A negative CTPA does not necessarily exclude CTEPD. The sensitivity of CTPA for CTEPD is lower than that of V/Q imaging, and can hence lead to false-negative results, as this case highlights. When there is a high clinical suspicion for CTEPD but a negative CTPA study, V/Q imaging should always be undertaken.

Keywords: False Negative Reactions • Pulmonary Embolism • Thromboembolism

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Background

Chronic thromboembolic pulmonary disease (CTEPD) is defined as persistent pulmonary vascular occlusion secondary to one or more thromboembolic events [1]. CTEPD is established as 1 of 5 main etiological groups responsible for pre-capillary pulmonary hypertension [2]. Idiopathic pulmonary hypertension, left-sided heart disease, chronic lung disease, and metabolic and miscellaneous disorders account for the remaining 4 pathologies [2].

Pre-capillary pulmonary hypertension is specifically defined as a mean pulmonary artery pressure of ≥20 mmHg at rest accompanied by a pulmonary artery wedge pressure ≤15 mmHg and a pulmonary vascular resistance ≥3 Wood units [3]. The identification of CTEPD is crucial, since undiagnosed and untreated CTEPD significantly increases the risk of chronic thromboembolic pulmonary hypertension (CTEPH, pre-capillary pulmonary hypertension specifically caused by CTEPD) and its sequelae, such as right-sided cardiac dysfunction and eventual failure [2].

The initial presenting symptoms of CTEPD can be subtle and non-specific, and may include exertional dyspnea and fatigue, with no obvious cause or prior history of venous thromboembolism [4]. Classic symptoms such as atypical chest pain, intermittent hemoptysis, and palpitations are not always present, meaning the diagnosis of CTEPD can often be delayed [2].

Computed tomography pulmonary angiography (CTPA) is the first-line investigation for suspected acute pulmonary embolism (PE), as opposed to ventilation/perfusion (V/Q) scintigraphy, for several reasons [5]. CTPA is non-invasive, allows direct visualization of filling defects in the pulmonary arterial vasculature, and is widely available, faster to perform, and more cost effective than a V/Q scan [6]. However, V/Q scintigraphy is the imaging modality of choice to exclude CTEPD and CTEPH, as well as in special circumstances where radiation and/or contrast exposure is contraindicated, such as pregnancy, renal failure, or contrast allergy [7].

Despite the merits of CTPA, several studies have shown that a negative CTPA study alone may not safely exclude PE [8,9]. For example, Moores et al [8] examined a cohort of 134 patients with a high probability of PE (based on Wells score) who each had a negative CTPA, yet thromboembolic disease was still detected in 6 patients. The employment of additional imaging, including V/Q scanning, in these patients led to the initiation of anticoagulation treatment, and subsequently minimized the risk of sequelae.

The presence of false-negative CTPA studies in patients with established pulmonary embolic disease observed by Moores et al [8] has been reaffirmed by several retrospective studies and systematic reviews [10-12]. In a cohort of 201 patients deemed to be at high risk for CTEPD (Wells score ≥6), Akhter et al [10] identified 16 patients with evident PE despite a negative CTPA study. Systematic reviews conducted by Hogg et al [11] and Kligerman et al [12] have demonstrated that false-negative CTPA studies is a ubiquitous issue in the investigation and diagnosis of CTEPD.

The higher detection rates for CTEPD with V/Q imaging may be attributed to an enhanced depiction of sub-segmental PEs, compared with CTPA [10]. This is because V/Q scintigraphy is known to provide improved contrast and better 3D representation of the pulmonary vascular tree without overlapping structures, leading to a greater overall sensitivity.

This case report is of a 60-year-old woman with a 6-week history of shortness of breath and intermittent chest pain due to CTEPD undetected by CTPA and diagnosed by V/Q imaging.

Case Report

Case Presentation

A 60-year-old woman was admitted to the hospital with a 6-week history of worsening shortness of breath. This was accompanied by a chronic dry cough, and intermittent, central chest pain that was non-radiating and dull in character. The onset of the chest pain was insidious. Importantly, the patient had no history of prior chest pain nor exertional chest pain. As a result of breathlessness at rest, her mobility and exercise tolerance had become greatly reduced, to the point at which she had become housebound. Her past medical history included chronic obstructive pulmonary disease (COPD), for which she had not previously required home oxygen, as well as pulmonary sarcoidosis, obesity, and a 20 pack-year history of smoking. Importantly, she had received all 3 COVID-19 vaccinations prior to admission, and had tested negative for COVID-19 by both rapid antigen testing and by polymerase chain reaction (PCR).

Clinical assessment found the patient to be tachycardiac, with a heart rate of 125 beats per minute (bpm) and with a blood pressure of 135/68 mmHg. At rest she required 3 liters of oxygen to maintain target oxygen saturations of 88-92%, yet would rapidly desaturate to 78% on minimal exertion despite supplemental oxygen therapy. Clear breath sounds were audible throughout both lungs.

The patient had been assessed by her general practitioner 1 week prior to hospital admission and diagnosed with a presumed chest infection. However, after completing a 7-day course of clarithromycin there was no symptomatic improvement
Laboratory and Radiological Tests

Initial blood tests revealed a D-dimer of 1585 ng/mL (0-250 ng/mL) and a C-reactive protein level of 40.7 mg/L (0-4.9 mg/L). The patient’s full blood count, including a white blood cell count of $9.3 \times 10^9$ (4-11 $\times 10^9$) was unremarkable. Serial Troponin-T tests were 52.3 and 64.4 ng/L (0-14 ng/L). Renal function remained within normal limits, with a creatinine level of 79 µmol/L (44-80 µmol/L) and urea of 7.8 mmol/L (2.5-7.8 mmol/L).

Given the raised serum Troponin-T levels, serial 12-lead electrocardiographs (EKGs) were performed to look for evidence of acute and progressive cardiac ischemia. EKGs showed non-dynamic, established T wave inversion in the anterior chest leads (V1-V4).

A Wells score was calculated to predict the likelihood of a PE. The overall Wells score was 6 based on a PE being the most likely differential diagnosis (3 points), tachycardia with a heart rate $>$100 bpm (1.5 points) and immobilization for at least 3 days (1.5 points), giving a high probability of PE.

An erect anterior-posterior chest radiograph was performed on admission in the emergency room to exclude the presence of pulmonary edema, as well as pneumonia. The chest radiograph exhibited bilateral prominent lung hila and increased interstitial markings, but no focal consolidation to indicate a pneumonia (Figure 1).

To exclude cardiac failure, echocardiography was undertaken. Echocardiography revealed no evidence of regional wall motion abnormalities. Instead, a severely impaired right ventricular contractility with grossly dilated right-sided cardiac anatomy was visualized. A significantly raised right ventricular systolic pressure of 75 mmHg (20-30 mmHg) was noted, along with a pulmonary artery systolic pressure of 45 mmHg ($<$25 mmHg), tricuspid regurgitation velocity of 4.3 m/s ($<$2.8 m/s) and pulmonary artery wedge pressure of 10 mmHg ($<$15 mmHg). These parameters were, overall, consistent with pulmonary hypertension. Left ventricular contractility was preserved, with a left ventricular ejection fraction of $>$55%.

The patient then underwent a CTPA on day 2 of admission. No evidence of PE was visible along the main pulmonary artery or the lobar, segmental, and subsegmental branches of the pulmonary tree (Figure 2A). More specifically, full vascularity of the right upper lobe was demonstrated (Figure 2B).
Following completion of the CTPA, an isotope V/Q scan was performed on day 6 of admission to look for evidence of CTEPD. At the right lung apex, a perfusion mismatch was seen in the posterior projections, indicating a high probability for PE (Figure 3A, 3B).

After the diagnosis of PE was confirmed, the CTPA was reviewed again by 2 independent consultant radiologists. Both radiologists concluded there to be no CT evidence of pulmonary emboli.

Differential Diagnosis

The markedly elevated D-dimer and 6-week history of breathlessness in the absence of any infective symptoms, raised infection markers, or radiographic evidence of pneumonia, led to a chronic PE being the most likely diagnosis. This was further supported by chest pain of a non-cardiac character, and non-dynamic electrocardiographic changes.

After the initial CTPA revealed no evidence of PE, an acute coronary syndrome needed to be excluded. At this point, the patient was reviewed by the cardiology team who arranged for a V/Q scan.

Treatment

The patient was initially managed with treatment-dose low molecular weight heparin and supplemental oxygen therapy, to maintain target saturations of 88-92%. Oxygen therapy was subsequently weaned off and the patient was switched to apixaban for ongoing anticoagulation. The patient was discharged after 12 days of admission.

Outcome and Followup

One month following discharge, the patient was unfortunately re-admitted into hospital following assessment in the respiratory outpatient clinic. She reported persistent breathlessness despite compliance to apixaban therapy, and was noted to have oxygen saturations of 84% on room air. She was managed for a non-infective exacerbation of COPD with oxygen therapy and a course of steroids. A repeat CTPA was performed which showed no evidence of acute PE.

Given that her symptoms represent severe CTEPH, the decision was made for the patient to be referred for a pulmonary endarterectomy at a tertiary center for more definitive management of her CTEPD.

Discussion

This is a case of a 60-year-old woman with a 6-week history of shortness of breath and intermittent chest pain due to CTEPD. The CTEPD, present at the right lung apex, was diagnosed only after V/Q imaging, with the initial CTPA study proving negative. This case highlights that V/Q imaging has a higher sensitivity for CTEPD vs CTPA, an observation supported by Tunariu et al [14] and Wang et al [15]. Specifically, Tunariu et al [14] showed that in a cohort of 78 patients with confirmed CTEPD, V/Q scintigraphy had an overall sensitivity of 96% (high probability in 75 patients, intermediate probability in 1 patient and low probability in 2 patients), whereas CTPA had a sensitivity of only 51%.
When there is a strong clinical suspicion of CTEPD (such as a Wells score ≥6), but a negative CTPA result, V/Q imaging should be performed. Correct diagnosis of CTEPD in the presence of pulmonary hypertension is essential, as these patients may be amenable to surgical intervention in the form of pulmonary endarterectomy, such as in the present clinical case.

Interestingly, several studies and systematic reviews have demonstrated the presence of PE despite a negative CTPA result [10,11]. For example, Akhter et al [10] determined the ability of a negative CTPA to exclude PE in high-risk patients (Wells score >6). A total of 201 patients underwent CTPA, of which 130 tested negative. However, 16 of these 130 patients (12.3%) were ultimately found to have a PE. Further analysis of these 16 patients revealed that 2 also had a negative D-dimer in combination with a negative CTPA. This highlights the potential of false-negative results when performing CTPA, which may not be able to conclusively exclude PE, even when combined with a D-dimer.

In our patient’s case, the use of V/Q imaging was integral to the final diagnosis of CTEPD. Other studies, such as Moores et al [8], Akhter et al [10] and Hogg et al [11] have also utilized V/Q imaging as well as lower limb doppler ultrasound to diagnose both acute and chronic PE and CTEPD following a negative CTPA. The latter 2 studies additionally included a retrospective follow-up period of up to 45 days after initial CTPA, with death secondary to PE indicative of a false-negative CTPA.

It is also important to be aware of the influence of human error in the correct diagnosis of CTEPD. This is illustrated by Kligerman et al [12], who identified 44 false-negative CTPA studies from a total of 6769 patients investigated for PE. PE was diagnosed in these 44 patients only after review of CTPA images by 3 independent senior thoracic radiologists.

Importantly, of note, the CTPA in our patient’s case was independently reviewed by 2 consultant radiologists, both of whom concluded there to be no evidence of CTEPD.

A potential explanation for why certain cases of CTEPD are not detected by CTPA is because they are subsegmental. The smaller size and highly distal location of subsegmental PEs can lead to not always being detected on CTPA. This may be of particular issue in single-detector CTPA studies, which use fewer slices and may therefore be more prone to false-negative outcomes [11].

Despite this, the diagnosis and management of subsegmental PEs remains an area of controversy. There is the argument that subsegmental PEs do not represent true thrombi, and are instead imaging artefacts or other non-thrombotic material [16]. Additionally, even if subsegmental PEs are confirmed to be true thrombi, there is debate as to their clinical significance, and whether or not they warrant anticoagulation therapy. Stein et al [17] conducted a meta-analysis evaluating the safety of withholding anticoagulation treatment in patients with subsegmental PE. In 105 untreated patients, there was no recurrence of PE, whereas there was a 7% incidence of major hemorrhagic events in those anticoagulated.

Nonetheless, with respect to our patient who was found to have CTEPH and impaired right ventricular function on echocardiography, it is reasonable to assume that her CTEPD was of clinical significance.

In spite of its high sensitivity for CTEPD and CTEPH, the predisposition of V/Q imaging for false-positive results must be recognized. False positives can result from a variety of causes, such as compression or entrapment of pulmonary vasculature from mass lesions such as bronchogenic carcinoma, pulmonary and mediastinal lymphadenopathy, fibrosing mediastinitis, and endogenous pulmonary artery stenosis [18]. Furthermore, conditions which cause air trapping such as interstitial lung disease, emphysema, pneumonia, and radiotherapy treatment can also lead to false-positive results. It is important to note that our patient had an established history of sarcoidosis and COPD, both of which are known to have upper lobe predominance. Therefore, the isolated right apical perfusion mismatch identified on V/Q imaging could be a false-positive finding.

Conclusions

Despite being established as the imaging modality of choice for acute pulmonary emboli, a negative CTPA result does not necessarily exclude CTEPD. CTPA has a lower sensitivity for CTEPD than V/Q imaging, and can thus be prone to false negatives. When there is a high clinical suspicion for CTEPD but a negative CTPA result, V/Q imaging should always be undertaken. The correct diagnosis of CTEPD is essential to minimize the risk of long-term sequelae such as CTEPH and right-sided cardiac dysfunction.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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