Novel Insights into Pulmonary Embolism with Negative D-dimer Results

Summary

A patient in his mid-40s presented with exertional dyspnoea and pleuritic chest pain persisting for six weeks. Despite repeated normal investigations, including D-dimer tests, chest X-rays, serial troponins, and electrocardiograms (ECGs), a CT pulmonary angiogram (CTPA) was performed to rule out pulmonary embolism (PE) or other pulmonary abnormalities, revealing a left main pulmonary artery thrombus with no evidence of right ventricular strain. The patient was managed with oral rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily for 6 months. The patient showed full recovery at six months follow-up. This case highlights the diagnostic challenges in patients with persistent symptoms, low risk of venous thromboembolisms (VTEs), and normal initial investigations. It is novel because previous case reports of PE with negative D-dimer results have predominantly involved patients with identifiable risk factors, such as prior VTEs, malignancy, or other conditions that increase the likelihood of PE. In contrast, this case demonstrates that PE can occur even in the absence of these risk factors, emphasising the importance of clinical diligence and the use of advanced imaging in diagnosing PE in atypical presentations.

Background

PE is a potentially life-threatening condition that can present with non-specific symptoms, complicating timely diagnosis (1). While negative D-dimer tests and imaging often rule out PE, persistent symptoms warrant further evaluation (2). This case emphasises the importance of considering PE in patients with ongoing exertional dyspnoea and pleuritic pain despite negative initial investigations. It also highlights the need for improved diagnostic pathways and the role of clinical judgment alongside algorithm-based tools.

Case Presentation

A patient in his middle 40s, working as a teacher, presented to the same-day emergency care (SDEC) unit with a six-week history of exertional dyspnoea and left-sided pleuritic chest pain. The pain, rated 2–3/10, was a dull ache with no relieving factors and did not limit daily activities. He reported no alarming symptoms, such as haemoptysis, weight loss, or night sweats. His Wells score for PE was 3.0, based on the criterion that ‘PE is the most likely or equally likely diagnosis’ (3 points), with no other criteria contributing to the score. This was

assigned due to the persistence of exertional dyspnoea and pleuritic chest pain despite normal initial investigations, raising clinical suspicion of PE.

The patient's medical history was unremarkable, with no prior VTEs malignancy, or significant cardiovascular or respiratory conditions. He denied recent travel, COVID-19 infection, vaccinations, or prolonged immobility. Family history was negative for VTEs or thrombophilia or any other comorbidities. On examination, he was haemodynamically stable with a respiratory rate of 18 breaths per minute, oxygen saturations of 98% on room air, a heart rate of 77 bpm, a temperature of 36.6°C, and a blood pressure of 135/81 mmHg, with no signs of respiratory distress.

Initial investigations included a normal D-dimer level of 210 ng/mL (normal range: <500 ng/mL; for patients aged >50 years, the age-adjusted threshold is calculated as age × 10 ng/mL, but this was not applicable here as the patient was in his mid-40s), normal chest X-rays, negative serial troponins (<13 ng/L, normal range: <13 ng/L), and ECGs (Figure 1) showing normal sinus rhythm.

Blood tests were unremarkable, including WBC: 6.1 × 10^9/L (normal range: 4–11 × 10^9/L), CRP: 2 mg/L (normal range: <5 mg/L), GFR >90 mL/min, creatinine: 74 µmol/L (normal range: 64–104 µmol/L), TSH: 2.3 mIU/L (normal range: 0.4–4.0 mIU/L), and Hb: 137 g/L (normal range: 130–170 g/L). Additional normal values included INR: 1.0 (normal range: 0.8–1.2), calcium: 2.35 mmol/L (normal range: 2.2–2.6 mmol/L), magnesium: 0.9 mmol/L (normal range: 0.7–1.0 mmol/L), pro-BNP: 45 pg/mL (normal range: <125 pg/mL) and lactate dehydrogenase: 180 U/L (normal range: 140–280 U/L). DDue to persistent symptoms, a CTPA was performed, revealing a left main pulmonary artery thrombus with no evidence of right ventricular strain. (Figure 2). The Pulmonary Embolism Severity Index (PESI) was calculated as 51 points, categorising the patient as Class I (very low risk), with an associated 30-day mortality rate of -1.6% in this group.

Differential Diagnosis

The initial differential diagnosis included acute coronary syndrome, pneumonia, aortic dissection, pericarditis, heart failure, sepsis and pneumothorax, which were excluded through electrocardiography, cardiac biomarkers, imaging (CT pulmonary angiography, chest X-ray, echocardiography), and clinical assessment.

Treatment

The patient was commenced on rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily for six months. He was referred to haematology for thrombophilia screening, which was negative for antiphospholipid syndrome

and other haematological abnormalities that might cause unprovoked PE. Routine CT abdomen and pelvis (CTAP) excluded malignancy. Anticoagulation therapy was discontinued after six months without complications.

Outcome and Follow-up

At six months follow-up, the patient reported complete resolution of symptoms and returned to full daily activities. No recurrence of PE or other complications were observed.

Discussion

PE remains a diagnostic challenge, particularly in cases with prolonged symptoms and negative initial investigations. The Wells score, while useful, contains a subjective criterion 'PE is the most likely or equally likely diagnosis' which lacks reproducibility and did not impact the outcome in this case. Although the Wells score is designed to determine whether D-dimer testing should be performed, clinical practice often deviates from strict adherence, with physicians ordering D-dimer based on symptom persistence rather than pre-test probability alone. In this case, the D-dimer was performed before formal Wells scoring, reflecting real-world emergency decision-making. The subsequent decision to perform a CTPA was driven by unexplained symptoms rather than strict algorithmic application. This highlights the necessity of integrating clinical judgment with structured diagnostic pathways to prevent misdiagnosis in atypical presentations of PE.

To date, several major clinical models have been developed and validated to determine the pre-test probability of PE. In addition, governing bodies and professional societies, including the British Thoracic Society, the European Society of Cardiology, and NICE guidelines for PE, have published recommendations for the evaluation of patients with suspected acute PE (4 and 5). While these guidelines consistently recognise the utility of D-dimer testing for excluding PE in low-risk patients, there is no universally agreed-upon definition of what constitutes "low risk."

In accordance with the 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of acute pulmonary embolism (PE), the standard diagnostic pathway involves an initial assessment of clinical pre-test probability using tools such as the Wells score. For patients with a low or intermediate probability, a D-dimer test is recommended to rule out PE; if the D-dimer is positive, imaging studies like CTPA are indicated. In our case, the patient presented with a Wells score of 3, categorising him as having an intermediate pre-test probability. Following the guidelines, a D-dimer test was performed, yielding a negative result (210 ng/mL), which would typically

exclude PE and preclude further imaging. However, due to the persistence of symptoms, a CTPA was conducted, revealing a left main pulmonary artery thrombus. This case underscores a limitation in the standard diagnostic algorithm: a negative D-dimer result, particularly in the context of a subacute or chronic PE, may lead to false reassurance and a missed diagnosis. Therefore, clinicians should maintain a high index of suspicion and consider advanced imaging in patients with ongoing symptoms suggestive of PE, even when initial D-dimer testing is negative.

The D-dimer assay is a highly sensitive test used in the evaluation of PE, measuring the presence of fibrin degradation products formed during clot breakdown (6). D-dimer has a half-life of 4–6 hours and typically remains elevated for approximately seven days following the onset of clot formation. Once clot organisation and adherence occur, D-dimer levels begin to decline (7). As a result, the timing of the assay is crucial for accurate interpretation. A false-negative result may occur if the test is performed too early or beyond the seven-day window, as fibrinolysis becomes less active in organised clots.

Despite its limitations, a negative D-dimer assay can safely rule out a large PE in low- and moderate-risk patients (8). However, in this case, the patient presented with persistently negative D-dimer results on two occasions, despite eventually being diagnosed with an extensive left-sided PE. This finding highlights the reduced sensitivity of the assay in prolonged symptomatology. Recent studies have examined the sensitivity of D-dimer assays in detecting PE. A systematic review and meta-analysis reported a pooled sensitivity of 97% for D-dimer in diagnosing PE, indicating that approximately 3% of patients with PE may have a negative D-dimer result (9). Another study focusing on patients with cancer found a D-dimer sensitivity of 96.9% for PE, suggesting that about 3.1% of such patients with PE could present with a negative D-dimer test (10).

It is essential to highlight that even with the application of age-adjusted D-dimer thresholds, as recommended by the latest European guidelines, this case would have remained undetected (16). The European Society of Cardiology (ESC) 2019 guidelines suggest adjusting the D-dimer cut-off in patients over 50 years of age to reduce false-positive results. Specifically, the threshold is calculated as the patient's age multiplied by 10 µg/L. For instance, in a 75-year-old patient, the adjusted cut-off would be 750 µg/L. However, our patient, being in his mid-40s, does not qualify for this adjustment, and the standard threshold of 500 ng/mL applies. Even if the patient were older, with a D-dimer level of 210 ng/mL, the result would still fall below the age-adjusted threshold, potentially leading to a missed diagnosis. This underscores the limitations of

relying solely on D-dimer levels, whether adjusted for age or not, and highlights the necessity of comprehensive clinical evaluation and consideration of advanced imaging modalities in patients with persistent symptoms suggestive of pulmonary embolism.

Although the radiological report described the PE as acute, it did not provide specific features to distinguish between acute and subacute PE. Given the patient's prolonged six-week history of symptoms and persistently negative D-dimer, a subacute presentation is a strong possibility. For instance, in subacute PE, D-dimer levels may normalise as clot organisation progresses, reducing fibrinolytic activity (17). This case highlights the importance of considering a subacute presentation in patients with prolonged symptoms and unexplained dyspnoea, even when initial investigations are inconclusive.

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The Wells score is a valuable tool for assessing the pre-test probability of PE (11). In this case, the patient’s Wells score of 3.0 indicated moderate risk. While algorithm-based approaches, such as the Wells score combined with D-dimer testing, are effective in many scenarios, they are not infallible. Persistent symptoms in moderate-risk patients should prompt further evaluation, even when initial test results are unremarkable. In addition, the simplified revised Geneva score is another validated tool that can be used to estimate pretest probability for PE, and its inclusion in clinical decision-making may further enhance risk stratification (18). This highlights the necessity of integrating clinical judgment with structured diagnostic pathways to prevent misdiagnosis in atypical presentations of PE.

CTPA remains the gold standard for diagnosing PE. Its high sensitivity and specificity make it the definitive imaging modality in cases where PE is strongly suspected or when initial tests are inconclusive (3). In this case, the decision to perform a CTPA was pivotal in identifying the left-sided PE, enabling appropriate treatment. However, the risks associated with radiation exposure and contrast-induced nephropathy necessitate judicious use of CTPA, particularly in low-risk patients. This underscores the need for a balanced approach that considers both the benefits and potential risks of advanced imaging.

Unprovoked PE accounts for approximately 30–50% of all PE cases and presents unique diagnostic and management challenges (12). In this case, the absence of identifiable risk factors, such as recent surgery, immobility, or malignancy, raised the possibility of underlying thrombophilia or malignancy. Comprehensive evaluation, including thrombophilia screening and malignancy workup, is essential in such cases to identify potential underlying causes and guide long-term management. Negative results in this patient’s haematology and malignancy workup were reassuring, allowing for anticoagulation therapy to be discontinued after six months.

The choice of rivaroxaban as the anticoagulant in this case aligns with current guidelines recommending direct oral anticoagulants (DOACs) as first-line therapy for PE (3). Rivaroxaban offers several advantages, including oral administration, fixed dosing, and minimal monitoring requirements, which improve patient adherence and convenience. Randomised controlled trials, such as the EINSTEIN-PE study, have demonstrated the efficacy and safety of rivaroxaban in the treatment of PE (13). This case further supports the use of rivaroxaban in managing unprovoked PE, with the patient experiencing no complications or recurrence during follow-up.

There is limited case reported similar to this case presentations as previous case reports, patients seem had risk factors, but patient had a PE despite negative d-dimer. For instance, the case by Al-Anbagi et al., (2024) describes a 47-year-old male who presented acutely with dyspnoea, tachycardia, and hypotension, eventually diagnosed with massive PE (14). Despite having significant risk factors, including obesity and a history of deep vein thrombosis (DVT), the patient's D-dimer result was falsely negative. In contrast, our patient was younger, had no identifiable risk factors such as previous venous thromboembolism (VTEs) or malignancy, and presented with persistent, non-severe symptoms over six weeks. These differences highlight the variability in PE presentations and the limitations of D-dimer testing across diverse clinical contexts.

The case by Breens et al., (2009) involves a 26-year-old female presenting with acute pleuritic chest pain and mild hypoxia, ultimately diagnosed with PE despite a negative ELISA D-dimer result. Similar to our case, this highlights the potential for false-negative D-dimer results in subacute or chronic presentations of PE. However, in the case described by Breens et al. (2009), the presence of hypoxia served as a critical clinical clue, prompting further diagnostic imaging (15). In contrast, our patient maintained normal oxygen saturations throughout the clinical course, further underscoring the diagnostic complexity when symptoms are mild, and laboratory findings are unremarkable. The persistence of symptoms over weeks rather than days in our case adds another layer of complexity, as D-dimer levels are known to normalise within 7–10 days of clot formation, reducing the sensitivity of the test in chronic or subacute presentations.

Learning Points/Take-home Messages

- Persistent exertional dyspnoea and pleuritic chest pain warrant thorough evaluation, even with normal initial investigations.
- Negative D-dimer results do not definitively rule out PE, particularly in patients with prolonged symptoms or moderate clinical probability, even no risk factors for VTEs.
- CTPA remains the gold standard for diagnosing PE in complex cases.
- Clinical judgment plays a crucial role alongside algorithm-based diagnostic tools in managing atypical presentations of PE.

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Figures

Figure 1: 12 lead Electrocardiogram (ECG) demonstrating a normal sinus rhythm

Figure 2: (A) Axial view of a CT pulmonary angiogram highlighting a filling defect in the left main pulmonary artery, as indicated by the red arrow, consistent with pulmonary embolism.

(B) Coronal view of a CT pulmonary angiogram demonstrating the same filling defect in the left main pulmonary artery, marked by the red arrow, confirming the presence of a pulmonary embolism.

Patient's Perspective

The patient expressed gratitude for the thorough evaluation and treatment. He noted initial frustration with repeated negative tests but appreciated the eventual diagnosis and care provided. The patient was relieved to resume normal activities and acknowledged the importance of ongoing vigilance for similar symptoms.

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Date: 15/01/2025

Figures

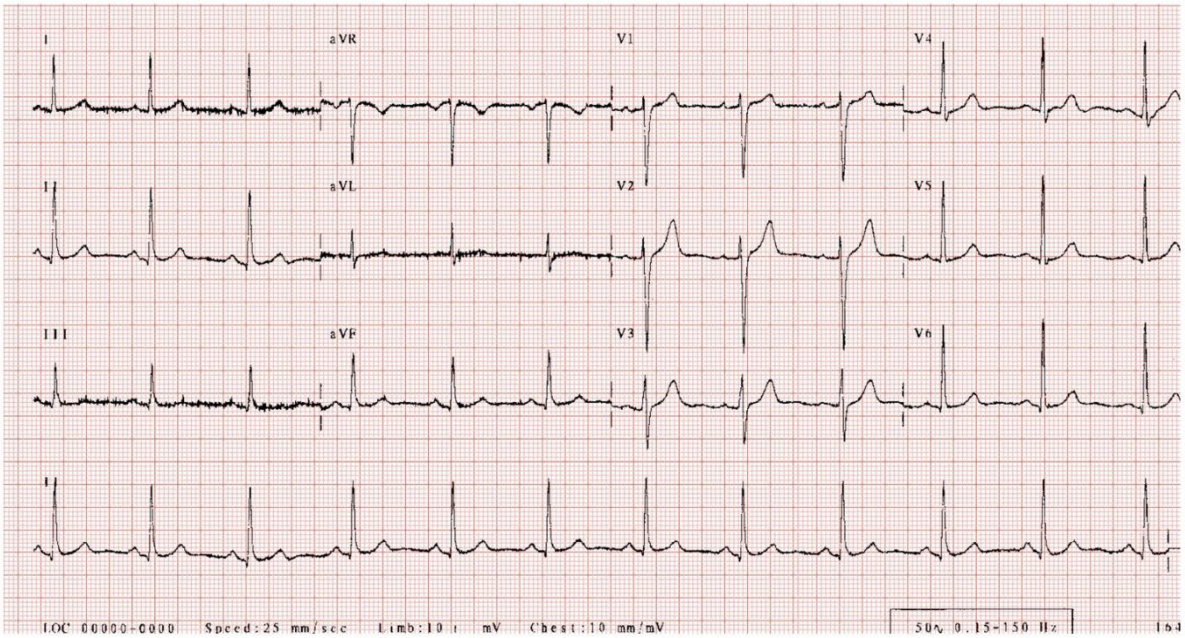

Figure 1: 12-lead electrocardiogram (ECG) demonstrating normal sinus rhythm

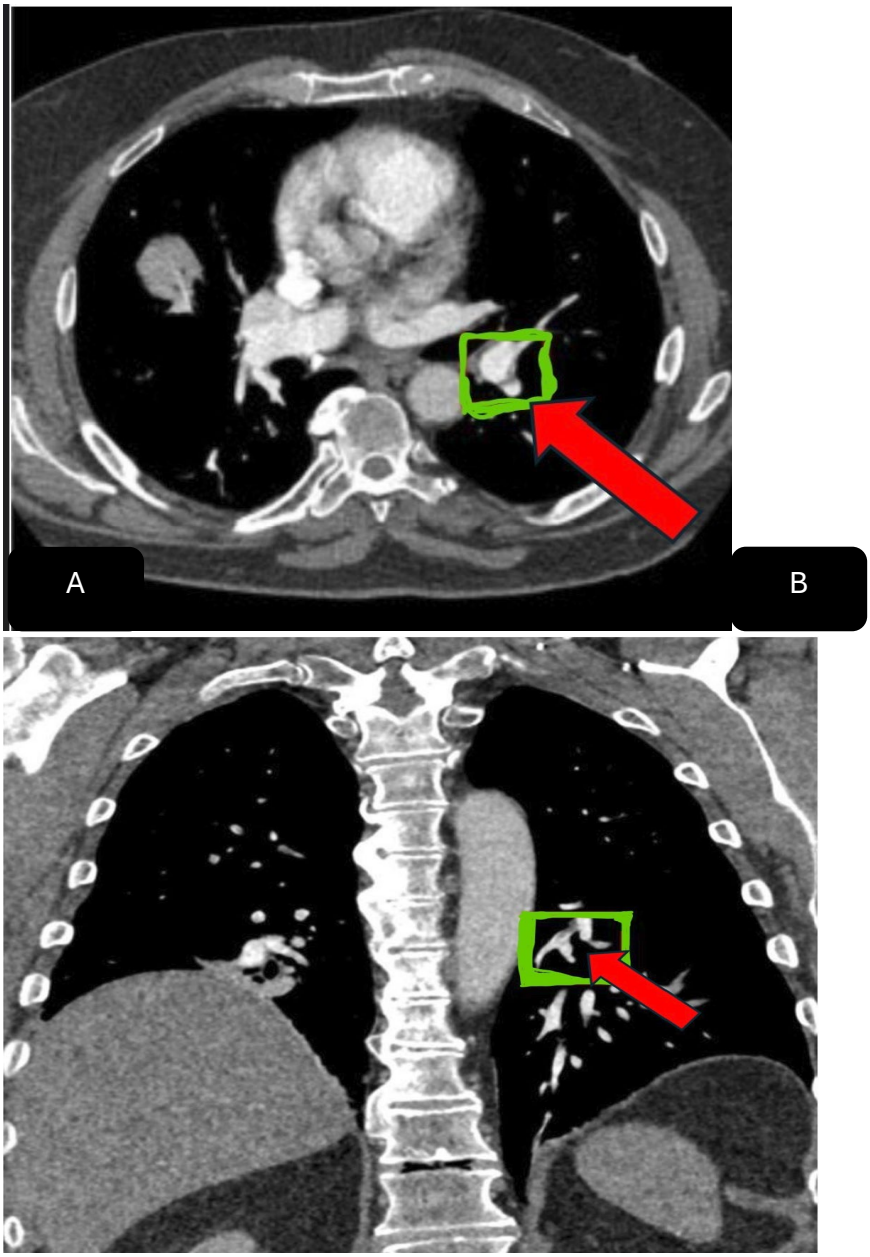

Figure 2: A: Axial view of a CT pulmonary angiogram with red arrow demonstrated filling defect in the left main pulmonary embolism.
B: Coronal view of a CT pulmonary angiogram with red arrow demonstrated filling defect in the left main pulmonary embolism

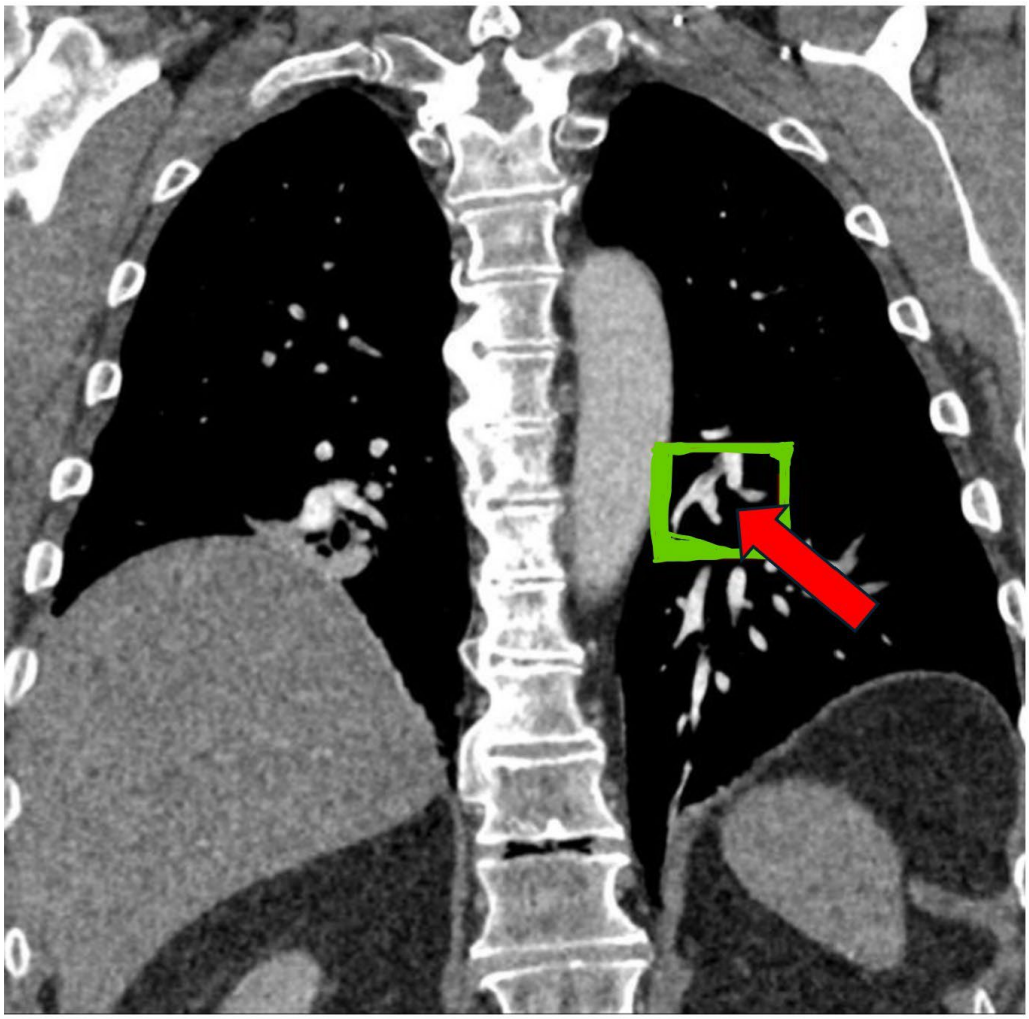

Figure 3: Coronal view demonstrating filling defects in the left pulmonary artery.