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# THE DIAGNOSIS OF PULMONARY EMBOLISM DESPITE A NEGATIVE D-DIMER ASSAY: THE IMPORTANCE OF INDIVIDUALISED CLINICAL ASSESSMENT AND OTHER INVESTIGATIONS

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## ABSTRACT

Pulmonary embolism is an important differential diagnosis in the work up of patients presenting with chest pain and respiratory symptoms. Left untreated, it carries a high mortality. Pulmonary embolism presents a diagnostic challenge as the clinical presentation varies widely. Hospitals in the United Kingdom frequently use the validated D-dimer assay as an initial 'rule-out' test for low-risk patients. We present the case of a 69-year-old woman, presenting with chest pain and cough. She was deemed low-risk for pulmonary embolism using validated scoring systems and had a negative D-dimer assay, however clinical suspicion and chest X-ray findings lead to further investigation with computed tomography pulmonary angiography. This revealed a suspected pulmonary infarct, and the diagnosis of pulmonary embolism was made. This report highlights that while the D-dimer assay and Wells score are useful tools in the work-up for pulmonary embolism, they should not replace careful clinical assessment. We also explore X-ray findings pertinent to this case and their association with pulmonary embolism.

## KEYWORDS

Pulmonary embolism, D-dimer, wells score, X-ray, Hampton's hump

## LEARNING POINTS

- The D-dimer assay is a useful test in the work-up for suspected pulmonary embolism when used alongside a validated risk stratification tool, however this should not replace careful clinical judgement.
- While typically used to rule out alternative pathology, chest radiographs can occasionally show changes related to pulmonary embolism.

## INTRODUCTION

The diagnosis of pulmonary embolism (PE) is a frequent clinical problem on the acute medical take. In the UK, for the period 2023-2024, there were over 69,000 hospital episodes in which PE was the primary diagnosis; resulting in over 36,000 admissions[1]. The National Institute of Clinical

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Excellence (NICE) guidelines support the use of the two-tier Wells score in the assessment of PE. Points are attributed for various features in the history and examination, as illustrated in *Table 1*. A score of less than 4 suggests low-risk, and patients should undergo D-dimer testing. If D-dimer assays are negative, then alternative diagnoses should be considered. This test has been shown to carry high sensitivity in detecting the presence of PE. The timely and accurate diagnosis of acute PE is crucial as it carries a high mortality if left untreated, with some studies suggesting up to 30%[2]. Chest radiographs are frequently requested for these patients, typically to rule out other pathology rather than aid in diagnosis, however there are some findings that have been shown to be relatively specific to PE.

| Clinical feature | Score |
|---|---|
| Clinical signs and symptoms of DVT | 3 |
| Alternative diagnosis less likely than PE | 3 |
| Tachycardia | 1.5 |
| Immobilisation over 3 days or surgery in the last 4 weeks | 1.5 |
| Previous DVT or PE | 1.5 |
| Haemoptysis | 1 |
| Malignancy | 1 |

**Abbreviations:** DVT, deep vein thrombosis; PE, pulmonary embolism.

*Table 1. Well's PE score.*

| | |
|---|---|
| **Basic observations** | Respiratory rate 20, $SpO_2$ 97% in room air<br>Heart rate 63, blood pressure 152/71<br>Temperature 36.2°C |
| **ECG** | Sinus rhythm, no acute changes |
| **Full blood count** | Hb 147 g/l, haematocrit 0.45 l/l, WCC $11.0^9$ $\times 10^9$/l, neutrophils 7.81 $\times 10^9$/l, lymphocytes 2.17 $\times 10^9$/l |
| **Biochemistry** | CRP 13 mg/l, creatinine 45 µmol/l, urea 5.6 µmol/l, Na 141 mmol/l, K 4.3 mmol/l, ALP 139 U/l, ALT 11 U/l, bilirubin 8 µmol/l, albumin 39 g/l, adjusted calcium 2.43 mmol/l |
| **Glucose** | 8.5 mmol/l |
| **Coagulation** | Prothrombin time 13.5 s, APTT 26.3s, Fibrinogen 5.0 g/l |
| **D-dimer (FEU)** | 0.33 mg/l |

**Abbreviations:** ECG, electrocardiogram; $SpO_2$, oxygen saturation; Hb, haemoglobin; WCC, white cell count; CRP, C-reactive protein; FEU, fibrinogen equivalent units.

*Table 2. Initial investigations including beside observations and blood tests.*

## CASE DESCRIPTION

Our patient is a 69-year-old woman. She presented to our medical ambulatory care service with right-sided chest pain. The pain started earlier that day after she woke up. It was initially severe but had eased somewhat prior to coming to hospital a few hours later. The pain was sharp in nature and localized to the right lateral aspect of her chest. It radiated to her upper back; there was no associated arm or jaw pain. The pain was exacerbated by deep breathing. A few days prior, she had developed a mild cough which was non-productive. She otherwise felt well in herself with no fevers. There was no history of haemoptysis. The patient had been under investigation for suspected chronic obstructive pulmonary disease (COPD) due to chronic breathlessness on exertion, this was not a confirmed diagnosis at the time. There was no history of previously diagnosed venous thromboembolism or malignancy. There were no clear provoking factors such as recent surgery, periods of immobility or long-distance travel. She had a history of insulin-dependent type 2 diabetes mellitus, obstructive sleep apnoea, bile acid malabsorption syndrome, anxiety and osteoarthritis. Her regular medications include aspirin, atorvastatin, biphasic insulin, empagliflozin, losartan, fluoxetine, lansoprazole and colesevelam. She also uses continuous positive airway pressure at night. She had no known allergies. She is retired and lives independently at home with her partner. She is an ex-smoker with a 25 pack-year history. There was no significant family history of any medical problems.

On examination, the patient appeared clinically well. Her baseline observations were reassuring, and her New Early Warning Score was 0. Cardiorespiratory examination was normal. There was no clinical evidence of deep vein thrombosis (DVT). The Pulmonary Embolism Rule out Criteria score was 1 (for age > 50). The calculated Wells PE score was 3 (PE was considered equally likely diagnosis). Our initial investigations are documented below in *Table 2* and *Figure 1*.

The brief history of cough, together with the mildly raised C-reactive protein and relative neutrophilia, raised the question of chest infection. However, there was little else from the history and examination to support this differential diagnosis. There was no productive cough, no history of fevers or malaise and chest auscultation was clear. The X-ray showed some left basal atelectasis and a peculiar wedge-shaped opacification in the periphery of the right lung. It was felt that this opacification could represent an area of infarction. On balance, given the lack of a clear alternative diagnosis and suspicious X-ray findings, we proceeded to investigate for PE further with computed tomography pulmonary angiography (CTPA) despite the low-risk Wells score and negative D-dimer. *Figure 2* shows an image from this scan.

The CTPA demonstrated a subtle hypoattenuation within a right subsegmental pulmonary artery, with an associated wedge-shaped opacification in the right upper lobe. This was in keeping with a pulmonary infarct, and the diagnosis

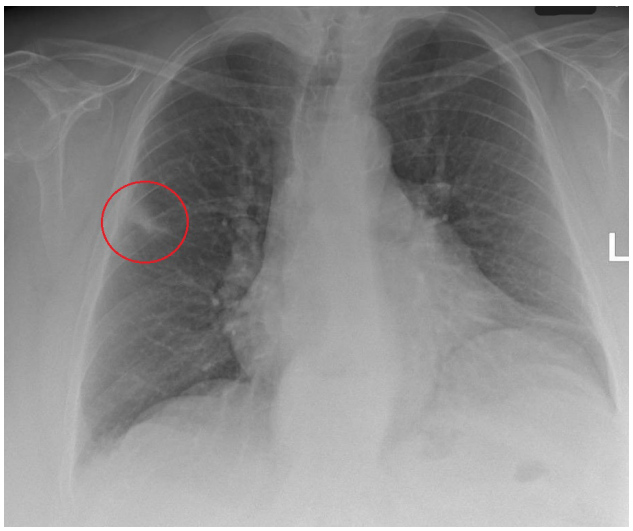


*Figure 1. Chest X-ray showing left basal atelectasis and a peripheral wedge-shaped opacity in the right lung (circled).*

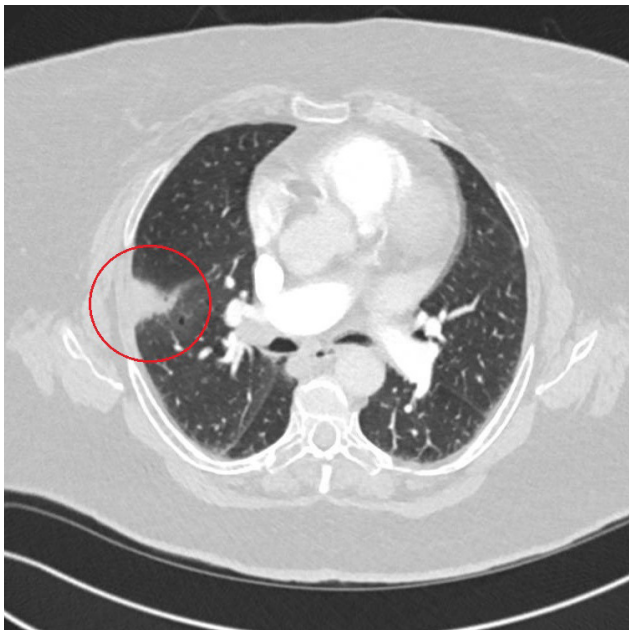


*Figure 2. Computed tomography pulmonary angiography image showing a subpleural wedge-shaped opacification in keeping with pulmonary infarction (circled).*

of unprovoked PE was made. Additionally, a small 3 mm pulmonary nodule was identified in the right lower lobe.

The diagnosis was explained to the patient, and we discussed treatment and follow up plans. We agreed to start anticoagulation with apixaban, this included an initial loading dose of 10 mg twice daily for seven days to be followed by a maintenance dose of 5 mg twice daily thereafter. Given that there was no clear provoking factor for this PE, the patient was referred to local thrombosis services for follow up in clinic. She was seen in thrombosis clinic 3 months later, and the anticoagulation was stopped at that stage. She was later seen by the respiratory team who made the diagnosis of COPD. Additionally, a surveillance computed tomography (CT) scan of the chest 6 months later reassuringly demonstrated no interval change in the pulmonary nodule detected during her attendance to ambulatory care.

## DISCUSSION

The D-dimer assay is frequently used in hospitals across the UK as part of the work-up for patients with suspected PE. It is most often applied in this context alongside the Well's score, which is a validated risk stratification tool for PE. Wells et al.[3] initially proposed the model in 1998, then it was further modified in 2000 to produce the scoring system widely used today. Large multi-centre studies, such as that by Van Belle et al.[4] in 2006, have demonstrated the high sensitivity and negative predictive value of the D-dimer assay when used in combination with a clinical decision tool such as the Modified Wells score. That said, our case and others reported in the literature also demonstrate the need for careful clinical assessment and avoiding over-reliance on such decision tools. Breen et al.[5] presents the case of a young patient diagnosed with PE despite two separate negative D-dimer assays on multiple hospital attendances. The D-dimer assay used in combination with the Wells Score is a useful clinical tool in the work up for PE, however it is not infallible. These pathways should be used alongside careful clinical judgement of the individual patient.

There were no clear provoking factors for PE from the history and examination of our patient. When considering this, together with a low-risk Wells score and negative D-dimer, it is easy to see how clinicians may feel PE is unlikely in these cases and therefore consider it low down on the list of differential diagnoses. Alsararatee[6] reports a similar case of a patient diagnosed with PE without any provoking factors, who had normal investigations including a D-dimer assay. Cases such as these remind us that PE can develop unexpectedly, without any particular clues from the history and assessment of the patient. Moreover, studies have shown that there is little diagnostic value in considering the presence or absence of individual clinical signs and symptoms in the work up for suspected PE. A meta-analysis by West et al.[7] examined the likelihood ratios of PE for various individual clinical features such as syncope, shock, DVT and others. They concluded that these only raise or lower the probability of PE very little. This highlights the challenges faced by physicians when assessing patients where PE is considered a differential diagnosis.

Most patients with suspected PE will undergo chest X-ray imaging. NICE guidelines in the UK advocate for the use of chest X-rays primarily to exclude other pathology, rather than to aid in the diagnosis of PE. A large multi-centre study by Elliot et al.[8] looked at the chest X-ray findings in patients diagnosed with acute PE. They concluded that the chest X-ray was normal in 25% of patients. Other non-specific findings included cardiomegaly in 27% and pulmonary artery enlargement in 19% of patients. Interestingly these associations did not correlate well with echocardiographic assessment of right heart strain indicating little application in looking at the severity of PE. That said, there are some rarer chest X-ray findings that are thought to be relatively specific to acute PE. Two of these signs include the 'Westermark sign' and 'Hampton's hump'. The former

describes pulmonary oligaemia due to collapse of blood vessels distal to the embolus, the latter refers to a peripheral wedge-shaped opacity due to pulmonary infarction. The chest X-ray from our patient *(Fig. 1)* demonstrated a wedge-shaped opacity visible in the periphery of the right lung. This finding was interpreted as concerning for an infarct, which in this context would most likely be caused by acute PE. Asides from case reports, there is limited evidence underscoring the significance of the 'Hampton's hump' sign in acute PE. However, a recent retrospective single-centre study by Kubiak et al.[9] examined the association in more detail. From over 400 patients diagnosed with acute PE, only 8% had the Hampton's hump sign on imaging. They suggested that there may be a correlation between severity of PE and the presence of Hampton's hump. A study by Worsley et al.[10] analysed radiographs from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) trial and found that the presence of Hampton's hump had a specificity of 82% for detecting PE. Although chest radiographs are typically used to rule out other pathology, there are some findings that raise the possibility of PE and can inform clinical decisions around further investigations.

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