CASE REPORT

The great deception: tranexamic acid and extensive pulmonary emboli

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SUMMARY

Pulmonary embolism (PE) is a common and life-threatening condition. The British Thoracic Society PE guidelines state that PE is reliably excluded in patients with low-intermediate clinical probability and a negative D-dimer. We are reporting the case of a 47-year-old lady, taking tranexamic acid for menorrhagia, who presented with shortness of breath and was diagnosed with extensive bilateral PE. She had a low clinical risk of PE as determined by her Wells score, and a subsequent negative D-dimer. This patient's D-dimer value of 15 ng/ml (HemosIL DD HS assay) was the lowest associated with any CT pulmonary angiogram (n=1645) recorded at our trust over a 2-year period. This lady was successfully treated with a heparin infusion and warfarin. No further thromboembolic events had occurred by 18-month follow-up. To our knowledge, this is the first case report to describe tranexamic acid causing an extremely low false-negative D-dimer masking PE.

BACKGROUND

Early diagnosis and treatment of pulmonary embolism (PE) is essential to reduce morbidity and mortality. The incidence of PE is 60–70 cases/100 000/year,¹ with around half occurring in hospital and long-term care, and half in the community.² Examination, bloods and basic investigations only help narrow the differential diagnoses, but ultimately, diagnosis is radiological with CT pulmonary angiography (CTPA) or ventilation/perfusion (V/Q) scanning. This case informs clinicians on how a commonly used antifibrinolytic drug can create an extremely low false-negative D-dimer, leading to the diagnosis of PE being missed.

CASE PRESENTATION

We present the case of a 47-year-old Afro-Caribbean lady who presented to our accident and emergency department with a 1-week history of shortness of breath and dizziness. This lady had a background of gastro-oesophageal reflux disease and obesity (body mass index (BMI) 38). She was a para 3, gravida 3, with three normal vaginal deliveries. She was diagnosed with uterine fibroids 24 years earlier which had been causing significant menorrhagia for the previous 2 years. She was taking omeprazole for reflux disease and tranexamic acid for menorrhagia. Her tranexamic acid regime was 1 g three times a day for 3–4 days during her menstrual period, and was last taken 7 days prior to presentation. She had been taking tranexamic acid for the last year and a half but did not use it with all menses.

Our patient reported no chest pain, cough, haemoptysis or symptoms suggestive of deep vein thrombosis (DVT). She was a lifelong non-smoker, and did not drink alcohol. She was not using any form of contraception and there was no known family history of cardiac or clotting disorders.

On admission, she was tachycardic at 107 beats/min, but was not tachypnoeic, and was saturating at 98% on room air. On examination, her chest was clear to auscultation; she had normal heart sounds; the internal jugular vein was not visible and there was no peripheral oedema. She had a palpable uterus up to her umbilicus. Calves were soft and non-tender.

Blood results showed a haemoglobin of 7.0 g/dl (mean corpuscular volume 61.2 fl), normal white cell count, C reactive protein of 14 mg/l, negative β -human chorionic gonadotrophin (hCG) and a D-dimer of 15 ng/ml (HemosIL DD HS assay, normal range ≤ 230 ng/ml).³

Arterial blood gas demonstrated a pH of 7.46, PaO₂ of 10.0 kPa and PaCO₂ of 4.40 kPa on room air; chest x-ray showed cardiomegaly (figure 1), and she was in sinus tachycardia on ECG.

The working diagnosis to explain her symptomatology was anaemia secondary to fibroid-induced menorrhagia. By Well's criteria for PE,⁴ she had a low pretest probability, scoring 1.5 for tachycardia. She did not meet any of the British Thoracic Society (BTS) major risk factors for PE, and only one minor risk factor (obesity).⁵ As per BTS guidelines, no further investigation for PE was undertaken.

She was admitted under the gynaecologists for a 3-unit red cell transfusion. With no symptomatic improvement post-transfusion, a persistent tachycardia and a large heart on her chest x-ray, our patient had an echocardiogram to exclude pericardial effusion. This demonstrated a dilated right ventricle, raised pulmonary artery pressure of 85 mm Hg, with no pericardial effusion and a normal ejection fraction. A CT pulmonary angiogram was subsequently arranged to exclude PE.

CTPA confirmed extensive bilateral PE (figure 2).

INVESTIGATIONS

- ▶ Haemoglobin 7.0 g/dl (mean corpuscular volume 61.2 fl), D-dimer 15 ng/ml, white cell count 8.4×10^9 and C reactive protein of 14 mg/l.
- ▶ Chest x-ray: cardiomegaly.
- ▶ ECG: sinus tachycardia, rate 110 beats/min.
- ▶ ABG on room air: pH 7.46, PaO₂ of 10.0 kPa and PaCO₂ of 4.40 kPa.
- ▶ Echocardiogram: dilated right ventricle, raised pulmonary artery pressure of

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Figure 1 Posteroanterior chest x-ray showing cardiomegaly (cardiothoracic ratio 16/29).

85 mm Hg with no pericardial effusion and a normal ejection fraction.

- CTPA: Thrombus in the main pulmonary artery on the right side with extension into segmental and subsegmental branches. Segmental and subsegmental thrombus on left side.

TREATMENT

Anticoagulation in thromboembolic disease is particularly challenging when there is an increased bleeding risk, such as in this case. Owing to the extent of our patient's PE, it was felt that the risk of further thromboembolic events outweighed the risk of bleeding. She was initially managed with an intravenous heparin infusion, rather than conventional low-molecular-weight heparin, to allow rapid reversal if significant blood loss

Figure 2 CT pulmonary angiography axial image demonstrating low-density filling defects within the segmental branches of the pulmonary arteries bilaterally.

occurred. She was subsequently loaded on warfarin and her tranexamic acid was stopped.

For completion, an ultrasound of her abdomen and pelvis demonstrated a large fibroid uterus with no inferior vena caval compression and ultrasound Doppler examination of her lower limbs was negative for DVT.

OUTCOME AND FOLLOW-UP

This lady was treated with warfarin for 6 months and did not suffer any further thromboembolic events at 18-month follow-up. During this period, she did not take any medication for menorrhagia and her haemoglobin was closely monitored. She was seen by the haematologists and her thrombophilia screen was normal. She was seen by the gynaecologists, and in view of her previous PE, comorbidities and raised BMI, a hysterectomy was not advised owing to the anaesthetic risk. She therefore opted for uterine artery embolisation.

DISCUSSION

To our knowledge, this is the first case describing a false-negative D-dimer, in a low-risk patient, on tranexamic acid, masking bilateral extensive PE. Of equal significance, is the patient's extremely low D-dimer value.

The BTS PE algorithm states that PE is reliably excluded in patients with low-intermediate clinical probability and a negative D-dimer when using a quantitative D-dimer assay.⁵ This has been shown to significantly reduce the need for V/Q scanning and CTPA in suspected PE.⁶

However, caution must be exercised when interpreting a D-dimer value, as many scenarios can make interpretation unreliable. There is good evidence to delineate the causes of a false-positive D-dimer such as sepsis with DIC,⁷ aortic dissection,⁸ and recent surgery/trauma,⁹ but little regarding the causes of a false-negative D-dimer.

Our patient's D-dimer value of 15 ng/ml is extremely low. On auditing all CTPA scans performed over a 2-year period in our Trust (n=1645), 903 had associated D-dimer values. 15 ng/ml was the lowest D-dimer value associated with any CTPA (range 15–7813 ng/ml), regardless of CTPA result. The next lowest D-dimer value in the dataset was 35 ng/ml. A very low value should prompt clinicians to consider alternative explanations for the result. Although, in a small proportion of cases, D-dimer may normalise by 7 days, the majority have an elevated D-dimer for up to 12 days.¹⁰

Other causes of a false-negative D-dimer include patients receiving therapeutic heparin treatment, and patients with suspected DVT during oral anticoagulant therapy.¹¹ One case report describes a false-negative D-dimer in a patient on tranexamic acid with DVT of the leg.¹²

Regarding tranexamic acid and thrombosis risk, two studies found no increased risk of thrombosis in women taking tranexamic acid for menstrual bleeding^{13 14}; this also extends to the surgical setting, where it is used to prevent postoperative blood loss.¹⁵

Tranexamic acid acts by competitively inhibiting the activation of plasminogen to plasmin by binding to specific sites on both plasminogen and plasmin, a molecule responsible for the degradation of fibrin.¹⁶ As D-dimer is a fibrin degradation product, its formation is inhibited in this setting.

In summary, as clinicians we must always consider basic biological principles when faced with any clinical problem; in this case, the production of D-dimer and pharmacodynamics of tranexamic acid in thrombus formation.

Learning points

- ▶ With extremely low D-dimers, always consider the possibility of defective fibrinolysis.
- ▶ Tranexamic acid can cause false-negative D-dimer results, which, if not appreciated by the clinician, can lead to a missed diagnosis of venous thromboembolism (VTE).
- ▶ Pulmonary embolism should always be considered when there is evidence of right heart strain on ECG or echocardiography.

Competing interests None.

Patient consent Obtained.

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