

A patient with pleuritic chest pain and abnormal blood clotting tests

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Abstract

We present the case of a 58 year old man who developed pleuritic chest while an in-patient; investigations revealed pulmonary embolism, despite a significantly raised Activated Partial Thromboplastin Time (APTT), which was subsequently attributed to Antiphospholipid syndrome (APS). The diagnosis and initial management of APS in the acute setting is discussed.

Key Learning points

- Antiphospholipid syndrome (APS) is a common cause for isolated elevation of APTT and may be primary or secondary; in acutely unwell patients, APS could be the result of a concurrent infection.
- Interpretation of isolated prolonged APTT in the acute setting should be correlated with the clinical presentation: clotting factor deficiency may present with bleeding whereas APS may result in thrombosis.
- Urgent laboratory investigation should be undertaken in liaison with the haematology team to establish the cause for a raised APTT, as this will help to determine the necessary treatment and thrombotic risk.
- Patients with APS are at high risk of both arterial and venous thrombosis and will usually require thromboprophylaxis during hospital admission, despite the raised APTT.
- If Venous Thromboembolism (PE or DVT) occurs as a result of APS, the patient should be started on treatment dose of low molecular weight heparin, even in cases where APTT is significantly raised.

Case report

A 58-year old man with Multiple Sclerosis, developed acute pleuritic right sided chest pain while an in-patient on a rehabilitation ward following treatment for sepsis from infected pressure sores. He was usually wheelchair bound and a non-smoker with no previous cardiac history. There was no family or past medical history of any bleeding or prothrombotic disorders.

On examination he was normotensive, slightly tachycardic (104bpm) and pyrexial (37.8 °C). His respiratory rate was 16/min and his oxygen

saturation 94% on air. Auscultation revealed right basal crackles. His ECG showed anterior T-wave inversion which had not been present on a previous ECG (Figure 1). Urgent bloods showed raised CRP (200 mg/L), WCC (16.7 10⁹/L) and neutrophils (13.7 10⁹/L). Urea and electrolytes were normal. Troponin at baseline and 12hours was normal. A chest x-ray (Figure 2) showed patchy consolidation at the right cardio-phrenic angle, which was deemed to be consistent with a hospital acquired pneumonia. He commenced treatment with intravenous antibiotics.

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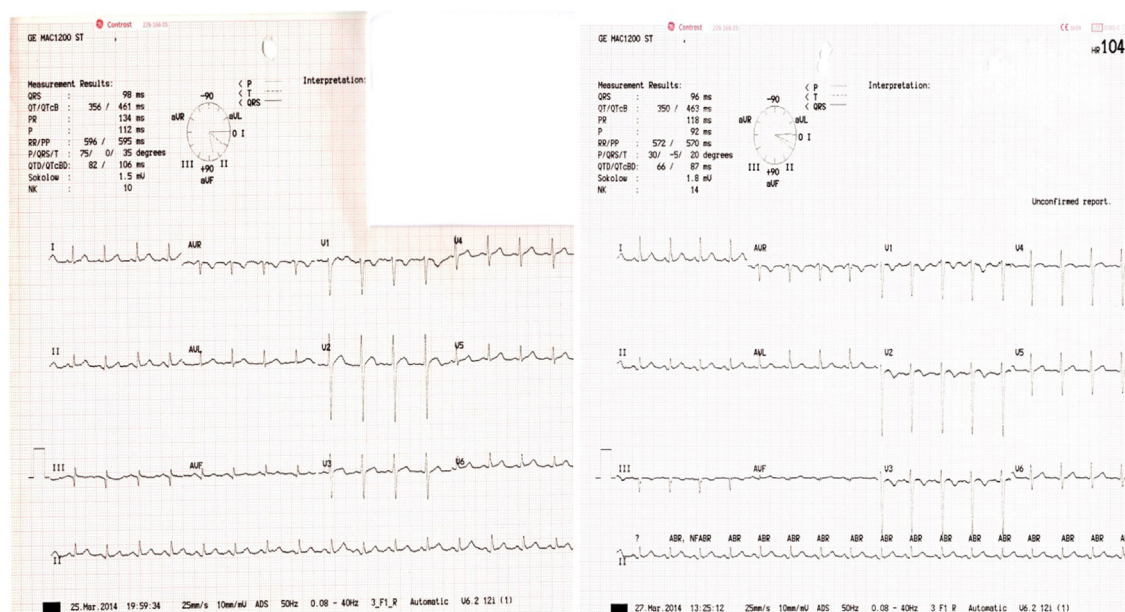


Figure 1. ECG prior and during the episode of chest pain

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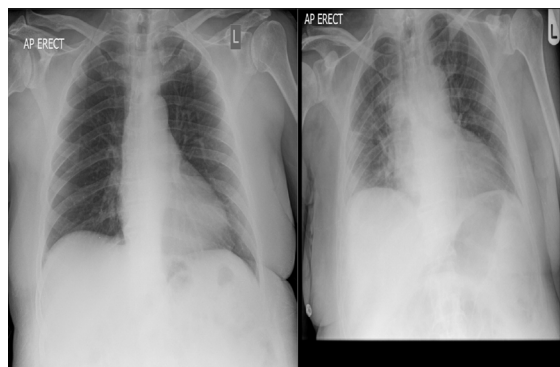


Figure 2. Chest X-ray on admission to ward and while acutely unwell with chest pain

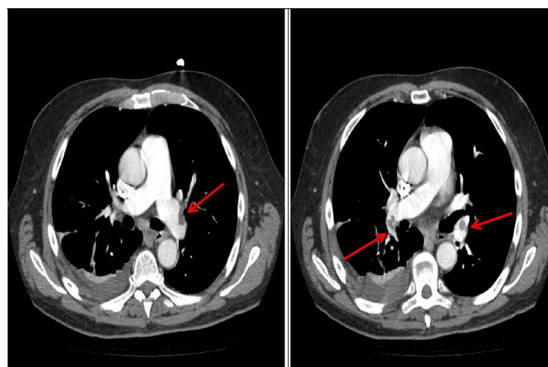


Figure 3. CTPA demonstrating bilateral lobar and segmental Pulmonary Embolism

On admission to the rehabilitation ward and a few days prior to the episode of chest pain he had been noted to have significantly raised Activated Partial Thromboplastin Time (APTT) (176 sec [normal 24–36 sec]) on routine blood tests. The cause was not clear and the case was immediately discussed with the local Haematology team who requested mixing tests, investigations for antiphospholipid antibodies and factor assays (haemophilia screening). In view of the high risk for Venous Thromboembolism (VTE), the absence of past or family history of bleeding and despite the prolonged APTT, the patient was started on prophylactic dose of LMWH while the results of further investigations for the raised APTT were awaited. A marginally elevated PT was also noted (16sec [normal 10–13sec]), although this self-corrected within a few days of hospital admission, and was attributed to malnutrition and vitamin K deficiency. The APTT remained abnormally prolonged on repeat testing.

Despite the initial diagnosis of pneumonia, the possible RV strain pattern seen on the ECG, the pleuritic type of chest pain and the abnormal clotting profile prompted further investigation for Pulmonary Embolism (PE). The D-dimer was raised to 1086 ng/mL and a subsequent CT Pulmonary Angiogram showed bilateral multiple filling defects in the lobar and segmental pulmonary arteries in keeping with acute PE (Figure 3).

The patient remained hemodynamically stable; further investigations into the cause of the prolonged

APTT revealed incomplete correction of the APTT when normal plasma was mixed with patient plasma at 20: 80 and 50:50 ratio suggesting presence of an inhibitor. The DRVVT (Dilute Russell's Viper Venom Time) test was positive (ratio 1.4), consistent with presence of Lupus Anticoagulant (LA). Following further discussion with the haematology team, he was commenced on therapeutic dose of Low Molecular Weight Heparin (LMWH). Results of factor assays demonstrated homozygous Factor 12 (FXII) deficiency (3.0 IU/ml assayed by CRV [50–150 IU/ml]), the significance of which in the above episode of PE was unclear.

The DRVVT (LA) test was repeated after twelve weeks and remained positive (1.7), which confirmed the diagnosis of Anti-phospholipid Syndrome (APS). Further tests for Systemic Lupus Erythematosus (SLE) and other autoimmune disorders were negative. There were no findings suggestive of underlying malignancy as a trigger for the APS. The APS with the complicating PE was most likely the result of his recent pressure ulcer infection or concurrent chest infection. During the patient's recent acute hospital admission for the pressure ulcer infection, he had been prescribed prophylactic dose of LMWH, although a clotting profile had at that time not been performed. A few days after the diagnosis of PE was made (and with the LA result already available) the patient was started on one of the novel oral anticoagulants (NOACs) which is expected to continue long-term, in view of the established diagnosis of APS.

Table 1. Causes of isolated raised APTT²

Factors VIII (Haemophilia A), IX (Haemophilia B), XI deficiency
Contact Factor deficiency (prekallikrein, Factor XII)
Factor VIII inhibitors
Antiphospholipid antibodies
Unfractionated heparin (LMWH has mild effect)
Laboratory error or artefact

Discussion

Activated partial thromboplastin time (APTT) assesses mainly intrinsic pathway factors (VIII, IX, XI), prekallikrein and factor XII. Significantly deranged isolated APTT usually signifies deficiency in the above factors and can be inherited (haemophilias) or acquired.¹ Causes of isolated raised APTT are shown in Table 1.²

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The inherited deficiencies of factors VIII, IX and XI (haemophilias) are associated with bleeding diathesis whereas the deficiency of factors XII and prekallikrein are not. Interestingly, acquired inhibitors of the intrinsic pathway factors are associated with bleeding (Factor VIII inhibitors), whereas the antiphospholipid antibodies (lupus anticoagulant type inhibitors) are associated in most cases with thrombosis.¹

Out of the anti-phospholipid antibodies, the most commonly seen is the Lupus Anticoagulant (LA) [others include the anti- β 2-glycoprotein I antibody (anti- β 2GPI) and the anticardiolipin antibody (aCL)]. Half of the patients with LA have prolonged APTT. Despite the prolongation in APTT, patients with positive LA have paradoxically increased risk of thrombosis.³ The antibodies may interfere with in vitro phospholipid-dependent coagulation tests as they are directed against plasma proteins which bind to phospholipids. The mechanisms through which they cause thrombosis are not clearly understood.⁴

The most updated Sapporo criteria define Antiphospholipid Syndrome (APS) as the combination of at least one clinical criterion with at least one laboratory criterion. The clinical criteria include vascular thrombosis (arterial or venous), whereas the laboratory include presence of one of the antiphospholipid antibodies on two occasions at least 12 weeks apart.⁵ Anti-phospholipid antibodies are seen in 1-5% of healthy people (Primary APS). However the antibodies could be related to other disorders such as connective tissue disease, infection and malignancy (Secondary APS). SLE is the commonest associated condition with 20-35% of SLE patients diagnosed with APS.^{2,6} The most frequently associated infections include skin infection (18%), HIV (17%), Pneumonia (14%) and Hepatitis C (13%).⁷ The most common clinical manifestations of APS include Deep Venous Thrombosis (32%), Livedo Reticularis (20%), CVA (13%) and PE (9%).⁸ Patients diagnosed with venous thromboembolism in association with APS should be treated with standard treatment dose of LMWH followed by warfarin with an INR target 2-3. The optimal duration of treatment is not clear. The expert task force recommends lifelong therapy in patients with definite APS (as described by Sapporo criteria) and up to 6 months in patients with isolated VTE, transient predisposing factor and low risk anti-phospholipid antibodies profile (isolated intermittently positive aCL or anti- β 2GPI at low-medium titres).⁹

Severe factor XII (or Hageman factor) deficiency is defined as factor XII activity less than 1% of normal and is inherited as an autosomal recessive trait. Affected patients have marked prolongation in APTT. Venous thromboembolism and myocardial infarction have been reported, however it remains unclear if factor XII deficiency leads to an increased risk of thrombosis. Risk for bleeding has not been reported. The deficiency is in most cases asymptomatic and therefore treatment is not usually required.^{10,11,12} There is an association between LA and Factor XII deficiency as it has been noted that FXII antibodies are present in a proportion of LA patients, which could falsely lead to a diagnosis of FXII deficiency. It is possible that such a relationship existed in our case.¹³

It is very important that clinicians undertaking risk assessment for VTE do not presume that the presence of a raised APTT will be protective. This case illustrates clearly the predisposition to VTE in patients with APS and the importance of thromboprophylaxis during hospital admission, despite the prolonged APTT. Prolonged APTT can also be a finding in patients with pathologies that predispose to bleeding. A careful history regarding previous bleeding (soft tissue, joint bleeding) or previous VTE (PEs, DVTs, miscarriages) together with assessment of the current presentation is crucial, along with urgent laboratory investigation. The initial step should be a mixing study of normal with patient plasma (20:80 and 50:50). This test is immediately available in most hospitals and is helpful in the differentiation between presence of an inhibitor and factor deficiency (failure of APTT to correct points towards presence of inhibitor).¹ The DRVVT test is recommended in current guidelines to look specifically for LA.¹⁴ Factor assays should follow if there is suspicion on the basis of clinical presentation (bleeding) or the results of mixing studies.¹ Once these investigations are completed and haemophilias are excluded the physician should ensure that prophylactic LMWH is prescribed unless other contra-indications exist. Similarly, prolonged APTT in patients presenting with suspected or confirmed VTE should not detract clinicians from prescribing treatment dose of LMWH, as in most cases this is due to APS. Urgent investigation of the possible secondary cause and early specialist opinion should be sought.

Conflict of interest

Nothing to declare

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