Antiphospholipid syndrome presenting as pulmonary thrombosis and pancreatitis in a young man

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SUMMARY

The antiphospholipid syndrome and protein-S deficiency are known prothrombotic conditions. The confirmation of the latter in a patient with a recent antiphospholipid syndrome-associated thrombosis may be difficult as protein-S levels are low in a patient in the wake of recent thrombosis, antiphospholipid antibodies themselves may be targeted against protein-S and oral anticoagulation with warfarin may further bring down protein-S levels. We report a case of a 29-year-old man presenting with widespread unprovoked thrombosis in the form of pulmonary thromboembolism, neck vein thrombosis and pancreatitis. He was found to have antiphospholipid syndrome with low protein-S levels on two occasions. He was anticoagulated with heparin and improved over a 24-day hospital stay marred by the development of an exudative pleural effusion.

BACKGROUND

A 29-year-old man presented with breathlessness and abdominal pain. On evaluation, he was found to have widespread venous thrombosis manifesting as pulmonary infarction, neck vein thrombosis and pancreatitis. He had a stormy indoor course, developing an infected pleural effusion. He was anticoagulated with heparin and later switched to warfarin. He was found to have the antiphospholipid syndrome along with low protein-S levels. In reporting the case we wish to sensitise the treating physician to pancreatitis being among the varied manifestations of venous thrombosis and to discuss the problems in interpreting low protein-S values in the presence of antiphospholipid antibodies.

CASE PRESENTATION

A 29-year-old male labourer was symptomatic since 20 days before admission with pain in his upper abdomen especially in the right hypochondrium for which complaint he was treated symptomatically in another hospital with proton-pump inhibitors. He presented to our hospital when he developed a swelling in the right side of his neck 2 days before admission, and pain in the right side of chest, most pronounced at the height of inspiration. On the day of admission he had had two episodes of streaky haemoptysis. He had pain in the upper abdomen, also worsening with deep breaths. There was no exertional breathlessness or angina, no painful swelling in the calves, pedal oedema, palpitations, fever or productive cough. He did not complain of significant weight loss, was never transfused with blood products in the past. He was a teetotaler and occasionally chewed tobacco. He had no discernible family history of thrombotic events. On examination, pulse was 84 beats per

minute, Blood pressure 120/80 mm Hg in the right brachial artery. The right aspect of his neck had a tender cord-like swelling extending from the base till the mastoid. He was tachypnoeic and auscultation of the chest revealed a pleural rub at the right base with reduced air entry. Abdominal palpation revealed tenderness in the epigastrium without any obvious visceral enlargement.

INVESTIGATIONS

Investigations at admission showed a haemoglobin of 11 g/dl, mildly raised total leucocyte counts ($15\,000/\text{mm}^3$) with a neutrophilic predominance, with normal platelet counts. Liver and renal functions were normal. He was also found to have significantly elevated levels of serum amylase and lipase (560 and 2241 IU, respectively). Arterial blood gases showed partial pressure of oxygen (pO_2) of 78 mm Hg and oxygen saturations (sO_2) of 86%. A chest radiograph showed a mild pleural effusion at the base of the right lung. An ultrasound of the neck demonstrated complete thrombosis of the right internal and external jugular veins. CT of the chest with pulmonary angiography revealed thrombosis of inferior branches of left and right pulmonary arteries (figure 1) with bilateral wedge-shaped ground glass opacities suggestive of pulmonary infarction (figure 2). It also showed that collaterals had developed on the right side of the thoracic wall, with a right-sided pleural effusion. CT scanning of the abdomen revealed a bulky pancreas and no signs of abdominal malignancy. A colour Doppler scan of the lower limbs ruled out a deep vein thrombosis.

TREATMENT

Samples were drawn for workup of thrombophilia and an infusion of unfractionated heparin at a rate of 1000 U/h was initiated. The patient had severe pain, which he rated at 7 on a scale of 10, and required opioid analgesia with pentazocine. A surgical reference was sought for the pancreatitis, and was managed conservatively. He developed a re-filling of his pleural effusion around the 10th day of admission with a worsening of dyspnoea, attributed to a superadded infection. Pleural fluid analysis revealed high protein (5.15 g%) and high white cell count ($1200/\text{mm}^3$, with 80% neutrophils) with no evidence of malignant cells. An intercostal drain was inserted and kept in situ for 5 days till it no longer drained fluid. His blood culture grew acinetobacter sensitive to meropenem, imipenem and colistin. He was initially given injectable amoxicillin-clavulanate, which was later changed to meropenem. His thrombophilia profile reports were received which showed low protein-S activity

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Figure 1 Thrombosis of inferior branches of left and right pulmonary arteries.

of 35% (normal 65–140%, using a clotting-based assay on an automated coagulometer) and the presence of lupus anticoagulant (using the dilute Russell's viper venom (DRVV) test, the screen showed prolongation to 75.7 s compared to a control of 38 (DRVV ratio 1.99), and was reconfirmed with a DRVV prolonged to 46.7 s as compared to control of 34 s). The other results of the thrombophilia profile showed the following: activated protein C resistance ratio 3.27 (<1.6 s/o resistance), Plasma antithrombin activity 94% (80–120%), anticardiolipin Ab (ACLA) IgM 2.26 (negative below 10 MPL units/ml), ACLA IgG 0.91 (negative), anti- β 2-glycoprotein I (anti- β 2gPI) levels negative, homocysteine levels 9.6 micromol/l. Protein C observed value 80% (70–130%), antinuclear antibodies, JAK-2 gene mutations and flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH) were all negative. Oral anticoagulation was initiated. The patient was discharged home after a total hospital stay of 26 days, 14 of which were in the medical intensive care unit.

OUTCOME AND FOLLOW-UP

On follow-up, the patient showed persistently elevated levels of lupus anticoagulant and is currently symptom free on a daily dose of warfarin, with an international normalised ratio (INR) of 2.6 at the last visit. Protein-S values were repeated 3 months after presentation (while on warfarin) and they continue to be low at 42% activity. He has been counselled to get his sister and

Figure 2 CT chest image showing wedge-shaped ground glass opacities suggestive of pulmonary infarction.

children screened for protein-S deficiency as soon as his financial circumstances permit it. Tests for lupus anticoagulant were also repeated at 3 months, which showed prolongation to 68 s with a control of 34.2 s (DRVV ratio 1.98).

DISCUSSION

This young patient presented to us with neck vein thrombosis. CT and other investigations revealed that his other symptoms were also rooted in venous thromboses at other sites; viz bilateral pulmonary vein thrombosis causing basal lung infarction. In the absence of an obvious aetiology, pancreatitis was also considered to be the sequel of the same. A repeated presence of lupus anticoagulant in the patient's plasma in this clinical setting led to a diagnosis of primary antiphospholipid syndrome (APS) according to the revised Sapporo criteria.¹ Clinical criteria include arterial, venous, or small vessel thrombosis, or the presence of pregnancy morbidity. Laboratory criteria include: (A) presence of lupus anticoagulant antibody, (B) medium or high titre (or >99 th percentile) IgG/IgM ACLA antibody or (C) IgG/IgM Anti- β 2gPI antibody (titre >99 th percentile). While the initial levels of lupus anticoagulant were done prior to anticoagulation, the DRVV test is reliable even if the patient is on warfarin.²

β 2gPI has been recently implicated as an independent factor in the pathogenesis of thrombosis. Patients with 'triple positivity' appear to be at greater risk of rethrombosis as compared with others, and may need longer anticoagulation.³ Pulmonary thromboembolism is the most common pulmonary manifestation of APS, others being pulmonary hypertension, adult respiratory distress syndrome and intra-alveolar haemorrhage.⁴ Pancreatitis has been previously reported among the various abdominal manifestations of APS.⁵ The pathogenesis of pancreatitis is not yet clear though preliminary autopsy reports suggests thromboembolism of the pancreatic blood vessels, without inflammation of the veins, as the most likely aetiology.⁵ The pancreatitis in APS is distinct from autoimmune pancreatitis which presents as chronic pancreatitis with mild symptoms; histopathology characteristically shows obliterated phlebitis throughout the pancreas.⁶

Deficiency of the vitamin K-dependent anticoagulant protein, protein S, may be hereditary or acquired and presents as venous thromboembolism. Thrombosis at an early age and a positive family history suggest inherited thrombophilia. Protein-S deficiency may be quantitative or functional, and tests for both are available. The co-existence of primary antiphospholipid syndrome and inherited protein-S deficiency is extremely rare but has been documented.⁷ It has been suggested that ACLAs may themselves produce an 'autoimmune' protein-S deficiency; endothelial cells which secrete protein-S may serve as the target of the anticardiolipin antibodies.⁸ A cross-sectional study found a significantly higher number of patients of systemic lupus erythematosus had low protein-S values when ACLA was positive when compared with ACLA-negative patients.⁹ In such cases of 'acquired' protein-S deficiency, protein-S levels will normalise on repeated testing, unless the patient is on vitamin K antagonists, as in our case.

In the treatment of APS, full anticoagulation with subcutaneous or intravenous heparin followed by warfarin therapy is recommended following a thrombosis. An INR target of 2.0–3.0 is reasonable for venous thrombosis, and recurrent thrombotic events while on anticoagulation warrant an INR of 3.0–4.0. In the presence of significant thrombotic events, as was the case in our patient, lifelong anticoagulation is the norm. At present, the classification of APS according to its underlying

pathogenetic mechanism and introducing targeted strategies is still underway.¹⁰ In the absence of genetic testing for mutations, it is difficult to dismiss an immediate post-thrombotic effect as the cause of low protein-S levels. Protein-S being a vitamin K-dependent protein will be reduced following warfarin therapy. The alternative of stopping anticoagulation before retesting would have been dangerous in the face of this life-threatening thrombotic event. The confirmation of an inherited protein-S deficiency will, furthermore, not affect the management of our patient but will have implications in the importance of family screening.

Learning points

- ▶ Venous thrombosis may present with varied manifestations including pancreatitis.
- ▶ Two procoagulant states may co-exist and may precipitate widespread thrombosis.
- ▶ Low levels of protein C, protein-S and antithrombin occur after a recent thrombosis and should not be considered causative unless confirmed by retesting off anticoagulants or genetic testing.
- ▶ Antiphospholipid syndrome may cause a secondary protein-S deficiency as it may be a target of the autoantibodies directed against membrane-associated phospholipids.

Competing interests None.

Patient consent Obtained.

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