CASE REPORT

PULMONARY EMBOLISM, THROMBOCYTOPENIA, AND ANTI-PHOSPHOLIPID SYNDROME

Talha Mahmud

Department of Pulmonology, Shaikh Zayed Hospital and Federal Post Graduate Medical Institute, Lahore, Pakistan

This case report describes a young non-smoker male masquerading under the diagnosis of community acquired pneumonia who was found to have respiratory symptoms attributed to bilateral pulmonary emboli. There was also evidence of thrombocytopenia and proximal deep venous thrombosis of right lower limb. He underwent further investigations and was found to have positive anti-cardiolipin antibodies, lupus anticoagulant and prolonged activated partial thromboplastin time due to anti-phospholipid antibody syndrome. This article highlights the importance of consideration of earlier diagnosis in younger patients with congenital thrombophilias that carries potential for prevention and treatment of life threatening thromboembolic manifestations.

Keywords: Anti-phospholipid antibody syndrome, activated partial thromboplastin time, aPTT, deep venous thrombosis, pulmonary embolism, thrombocytopenia

INTRODUCTION

The anti-phospholipid syndrome (APS) is defined by two major components: occurrence of at least one clinical feature, vascular event or pregnancy morbidity; and presence of at least one type of autoantibody known as an anti-phospholipid (aPL) antibody on two separate occasions at least 12 weeks apart.[1] APL are directed against serum proteins bound to anionic phospholipids and may be detected by lupus anticoagulant (LA) tests, anti-cardiolipin antibody ELISA, anti-ß2 glycoprotein-I ELISA.[2] The risk of both venous and arterial thrombosis and/or thromboembolism is increased in individuals with positive tests for LA activity (odds ratio [OR] of 11, or medium or high levels of aPL (OR 1.6).[3]

CASE REPORT

A 22-year-old non-smoker male college student, resident of Lahore, Pakistan presented with history of mild cough accompanied by occasional blood tinged sputum, right sided pleuritic chest pain, low grade intermittent fever and moderate progressive exertional dyspnoea of three weeks duration. There was no history of orthopnoea, nocturnal awakenings due to shortness of breath or wheezing during or prior to this illness. His initial chest radiograph showed a semi-rounded opacity at the left base along with obliteration of costophrenic angle (Figure-1a, b). In the suspicion of pneumonia, he was prescribed azithromycin and cefuroxime by his family physician but there was no improvement in symptomatology. Prior to this illness, he admitted for a recent six hours road travel to Sakardu for a recreational trip with his friends where the above symptoms triggered after prolonged walking at hiking tracks. His review of systems revealed that he also had right lower limb pain with mild calf swelling which he attributed to the excursion trip but no trauma. There was no evidence of weight loss and rhinitis or sinusitis including other systemic complaints. In the past, he was never hospitalised for any medical or surgical ailment. He kept no pets at home and revealed no history of any job or work having an aerosol or chemical exposure and his family history was also benign for any chronic disorder.

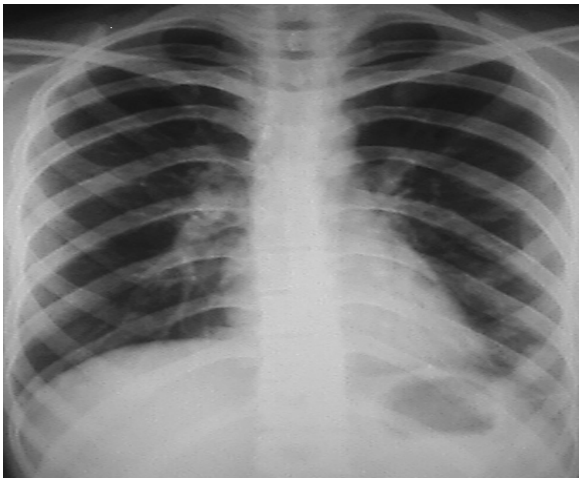

Figure-1a: CXR-PA: Opacity at left base with obliteration of costophrenic angle

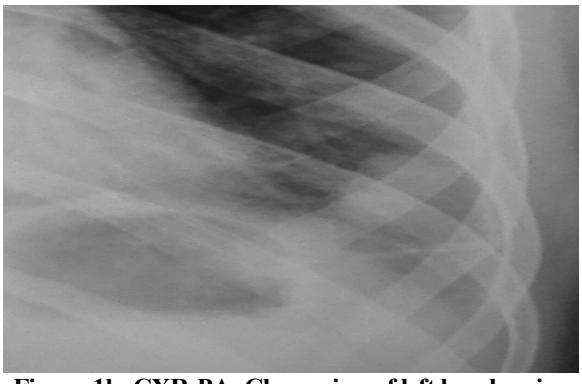

Figure-1b: CXR-PA: Closer view of left basal region showing a rounded opacity with unclear lateral border, atelectatic band and obliteration of costophrenic angle

On general physical examination, he was alert and cooperative, afebrile with pulse of 110/m, blood pressure 125/75 mmHg, and respiration 20/m with 92% saturation on pulse oximeter. His right leg was slightly oedematous with mild tenderness in calf having normal peripheral pulses. Chest examination was consistent with slightly reduced breath sounds intensity and occasional rales in both basal regions of chest. Remaining general and systemic examination revealed no abnormality. In the presence of right leg deep venous thrombosis (DVT), this clinical picture raised suspicion of pulmonary embolism for which he was further evaluated.

Laboratory evaluation included complete blood cell count that revealed haemoglobin 12.9 g/dL, WBC $10.41\times10^3/\mu L$ (differential count: neutrophils 68%, lymphocytes 20.9%, monocytes 6.4%, eosinophils 4.3% and basophils 0.4%) and platelets $77\times10^3/\mu L$. He had a prothrombin time (PT) of 12 seconds (control=12), international normalised ratio (INR) 1.2 and activated partial thromboplastin time (aPTT) 42 seconds (control 22–31). Thrombocytopenia and prolonged aPTT were confirmed with repeated levels of platelets (105 and 82) and aPTT (46 and 40) in the two consecutive specimens. Plasma D-dimer levels were raised to ≥2.0<4 (normal <0.5 µg/dL). Serum biochemistry showed blood urea nitrogen 17 mg/dl, creatinine 0.8 mg/dl, alanine aminotransferase (ALT) 30 U/L, aspartate aminotransferase (AST) 35 U/L, alkaline phosphatase 108, bilirubin 1.1 mg/dl, sodium 137 mmol/L, potassium 4.0 mmol/L. Urine routine examination was normal. Arterial blood gas analysis revealed *p*H 7.44, Po_2 71 mmHg, Pco_2 36.1 mmHg and HCO_3 31.1 mmol/L. Sputum evaluation showed no growth on pyogenic culture, negative Gram stain and two consecutive smears for acid fast bacilli were also negative. ECG showed S_1, Q_3, insignificant ST segment elevation in leads II, III and aVF and inverted T waves in V_1, and V_2 (Figure-2), echocardiography was normal and troponin-I levels were <0.20 (normal <1.0).

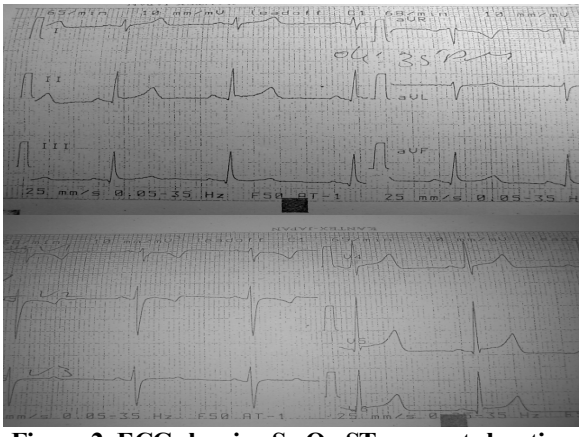

Figure-2: ECG showing S_1, Q_3, ST segment elevation in leads II, III and aVF and inverted T waves in leads V_1, and V_2

Venous Doppler ultrasonogram of right lower limb showed partial thrombus involving common femoral, deep femoral and popliteal veins without any evidence of thrombosis in left lower limb. Computerised tomographic pulmonary angiogram (CTPA) confirmed bilateral thrombo-embolism in the distal parts of right and left pulmonary arteries extending into their main lower lobe branches and segmental branches of all the lobes (right>left and lower>upper). A large peripheral wedge shaped opacity seen in middle lobe was suggestive of infarction, smaller sub-pleural opacities in lingular and right lower lobes and small right sided pleural effusion was also seen (Figure-3, 4, 5, 6).

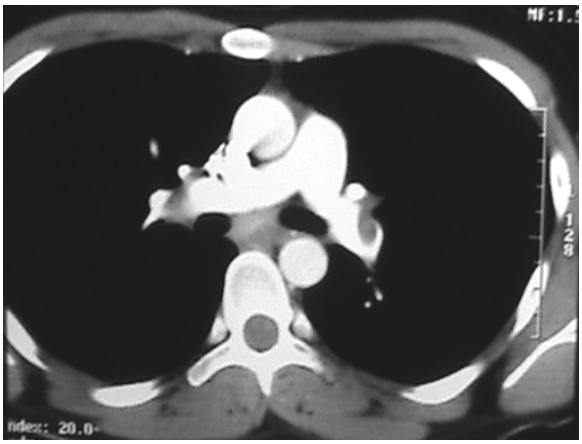

Figure-3: CT pulmonary angiogram showing bilateral thrombus formation in the distal parts of right and left pulmonary arteries

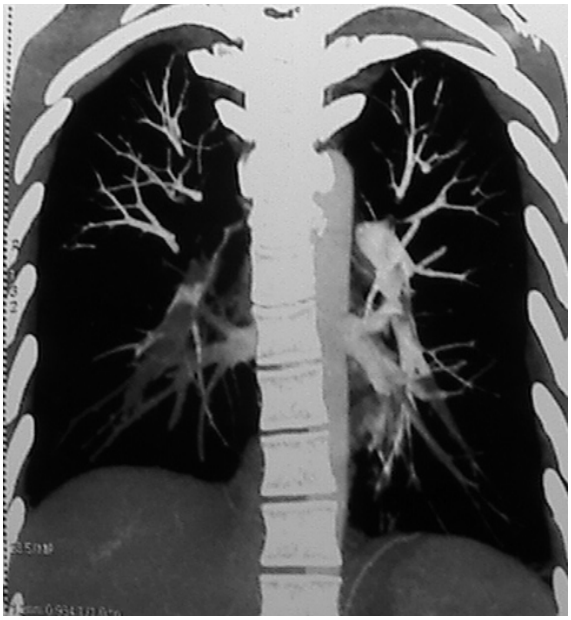

Figure-4: Computerised tomographic pulmonary angiogram showing bilateral thrombo-embolism in distal parts of right and left pulmonary arteries extending into main lower lobe and segmental branches of all lobes

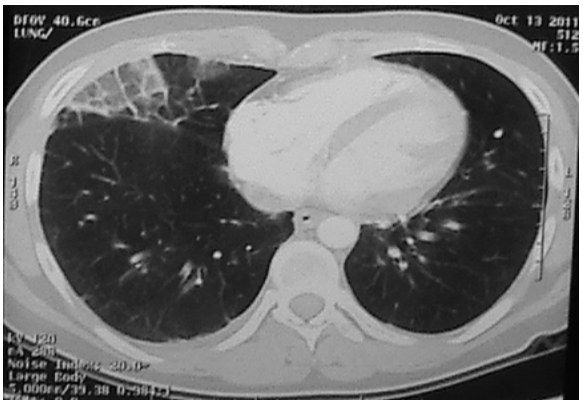

Figure-5: CT chest (lung window) showing peripheral wedge shaped opacity in right middle lobe suggestive of infarction

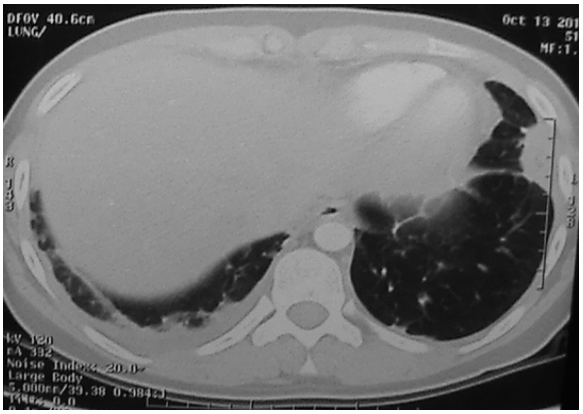

Figure-6: CT chest (lung window) showing smaller sub-pleural opacities in lingular and both lower lobes along with small right sided pleural effusion

At this stage the diagnosis of right leg DVT and bilateral pulmonary emboli was established, but the question was to investigate its underlying cause and to initiate the treatment. Prior to starting anticoagulants, his blood was sent for evaluation of pro-coagulant states including protein C, protein S, factor V Leiden, antithrombin III, anticardiolipin antibodies, plasma homocysteine, vitamin B_{12} and folate levels. He was started with enoxaparin 60 mg sub-cutaneous twice a day and warfarin 10 mg daily. Enoxaparin was discontinued after achieving INR of 2.3 at day five of treatment while warfarin was continued. His anticardiolipin antibodies IgM were borderline raised to 10.4 MPL/ml (negative ≤10) and IgG were moderately raised to 35.5 GPL/ml (negative ≤10) while protein C 87% (72–106), protein S 84% (60–110), factor V Leiden 1.04 ratio (0.9–2.9), antithrombin III 106% (80–120), plasma homocysteine 12 (4.72–14.05), vitamin B_{12} 244.70 ρg/ml and folate 5.27 ηg/ml also were within normal ranges. He became asymptomatic after a few weeks of treatment; his anticardiolipin antibodies were repeated after 3 months of treatment and were again positive (patient's rate 1.330, cut-off 0.440). Keeping in view of strong association of antiphospholipid antibodies with systemic lupus erythematosis (SLE), connective tissue profile screening was done that included ANA (negative), RA factor (negative, quantitative 6.60 IU/mL), anti-smooth muscle and anti-mitochondrial antibodies (negative). His anti-ds DNA were significantly raised to 116.727 U/mL (range <25) while complement levels were normal (C_3 110 mg/dL and C_4 14 mg/dL), lupus anticoagulant (LA) was also positive but venereal disease research laboratory/rapid plasma reagin (VDRL/RPR) test for syphilis was non-reactive. ENA profile showed anti-Sm/RNP 0.56, anti-RO (SS-A) 0.39, Anti-LA (SS-B) 0.26, anti-Sm 0.40 and anti Scl-70 0.31 (quantitative cut-off <0.95=negative).

In the light of thrombocytopenia, prolonged aPTT and positive LA test, raised aCL, DVT and bilateral pulmonary emboli, he was finally diagnosed as having anti-phospholipid antibody syndrome due to undifferentiated connective tissue disease (just positive anti-ds DNA, thrombocytopenia and negative other clinical and immunological criteria for SLE). He was followed during his treatment on monthly basis and was found to have clinical improvement while continuing warfarin maintaining his INR between 2 and 3. After 6 months of treatment, his perfusion ventilation scintigraphy was performed that showed insignificant sub-segmental perfusion defects in lateral basal, anterior and posterior basal segments of right lung and normal tracer distribution in the left lung (Figure-7).

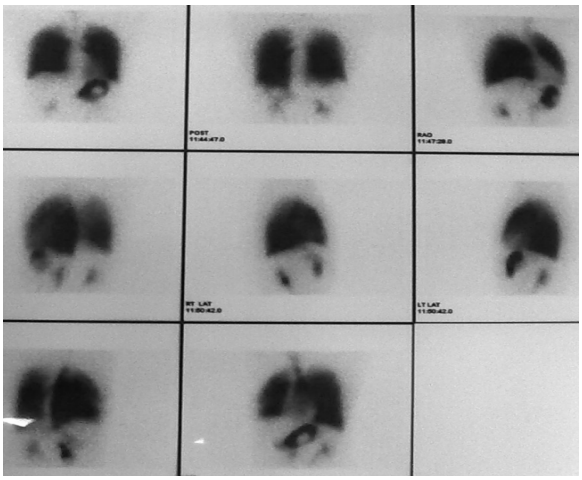

Figure-7: Perfusion ventilation scintigraphy showing insignificant sub-segmental perfusion defects in lateral basal, anterior and posterior basal segments of right lung and normal tracer distribution in the left lung

He was otherwise fully asymptomatic having normal plasma D-dimer <0.5, normal ECG, normal right leg venous doppler ultrasonography and a clear chest radiograph (Figure-8). He was counselled for this disease having future risks of arterial and venous thrombosis and was strongly advised to continue warfarin on life-long basis.

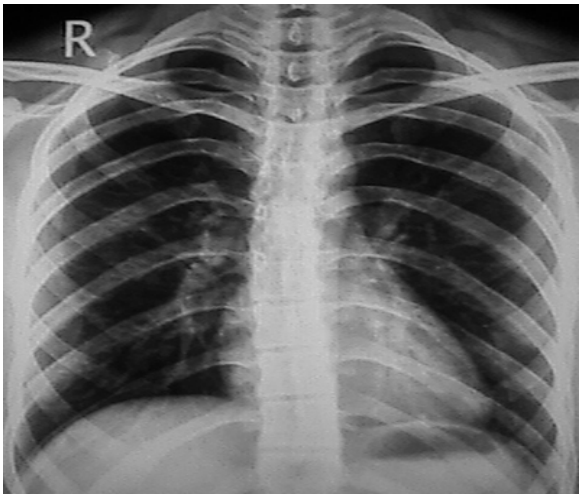

Figure-8: Follow-up radiograph showing clearing of left basilar shadowing

DISCUSSION

Inherited thrombophilia is a genetic tendency to venous and/or arterial thromboembolism.[1] The commonest causes of a primary hypercoagulable state are the factor V Leiden mutation and the prothrombin gene mutation accounting for 50–60% cases.[4] Defects in protein S, protein C, and antithrombin account for most of the remaining cases, while various dysfibrinogenemias are responsible for some of the rare causes.[1,4] These disorders are suspected when an episode of venous thrombosis occurs in an individual of younger age having no or minimal apparent trigger/risk factors for thrombosis.[5] In anti phospholipid antibody syndrome, the risk of both venous and arterial thrombosis and/or thromboembolism is increased in individuals with positive tests for LA activity including IgG and/or IgM aCL in moderate or high titre, antibodies to ß2-GP-I of IgG or IgM isotype and lupus anticoagulant.[6]

The pathogenesis of APS associated clinical features appears to result from a variety of aPL effects on coagulation pathways including pro-coagulant actions of these antibodies upon protein C, annexin V, tissue factor, platelets, serum proteases, toll-like receptors (TLR), and via fibrinolysis impairment.[7] Clinical suspicion for APS should be raised in the following scenarios: occurrence of one or more otherwise unexplained thrombotic or thromboembolic events, one or more specific adverse outcomes related to pregnancy and/or otherwise unexplained thrombocytopenia or prolongation of a test of blood coagulation (e.g., PT or aPTT).[8]

Secondary APS refers to those with SLE who also have aPL or positive tests for LA activity, which are associated with menorrhagia, prolonged clotting times, unexplained thrombosis, and stroke.[9] The diagnosis of SLE is made when at least 4 positive criteria of American College of Rheumatology (ACR) are met and patients who, despite manifesting multiple non-specific clinical or serologic abnormalities, do not meet ACR criteria for the diagnosis of a specific rheumatic disease are said to have undifferentiated connective tissue disease who may develop a definite connective tissue disorder within two to five years.[10]

The therapy for APS is largely the same regardless of whether the disorder is classified as primary APS or being secondary to SLE and the initial approach to thrombosis in APS is identical to that of many other thromboses. Heparin is overlapped simultaneously with warfarin for 4–5 days until the INR is within the therapeutic range of 2–3 for two consecutive days followed by long term use of warfarin.[11]

REFERENCES

1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
2. Reber G, Tincani A, Sanmarco M, de Moerloose P, Boffa MC. Proposals for the measurement of anti-beta2-glycoprotein I antibodies. Standardization group of the European Forum on Antiphospholipid Antibodies. J Thromb Haemost 2004;2:1860–2.
3. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003;101:1827–32.
4. Dahlback B. Advances in understanding pathogenic mechanisms of thrombophilic disorders. Blood 2008;112(1):19–27.
5. Crowther MA, Kelton JG. Congenital thrombophilic states associated with venous thrombosis: a qualitative overview and proposed classification system. Ann Intern Med 2003;138:128–34.
6. Pengo V, Ruffatti A, Legnani C, Gresele P, Barcellona D, Erba N et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost 2010;8:237–42.
7. Bu C, Gao L, Xie W, Zhang J, He Y, Cai G et al. Beta 2-glycoprotein is a cofactor for tissue plasminogen activator-mediated plasminogen activation. Arthritis Rheum 2009;60(2):559–68.
8. Bobba RS, Johnson SR, Davis AM. A review of the Sapporo and revised Sapporo criteria for the classification of antiphospholipid syndrome. Where do the revised sapporo criteria add value? J Rheumatol 2007;34:1522–7.
9. Schmugge M, Revel-Vilk S, Hiraki L, Rand ML, Blanchette VS, Silverman ED. Thrombocytopenia and thromboembolism in pediatric systemic lupus erythematosus. J Pediatr 2003;143:666–9.
10. Mosca M, Tani C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a new frontier for rheumatology. Best Pract Res Clin Rheumatol 2007;21:1011–23.
11. Saadoun D, Piette JC, Wahl D, Costedoat-Chalumeau N. Management of antiphospholipid syndrome. Rev Med Interne. 2012; 217–22.

Address for Correspondence:

Dr. Talha Mahmud, Head, Department of Pulmonology, Shaikh Zayed Hospital and Federal Postgraduate Medical Institute, Lahore, Pakistan. **Cell:** +92-301-4397549, **Fax:** +92-42-35830639

Email: drmtalha@hotmail.com