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Case report

Acute pulmonary embolism in Protein S deficiency: 2 rare case reports of young male presenting with breathlessness

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Abstract

Acute pulmonary embolism is a common, treatable, but potentially fatal condition which is currently the third most common cause of cardiovascular death. We describe 2 case reports of young active otherwise healthy male, presenting with dry irritating cough and shortness of breath of short duration .A persistent tachycardia, tachypnea, negative Troponin T test, with dilated right atrium (RA), right ventricle (RV) and elevated pulmonary artery (PA) pressure on echocardiography made us suspect pulmonary artery embolism. Computed tomography pulmonary angiography (CTPA) done urgently confirmed diagnosis of pulmonary artery thrombosis. Prompt treatment with antifibrinolytic and anticoagulant relieved them from symptoms and saved them from a mortal condition. Later on Protein S deficiency was established.

Key words: Protein S deficiency, Pulmonary embolism, Shortness of breath, Young male

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Pulmonary embolism (PE) is defined as a blockade of a pulmonary artery or one of its vessels by a substance that has moved from elsewhere in the body through the blood stream (embolism). Most commonly it is a consequence of thrombus formation in deep veins of the lower extremity. Approximately 51% of deep venous thrombi will embolize to the pulmonary vessels and one of the frequent cause of death in India and worldwide[1]. A small proportion of cases are due to the embolization of fat, amniotic fluid, air, tumor (especially choriocarcinoma), septic emboli (from endocarditis).

Pulmonary embolism occurs in around 1% of all patients admitted to hospital and accounts for around 5% of in-hospital deaths. It is a common mode of death in patients with cancer and stroke and remains the most common cause of death in pregnancy[2]. An autopsy series in a tertiary centre with 1000 patients revealed PE was present in 15.9% of the cases and also reported that 79.8% were below the age of 50 years[3].

Signs of massive pulmonary embolism are tachycardia, hypotension, raised JVP, right ventricular gallop rhythm, split P2, severe cyanosis and decreased urinary output[1]. Acute small/medium pulmonary embolism presents as pleuritic chest pain, restricted breathing and hemoptysis. Chronic pulmonary embolism shows signs of right heart failure.

Thrombotic event in a healthy under the age 40 years patient is uncommon in the absence of a provoking factor. People with hereditary Protein S deficiency have 2 to 11 fold increased risk for de-

veloping deep vein thrombosis (DVT) or PE in comparison with those without a deficiency[4,5].

Case report 1

A 38-year-old young, active male admitted with complaints of persistent irritating dry cough for 4 days and one episode of hemoptysis. He had no fever, chest pain or recent trauma. He was non smoker, non diabetic, normotensive. He did not have any family history of pulmonary tuberculosis. In his family his elder brother had coronary heart disease and undergone Percutaneous transluminal coronary angioplasty (PTCA).

On arrival to the emergency department he had a blood pressure (BP) of 110/78 mm Hg, heart rate (HR) of 130 beats per minute and respiratory rate (RR) of 30 breaths per minute and oxygen saturation (SpO_2) of 92% at room air. Laboratory findings: complete blood count, coagulation profile, liver function test, electrolytes, urea, creatinine, blood glucose, lipid profile were within normal limits. Chest X ray was normal. Troponin T was negative. Initial electrocardiogram (ECG) showed sinus tachycardia at a rate of 130 beats per minute. His arterial blood gas had pH of 7.5, pCO_2 of 24 mm Hg and pO_2 of 102 mm Hg with 3 liters of oxygen in high flow mask. Patient remained to be symptomatic with persistent tachycardia and tachypnea. Two dimensional echocardiogram (2D ECHO) revealed no regional wall motion abnormality, good left ventricle (LV) function, mild diastolic dysfunction, dilated RA, RV, mild pulmonary arterial hypertension (PAH), tricuspid regurgitation (TR) gradient 39 mm Hg, possibility of PE was thought. The D Dimer was positive. Computed tomography pulmonary angiography (CTPA) done was suggestive of thrombosis in right and left pulmonary artery with patchy pulmonary infarcts (Fig 1). Venous doppler of lower limb showed focal thrombosis in left popliteal vein. He was thrombolyzed with alteplase 10 mg bolus followed by 90 mg over 2 hours followed by unfractionated heparin infusion for 2 days and low molecular weight heparin (LMWH) - enoxaparin 60 mg subcutaneously twice daily for 3 days. APTT was maintained between 60- 90 seconds, he was started on oral anticoagulant with strict monitoring of international normalized ratio (INR). There was improvement in his oxygen saturation and heart rate during and after thrombolysis. His repeat angiography showed partial resolution of thrombus. 2D ECHO was normal. He was discharged on day five with oral anticoagulant. He was followed up in outpatient department after 15 days with PT and INR report. He was asymptomatic with HR of 60/sec and RR of 20/min. Further investigation (after 3 weeks of stoppage of oral anticoagulant) showed Antithrombin III of 102 %, homocysteine = 6.53µmol/l, antinuclear antibody was negative, Protein C was 132% but his Protein S (total protein) level was low at 26% (Normal= 77- 143%).

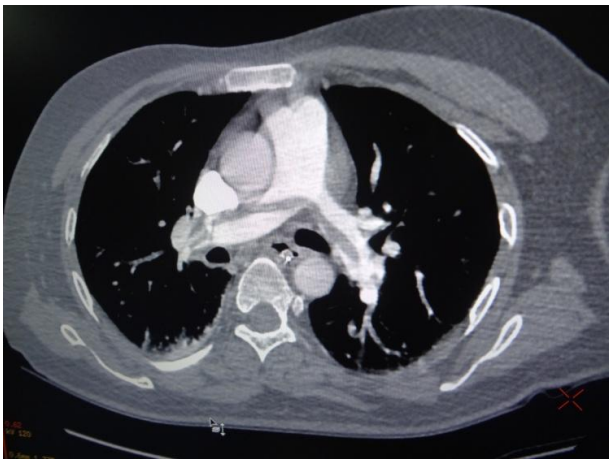

Fig 1. CT showing thrombus in both pulmonary artery extending from bifurcation

Case report 2

A 29-year-old active male presented with shortness of breath and palpitation for 3 days. No personal history of diabetes mellitus, hypertension or coronary artery disease. He had no fever, cough, hemoptysis or any recent trauma. No history to suggest cardiovascular risk factor.

Physical examination revealed a well developed and well nourished man with BP of 90/60 mm Hg, HR - 120/min, RR - 18/min and SpO_2 - 97% at room air. Routine investigation: Hb-16.3 gm/dl, TLC-11,300/cu.mm with (Nutrophils-70%, Lymphocytes-28%), INR-1.3, Sodium-136mEq/liter, Potassium - 4.4 mEq/liter, liver function and renal function test were normal. Chest X ray was normal. Troponin T was negative. ECG showed sinus tachycardia and 2DECHO showed dilated RA, RV and moderate TR with severe PAH (75 mm Hg). Contrast enchanced computed tomography (CECT) thorax showed thrombus in main pulmonary artery (MPA), hepatic vein and inferior vena cava (IVC) extending up to renal vein (Fig 2 and 3). USG abdomen and pelvis showed thrombus in hepatic veins, IVC extending up to right renal vein. Venous doppler of lower limb was normal. He was thrombolyzed with Tenectiplase 40 mg over 2 minutes followed by unfractionated heparin for 48 hours then with LMWH enoxaparin 60 mg subcutaneously twice daily for 5 days. INR was maintained between 2 to 3. Warfarin was started on day 2. Repeat CECT thorax was done on third day showed small thrombus in MPA. ECHO screening

revealed decrease in PA pressure (37 mm Hg). Patient became stable and was discharged on day 5. Followed up in OPD and was asymptomatic. Further investigation (after stoppage of oral anticoagulant for 3 weeks) showed Antithrombin III - 98 %, homocysteine – 9.24 µmol/l , antinuclear antibody was negative, Protein C - 98%, but he had Protein S (total protein) deficiency with value of 30% (Normal= 77-143%).

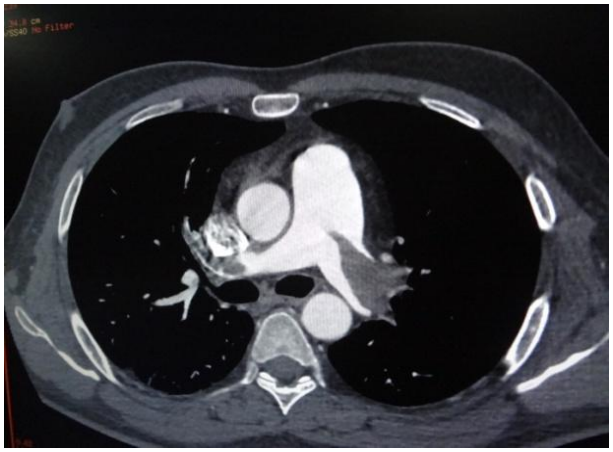

Fig 2. Axial section showing thrombus in distal segment after bifurcation

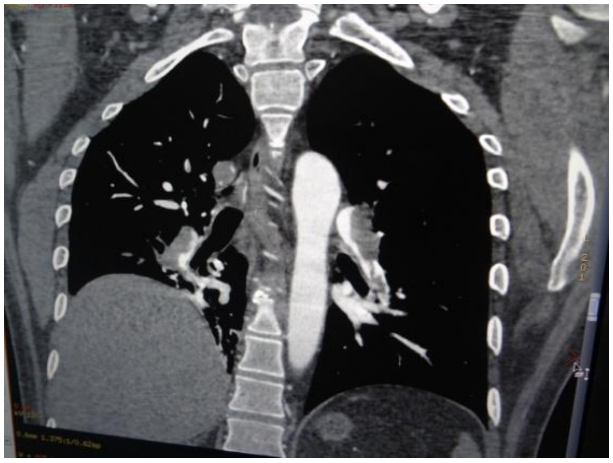

Fig 3. Coronal section showing thrombus in distal segment after bifurcation

Discussion

Acute pulmonary embolism is a common, treatable, but potentially fatal condition which is currently the third most common cause of cardiovascular death. The varied clinical presentation, non specific nature of the physical signs and the lack of sensitive and specific diagnostic test can make the diagnosis of pulmonary embolism difficult.

The clinical features of pulmonary embolism depend largely upon the size of embolism and comorbidity. Recognized risk factors i.e. recent surgery, trauma, immobilization, pregnancy, pelvic malignancy etc are present in 80% to 90% of patients.

Diagnosis of pulmonary embolism relies upon cautious utilization of the available tests. Simple tests such as chest radiograph, ECG, D-dimers, arterial blood gas help in enhancing the clinical probabilities.

Though chest radiograph is the first investigation in patients with suspected pulmonary embolism, unfortunately these radiographic features are usually non specific. Hampton's hump, the peripheral wedge shaped consolidation with its base against the pleural surface, raised ipsilateral hemidiaphragm, small pleural effusion, Westermark sign (oligemia of lung beyond the occluded vessel), Fleischner sign (prominent central pulmonary artery), are now well known signs of pulmonary infarction. Normal chest radiograph have been reported in 12-30% of patients. The most important role of the chest x-ray is to exclude key differential diagnosis such as heart failure, pneumonia, pneumothorax or tumor.

The ECG is also useful in excluding other important differential diagnosis such as acute myocardial infarction and pericarditis, right ventricular dysfunction. Sinus tachycardia and anterior T wave changes are common findings in pulmonary embolism.

Ventilation-perfusion scanning has been the most popular method in the diagnosis of pulmonary embolism, when the chest x-ray is normal and there is no significant cardio-pulmonary disease, however it is only available in tertiary care centers.

Perfusion scintillography demonstrates the distribution of lung perfusion using a technetium-labeled albumin tracer in the form of small particles. The particles are of such a size (15-70µm) that they will be trapped in the pre-capillary arterioles of the lung in their first passage after intravenous injection.

Ventilation scintillography demonstrates the distribution of lung ventilation using an inhaled tracer. Krypton-81m (81mKr) is a radioactive gas with gamma emissions used for scanning because of its short half-life. Distribution of 81mKr in the lung is proportional to the regional ventilation, does not allow time for equilibration, and only a small proportion of the inhaled tracer is expired. 81mKr is also insoluble in blood so there is no vascular contamination of the ventilation images. Because its gamma emission energy is distinct from that of technetium - 99m, perfusion and ventilation can be measured sequentially or simultaneously if a dual energy acquisition system is used.

Interpretation based on identifying areas of ventilation without perfusion (mismatched defects) and is classified as high probability, intermediate probability, low probability and normal scan as follows:

- High probability: 2 or more large (>75% of a segment) mismatched perfusion defects with no corresponding CXR abnormalities; or 1 large and ≥ 2 moderate sized (25-75% of a segment) mismatched perfusion defects with no corresponding CXR abnormalities; or 4 or more moderate sized mismatches with no corresponding CXR
- Low probability: Multiple matched VQ defects, regardless of size, with normal CXR; or Matched VQ defect plus CXR lesion in same area i.e. upper or mid zone; or Perfusion defects surrounded by normally perfused lung; or Matched VQ defect with large effusion; or Any perfusion defect with a substantially larger CXR abnormality; or Non segmental defect i.e. cardiomegaly, aortic impression, enlarged hila
- Intermediate probability: A mixture of matched or unmatched defects; or Single moderate sized mismatch with normal CXR; or Matched VQ defect plus CXR lesion in lower lung zone; or Matched VQ defect with small effusion; or 1 moderate to <2 large mismatches with no corresponding CXR abnormalities.

The prospective investigation of pulmonary embolism diagnosis (PIOPED) study showed that a high VQ probability has a high positive predictive value, with the likelihood of having pulmonary embolism to be as high as 87%, though a few patients will have false positive results. The predictive value of VQ scan can be increased or decreased further, if combined with clinical probability and clinical scoring systems.

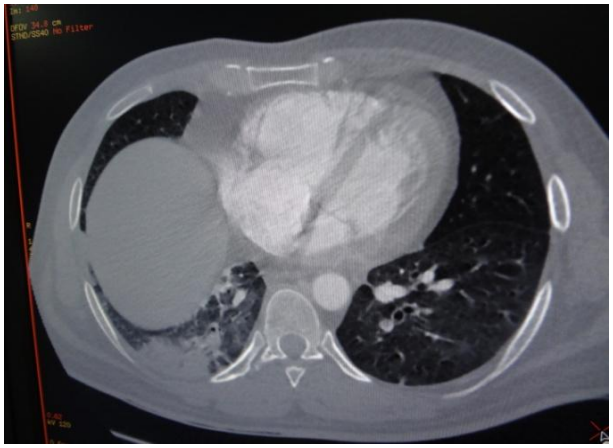

Fig 4. Axial section showing wedge shaped infarct in right lung peripherally

Computed tomography pulmonary artery (CTPA) is investigation of choice for diagnosis of pulmonary embolism[6] and has largely replaced conventional angiography. CTPA may not only exclude pulmonary embolism but highlight an alternative diagnosis. In patients clinically detected deep vein thrombosis, a leg venous doppler can be used as a screening test to confirm venous thromboembolism[7].

We suggest doing 2DECHO which is readily available and it is a surrogate maker of pulmonary embolism in the form of dilated RA and RV and raised TR gradient. Once pulmonary embolism is suspected CTPA and thrombophillia screening can be done to confirm the diagnosis and its predisposing factor. Literature searching for pulmonary embolism in young active person has resulted in causes like medical or surgical conditions, calf pain secondary to DVT, OCP intake, high altitude exposures, Paget-Schroetter syndrome (effort thrombosis) and thrombophillia (Protein C and S deficiency)[8,9].

Protein S is a vitamin–K dependent plasma glycoprotein, synthesized in liver, endothelial cells and megakaryocytes. The half–life of protein S is 42 hours. Protein S acts as non-enzymatic cofactor for protein C in the inactivation of Factor Va and VIIIa. Decreased levels or impaired function of protein S leads to decreased degradation of factor Va and factor VIIIA and increased susceptibility to venous thrombosis. Protein S circulates in human plasma in two forms. Approximately 60% is bound to complement component C4b β-chain while the remaining 40% is free. Only free protein S has activated protein C cofactor activity. Around 1-5% of cases of protein S deficiency are associated venous thrombosis, < 0.5% with arterial thrombosis[10-12]. Protein S deficiency is now known to be related to genetic defect.

Thrombophillia is associated with venous thromboembolism which comprises of pulmonary embolism and deep vein thrombosis, however thrombophillia per se is not usually associated with pulmonary embolism. It is rare that in our 2 cases they had thrombophillia but without any precipitating factor to cause PE.

Conclusion

PE encompasses a spectrum like cardiovascular collapse to small emboli with few or no hemodynamic consequences. There is always difficulty in diagnosis PE because of lack of a conclusive simple, low cost, low-risk tests[13,14]. Any young person with unexplained tachycardia and tachypnea

should be evaluated intensively, at least with 2DECHO to rule out pulmonary embolism. Pulmonary angiography, remains the gold standard for diagnosis, but has been superseded by CTPA. CTPA not only exclude PE, but also highlights alternative diagnosis. High-probability ventilation–perfusion scan indicates a 90% probability for PE.

Therapeutic approach like heparin and long term warfarin are generally recommended. Low dose and long term infusion should be suggested to avoid complication like fragmentation of thrombus.

Thrombophillia work up should be done in every patient of venous thromboembolism as protein C and S deficiencies are not so rare diseases in our clinical practice.

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Conflict of interest: None

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