CASE REPORT

A Case of Multiple Episodes of Venous Thrombosis Causing Deep Vein Thrombosis, Cerebral Venous Sinus Thrombosis and Pulmonary Embolism in a Patient With Hyperhomocysteinemia

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Abstract:

Venous thromboembolism, causing Pulmonary Embolism (PE), is one of the major cardiovascular causes of death. Hyperhomocysteinemia can increase the risk of pulmonary embolism. We are reporting a 30 year sedentary male presented with acute onset shortness of breath since the previous morning with chest discomfort, palpitations and perspiration with past history of superior sagittal sinus thrombosis causing non-haemorrhagic venous infarct and deep vein thrombosis of right lower limb. His serum homocysteine level was 42micromol/l (high) and D-Dimer with value of 3.2 (positive). The electrocardiogram showed S1Q3T3 pattern, low voltage pattern, poor progression of 'R' wave, resting tachycardia, heart rate of 160/min with 'P' pulmonale RV strain. Chest radiograph was showing Hamptons hump and Wistermark striae. The echocardiography RV dysfunction with RV apical sparing (positive Macuon sign) with PAP: 45 mmHg with LV diastolic dysfunction and LVAE of 56%. Considering clinical, laboratory parameters and imaging profile diagnosis of acute pulmonary embolism was considered in background of deep vein thrombosis (DVT) and hyperhomocysteinemia with past history of cortical venous sinus thrombosis. Patient was treated with fibrinolytic agent (streptokinase) and other standard supportive line of treatment and was discharged on oral anticoagulant, folate, vitamin B6 and vitamin B12 supplementations.

Keywords: Pulmonary embolism, Hyperhomocysteinemia, Cortical Venous Sinus Thrombosis, deep vein thrombosis

Introduction:

Venous thromboembolism (VTE), which encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE), is one of the three major cardiovascular causes of death, along with myocardial infarction and stroke. [1] Approximately three of four symptomatic VTE events occur in the community and the remaining is hospital acquired. [1] Prothrombotic states or thrombophilia contributes to the risk of venous thrombosis. The two most common autosomal dominant genetic mutations are factor V Leiden, which causes resistance to activated protein C (which inactivates clotting factors V and VIII), and the prothrombin gene mutation, which increases the plasma prothrombin concentration. Antithrombin, protein C, and protein S are naturally occurring coagulation inhibitors. Deficiencies of these inhibitors are associated

with VTE but are rare. Hyperhomocysteinemia can increase the risk of VTE, but lowering the homocysteine level with folate, vitamin B6, or vitamin B12 does not reduce the incidence of VTE. Antiphospholipid antibody syndrome is the most common acquired cause of thrombophilia and is associated with venous or arterial thrombosis [1]. Other common predisposing factors include cancer, systemic arterial hypertension, chronic obstructive pulmonary disease, long-haul air travel, air pollution, obesity, cigarette smoking, eating large amounts of red meat, oral contraceptives, pregnancy, postmenopausal hormone replacement, surgery, and trauma. About one-half of patients with pelvic vein thrombosis or proximal leg DVT develop PE, which is often asymptomatic. Progressive right heart failure is the usual cause of death from PE. [1, 2, 3]

Case Report:

A 30 year sedentary male presented with acute onset shortness of breath since previous morning with chest discomfort, palpitations and perspiration. On examination patient was tachypnic with a respiratory rate of approximately 50/min, heart rate was 160/min, BP was 80/60 mm Hg, SpO_2 was 81%, RV gallop and hypotension. He had swelling of right lower limb from groin to ankle for previous two years, which was painful but all his peripheral pulses were well-felt. Patient's chest examination revealed bilaterally equal breath sounds with no adventitious sounds. There was past history of left sided hemiparesis secondary to superior sagittal sinus thrombosis with non-haemorrhagic venous infarct in right frontal lobe about 12 years ago [Fig.1 (D)]. He had undergone trans-catheter thrombolysis of superior sagittal sinus with urokinase, which showed successful thrombolysis of superior sagittal sinus with good flow but anterograde flow was established, gradually patient recovered from weakness and was discharged on long term oral anticoagulants. Two years earlier he was diagnosed to have deep vein thrombosis of right lower limb with acute pulmonary thrombo-embolism which was managed conservatively on low molecular weight heparin and oral anticoagulants. He recovered from the same uneventfully but stopped taking treatment at home. Differential diagnosis of PTE was ruled out by appropriate investigations, for various disease states including pneumonia, asthma, chronic obstructive pulmonary disease, congestive heart failure, pericarditis, pleurisy: viral syndrome, costochondritis, musculoskeletal discomfort, rib fracture, pneumothorax and Acute Coronary Syndrome (ACS). Patient in this case report had score favoring acute pulmonary embolism [tenderness along distribution of deep veins: 1, entire leg swelling: 1, unilateral calf swelling >3 cm:1, pitting edema: 1 with total score : 4; (i.e high-likelihood score is 3 or greater) positive signs and symptoms of DVT:3, alternative diagnosis less likely than PE:3, heart rate >100/min:1.5 with total score of 7.5 (i.e high clinical likelihood of pulmonary embolism) in clinical scenario, in the background of hyperhomocysteinemia**.** Nonimaging tests were utilized in combination with clinical likelihood assessment of PE (Table 1).

Table 1: Point Score Methods are Useful for Estimating the Clinical Likelihood of DVT and PE

Sr. No.	Clinical Variable	Score
1	Active cancer	1
2	Paralysis, paresis, or recent cast	1
3	Bedridden for >3 days; major surgery <12 weeks	1
4	Tenderness along distribution of deep veins	1
5	Entire leg swelling	1
6	Unilateral calf swelling >3 cm	1
7	Pitting edema	1
8	Collateral superficial non-varicose veins	1
9	Alternative diagnosis at least as likely as DVT	-2
	Total Score	4
	High Clinical Likelihood of PE if Point Score Exceeds 4	
	Clinical Variable	**Score**
1	Signs and symptoms of DVT	3.0
2	Alternative diagnosis less likely than PE	3.0
3	Heart rate >100/min	1.5
4	Immobilization >3 days; surgery within 4 weeks	1.5
5	Prior PE or DVT	1.5
6	Hemoptysis	1.0
7	Cancer	1.0
	Total Score	7.5

Low Clinical Likelihood of DVT if Point Score is Zero or Less, Moderate-Likelihood Score Is 1 to 2, High-Likelihood Score is 3 or Greater [1]

Investigations:

Hb 12.2 gm%, total leukocyte count 14200 [DLC P-75%, L- 22% E-3%], prothrombin time (PT) 15 sec with INR 1.3, random blood glucose level: 96mg%, blood urea: 33mg%, serum creatinine: 1.1mg%, serum potassium: 4.2meq/l, serum sodium: 138meq/l. D-Dimer: 3.2 (positive) was reported. His previous coagulation profile showed, protein-C levels of 52%, Protein-S: 78%, lipoprotein-A was 50 mg% [normal value: 0-30mg/dl], serum homocysteine was 42micromol/l (high) [normal value: 5.9-16 micromol], CRP 9.8mg% [normal value: 0-5]. The quantitative plasma d-dimer Enzyme-Linked Immunosorbent Assay (ELISA) rises in the presence of DVT or PE because of the breakdown of fibrin by plasmin. The sensitivity of the d-dimer is >80% for DVT (including isolated calf DVT) and >95% for PE. The d-dimer is less sensitive for DVT than for PE because the DVT thrombus size is smaller. The d-dimer is a useful "rule out" test. More than 95% of patients with a normal (<500 ng/mL) d-dimer do not have PE. The d-dimer assay is not specific. **Chest radiograph** shows right lower zone, mid zone haziness with ***Hamptons hump*** (peripheral wedged-shaped density above the diaphragm), ***Wistermark striae*** (focal oligemia) ***Palla's sign*** (enlarged right descending pulmonary artery) favouring the diagnosis of acute pulmonary embolism. [Fig. 1 (A)] **Electrocardiogram** showed S1Q3T3 pattern, low voltage pattern, poor progression of 'R' wave, rest shows tachycardia, heart rate of 160/min with 'P' pulmonale RV strain ['T' wave inversion in V2-V5 most common abnormality] suggestive of acute pulmonary embolism. [Fig.1 (B)] **Echocardiography** *RV dysfunction* with *RV apical sparing* (positive ***Macuon sign***) moderate tricuspid incompetence with moderate pulmonary artery hypertension (PAP: 45 mmHg) with IVS flattening with dilated RA/RV with LVEF of 45%. [Fig.1 (C)] **Venous Doppler study:** Venous flow dynamics examined with Doppler imaging. Normally, manual calf compression causes augmentation of the Doppler flow pattern. Loss of normal respiratory variation is caused by an obstructing thrombus was seen in of right lower limb deep veins suggestive of DVT. [Fig.1 (E)] The DIC profile was negative. Patient was treated in emergency department with fibrinolytic agent (streptokinase) in the dose of 24 lakh IU over a period of 24 hours along with oxygen supplementation and non-invasive ventilation after 24 hours patient had drastic relief in his breathlessness and chest discomfort. His blood pressure came back to normal with heart rate of 106/min. Then he was started with enoxaparin (LMWH) 60 mg 12 hourly for 5 days and metoprolol 25 mg, furosemide (as and when required), then he was put on warfarin (oral anticoagulant) 5mg daily. On 5th day patient had mild chest discomfort with room air spo2 of 93%. Patient was discharged on 10th day on oral anticoagulants. He is doing well with regular follow-up for last one year with PT-INR around 2 with no cardio-respiratory and neurological symptoms with resolving right lower limb DVT as well.

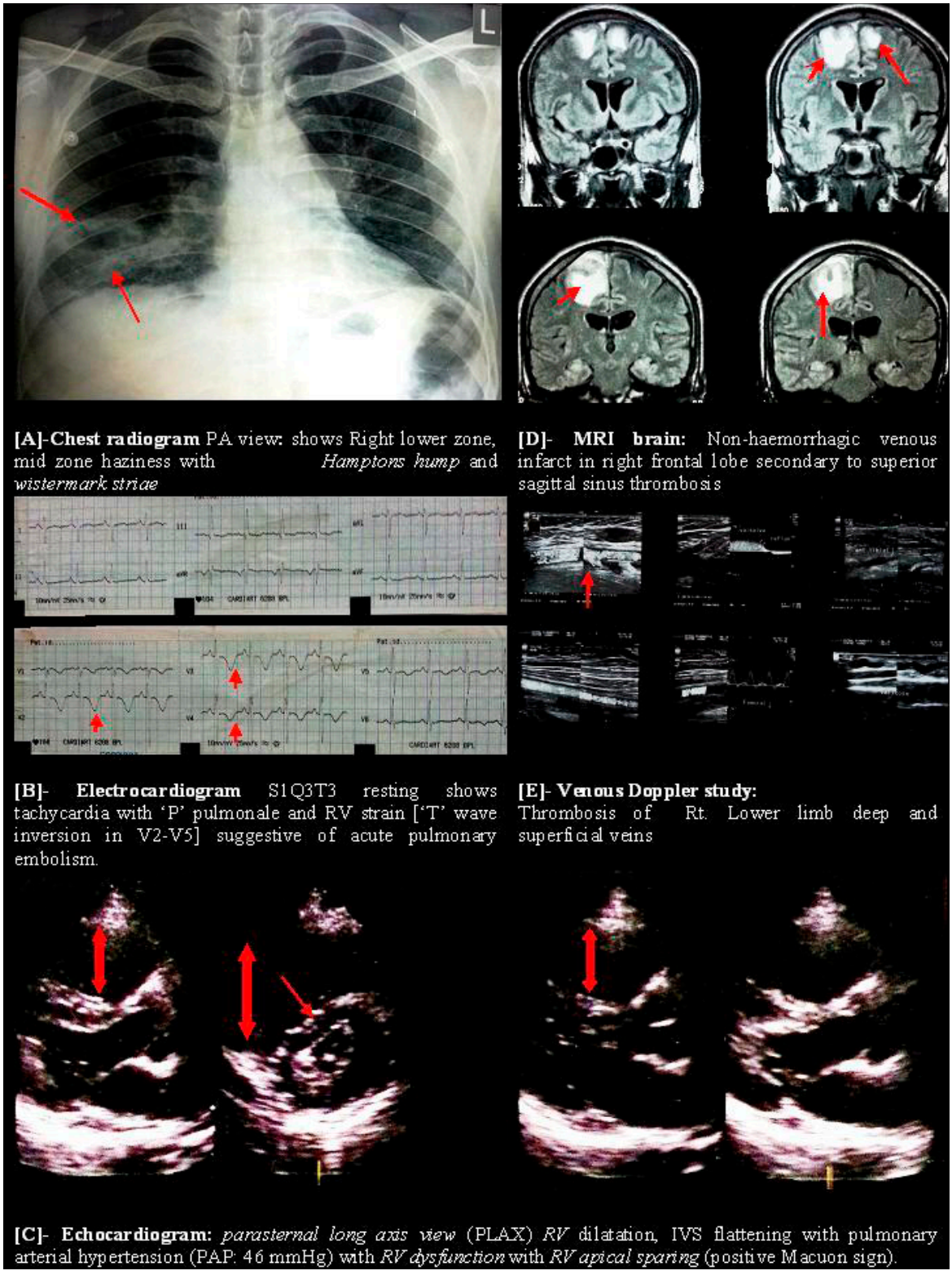

Fig. 1: [A] Chest radiogram, [B] Electrocardiogram (S1Q3T3), [C] Echocardiogram, [D] MRI brain (CVST) with venous infarct and [E] Right lower limb venous Doppler study (DVT).

Discussion:

The patients who have PE, the most common symptom in the history is unexplained breathlessness. The most common gas exchange abnormalities are hypoxemia (decreased arterial PO_2) and an increased alveolar-arterial O_2 tension gradient, which represents the inefficiency of O_2 transfer across the lungs. Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries. The increased pulmonary vascular resistance, impaired gas exchange, alveolar hyperventilation, increased airway resistance and decreased pulmonary compliance are the pathophysiological consequences of acute PTE. VTE mimics other illnesses, and PE is known as "the Great Masquerader" making diagnosis difficult. This scenario is a clinical clue to the possible coexistence of PE. For patients who have DVT, the most common history is a cramp in the lower calf that persists for several days and becomes more uncomfortable as time progresses. Dyspnea is the most common symptom of PE, and tachypnea is the most common sign. Dyspnea, syncope, hypotension, or cyanosis indicates a massive PE, whereas pleuritic pain, cough, or hemoptysis often suggests a small embolism situated distally near the pleura. They may have dyspnea only with moderate exertion. They often lack "classic" signs such as tachycardia, low-grade fever, neck vein distention, and an accentuated pulmonic component of the second heart sound. Patients with *massive PE* present with systemic arterial hypotension and usually have anatomically widespread thromboembolism. As pulmonary vascular resistance increases, RV wall tension rises and causes further RV dilation and dysfunction. RV contraction continues even after the left ventricle (LV) starts relaxing at end-systole. Consequently, the interventricular septum bulges into and compresses an intrinsically normal left ventricle. Diastolic LV impairment develops, attributable to septal displacement, and results in reduced LV distensibility and impaired LV filling during diastole. Increased RV wall tension also compresses the right coronary artery, diminishes subendocardial perfusion, limits myocardial oxygen supply, and may precipitate myocardial ischemia and RV infarction. Underfilling of the LV may lead to a fall in left-ventricular cardiac output and systemic arterial pressure, thereby provoking myocardial ischemia due to compromised coronary artery perfusion. Eventually, circulatory collapse and death may ensue. Those with moderate to large PE have RV hypokinesis on echocardiography. Patients with small to moderate PE have both normal right heart functions with an excellent prognosis with adequate anticoagulation. Rapid and accurate risk stratification is critical in determining the optimal treatment strategy. The presence of hemodynamic instability, RV dysfunction, RV enlargement, or elevation of the troponin level due to RV microinfarction can identify high-risk patients. RV hypokinesis on echocardiography,

RV enlargement on chest CT, and troponin elevation predict an increased mortality rate from PE. Primary therapy should be reserved for patients at high risk of an adverse clinical outcome. When RV function remains normal in a hemodynamically stable patient, a good clinical outcome is highly likely with anticoagulation alone [1]. Cho *et al* [2] have reported that, PTE due to severe hyperhomocysteinemia and was successfully managed with antithrombotics, folate, and vitamin B_6. There is clear evidence that the very high VTE risk of patients with severe hyperhomocysteinemia is due to cystathione β-synthase deficiency, which get dramatically reduced with vitamin supplementation, thereby lowering the very high plasma Hcy levels. Shen et al reported a case of familial hyperhomocysteinemia-related cerebral venous sinus thrombosis and pulmonary embolism in a 21-year-old man. Elevated plasma homocysteine levels are associated with an increased risk of deep vein thrombosis. The MRI brain showed cerebral venous thrombosis in right transverse and sigmoid venous sinus. The only risk factor was an elevated serum homocysteine level (46.23 μM/L) which was most likely related to familial hyperhomocysteinemia [3]. These findings are comparable with our patient in which presentation was acute pulmonary embolism in background of DVT with past history of CVST with serum homocysteine level of 42micromol/l (high). Narayan et al reported hyperhomocysteinemia in 78 (18.2%) patients with CVST with overall good prognosis. Similarly our patient recovered from CVST with no obvious residual neuro-deficit. Aaron *et al* [4] have stated that Methylene Tetrahydro-Folate Reductase (MTHFR) heterozygosity (19.5%) and hyperhomocysteinemia (34%) were the commonest genetic markers adding Mortality rate by odds of 1.3 for every additional prothrombotic marker. Shariati *et. al* [5] have reported the first case of septo-rhinoplasty with consecutive thrombotic events in different parts of the venous system. Similarly, our patient had past history of DVT with CVST and presented with acute pulmonary embolism, which was successfully treated with thrombolytic agent and long term anticoagulation with regular monitoring for PT-INR and vitamin B12 and folic acid supplementation.

Conclusion:

Our patient had pulmonary embolism with history of deep venous thrombosis, as well as stroke (CVST). His blood circulation was always in a hypercoagulable state as evidenced by hyperhomocysteinemia and positive D-dimer test. He was successfully treated with fibrinolytic agent, anticoagulants, vitamin B12, folic acid supplementations and other supportive line of treatment. The multiple episodes of venous catastrophic events in young age should be thoroughly investigated for hypercoagulable states like hyperhomocysteinemia and other. Although it is uncertain whether treatment with vitamins in patients with mild to moderate hyperhomocysteinemia decreases the risk for PTE,

can be successfully managed with inexpensive and safe vitamin supplementation. No side effects have been reported in trials in which folic acid with or without other vitamins were used for various indications. To conclude we should keep in mind that a patient with a PTE due to severe hyperhomocysteinemia along with other venous thrombosis as they are life threatening medical condition which require emergency medical treatment and financial burden as well.

Acknowledgement:

I would like to thank the residents and hospital staff for their sincere care and support in managing this patient.

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