CASE REPORT

A Case of Vitamin B12 Deficiency and Hyperhomocysteinemia-induced Sub-massive Pulmonary Thromboembolism

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Abstract

The relation between pulmonary embolism and hypercoagulable state has been a debate in medical literature. There have been articles describing role of hyperhomocysteinemia in vascular injuries leading to prothrombotic state. We herein present a case of unprovoked sub-massive pulmonary thromboembolism secondary to hyperhomocysteinemia due to hypovitaminosis B12. The patient was investigated thoroughly and was managed with proper anticoagulants.

Keywords: Anticoagulant, Case report, Hyperhomocysteinemia, Pulmonary embolism, Thrombosis, Vitamin B12.

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Introduction

In a study from India, the incidence of pulmonary embolism was 2%.[1] Increase in the level of homocysteine by 5 µmol/L was associated with 60% higher chance of thromboembolism.[2] Hyperhomocysteinemia was associated in 95.3% of the cases with vit B12 deficiency.[2] Such a case of pulmonary embolism associated with hyperhomocysteinemia was evaluated and treated in our institution.

Case Presentation

A 55-year-old male presented with complaint of shortness of breath NYHA class 2 for 12 days and cough for 2 weeks with one episode of hemoptysis without any fever. There was no history of any chest pain. There was no pallor, cyanosis, clubbing, or icterus. There was mild edema. Blood pressure was 140/84 and 99 bpm. Jugular venous pulsation was not elevated. On examination, bilateral chest was clear and normal vesicular breath sound was heard.

The patient was diabetic, hypertensive, and hypothyroid. The patient had history of COVID-19 4 years back. The patient was previously evaluated with CT angiogram of coronary vessels for chest pain 4 years back which revealed normal coronaries with calcium score 3.5.

Chest X-ray PA view revealed subtle inhomogeneous opacity in left mid-zone and an enlarged right pulmonary artery (Fig. 1). Hemoglobin was 12.8 g/dL [Normal 13–17 gm/dL], Total leukocyte count 10,900/cmm [Normal 4,000-11,000/cmm], C-reactive protein (CRP) was raised to 49.55 (normal range), serum creatinine was 1.01 [Range], Fasting blood glucose was elevated to 144 [Range], and lipid profile was also deranged-cholesterol-213, triglyceride-113, HDL-25, LDL-175, VLDL-13. Prothrombin time was 14.4 (control 11.0) and INR was 1.34. ECG showed sinus rhythm. Echo showed the following:

- Dilated right atrium and right ventricle with reduced free wall motion (TAPSE 17 mm) with preserved apical motion (McConnell's sign).
- Severe tricuspid regurgitation (peak pressure gradient 64 mm Hg).
- Severe pulmonary arterial hypertension (PAH) (estimated PASP 70 mm Hg).
- Mild LA enlargement, concentric left ventricular hypertrophy with good LV systolic function (LVEF 60%).

Valves showed normal morphology with no vegetation.

Serum troponin was mildly raised to 10.7 (normal <6 ng/dL). This raised the suspicion of pulmonary thromboembolism. Further evaluation revealed that NTproBNP was 222 pg/mL (normal <125 pg/mL), D-dimer was 1170 ng/mL (normal <250 ng/mL). Computed tomography pulmonary angiogram was performed and it revealed:

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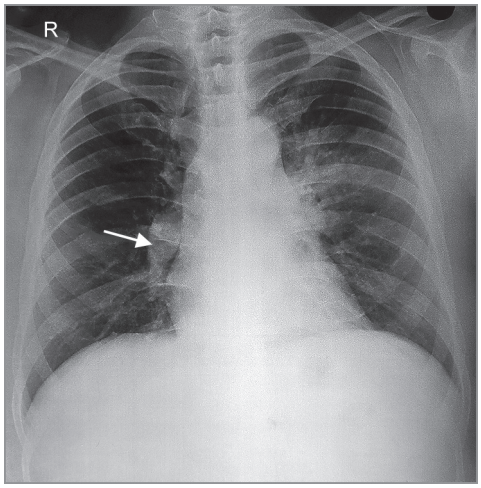

Fig. 1: Chest X-ray PA view shows enlarged right pulmonary vasculature (arrow)

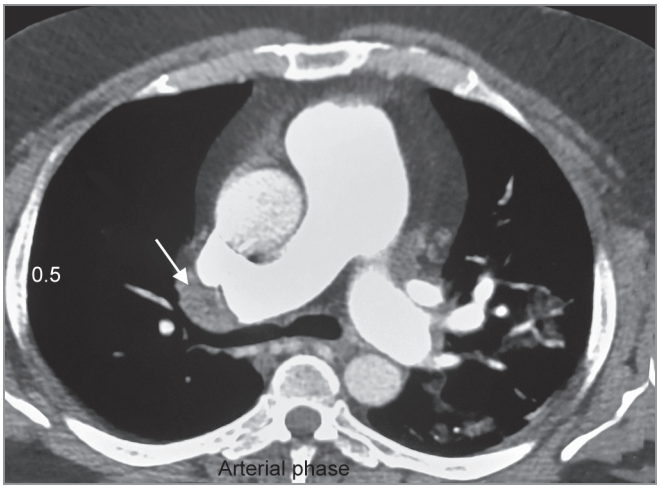

Fig. 2: CT pulmonary angiography showing large embolus in right pulmonary artery (arrow)

- Large embolus in right pulmonary artery with small emboli noted in lower lobar branch to right pulmonary artery (Fig. 2).
- Small emboli noted in upper and lower lobar branches of left pulmonary artery.
- Ischemic pulmonary hemorrhage in left upper lobe and superior basal segment of left lower lobe (Fig. 3).
- Right lung field was clear.

So, the diagnosis of pulmonary thromboembolism was confirmed. The patient was started on subcutaneous Enoxaparin 80 mg twice daily.

To search for etiology, bilateral lower limb arterial and venous Doppler were done to rule out the presence of any deep venous thrombosis. Evaluation was done before starting enoxaparin to check for any hypercoagulable state (Table 1).

As the patient had severe hyperhomocystemia, vitamin B12 and folate level were assessed. Vitamin B12 level was 138 (normal range 191–946) and folate level was 4.91 (normal range 4.6–19.3). The patient was started on vitamin B12 supplementation along with anticoagulation and vitals monitored strictly.

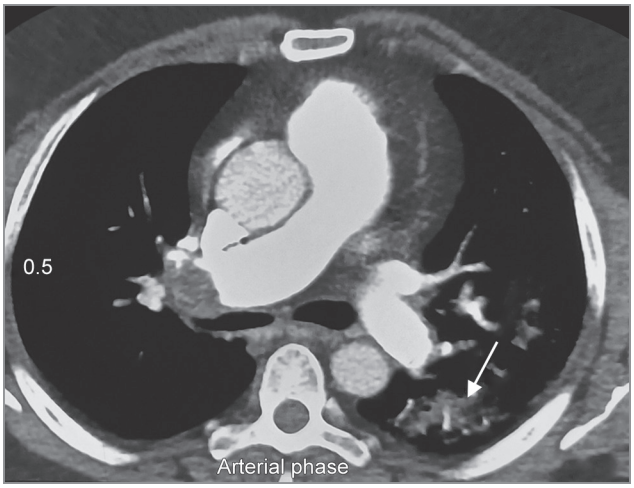

Fig. 3: Pulmonary angiography showing ischemic pulmonary hemorrhage in left upper lobe (arrow)

Table1: Summary of tests done for evaluation of hypercoagulable state

Parameters	*Obtained value*	*Normal reference range*
Factor V mutation detection Exon 10 c.1691G>A(p.R506Q)	Not detected	Not detected
Plasma protein C activity	83	67–195
Plasma free protein S activity	127	70–148
Plasma antithrombin activity	102	70–122
Plasma PTT (test)	33.5	29.58–36.62
PTT control	31.4	31.2–34.8
PTT (test + control, 1:1)	33.6	
Plasma DRVV screen test	47.50	32.82–48.90
Plasma DRVV confirm	43.30	32.83–48.90
Plasma DRVV screen	1.1	0.82–1.22
Lupus anticoagulant	Absent	Normal
Plasma homocysteine level	>100	Without folate supplement <15

Repeat echocardiography revealed prominent right ventricle with normal right ventricular function, normal right atrium, PASP was 65 mm Hg. Repeat trop I was within normal range (2.08 ng/L). Patient improved clinically and was discharged in hemodynamically stable condition with anticoagulant and vitamin supplements along with other drugs for comorbidity management.

Discussion

Hyperhomocysteinemia is a known prothrombotic factor that can lead to the development of thromboembolism, coronary artery disease and stroke.[3] Homocysteine is an important intermediary in pathway of cysteine formation from methionine. It is involved in transfer of methyl group from N-methyl tetrahydrofolate (Fig. 4). The reaction is hampered in methylenetetrahydrofolate reductase MTHFR mutation, vitamin B6, B12, folate deficiency. All these lead to hyperhomocysteinemia.[4] There are many case reports

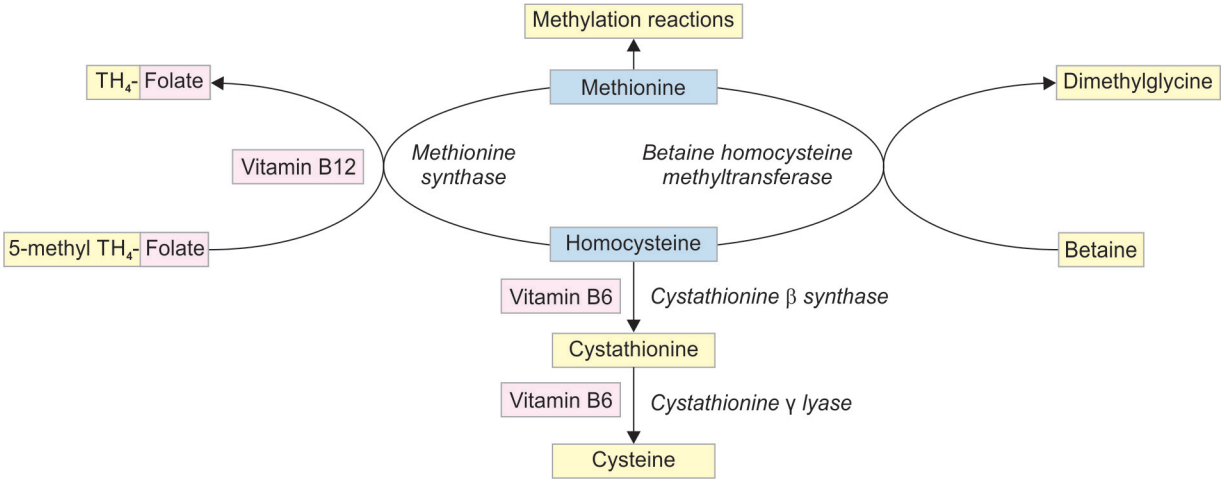

Fig. 4: Pathway of conversion of homocysteine to essential amino acids and its relation with vitamin B12, B6, folate

depicting association of hyperhomocysteinemia and unprovoked thromboembolism.[5–7]

Hyperhomocysteinemia can lead to thrombosis in many ways including:[8,9]

- Homocysteine-induced vascular wall damage evidenced by intimal thickening, elastic lamina disruption, smooth muscle hypertrophy, and impaired nitric oxide availability.
- Increased platelet turnover secondary to platelet consumption due to endothelial damage.
- Increased activity of tissue factor.
- Increased activity of factor vii.
- Decreased activity of protein C and S.
- Reduced activity of antithrombin.
- Decreased permeability of clots.

Hyperhomocysteinemia either primary or secondary to vitamin B12 deficiency may cause thromboembolism.[10–12]

Our case presented like a case of lower respiratory tract infection but was picked-up due to the presence of characteristic findings of PE in echocardiography. For example, right ventricle dilatation and right ventricle reduced the free wall motion with preserved apical motion, tricuspid regurgitation, and raised PASP.[13] Chest X-ray was also suggestive of pulmonary artery enlargement.[14] The patient had raised troponin I and D-dimer according to YEARS algorithm for pulmonary embolism.[15] Now the patient showed high probability of pulmonary embolism with raised biomarkers. CT pulmonary angiography was done. It showed the presence of embolus with pulmonary infarction.[16,17]

Our case was a case of pulmonary embolism, but the patient was hemodynamically stable and systemic pressure was maintained. However, there was right ventricular strain, elevated trop-I, and NTproBNP. So, it was diagnosed to be a case of intermediate risk sub-massive pulmonary embolism.[13,18–20] The patient was admitted, treated with low molecular weight heparin (LMWH) and vitals were monitored strictly. The patient was discharged on oral novel oral anti-coagulants (NOAC) after the improvement of clinical and echocardiographic findings.[13,21]

Conclusion

The case depicts the importance of thrombophilia profile in a patient of unprovoked pulmonary embolism. This case report depicts the mechanisms involved in the development of a life-threatening condition like pulmonary embolism from deficiency of a vitamin. Pulmonary embolism requires urgent recognition and prompt appropriate thrombolysis and anticoagulation. Early diagnosis and categorization of pulmonary embolism leads to better outcome with respect to resolution and complication.

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