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CASE REPORT OF HOMOCYSTEINEMIA LEADING TO DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM IN YOUNG MALE

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ABSTRACT:

The sulfur-containing amino acid called homocysteine is created as a byproduct of the metabolism of methionine. 5 to 15 micromoles per liter (μmol/L) is the normal range for plasma homocysteine levels. Three levels of increased homocysteine are classified either moderate (12–30 μmol/L), medium (31–100 μmol/L), as well as severe (>100 μmol/L) hyperhomocysteinemia. A higher risk of cardiovascular conditions, such as atherosclerosis, stroke, especially coronary heart disease, is linked to elevated homocysteine levels. artery disease, due to mechanisms involving oxidative stress, endothelial dysfunction, & thrombogenesis.

Addition to arterial vascular diseases, hyperhomocysteinemia is a recognized but underdiagnosed risk factor for venous thromboembolism(VTE) encompassing conditions such as deep vein thrombosis (DVT) & pulmonary embolism (PE). This case report describes a young male with no prior medical history who presented with DVT and PE. Subsequent investigations revealed hyperhomocysteinemia as the underlying etiology. The patient was managed with anticoagulants and vitamin supplementation, leading to clinical improvement. This case highlights the importance of identifying and addressing hyperhomocysteinemia among the individuals who have been diagnosed thromboembolic events which reduce hazard recurrence along with long-term complications.

Key words: Homocysteine, homocysteinemia, deep vein thrombosis(DVT), pulmonary embolism(PE)

INTRODUCTION:

Homocysteinemia, also referred to as hyperhomocysteinemia, is defined as an increase in homocysteine levels, a sulphur-containing amino acid involved in methionine metabolism. Normal plasma homocysteine level ranges between 5 and 15 micromoles per litre [1]. Fasting homocysteine levels above 12 mmol per litre appear to be linked to an elevated likelihood of atherosclerotic vascular disease. Plasma levels between 12 - 30 mmol per litre are referred to as moderate hyperhomocysteinemia, intermediate hyperhomocysteinemia (levels between 31 and 100 mmol/L), and severe hyperhomocysteinemia (concentrations exceeding 100 micromoles/L) [2]. One independent risk factor for atheroembolic vascular disease is elevated plasma homocysteine levels. The

pathophysiology of hyperhomocysteinemia involves oxidative stress, endothelial dysfunction, and promotion of prothrombotic states. Homocysteine auto-oxidation generates reactive oxygen species (ROS), reducing nitric oxide bioavailability and impairing vascular relaxation. Additionally, elevated homocysteine increases platelet activation and enhances inflammatory cytokine expression, contributing to atherosclerotic plaque formation [3].

Hyperhomocysteinemia can arise due to genetic mutations in methylenetetrahydrofolate reductase (MTHFR) gene, nutritional deficiency in folate, vitamin B6, or vitamin B12 which are necessary for the breakdown of homocysteine. Other causes include renal insufficiency, hypothyroidism, and certain drugs [4]. While often underdiagnosed, hyperhomocysteinemia plays a significant role in both arterial and venous thromboembolic events. In the context of venous thromboembolism (VTE), elevated homocysteine impairs anticoagulant mechanisms and promotes thrombus formation.

A clinical presentation, diagnosis, as well as therapy of a young patient are highlighted in this case study with pulmonary thromboembolism (PTE) & hyperhomocysteinemia, emphasising the importance of identifying this modifiable risk factor to prevent recurrent thrombotic events.

CASE REPORT:

A 28-year-old male who had no previous medical conditions presented to our emergency room with complaints of giddiness and fall, accompanied by breathlessness and palpitations lasting for one day. Giddiness was sudden in onset, followed by a fall and loss of consciousness. He regained consciousness after 10 seconds. He denied any history of nausea or vomiting. The patient also had complaints of sudden onset breathlessness for one day, Class-3 NYHA, associated with palpitations. He denied any history of orthopnea or paroxysmal nocturnal dyspnea. He denied any complaints of chest pain. Patient had no previous co-morbidities. Patient was a non-smoker, non-alcoholic. Patient was not on any drugs. The patient had no family history of vascular events like stroke or coronary artery disease. Patient was on a vegetarian diet.

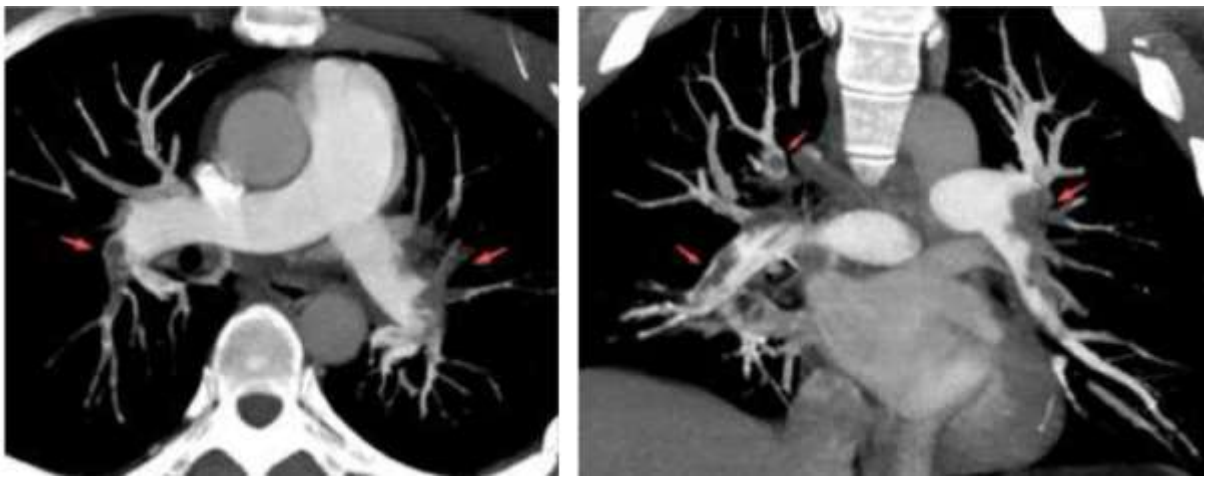
Upon assessment, the patient's blood pressure was 140/100 mm Hg, pulse rate was 128/min, and room air SpO2 of 97%. Systemic examination was uneventful. Electrocardiogram revealed sinus tachycardia with no ST alterations. The chest X-ray was not contributory. Initial diagnostic workup including Complete blood count(CBC) and peripheral smear, indicated macrocytic anaemia. Tests for both kidneys and liver function were within normal ranges.Serum electrolytes, and cardiac markers were unremarkable. His thyroid function test(TFT) and fasting lipid profiles(FLP) were normal.

To investigate the sudden onset of breathlessness and tachycardia, 2D echocardiogram was performed, which showed evidence of right ventricular(RV) strain, raising the suspicion of pulmonary embolism.During the hospital course, the patient developed acute left lower limb pain. A focused vascular examination revealed tenderness and diminished pulses in the left lower limb. A lower-limb Doppler ultrasound was performed which revealed an echogenic thrombus with trickle flow in the left femoral and popliteal veins.

Additional investigations were performed to confirm the suspected diagnosis of pulmonary embolism.D-dimer levels were elevated at 4816 ng/mL indicative of ongoing thrombosis.Coagulation tests showed an INR of 1.28 seconds and an aPTT of 30.7 seconds.

LAB VALUES	RESULTS	NORMAL RANGE
Hemoglobin	9.2gm/dl	Males: 13-17g/dl
MCV	127.5fl	83-101fl
MCH	43.6pg	27-32pg
D-dimer	4816ng/ml	<500ng/ml
Prothrombin time	14.7 seconds	11-13.5 seconds
INR	1.28	1.0-1.5(normal individuals who are not on anticoagulation)
Aptt	30.7seconds	21-35 seconds
Vitamin-B12	159pg/ml	239-931pg/ml
Folic acid levels	20ng/ml	6-28 mmol/L

Table.1: Laboratory workup, including CBC, D-dimer, PT, INR, APTT, Vitamin-B12, folic acid levels.
A CT pulmonary angiography demonstrated pulmonary thromboembolism involving the bifurcation, descending pulmonary arteries, and segmental and subsegmental branches of bilateral pulmonary arteries.



Figures 1 and 2: **CT-Pulmonary Angiography** - Filling defect (red arrow) noted in the bifurcation pulmonary arteries and descending pulmonary arteries (Figure 1). Filling defects were noted in segmental and subsegmental branches of bilateral pulmonary arteries (Figure 2).

Given the absence of traditional risk factors for thromboembolism, a thrombophilia workup panel was initiated to identify the underlying prothrombotic conditions. The results showed high levels of homocysteine (46 micromoles/L). APLA profile was negative. It was discovered that antithrombin-3, protein-C, and protein-S were all within normal ranges. These findings suggested hyperhomocysteinemia as the primary contributing factor to the patient's thromboembolic event.

The patient was initiated on intravenous unfractionated heparin to achieve rapid anticoagulation. As he stabilised, he was transitioned to oral anticoagulation therapy with Apixaban(a direct oral anticoagulant). Given the elevated homocysteine levels, the patient was prescribed with folic acid, vitamin B12 and vitamin B6 supplementation. These supplements aim to help improve its metabolism while decreasing homocysteine levels.

The patient showed significant symptomatic improvement within days of initiating therapy. His tachycardia and breathlessness resolved, and his left lower limb pain subsided. He was discharged on Apixaban (5mg twice daily) along with Vitamin-B12, vitamin-B6 and folic acid supplementation. The patient was instructed to attend the outpatient clinic on routine monitoring in coagulation parameters and homocysteine levels. Lifestyle modifications, including a balanced diet rich in folate and Vitamin-B supplements were emphasized.

DISCUSSION:

The subject of this case report is a 28-year-old man who displayed a number of symptoms like giddiness, breathlessness and palpitations. The results of routine blood investigations revealed macrocytic anaemia, with low levels of vitamin B12 and folate. Initial investigations revealed sinus tachycardia and right ventricular strain. He developed acute left lower limb pain, and Doppler ultrasound confirmed deep vein thrombosis (DVT). CT pulmonary angiography showed pulmonary thromboembolism (PTE). Elevated homocysteine levels (46 μmol/L) indicated hyperhomocysteinemia as the underlying cause. The patient was treated with intravenous heparin, transitioned to oral Apixaban, and prescribed folic acid, vitamin B6, and B12 supplements. He improved symptomatically and was discharged with anticoagulation therapy and supplements. This case highlights hyperhomocysteinemia as an independent risk factor for thromboembolism.

Homocysteine is a sulfur-containing amino acid which is converted to methionine and cysteine with the help of B-complex vitamins like vitamin B6, B12, and folate and with the enzyme tetrahydrofolate reductase (MTHFR). Homocysteine is metabolised in the body by three pathways: i) transsulfuration; ii) methionine synthase with vitamin B12 or folate remethylates homocysteine to methionine; and iii) betaine homocysteine methyltransferase (BHMT) remethylates homocysteine to methionine[5]. These pathways play a critical role in regulating homocysteine levels and maintaining vascular health. The activity of these pathways is critical for maintaining appropriate homocysteine levels.

Pathogenesis of hyperhomocysteinemia is complex. A study by Huang, Tao et al[5] has reported that endothelial injury is the earliest and a key event preceding vascular abnormalities like atherosclerosis and thrombosis. Homocysteine has a direct toxic action on endothelium by decreasing Endothelin-1, a vasoactive peptide synthesised by endothelial cell which is required for normal vasomotor function. Additionally, homocysteine raises VEGF (vascular endothelial growth factor) expression, which leads to impaired synthesis of vasoactive substances like Nitric Oxide(NO) resulting in endothelial dysfunction. Homocysteine can also be converted to thiolactone which affects the body proteins. This leads to endothelial inflammatory response contributing to atherosclerosis. High levels of homocysteine causes an imbalance between blood clotting and fibrinolysis which leads to increase in blood viscosity.

Homocysteine metabolism is reliant upon three vitamins; iii) Folic acid, iii) Vitamin B6 (pyridoxal phosphate), and iii) Vitamin B12 (cobalamin). One important cofactor that is necessary for methionine synthase activity is vitamin B12, also known as cobalamin. Reduced vitamin-B12 levels leads to increase in homocysteine by reduced enzymatic activity of methionine synthase. Decrease in methionine synthase activity leads to impairment of 5-methyl Tetrahydrofolate metabolism which leads to increase in Tetrahydrofolate levels. The cellular synthesis of Tetrahydrofolate (THF), a precursor to 5-Methyltetrahydrofolate, depends on folic acid. Vitamin-B6 or pyridoxine phosphate acts as a cofactor for normal enzymatic activity of Cystathionine Beta Synthase (CBS). Since these vitamins are essential for homocysteine metabolism, deficiency in vitamins B12, folate, and B6 may result in higher homocysteine levels[6].

Brattström et al. reported that when homocysteine levels were raised in the context of vitamin B12 deficiency, vitamin B12 replenishment decreased the levels of homocysteine[7].Apart from nutritional deficiency, other causes for hyperhomocysteinemia include mutations in MethyleneTetrahydrofolate reductase (MTHFR) gene,acute lymphoblastic leukemia, psoriasis, breast and ovarian malignancy, drugs like methotrexate, phenytoin, hypothyroidism. Smoking can lead to hyperhomocysteinemia. Hyperhomocysteinemia is also seen in individuals suffering from end-stage renal failure. A rise in homocysteine causes the glomerular filtration rate (GFR) to be impaired.

Clinical features of hyperhomocysteinemia include:i)Vascular disorders: Elevated homocysteine levels causes thrombosis and endothelial dysfunction, which in turn causes peripheral arterial disease, cerebrovascular accidents, and coronary artery disease (CAD), ii) Thromboembolism: Increased procoagulant activity leads to deep vein thrombosis and pulmonary embolism, iii) Neurologic manifestations like dementia, Alzheimer's disease, mood disturbances leading to depression, iv) Skeletal anomalies like osteoporosis and fractures due to disrupted collagen cross-linking, v) Pregnancy complications like preeclampsia and placental abruption[8]. Other clinical manifestations include retinal vascular conclusions, optic neuropathy due to pro-thrombotic effects, cutaneous ulcers, muscle weakness and fatigue and impaired wound healing.

Management of homocysteinemia includes; i)Dietary modifications which includes foods rich in folate like green leafy vegetables, legumes, citrus fruits and fortified grains. Food sources like fish, poultry, dairy products which are rich in Vitamin-B12 must also be included, ii)Supplementation with folic acid (0.4-5 mg/day), vitamin-B6(10-50mg/day) and vitamin-B12 (1-2 mg/day) are also effective. Supplementation of Vitamin-C & Vitamin-E may aid in lowering oxidative stress, which makes vascular damage worse in homocysteinemia. Supplementation with L-arginine acts as a nitric oxide precursor and may help counteract homocysteine-induced endothelial dysfunction. iii)Lifestyle modifications like cessation of smoking and alcohol, regular physical activity may also help in reducing homocysteine levels, iv)Genetic mutations in MTHFR genes may require high dose of folate or methylated forms of folate(L-methylfolate), iv) Antiplatelets like aspirin or clopidogrel mate be prescribed to reduce thrombotic risks in high-risk patients. In case of documented thrombotic events, anticoagulation with warfarin or direct oral anticoagulants is indicated[8].

In our case report, the patient had both vitamin B12 and folate deficiency, which caused elevated homocysteine levels, which led to vascular events like pulmonary embolism & deep vein thrombosis. Management involved oral anticoagulants and vitamin supplementation. Falcon, C R et al[9] reported that moderate homocysteinemia is linked to a higher risk of thrombosis at young age. To evaluate the effectiveness of treatment and stop issues from getting worse, homocysteine levels must be regularly measured. Individuals with thrombosis should have their monitoring periods prolonged because of the higher prevalence of recurrence of vascular events [10].

CONCLUSION:

This case underscores the critical importance of adequate nutrition in preventing severe health outcomes, particularly in young individuals who might not normally be regarded as being at high risk for vascular events. The patient's pulmonary embolism was a direct consequence of hyperhomocysteinemia, which was primarily driven by deficiencies in vitamin B12 and folate. These deficiencies were likely due to the patient's vegetarian diet, which lacked adequate amounts of these essential nutrients. The case highlights the significant interplay between dietary habits and vascular health, emphasizing the need for balanced nutrition to prevent serious complications such as thromboembolism.

The correct metabolism of homocysteine, an amino acid that, when high, can cause endothelial dysfunction, increased clotting, and vascular damage, depends on vitamin B12 and folate. Deep vein thrombosis (DVT) and pulmonary embolism (PE) were directly caused by the patient's elevated homocysteine levels, which resulted from insufficient amounts of these vitamins. Additionally, this instance highlights how critical it is to identify and treat hyperhomocysteinemia as soon as possible in order to reduce its detrimental effects, particularly in individuals who may not exhibit typical risk factors for thrombotic events.

For individuals following vegetarian or vegan diets, the risk of vitamin B12 deficiency is heightened due to the nutrient's primary presence in animal-based foods. This underscores the need for routine dietary assessments, early identification of deficiencies, and preventive strategies such as supplementation or the inclusion of fortified foods. It is essential to monitor these at-risk populations for potential nutrient imbalances to prevent complications related to elevated homocysteine levels.

This study also highlights the importance of multidisciplinary methods to patient care. Dietitians, healthcare providers, and specialists must collaborate to ensure that individuals following restrictive diets receive proper guidance on meeting their nutritional needs. Education regarding fortified plant-based foods, supplementation, and the importance of regular monitoring can help individuals maintain a balanced diet while still adhering to their dietary preferences.

In conclusion, this case demonstrates the far-reaching effects of nutritional deficiencies on vascular health. Proactive measures, including regular monitoring of homocysteine levels, early detection of deficiencies, and supplementation, are vital in preventing life-threatening conditions like pulmonary embolism. Addressing these issues early on can prevent complications and lead to better long-term health outcomes for individuals at risk.

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