Hyperhomocysteinemia Masquerading as Pulmonary Embolism

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Abstract
We describe a 30-year-old male who presented with acute onset of breathlessness, tachycardia, and palpitations associated with distension of jugular vein and clear lungs on physical examination. The chest X-ray was normal and ECG was showing S1Q3T3 and right ventricular strain pattern. His 2-D echocardiography was showing dilated right atrium, right ventricular dilatation and moderate pulmonary arterial hypertension. He was fond to have thrombosis involving left side of deep venous system with normal superficial venous system (Doppler proved). All routine blood investigations for etiology of recurrent DVT were normal except serum homocysteine level, which was significantly raised. Megaloblastic anemia on peripheral smear and hyperhomocysteinemia prompted us to search for its cause, which was subsequently found to be vitamin B12 deficiency. Such an association of megaloblastic anemia due to vitamin B12 deficiency leading to hyperhomocysteinemia and subsequent thrombosis in left venous system presenting as acute pulmonary embolism has not been described earlier in the medical literature.

INTRODUCTION
Hyperhomocysteinemia is a disorder of methionine metabolism. Several studies have shown a good relation between hyperhomocysteinemia and thrombo-vascular disease. However, we report a case of acute pulmonary embolism due to deep vein thrombosis in a young man with hyperhomocysteinemia and megaloblastic anemia due to vitamin B12 deficiency.

CASE REPORT
A 30-year-old gentleman was admitted to our hospital with acute onset of breathlessness, palpitation and profuse perspiration since one day. He was a known case of recurrent deep vein thrombosis involving right lower limb since three years. On admission, his physical examination showed tachycardia, tachypnoea, distended neck veins with clear lungs and normal blood pressure. The chest X-ray (PA view) was normal but arterial blood gas analysis (ABG) showed pH = 7.39; pO2 = 50 mm Hg; saturation of O2 = 84% and pCO2 = 40 mm Hg and electrocardiogram showed S wave in lead I and Q wave with T wave inversion in lead III (S1Q3T3) with sinus tachycardia and right ventricular strain pattern in leads V1-V4.

The 2-D echocardiography showed dilated right atrium and right ventricle with mild tricuspid regurgitation and moderate pulmonary arterial hypertension (right ventricular systolic pressure = 62 mm Hg) with normal left and right ventricular function.

The laboratory study showed hemoglobin (Hb) = 16 gm%; hematocrit (Hct) = 46.6%; red blood cell count = 4.35 x 1012/L; total WBC count = 9.5 x 109/L with normal differential count; Platelet Count = 243 x 109/L; reticulocyte count = 1.2%. MCV = 107 fl; MCH = 38.6 pg; MCHC = 34.3; RDW = 15.5%. The erythrocyte sedimentation rate was 20 mm at the end of one hour. The peripheral smear showed hypersegmented neutrophils with anisopoikilocytosis and macro-ovalocytosis. Blood urea, serum creatinine, blood glucose, serum electrolytes, serum bilirubin, amylase, aminotransferase enzymes and alkaline phosphatase were normal. Prothrombin time and activated partial thromboplastin time were normal.

The lupus anticoagulant was negative and anticardiolipin antibody IgM was 6 MPL (normal < 10 MPL) and IgG was 2 GPL (normal < 10 GPL). The paroxysmal nocturnal hemoglobinuria workup was negative. Euglobin lysis time of patient was 2 hrs 50 min. with 2 hrs 40 min. as control. Serum LDH was 475 IU/L (200-400 IU/L); serum vitamin B12 was 159 pg/ml (223-1132 pg/ml). The protein C and protein S activity was normal. The antigenic antithrombin (AT-III) concentration was 70%. Right lower limb venous system
showed significant recanalization with mild changes of chronic venous insufficiency. His ultrasonography of abdomen was normal.

He was thereby diagnosed as having acute pulmonary embolism due to deep vein thrombosis of the left sided venous system with megaloblastic anemia due to vitamin B₁₂ deficiency which was also responsible for his hyperhomocysteinemia.

The patient was then treated with low molecular weight heparin-Enoxaparin at a dose of 1 mg/kg subcutaneously twice a day for 3 days along with complete bed rest and graded compression stockings. Oral anticoagulant in form of warfarin (5 mg) was started along with folic acid and vitamin B₁₂ intramuscularly daily for first 15 days along with potassium supplementation. Then the injections were given twice a week for next six weeks along with iron supplementation and then once a week for further six weeks, followed by once every 15 days for 3 months and then once a month for next 3 months.

The patient was followed up at regular intervals with clinical evaluation and echocardiography, which showed markedly improved right and left ventricular function with the right systolic pressure coming down to 35 mm Hg after six months. The serum homocysteine level dropped down to 14 µmol/L after six months of therapy.

**DISCUSSION**

Homocysteine is a naturally occurring molecule in the body, which is a sulfur-containing aminoacid, produced during the metabolism of essential aminoacid methionine. Homocysteinemia was first described in 1962 in mentally retarded.

Children with skeletal and visual problems, but association with vascular disease and early atherothrombosis was clearly described by McCully in 1969.

Homocysteinemia, an autosomal disease with considerable genetic heterogeneity, is the second most common inborn error of aminoacid metabolism. While the full genetic disorder affects only 1:20,000 live-births, abnormal homocysteine metabolism due to genetic (hereditary) or nutritional deficiency (acquired) appears to be surprisingly common.

Mutation in any of the enzymes involved in the metabolism of homocysteine will lead to hyperhomocysteinemia. Patients who are homozygous for the defect can develop homocysteinemia. Apart from hereditary factors, there are certain acquird factors, which can influence and can associate with raised levels of plasma homocysteine like:-

1. Vitamin B₁₂ and folic acid deficiency.
2. Drugs : Metformin, methotrexate, phenytoin, carbamazepine, niacin, theophylline.
3. Diabetes mellitus, renal failure, hypothyroidism.
4. Rheumatoid arthritis, SLE, psoriasis etc.

Hyperhomocysteinemia is associated with significant increased risk of coronary, peripheral, cerebral and retinal vasculo-occlusive disease.

Kang and co-workers have classified hyperhomocysteinemia as follows:

1. **Moderate Risk : 15-30 µmol/L**
2. **Intermediate Risk : 30-100µmol/L**
3. **Severe Risk : > 100 µmol/L**

Apart from genetic defects in the enzymes leading to hyperhomocysteinemia, commonest cause contributing to it is the nutritional deficiencies in vitamin cofactors. Selhub et al demonstrated inadequate plasma concentrations of one or more B vitamins contributed to 67% of the cases of hyperhomocysteinemia. Thus, providing the fact that vitamin supplementation is going to be the mainstay of the treatment for hyperhomocysteinemia. In various studies it is conclusively shown that the normalization of hyperhomocysteinemia occurs after nutritional supplementation and on an average it takes 4-6 weeks after initiation of therapy.

In a case-control study, Falcon et al, found that hyperhomocysteinemia was a risk factor for venous thrombosis in people less than 40 years of age and also a risk factor for recurrent deep vein thrombosis in general population between 20 to 70 years of age.

Here in our case report, the patient falls into moderate risk group (Kang classification). Our patient presented with a constellation of symptoms and signs, which were highly suggestive of pulmonary embolism due to deep vein thrombosis that had developed because of hyperhomocysteinemia secondary to vitamin B₁₂ deficiency. However, with treatment in the form of vitamin B₁₂, folic acid supplementation and anticoagulation, patient recovered completely. After six months of therapy, the patient showed remarkable improvement in right ventricular function on 2-D echocardiography and the serum homocysteine level came down from 28.5µmol/L to 14µmol/L.

Early recognition and treatment of such a condition can not only reverse but also prevent further recurrence of venous thromboembolic episodes.

**REFERENCES**