European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 08, 2020

Pulmonary Embolism In A Young Healthy Male With Hyper Homocysteinemia

Mohd Shahid[1], RameshwarR[2], MeenakshiKadiyala[3], J Vinoth Kumar[4],Damodaran J[5]

[1,2]*Senior resident , Saveetha Medical College and Hospital, Chennai, Tamilnadu*
[4]*Juniour resident, Saveetha Medical College and Hospital, Chennai, Tamilnadu*
[3,5]*Professor, Saveetha Medical College and Hospital, Chennai, Tamilnadu*

Email- rame5193@gmail.com

ABSTRACT: Pulmonary thromboembolism can be a cardiovascular killer particularly during prolonged hospitalisations for surgical or medical illnesses. It is usually consequent to deep venous thrombo embolism but can also be due to hypercoaguable states. We report a rare case of acute Pulmonary Thromboembolism, diagnosed clinically and proven by CT pulmonary angiography in a 27 year old male with hyperhomocysteinemia, who was treated successfully with anticoagulants, folic acid and pyridoxine.

1. INTRODUCTION

Homocysteine, a sulfur-containing amino acid is an intermediate in the metabolism of methionine.(1). Normal levels of homocysteine in the blood is <15micromoles /L. Thrombophilia, congential or acquired should be high up in the list when pulmonary embolism occurs in a non obese and mobile patient and hyperhomocysteinemia is one such cause of thrombophilia. Other causes include deficiency of protein C, protein S, anti-thrombin, Factor V Leiden, and acquired disorders such as collagen vascular diseases, anti-phospholipid antibody syndrome and malignancy.(2)

2. CASE SUMMARY

A 27year old male, keyboard player by occupation presented to emergency department with complaints of acute onset and gradually progressive breathlessness of 5 days duration . There was no history of chest pain, palpitations, fatigability, giddiness or any significant history of prior illness. On examination Pulse rate was 115/min regular, good volume, blood pressure-110/70 mmHg in right upper limb, saturation-82% in room air, respiratory rate of 20/min and temperature of 99.6 F. Cardiovascular system examination revealed accentuated second heart sound and a right ventricular S3 gallop. The haemoglobin was 17.0 gm/dl, RBC of 6.01million/mm3, TC-14600/mm3. Blood urea was 29mg/dl, serum creatinine 0.9 mg/dl, sodium-140 mEq/L, potassium-4.4 mEq/L. Liver function test revealed serum bilirubin total of 4.9 mg/dl and indirect bilirubin of 1.2 mg/dl, alkaline phophatase of 153 U/L, SGOT-49 U/L, SGPT-59 U/L), total protein-7.9 gms/dl and albumin-4.1 gms/dl. D-dimer was elevated (3939 ng/ml).

Electrocardiogram showed sinus tachycardia (115) with S1Q3T3 pattern and T wave inversion in V1-V4.(Fig1)

Echocardiography revealed dilated right atrium and right ventricle(RV), severe tricuspid regurgitation(Fig 2) and pulmonary hypertension of 78 mmHg. There was right ventricular(RV) dysfunction with a TAPSE of 9mm. No thrombus was picked up by ECHO in the pulmonary artery. The global LV systolic function was normal with an ejection fraction of 66% .

Chest X-ray showed increased CT ratio and elevated right dome of the diaphragm . There were no opacities in the lung fields.

Ultrasound abdomen revealed congestive hepatomegaly.

Evaluation of the Thrombotic profile revealed elevated Homocysteine level (88.6 micro mols/L), normal Protein C levels (0.86IU/ml) and Protein S levels (1.02IU/ml) and he was APLA negative .

Venous Doppler of all 4 limbs was performed, which revealed an echogenic thrombus measuring 3.5 cm in right politeal vein causing near complete occlusion of the vein.(Fig 3)

With a clinical diagnosis of acute pulmonary embolism, CT pulmonary angiogram was performed and showed multiple filling defect in right pulmonary artery, at the bifurcation and extending into the lobar and segmental branches consistent with thrombi. Left pulmonary artery also showed multiple filling defects consistent with thrombi at the bifurcation into lobar and segmental branches.(Figs 4,5,6)

Patient was treated in the intensive care unit and was give a bolus of 2.5lakhs units of streptokinase, followed by an infusion of 1lakh unit/hour for 24 h. This was followed by an infusion of unfractionated heparin which was allowed to overlap with acitrom 2mg for a period of 3days and the INR was maintained between 2-2.5 following which heparin was stopped. He was also put on capsule homocheck which contains Folic acid, Pyridoxin and methylcobalamine. Patient responded well to treatment, improved symptomatically and was discharged on day 10 with the advice to continue anticoagulants and other drugs for a period of 3 months . Tests to rule out a genetic defect were not done. However he was advised to take a folate rich diet like green vegetables, orange juice and beans and to abstain from drinking alcohol. On follow up after 2 weeks, patient remained asymptomatic and his Echocardiogram showed significant improvement in RV dimension and function with a TAPSE of 14mm and reduction of PHT to 42mmHg. His homocysteine levels were now 22 micro mols/L. He was advised to continue the same management along with regular follow up.

3. DISCUSSION

Hyperhomocysteinemia can occur due to aging, nutritional vitamin deficiency, renal failure, thyroid dysfunction, cancer and chronic alcohol intake or can be due to a genetic defect. Genetic hyper homocysteinemia is a rare disorder generally due to the deficiency of the enzyme cystathionine synthase, although other enzyme deficiencies may be also responsible.(2).These Patients can be asymptomatic or be associated with involvement of systems like the connective tissue, vascular system, liver, central nervous system and the eye.(3). Our patient was totally asymptomatic till he presented with acute pulmonary

embolism. He did not have any of the other manifestations reported in literature including ectopia lentis which has been reported to occur in almost 70% of the genetic cases. By far the most important and life threating presentation is the involvement of the vascular system leading to throbophlebitis, thrombo embolism and even fatal pulmonary embolism.

Vascular thrombosis can involve both small to large sized arteries and veins.(3). Pulmonary thromboembolism as was observed in our case can occur and is diagnosed by Echocardiography and CT Pulmonary angiography as was done in our patient. Hyperhomocystinemia should be thought when pulmonary embolism occurs in non traumatic, non surgical and mobile patients, although other causes of thrombophilia should be ruled out as we did in our case. In literature, myocardial infarction can also occur, though at a lesser frequency (4%) than pulmonary thromboembolism. (3). The association of hyperhomocysteinemia with thrombosis has been shown to be independent of risk factors like smoking, hyperlipidemia, hypertension, and diabetes .

Based on fasting total plasma homocysteine levels, hyperhomocysteinemia can be classified as mild (12 - 30 mmol/), moderate (31- 100 mmol/l or severe (>100mmol/l).Our patient falls into the moderate category. High homocystein levels can also cause endothelial dysfunction and can promote atherosclerosis.(4).

Diagnosis is clinched by determining fasting blood levels of homocysteine, urinary Cyanide nitroprusside test, urinary amino acid analysis by chromatography and direct enzyme analysis.

Diagnosis can be confirmed by analysis of liver biopsy specimen and cultured skin fibroblast. Molecular diagnosis of this disorder holds good promise.

It is mandatory to monitor homocystinuria patients who want to become pregnant and they have to be supplemented with pyiridoxin to prevent intra uterine growth retardation, abruptio placenta, fetal loss and the 2to 3 fold increased risk of pregnancy induced hypertension and the risk of pulmonary embolism. (5,6).

Treatment includes: drugs, diet and thrombolysis in the event of a thromboembolism. 50% of Homocystinuria patients can be pyridoxine responders and the rest are partial or non responders requiring a special diet and additional drugs to thwart complications.(7).

In pyridoxine non-responders, choline or betaine (4-6 gm/day) is given.(3). Intake of green leafy vegetables, oranges and beans should be encouraged Genetic counselling can be done after a Prenatal diagnosis is made using pinch biopsy from forearm of both mother and father, from amniotic fluid at 16 weeks gestation or from the base of the new borns umbilical cord.(8).

Thrombolytic therapy is the treatment of choice in the event of a pulmonary embolism. Surgical pulmonary embolectomy or catheter embolectomy is alternative in patients with high-risk PE in whom thrombolysis is absolutely contraindicated or has failed . Our patient underwent IV thrombolysis.(9).

Long term anticoagulation along with diet plan for atleast 3 months is necessary and the further anticoagulant intake to be determined by the homocysteine levels at 3 months. Our patient was also asked to continue anticoagulants for 3months with review every 2weeks. He would be reassessed at the end of 3 months to decide on continuation or not of anticoagulant therapy.

4. CONCLUSION

Hyperhomocysteinemia is one on the list of causes of Pulmonary Thromboembolism in an ambulant non obese patient and it may be the only manifestation although it could be a part of a multisystem involvement and associated with thromboembolism elsewhere.
A high index of suspicion and prompt therapy may help in reducing recurrent episodes. Prognosis in pyridoxine responsive patients is excellent if treated early.

5. REFERENCES

[1] S. Harvey Mudd, FlemmingSkovby, Harvey L. Levy, Karen D. Pettigrew, Bridget Wilcken, Reed E. Pyeritz,, et al.The natural history of homocystinuria due to cystathionine β-synthase deficiency. Am J Hum Genet. 1985 Jan; 37(1): 1–31.

[2] Paul Gangulyand Sreyoshi Fatima Alam. Role of homocysteine in the development of cardiovascular disease. Nutrition Journal2015**14**:6. https://doi.org/10.1186/1475-2891-14-6

[3] MalleshKariyappa, Navin Agrawal*, Shankar Somanna,SadashivappaSurhonne, Prakash, Kumaraswamy Veerappa,ManjunathcholenhallyNanjappa. Unprovoked pulmonary thromboembolism predisposed by hyperhomocysteinemia. journal of indian college of cardiology 4 (2014) 239 – 242

[4] Graham IM[1], Daly LE, Refsum HM, Robinson K, Brattström LE, Ueland PM, et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. JAMA. 1997 Jun 11;277(22):1775-81.

[5] Steegers-Theunissen RP, Boers GH, Blom HJ, Trijbels FJ, Eskes TK. Hyperhomocysteinaemia and recurrent spontaneous abortion or abruptio placentae. Lancet. 1992 May 2;339(8801):1122-3.

[6] Nelen WL[1], Blom HJ, Steegers EA, den Heijer M, Thomas CM, Eskes TK. Homocysteine and folate levels as risk factors for recurrent early pregnancy loss. Obstet Gynecol. 2000 Apr;95(4):519-24.

[7] Bradley A. Maron, and Joseph Loscalzo. The Treatment of Hyperhomocysteinemia. Annu Rev Med. 2009; 60: 39–54.

[8] doi: 10.1146/annurev.med.60.041807.123308

[9] Saima Salam, Saba Mushtaq, Khalid Mohi-ud-Din, Irfan Gul*, Asifa Ali.. Maternal and fetal outcome in pregnancy with heart disease in tertiary care hospital in India. Int J Reprod Contracept Obstet Gynecol. 2017 Sep;6(9):3947-3951

[10] Martin den Heijer M[1], Koster T, Blom HJ, Bos GM, Briet E, Reitsma PH, Vandenbroucke JP, Rosendaal FR. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med. 1996 Mar 21;334(12):759-62.

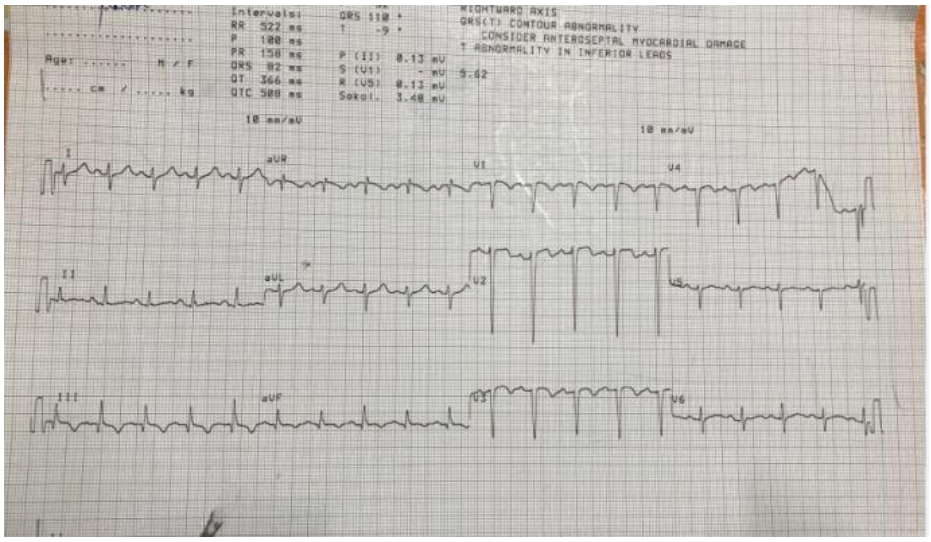

Fig 1. 12 lead ECG
Sinus tachycardia with S1 Q3 T3 pattern. r/S complexes from V1-to V5

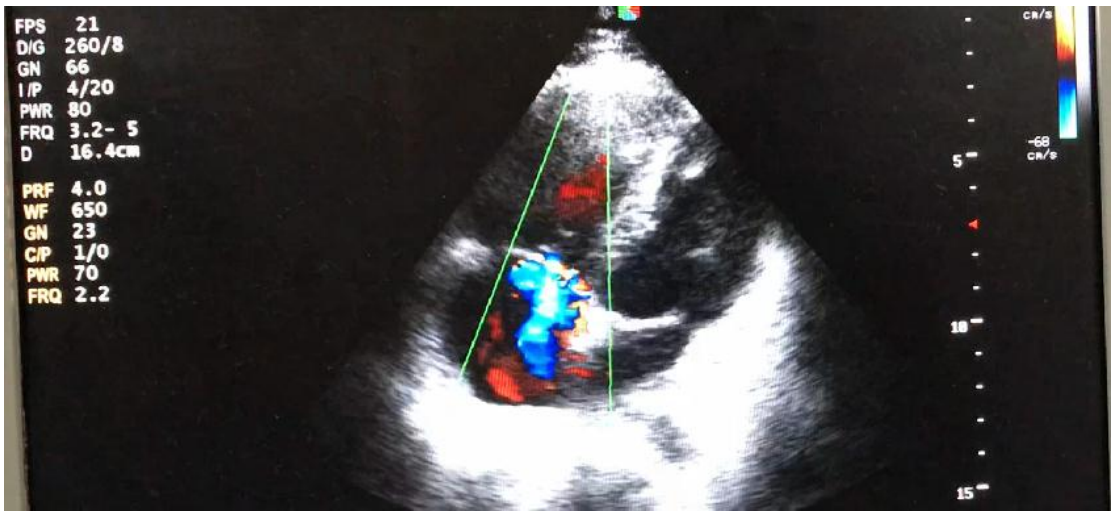

Fig 2- Trans thoracic ECHO
Apical 4 chamber view showing the dilatation of the right atrium and ventricle with tricuspid regurgitation jet.

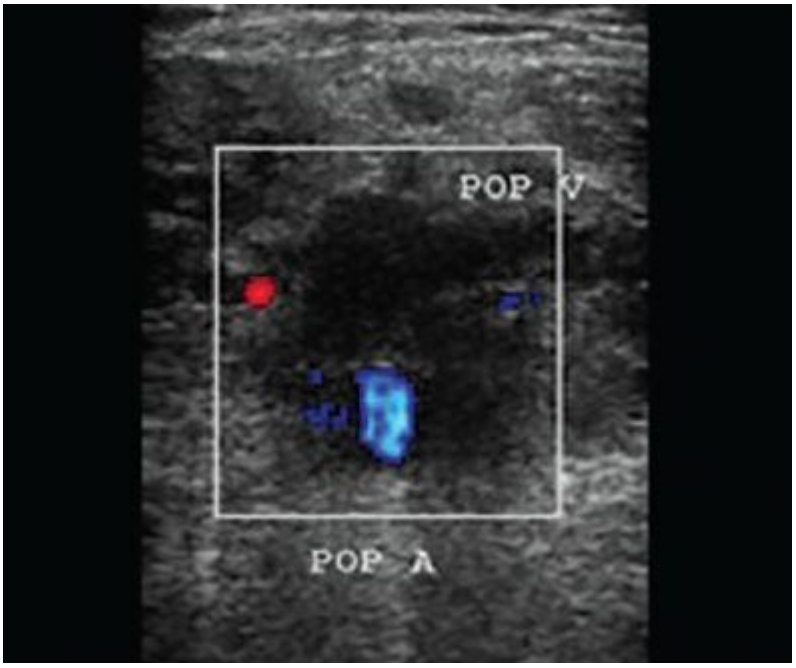

Fig 3. Transverse color mode image showing absence of color flow in popliteal vein with echogenic lumen suggestive of thrombus. The vein size has also increased substantially as compared to the popliteal artery. Color flow is seen in popliteal artery (blue)

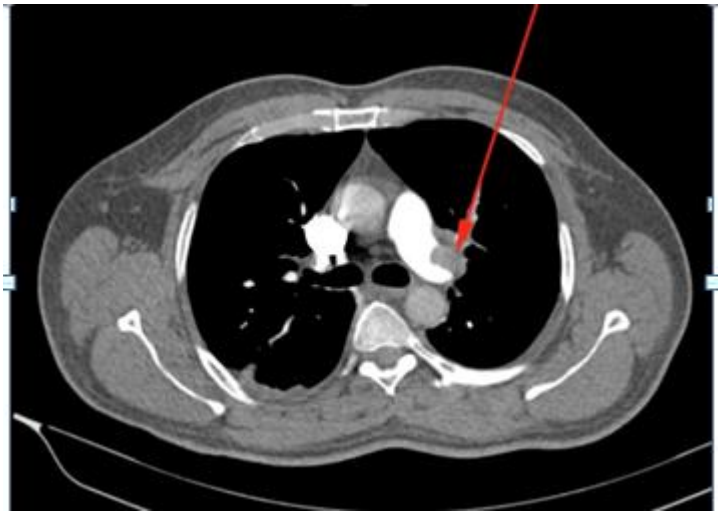

Fig4 CTPA- Axial
Eccentric filling defect in the left Pulmonary artery distal to the bifurcation in its proximal portion

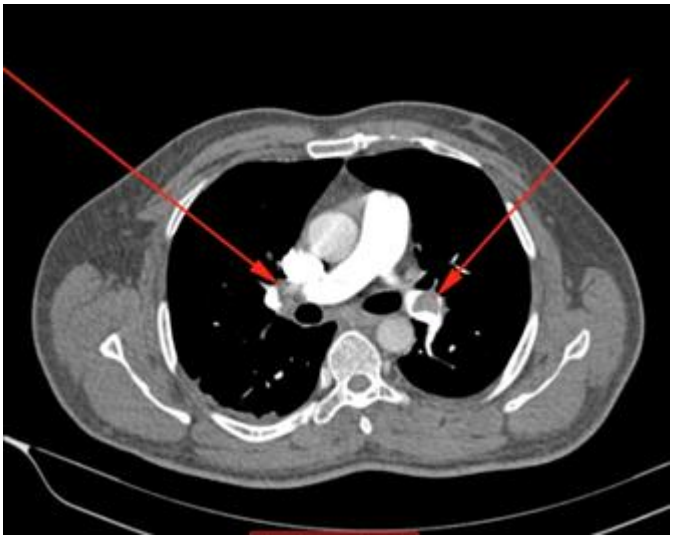

Fig5. CTPA- Axial
Focal central filling defect involving the distal right pulmonary artery (prior to its bifurcation) and distal left pulmonary artery with no significant proximal dilatation.

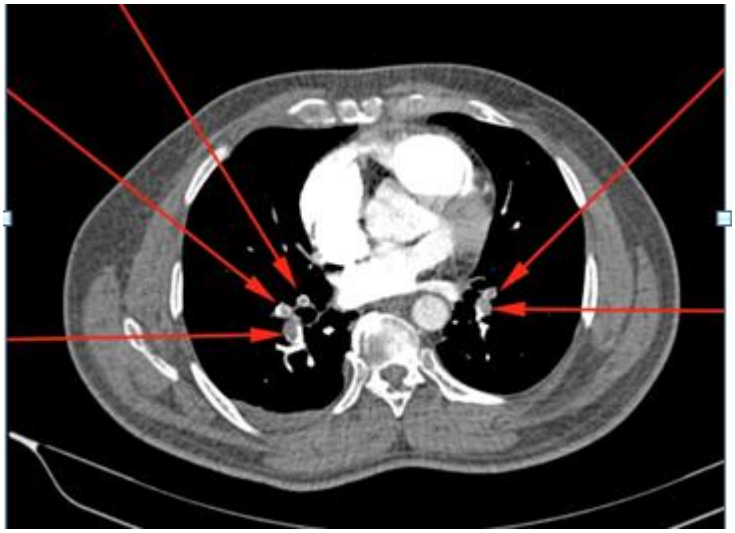

Fig 6. CTPA –Axial
Focal central filling defects involving the lower interlobar divisions of both right & left pulmonary arteries