

Pulmonary Thromboembolism due to Vitamin B12 Deficiency: A Case Series

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Abstract

We have described three cases of pulmonary thromboembolism (PTE) with/without myocardial infarct due to vitamin B12 deficiency and hyperhomocysteinaemia. Two of the patients had the deficiency due to vegetarian diet and one had mal-absorption syndrome. The long term management for prevention of PTE is dependent on: 1. PTE is unprovoked or otherwise, 2. bleeding risk and 3. presence of coagulopathy. In this case series, identifying the cause of vitamin B12 deficiency, correcting vitamin B12 deficiency appropriately, use of newer oral anticoagulant for 3 months atleast and then stopping the anticoagulants once correction was achieved was the key to the long-term management. None of the patients had recurrence two years after stopping anticoagulants. This is the first case series where vitamin B12 deficiency and homocysteinaemia was systemically implicated as the cause of PTE, identified the cause of vitamin B12 deficiency, treating it appropriately and showing the absence of recurrence after stopping the anticoagulants.

Keywords: Pulmonary Thromboembolism (PTE); Vitamin B12

Introduction

Pulmonary thromboembolism (PTE) is relatively common cardiovascular emergency, yet it is under-recognized and under-diagnosed [1]. There is a consensus regarding diagnosis and management of acute PTE [2]. The long-term management however varies. If a treatable underlying cause is identified it prevents recurrence of the disease after stopping the anticoagulants [1]. We have described three cases of PTE with varied manifestation having common underlying etiology i.e. vitamin B12 deficiency.

Case 1

A 35-year-old man, non-smoker, driver presented with hemoptysis and blood streaked sputum of 3 months duration. He had history of myocardial infarction 1 year ago. There was no history of diabetes mellitus or hypertension. On examination, the vital parameters and systemic examination was normal. The chest radiograph and electrocardiograph were normal. His hematological and biochemical investigations were normal. His lipid profile was as follows: triglyceride - 208 mg%, cholesterol - 230 mg% and HDL - 51 mg%.

Two-dimensional echocardiography showed an organized thrombus extending from apex to septum in the left ventricle of 4.6 cm X 2.2 cm in size. The ejection fraction was 30%. The computed tomography (CT) of chest, CT angiography and CT venography showed bilateral lower lobe pulmonary infarct, common iliac vein thrombosis and left ventricular thrombus (Figure 1-3). The investigations for

hypercoagulable state, homocysteine level, folic acid and serum vitamin B12 are given in table 1 and 2. It showed homocysteinaemia due to vitamin B12 deficiency.

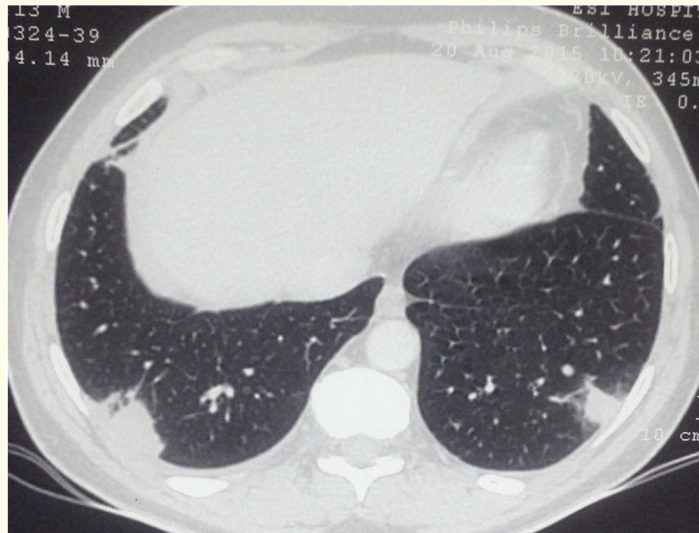


Figure 1: Case 1- Contrast enhanced CT thorax, lung window at the level of lower lobe showing bilateral lower lobe wedge shaped infarct.

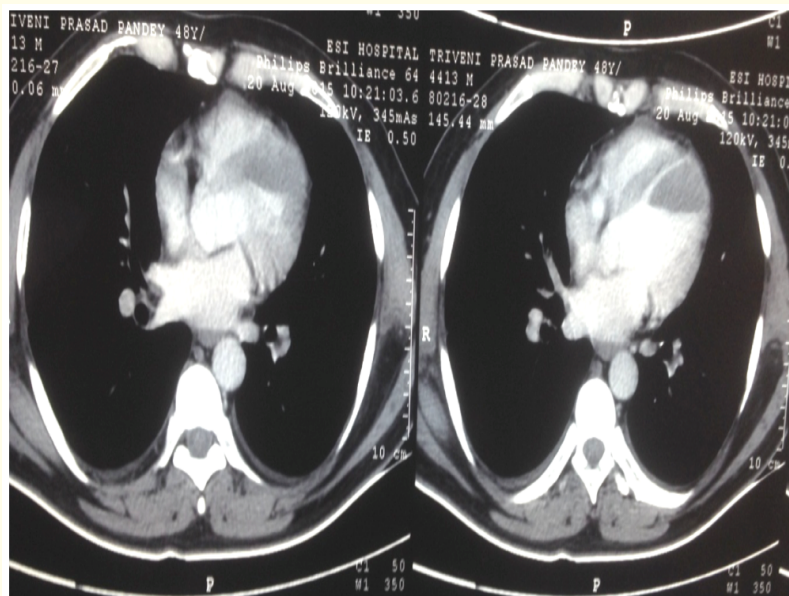


Figure 2: Case 1- Contrast enhanced CT thorax, mediastinal window showing a large thrombus in the left ventricle.



Figure 3: Case 1- CT abdomen showing inferior vena cava thrombus.

He was a vegetarian but consumed 1 litre milk daily. So, he was investigated for vitamin B12 deficiency. The upper gastrointestinal endoscopy and duodenal biopsy were normal. Serum tissue trans glutaminase and serum gastrin were normal. Anti-parietal cell antibody was negative. Since, tests for malabsorption were negative, intrinsic factor deficiency was diagnosed as diagnosis of exclusion. He was given intramuscular injections of vitamin B12- 1 mg once every month and rivaroxaban 10 mg once a day. Three months later, the serum homocysteine and vitamin B12 normalized (Table 2) and the intra-ventricular thrombus resolved (Figure 4). He has been asked to continue injectable vitamin B12 life long.

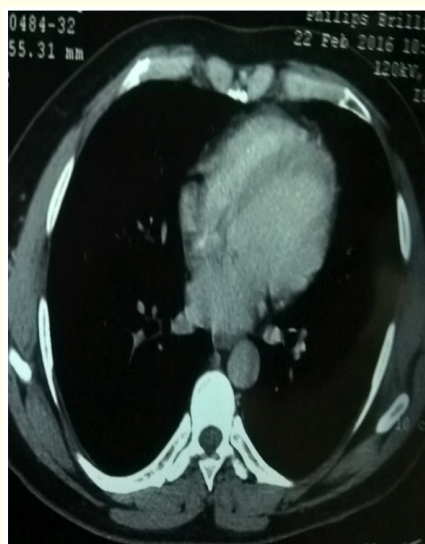


Figure 4: Case 1- CT thorax mediastinal window after treatment showing resolution of left ventricular thrombus.

Case 2

A 38-year-old man, non-smoker, driver presented with sudden onset dyspnea at rest of one day duration. He had no other significant past history or comorbidity. At presentation the respiratory rate, pulse rate and blood pressure were 22/min, 147/min and 112/80 mm of Hg respectively. His chest radiograph was normal. Electrocardiogram showed tachycardia. The arterial blood gas analysis showed pH - 7.46, PCO_2 - 27.8 mm of Hg, PO_2 - 53 mm of Hg, HCO_3^- - 19 mmol/l. The routine biochemical parameters were normal. 2-dimensional echocardiography showed dilatation of right atrium and ventricle with severe pulmonary hypertension. CT pulmonary angiography showed embolus in the bifurcation of right main pulmonary artery, left lower lobe and left upper lobe pulmonary artery (Figure 5). His pro-brain natriuretic peptide (BNP) was 3254 pg/ml (normal < 450 pg/ml). His pulmonary embolism severity index (PESI) score was class IV category. He was managed conservatively with heparin in intensive care unit. Investigation for thrombophilia, homocysteine, vitamin B12 and folic acid are given in table 1 and 2. He consumed non-vegetarian diet occasionally (once/month) and did not consume milk. He was treated with rivaroxaban 15 mg twice daily and oral vitamin B12 supplement of 1000 mcg/day. The vitamin B12, homocysteine and pulmonary artery pressure normalized on treatment. A residual thrombus in the pulmonary artery remained. Two year after stopping the treatment he has remained asymptomatic.

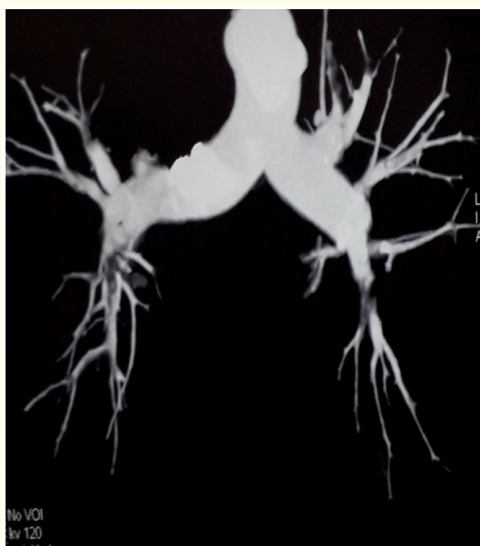


Figure 5: Case 2- CT pulmonary angiography showing right pulmonary artery thrombus.

Case 3

A 38 year old man, non- smoker, guard was referred for evaluation of deep vein thrombosis. He had incurred an acute episode of PTE 1 year ago. He had undergone thrombolysis when he suffered from saddle shaped pulmonary embolism and was started on warfarin 5 mg/ day after that. Detailed enquiry of his previous records of that time revealed complete resolution of pulmonary emboli. So, at the time of presentation to us, he did not have complaints. There was no other comorbidity or noteworthy past history. Colour doppler study of both lower limbs showed partial filling defect with recanalization in the right leg (popliteal vein) consistent with chronic thrombosis. He was a vegetarian with inadequate consumption of milk. The homocysteine, vitamin B12, folic acid and the other coagulation profile are given in table 1 and 2. The vitamin B12 and homocysteine normalized after treatment and. He has not had recurrence of embolism for last 1 year after correction of vitamin B12 and stopping anticoagulants.

Tests for Hypercoagulability	Case 1	Case 2	Case 3
Prothrombin gene mutation	Not detected	Not detected	Not detected
Anti-phospholipid Antibody IgG (N <10)	4.2 IU	5.2 IU	3.65 IU
Anti-phospholipid Antibody IgM (N < 10)	4.6 IU	3.7 IU	3.03 IU
Protein C (N 67 - 195%)	120%	132%	100%
Protein S (N 55 - 123%)	70%	87%	58%
Protein C Functional (N 100 - 150%)	132%	121%	104%
Factor V assay (N 70 - 140%)	88%	95%	85%
Anti-Thrombin III (N 70 - 122%)	102%	87%	74%

Table 1: Results of test for hypercoagulability.

Test	Case 1		Case 2		Case 3	
	Pre treatment	Post treatment	Pre treatment	Post treatment	Pre treatment	Post treatment
S. Homocysteine (N 5.9 - 15 umol/L)	42.7	12.2	380	14.3	80	11
S. Vitamin B 12 (N 200 - 900 pg/ml)	82	800	66	560	46	678
S. Folic acid (N 2 - 10 ng/ml)	11	10	5.5	8.6	10.2	11.6

Table 2: Levels of serum homocysteine, vitamin B 12 and folic acid (pre and post treatment).

Discussion

The treatment of PTE is divided into two parts: acute management and prevention of recurrence. The acute management consists of risk stratification with blood pressure, PESI, 2-dimensional echocardiography, troponin T test and pro-BNP [1]. The patients are then grouped into high, intermediate high, intermediate low and low risk as per European Society of Cardiology (ESC) [1]. The acute management consists of intensive care monitoring, anticoagulation and/or thrombolysis based on the risk stratification. Our second patient had presented with acute PTE. He was classified into high intermediate category and treated accordingly with monitoring and anticoagulant. Non-severe mild cases require only outpatient management like the first case [2]. The third case had been treated with thrombolysis elsewhere.

The prevention of recurrence of PTE requires anticoagulants atleast for 3 months. Rivaroxaban is the first newer oral anticoagulant to receive regulatory approval for the acute and continued treatment of DVT and PE, and for the secondary prevention of VTE [3,4]. The continuation of anticoagulant is dependent on if PTE is provoked, bleeding risk and coagulopathy. Unprovoked PTE as seen in our patients require treatment for extended period i.e. no schedule stop date if the bleeding risk is low or moderate as per the ESC and Chest guidelines [1,4]. The indications for coagulopathy or thrombophilia testing are given in table 3 [5]. All 3 patients were young active men with 3 - 4 hours of sitting or standing (minor provocation) and require the testing as per the guidelines. If thrombophilia is proven to be due to the prothrombin gene mutation (real time PCR) G20210A, protein C, protein S, factor V assay (Layden), antithrombin III assay it can serve to reinforce adherence to lifelong prophylaxis [5]. Hyperhomocysteinemia due to methyl tetra hydro folate reductase enzyme (MTHFR) gene has been studied extensively and has not been indicated anymore [5,6]. There are no definite guidelines regarding the role

of vitamin B12 in the management of PTE. Studies have shown that vitamin B12 deficiency leads to PTE [7-10]. Though, studies on the role of administering vitamin B12 to patients with PTE have found that vitamin B12 administration is not useful [11-13]. These studies, however had not identified vitamin B12 deficiency as the cause of PTE [7-9]. Vitamin B12 was administered irrespective of deficiency. Also, the cause of deficiency was not investigated [8]. Ours is the first case series where we have shown that vitamin B12 deficiency led to hyperhomocysteinaemia and PTE by ruling out other causes of thrombophilia and normalized the level of both homocysteine and vitamin B12 with appropriate treatment (injectable or oral), stopped the anticoagulant and followed up the patients for one and half to three years to show that there was no recurrence.

1) Age < 50 years especially in association with weak provoking factors like minor surgery, oral contraceptives, or immobility or unprovoked VTE
2) Family history of venous thromboembolism
3) Recurrent episodes of unexplained venous thromboembolism
4) VTE in unusual sites such as splanchnic or cerebral veins

Table 3: Indications for thrombophilia testing.

One of the patients with vitamin B12 deficiency had malabsorption syndrome and the other two had the deficiency due to vegetarian diet. The common cause of vitamin B12 deficiency has been shown to be malabsorption. However, two of our patients had deficiency due to vegetarian diet. 29 - 40% of Indian population consumes vegetarian diet, which is far higher than any other country [14]. It has been shown that vegetarians have lower vitamin B12 bioavailability [15]. However, there are no studies on PTE and/or ischemic heart disease and vitamin B12 deficiency from India.

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