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Venous Thromboembolism in a Patient with Vitamin B-12 Deficiency and Apla Syndrome

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ABSTRACT

Deep vein thrombosis is an entity that can have multiple predisposing factors. Identification of each of these is essential for better outcomes and requires a holistic approach. Here we report the case of a 41 year old female who presented with deep vein thrombosis in whom the initial diagnosis was vitamin B-12 deficiency with secondary hyperhomocysteinemia was made beyond doubt. However, since she had one spontaneous first trimester abortion, loud P2 suggesting possible pulmonary hypertension with history suggestive of recurrent pulmonary embolism, a coexistent APLA syndrome was also suspected clinically, which was confirmed by prolonged aPTT, positive VDRL and ANA positivity. The case is reported to highlight importance of looking for other etiological factors for any clinical syndrome, if the clinical indications are strong. Hence the presence of one definite etiologic factor does not necessarily indicate the absence of others. A holistic clinical approach is absolutely essential to help the patients rather than believing only the laboratory.

INTRODUCTION

Deep vein thrombosis (DVT) is a major preventable cause of morbidity and mortality. It has to be prevented by all possible means but when it develops, prompt clinical diagnosis and early management should not be delayed even if radiological evidence is not available since the sensitivity of ultrasound Doppler is poor especially for distal deep vein thrombosis. While early recognition of the condition is important, equally important is the identification of possible etiological factors. Each patient with venous thrombosis has multiple factors responsible for venous thrombosis. Hence a holistic approach in the form of detailed history, including dietary history, adequacy of hydration, immobilization, travel, prolonged unusual postures and physical examination and necessary investigations are needed to solve the clinical problems.

CASE DESCRIPTION

41 year old female who was apparently normal before the onset of symptoms presented with 2 weeks history of insidious onset progressive right lower limb oedema and pain mainly confined to the leg and dorsum of foot not associated with fever **(Figure 1)**. There was no history of any trauma/wound in the concerned limb. There was no history of prolonged immobilisation/recent surgeries. There was no history of polyarthralgia/skin lesions/oral ulcers or hematuria. There was no history of weight loss/fever. She was not on any medications. Two days after she was admitted for evaluation, she developed sudden onset

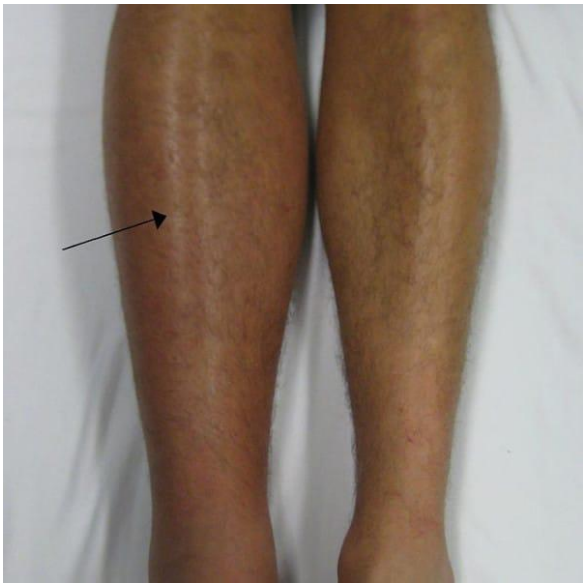

Figure 1. Deep vein thrombosis.

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breathlessness as well after walking a few steps. She gave a history suggestive of similar two episodes in the past few years although the severity of the present episode was much higher. She was a pure vegetarian and her dietary history suggested poor intake of fruits and green leafy vegetables as well. She also gave a history of tingling sensation of her lower limbs for the past few years. As far as her obstetric history was concerned, she had one spontaneous abortion in first trimester of her pregnancy at the age of 20. Her next two pregnancies were uneventful. There was no history of any similar complaints in her family to her knowledge. On examination she was overweight with a BMI of 27. Pallor was present. She had a pulse rate of 100/min and normal blood pressure. Her respiratory rate was 24/min. Her right lower leg was swollen and tender with no local rise in temperature or redness. Chest was clear on auscultation. Cardiac auscultation revealed loud P2. Abdominal and pelvic examination was normal. Neurological examination was normal except for absent ankle jerk. Hence the provisional diagnosis was deep vein thrombosis with possible pulmonary venous thromboembolism with an underlying vitamin B-12 deficiency (because of anaemia and strict vegetarian diet) which might be responsible for a secondary homocysteinemia and hyper coagulable state. Since the patient gave a history suggestive of a recurrent pulmonary embolism and a history of spontaneous first trimester abortion a possibility of APLA syndrome as an additional possibility was also considered. Hence she was advised bed rest and limb elevation and was started on anticoagulation with Heparin after sending the blood sample for aPTT and other relevant investigations. Meanwhile the following were her investigation results. Her Hb was 106 g/L (120-155 g/L), MCV was 98 fL (80-96 fL), WBC count was 7.4 cells*10^9/L (4.5-10 cells*10^9/L), platelet count was 420 cells*10^9/L, ESR was 82 mm/h, vitamin B-12 levels were 62 pmol/L (147-664 pmol/L), VDRL was reactive.

Thus it was clear that the patient had vitamin B-12 deficiency and hence she was started on parenteral hydroxycobalamine and other oral multivitamins as well in addition to the necessary dietary advice. Five days after inpatient care, she was symptomatically better with regard to her lower limb edema and dyspnea. By this time a diagnosis of probable APLA, suspected upon clinical grounds, was reaffirmed as the aPTT was prolonged, VDRL was reactive and ANA was positive. Although the APLA antibodies came out to be negative, the clinical history together with indirect laboratory evidence of anti-cardiolipin antibody (positive VDRL) was sufficient enough to make an early diagnosis of APLA syndrome in this patient so that early intervention to prevent further thrombotic events could be initiated. Hence the patient was started on steroids, Azathioprine and Dabigatran as well in addition to the necessary dietary advice for weight reduction and was discharged to be kept under follow up. On follow up she has been asymptomatic for the last one year. There have not been any further episodes suggestive of thrombotic events.

DISCUSSION

Deep vein thrombosis is a clinical diagnosis. Venous Doppler should not be relied upon for a diagnosis of DVT since the sensitivity of the same is poor especially for distal vein thrombosis [1]. Hence its significance in a clinically evident case of deep vein thrombosis is questionable since the absence of radiological evidence can misguide us in the diagnosis and most importantly would cause a delay in the diagnosis and management of the condition. There was no alternative diagnosis in this patient other than DVT and recurrent pulmonary embolism after history and physical examination. Hence this patient was started on heparin soon after admission. This patient was a pure vegetarian with low intake of vegetables and fruits. Thus it was clear that she was having vitamin B-12 and folic acid deficiency which was suggested by her hemogram showing anemia with high MCV. Even her vitamin B12 levels were low, although it is not necessary to assess the same as vitamin B-12 assay can be normal in some patients with vitamin B-12 deficiency. Thus ultimately, what led us to the diagnosis of vitamin B-12 deficiency in this patient was her dietary history and hem orgasm. Vitamin B-12 deficiency is a well-recognized cause of hyperhomocysteinemia and the latter is a well-recognized cause of thrombosis [2]. Among the various biochemical function of vitamin B-12, the one involved in the synthesis of methionine from homocysteine is clinically important with regard to the occurrence of hyperhomocysteinemia and subsequent predisposition to venous thrombosis in patients with vitamin B-12 deficiency [3]. Hyperhomocysteinemia causes venous thrombosis by variety of mechanisms such as endothelial dysfunction, increase in synthesis of thromboxane and impaired fibrinolysis.

Vitamin B-12 deficiency is extremely common in India. The reasons for this are too many and related to diet, lifestyle and social and cultural issue. In spite of it being a common disorder, its recognition is delayed or missed because the manifestations are diverse in nature, affecting all organs and systems and is often subclinical [4].

Hence, she was started on parenteral hydroxycobalamine, folic acid and other oral multivitamins in addition to the dietary modifications. Although we identified one definite risk factor for thrombosis in this patient, there was still a suspicion of an additional underlying APLA syndrome since she had recurrent episodes of exertional dyspnea, loud P2 on auscultation and one spontaneous abortion at the age of 20 years. Hence aPTT, APLA antibodies and VDRL was tested. The aPTT was prolonged and VDRL was positive although IgG APLA was negative. ANA-IF was positive as well. Thus a diagnosis of probable APLA based on clinical clues and indirect evidence of anti-cardiolipin antibody was made. Here again APLA syndrome secondary to an underlying collagen vascular disorder was diagnosed in the setting of a

thrombotic event and suggestive clues in history, examination and investigations. One should not wait for all the laboratory criteria to be satisfied in such a case. There have been case reports of seronegative APLA syndrome as well [5]. For the same reason, she was started on azathioprine and tapered regimen of steroids. Thus we could identify vitamin B-12 deficiency and APLA syndrome as two potential risk factors in this patient with venous thromboembolism.

CONCLUSION

Clinical evaluation and decision making should remain the cornerstone in the diagnosis and management of any patient. Radiological investigations and laboratory criteria should not be heavily relied upon when the diagnosis is obvious clinically since the patient may benefit remarkably from early intervention. Finally, identifying a potential risk factor for venous thrombosis does not necessarily obviate the need to look for other additional factors contributing to the same.

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