Vitamin B_{12} deficiency presenting with pulmonary embolism: An unusual presentation

To the editor: Thrombotic disease may involve the arterial or venous systems. Arterial thrombosis (AT) typically occurs through erosion and rupture of an atherosclerotic plaque or via platelet-mediated thrombi. Important drivers of AT include inflammation, immune activation and hyperlipidaemia.[1] Venous thrombosis is widely accepted as a combination of stasis and hypercoagulability rather than endothelial damage. Venous thrombi typically consist of fibrin and red blood cells, unlike platelet-rich atherosclerotic plaques.[1]

Hyperhomocysteinaemia appears to traverse the arterial and venous systems as a thrombotic risk factor. It is a documented cause of AT and a theoretical risk factor for venous thrombosis.[2] One important cause of raised homocysteine levels is vitamin B_{12} deficiency.

We present a case of chronic pulmonary thromboembolic disease (TED) in which, after extensive investigation, it was postulated that vitamin B_{12} deficiency with resultant elevated homocysteine was the cause.

A 40-year-old woman with a 1-year history of dyspnoea, palpitations and bilateral lower limb oedema presented with worsening dyspnoea, left-sided pleuritic chest pain, and an intermittent cough that had been occurring for 1 week.

The patient had a significant past medical history of thromboembolic disease. At the age of 19, she had experienced a stroke, with the oral contraceptive being the only identifiable prothrombotic risk factor. A computed tomography pulmonary angiogram (CTPA) 3 months before the current admission confirmed the presence of chronic thromboembolic disease, and the patient had therefore been initiated on warfarin treatment. However, the initial work-up to identify an underlying prothrombotic risk factor did not provide any enlightening results. On further questioning of the patient, a seemingly unrelated history of repeated admissions for symptomatic anaemia emerged. An incomplete work-up for the underlying cause was noted, and treatment with intermittent ferrous sulphate and oral folic acid was started.

Clinical examination at the current admission revealed that the patient was pale with mild jaundice, grade 1 pedal oedema and an oxygen saturation of 83% on room air. There was no neurological fall-out or evidence of lower limb deep-vein thrombosis.

The electrocardiogram (ECG) revealed sinus tachycardia and right heart strain, and dilated pulmonary vessels were noted on the chest radiograph (available as supplementary material online at https://www.samedical.org/file/2066). A repeat CTPA (available as supplementary material online at https://www.samedical.org/file/2069) showed a worsening filling defect compared with the previous image. Echocardiography confirmed a preserved ejection fraction with right ventricular systolic pressures of 70 + 15 (85) mmHg. A bubble test excluded a patent foramen ovale, and a Holter ECG excluded a paroxysmal arrhythmia predisposing to thrombosis.

The laboratory work-up during the current admission (Table 1) revealed grade 2 macrocytic anaemia and grade 2 thrombocytopenia. The international normalised ratio was within the therapeutic range at visits prior to and at the current presentation. The vitamin B_{12} level was low with both positive antiparietal cell and anti-intrinsic factor antibodies. The results of serum folate and iron studies were normal. Gastroscopy showed atrophic gastritis. Further investigation revealed an elevated homocysteine level, postulated as the possible cause of the recurrent TED.

Biochemical work-up (Table 1) also indicated the presence of non-immune haemolysis. This was evidenced by low haptoglobin, raised lactate dehydrogenase, unconjugated hyperbilirubinaemia and a negative direct Coombs test. In addition, few schistocytes were seen on the peripheral smear. In the context of vitamin B_{12} deficiency, ineffective erythropoiesis with resultant intramedullary cell death was the suspected cause of the haemolysis.

Intravenous vitamin B_{12}, oral folate and ferrous sulphate were instituted, resulting in an improvement of the peripheral counts, a decrease in homocysteine levels and resolution of the haemolysis. Warfarin was continued.

Infectious diseases and inherited thrombophilia were ruled out. Vitamin B_{12} deficiency with hyperhomocysteinaemia was presumed to have contributed to the patient's history and subsequent presentations.

Homocysteine is a non-proteinogenic α-amino acid. It is formed by removing the terminal C methyl group from methionine. Although similar to cysteine, it differs by the presence of an additional methylene bridge. In the body, it can be recycled into methionine or converted into cysteine with the assistance of B vitamins.

Hyperhomocysteinaemia is well documented in AT, but its role in venous thromboembolism is controversial.[2] The proposed mechanisms are modified factor V activity, increased tissue factor expression, diminished anticoagulant processes, disrupted fibrinolysis, vascular and endothelial injury, enhanced platelet reactivity and increased thrombin generation.[3] There has previously been interest in hyperhomocysteinaemia as a risk factor for thrombosis, but it lost favour over the past decade because several studies failed to demonstrate a significant association.[4,5] A further confounder in the literature is that treatment of vitamin B_{12} deficiency and the subsequent reduction in homocysteine levels are not associated with a reduction in thrombosis risk.[6]

Vitamin B_{12} deficiency is frequently a result of pernicious anaemia. Our case confirmed this by the presence of antiparietal cell and anti-intrinsic factor antibodies. In addition, our patient's significant and recurrent history of both arterial and venous TED is postulated to be due to hyperhomocysteinaemia secondary to pernicious anaemia.

The delay in diagnosis of the vitamin B_{12} deficiency and *ad hoc* folic acid supplementation may have resulted in an intermittent lowering of the homocysteine level, thereby altering the risk of thrombosis. The homocysteine-lowering properties of folic acid have been documented in the literature.[7]

A rare presentation of vitamin B_{12} deficiency with hyperhomocysteinaemia is that of pseudomicroangiopathy. This entity is characterised by schistocytes, with biochemical evidence

Table 1. Complete patient work-up*

Coagulopathy screen	
Protein C (55 - 123 IU/dL)	66
Protein S (70 - 130 IU/dL)	74
Factor V Leiden mutation	Negative
Prothrombin 20210A mutation	Negative
Autoimmune screen	
Intrinsic factor antibodies	Positive
Antiparietal cell antibodies	Positive
Anti-Sm antibodies	Negative
Anti-ribonucleoprotein antibodies	Negative
Anti-Sjögren's syndrome antigen, A and B	Negative
Anticardiolipin antibody	Negative
Lupus anticoagulant	Negative
Rheumatoid factor (<20 IU/mL)	<10
Full blood count	
Haemoglobin (13.4 - 17.5 g/dL)	8.2
Mean cell volume (83.1 - 101.6 fL)	105.1
White cell count (3.92 - 10.40 × 109/L)	4.29
Neutrophils (1.6 - 8.3 × 109/L)	2
Platelet count (171 - 388 × 109/L)	85
Liver function tests	
Total bilirubin (5 - 21 µmol/L)	57
Direct bilirubin (0 - 3 µmol/L)	7
Coagulation	
D-dimer (0.0 - 0.25 mg/L)	1.65
Anaemia work-up	
Vitamin B12 (141 - 489 pmol/L)	37
Serum folate (8.8 - 60.8 nmol/L)	30
Haptoglobin (0.30 - 2.0 g/L)	0.01
Iron (9.0 - 30.4 µmol/L)	7.7
Transferrin (2.5 - 3.8 g/L)	2.22
Transferrin saturation (15 - 50%)	14
Ferritin (15 - 150 µg/L)	65
Reticulocyte production index	0.4
Other	
Homocysteine (5.1 - 15.4 µmol/L)	20.1
Direct Coombs	Negative
Lactate dehydrogenase (100 - 190 U/L)	>2 500
HIV	Negative

*The values in parentheses are the normal laboratory values.

of haemolysis. The most common mechanism of schistocyte development is marked anisopoikilocytosis secondary to ineffective erythropoiesis. It is also proposed that hyperhomocysteinaemia has the potential to induce endothelial damage, driving red cell fragmentation.[8]

This case highlights the importance of considering rarer causes of TED in patients with young-onset and recurrent thrombosis. In cases of hyperhomocysteinaemia, a vitamin B_{12} deficiency should be sought, and lifelong replacement therapy should be instituted to prevent recurrence of TED.

In conclusion, in patients with young-onset and recurrent TED of unexplained aetiology, hyperhomocysteinaemia secondary to vitamin B_{12} deficiency should be considered a possible cause.

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