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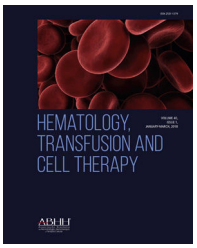

Case Report

Simultaneous pulmonary thromboembolism and superior mesenteric venous thrombosis associated with hyperhomocysteinemia secondary to pernicious anemia-induced vitamin B12 deficiency

Leonardo Rodrigues de Oliveira, Jordana Rafaella Fonseca*

Universidade Federal do Triângulo Mineiro (UFTM), Uberaba, MG, Brazil

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Introduction

The identification of conditions predisposing a patient to thrombosis is essential for the prevention and treatment of acute myocardial infarction, stroke, pulmonary embolism, and venous thrombosis. Accordingly, this knowledge should reduce the morbidity and mortality rates of patients with venous or arterial thrombosis.

Hyperhomocysteinemia is associated with an increased risk of arterial thrombosis (e.g. myocardial infarction, stroke, peripheral vascular disease) and may be associated with a higher risk of venous thrombosis.[1,2] Therefore, clinical conditions normally associated with hyperhomocysteinemia, such as folic acid and vitamin B12 deficiencies, may also be associated with a higher risk of thrombosis.

The present report presents an unusual case of multiple and simultaneous venous thromboses in a patient with hyperhomocysteinemia secondary to pernicious anemia-induced vitamin B12 deficiency, who was treated with short-term anticoagulation therapy and vitamin B12 and folic acid supplementation.

Case report

A 58-year-old man was admitted to the emergency room owing to acute pain in the right hemiabdomen lasting three days. No fever, jaundice, or respiratory, urinary, or gastrointestinal changes had occurred. The patient's comorbidities included Chagas disease (indeterminate chronic phase) and systemic arterial hypertension (regular losartan use). He had no history of tobacco or alcohol use, recent surgery, or prolonged immobilization (including long trips). A physical examination at the time of admission revealed normal findings, with no signs of peritoneal irritation.

Laboratory tests revealed discreet normocytic-normochromic anemia [hemoglobin (Hb): 12.0 g/L; mean corpuscular volume (MCV): 98.1 fL; and mean corpuscular hemoglobin: 33.1 pg] and increased serum lactate

* *Corresponding author at*: Oncology, Radiotherapy, Hematology and Hemotherapy Unit, Universidade Federal do Triângulo Mineiro (UFTM), Rua Getulio Guarita, sn° CEP: 38025-180 Uberaba, MG, Brazil. Tel.: +55 34 33185158.
E-mail address: leonardorodoli@hotmail.com (L.R. Oliveira).

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dehydrogenase (238 U/L; reference range: 135–225 U/L) and ferritin levels (671 ng/dL; reference range: 30–300 ng/dL). Furthermore, the following exams yielded normal results: total bilirubin (0.84 mg/dL; reference range: <1.2 mg/dL), amylase (33 U/L; reference range: 0–86 U/L), aspartate aminotransferase (19 IU/L; reference range: <40 IU/L), alanine aminotransferase (17.7 IU/L; reference range: <42 IU/L), creatinine (0.7 mg/dL; reference range: 0.6–1.2 mg/dL), alkaline phosphatase (205 IU/L; reference range: <270 IU/L) and γ-glutamyl transferase (29 IU/L; reference range: 7–45 IU/L). An initial hemostasis evaluation yielded the following values: activated partial thromboplastin time (TTPa): 34.8 seconds (reference range: 25–34 seconds), prothrombin time: 15.2 seconds (reference range: 10–15 seconds), international normalized ratio (INR): 1.3 and fibrinogen: 275 mg/dL (reference range: 200–400 mg/dL).

The result of an abdominal ultrasonography was normal. An intravenous contrast-enhanced computed tomography of the abdomen, performed because of persistent pain, indicated superior mesenteric vein thrombosis and pulmonary infarction (lower lobe of right lung). Chest angiotomography confirmed the pulmonary embolism, and echo Doppler ultrasound of the lower limbs revealed deep vein thrombosis (total occlusion of the right superficial femoral vein). Transthoracic echocardiography did not detect any intracardiac thrombus, dysfunction of the right heart chambers or any sign of pulmonary hypertension. There was no evidence of malignancy.

Treatment was initiated with enoxaparin (1 mg/kg subcutaneously every 12 hours) followed by the oral anticoagulant warfarin to achieve an INR between 2 and 3. Furthermore, the observation of multiple simultaneous thromboses led to an outpatient investigation of thrombophilia. Antinuclear antibody, rheumatoid factor, venereal disease research laboratory (VDRL), serology (human immunodeficiency virus, human T cell lymphotropic virus and viral hepatitis B and C), lupus anticoagulant, anticardiolipin (IgG and IgM) and anti-β2-glycoprotein 1 (IgG and IgM) tests were negative. Furthermore, this investigation did not detect the paroxysmal nocturnal hemoglobinuria clone (using a flow cytometry technique), JAK2 V617F mutation, factor V Leiden mutation or the prothrombin gene G20210A mutation.

The patient's antithrombin, protein C and protein S activities were 102% (reference range: 79–125%), 109% (reference range: 72–106%) and 58% (reference range: 55–160%), respectively at eight weeks after completing the oral anticoagulation treatment. His fasting serum homocysteine level was high (65.5 μmol/L; reference range: 5.4–16.2 μmol/L), and he exhibited a vitamin B12 deficiency (30 pg/mL; reference range: 211–946 pg/mL) while maintaining a normal serum folic acid level (15.8 ng/mL; reference range: 4.6–18.7 ng/mL). A diagnosis of secondary hyperhomocysteinemia attributed to pernicious anemia-induced vitamin B12 deficiency was made establishing a thrombophilic etiology indicated by reactivity to an anti-parietal cell antibody and the exclusion of methyltetrahydrofolate reductase gene C677T and A1298C mutations.

The treatment of this patient comprised parenteral vitamin B12 replacement (associated with vitamin B6 and thiamine) and oral folic acid replacement (5 mg/day). Vitamin replacement therapy was maintained regularly even after the anemia was corrected (Hb: 16.2 g/L; MCV: 80.1 fL). During outpatient follow up, the patient continued to receive anticoagulation therapy for ten months. The oral anticoagulation was suspended after his serum vitamin B12 level had normalized (579 ng/dL) and his serum homocysteine level had decreased (19.2 μmol/L). No thrombotic recurrences were detected in a 26-month follow-up evaluation.

The patient's monozygotic twin brother was invited to undergo clinical and laboratory evaluations, during which a vitamin B12 deficiency, mildly elevated homocysteine levels (20 μmol/L) and seroreactivity to anti-parietal cell antibodies were detected. Despite the absence of cytopenia or a history of thrombosis, folic acid, vitamin B6 and vitamin B12 treatment was initiated for the patient's twin.

Discussion

Venous thromboembolism (VTE) is an important cause of intra- and extra-hospital morbidity and mortality. Thus, it is essential to identify the factors associated with an increased thrombotic risk during the establishment of measures to prevent and treat thromboses.

Hyperhomocysteinemia, although a risk factor for thrombosis, is more consistently associated with arterial events such as stroke, myocardial infarction and peripheral vascular disease.[1,2] The association between hyperhomocysteinemia and venous thrombosis remains highly controversial.[1–8] Previous studies have reported two- to three-fold higher risks of VTE among patients with hyperhomocysteinemia.[4,9,10] Furthermore, a meta-analysis of 24 retrospective and three prospective epidemiological studies reported a modest, although real, association between hyperhomocysteinemia and VTE (27% increase in risk in the prospective studies, and 60% increase in retrospective studies for every 5-μmol/L increase in serum homocysteine levels).[11] Moreover, an increased incidence of venous thrombosis has been observed among Brazilian patients with hyperhomocysteinemia.[12]

Hyperhomocysteinemia is the result of defective renal homocysteine excretion or deficiencies in enzymes or cofactors associated with pathways that convert homocysteine to methionine or cysteine via remethylation or transsulfuration, respectively.[2,3,9] Several mechanisms have been proposed to link hyperhomocysteinemia with endothelial damage/dysfunction and consequently an increased risk of thrombosis, including decreased levels of nitric oxide, asymmetric dimethylarginine catabolism reduction, vascular smooth muscle proliferation, platelet activation via increased thromboxane A2 biosynthesis, leukocyte activation, disruption of the hemostatic balance between coagulant and anticoagulant endogenous systems and inhibition of fibrinolysis.[1,3,7]

Dietary restriction, nitric oxide abuse, malabsorption states (e.g., pernicious anemia, celiac disease, *Helicobacter pylori* infection) and adverse effects of various drugs (e.g., metformin, omeprazole, oral contraceptives) are known causes of vitamin B12 deficiency.[8,9] Pernicious anemia is an autoimmune condition that may co-occur with a loss of vitamin B12 absorption and consequent increase in the homocysteine serum levels. Accordingly, patients with pernicious anemia would be expected to have a higher incidence of thrombosis.[13,14] The present case is peculiar because it

involves a patient with multiple simultaneous thromboses (including the abdominal vein) and a moderately elevated serum homocysteine level caused by a pernicious anemia-induced vitamin B12 deficiency. Few previous articles have reported an association between pernicious anemia and thrombosis[9,14] although some authors have reported recurrent or unusual vascular bed thrombosis in patients with vitamin B12 deficiency.[6,8,15]

Currently, no treatment has been established for hyperhomocysteinemia.[3] Although folic acid and vitamin B6 and/or vitamin B12 supplementation can reduce serum homocysteine levels, this does not necessarily confer a reduced risk of thrombosis. Accordingly, this failure to mitigate risk raises questions regarding the actual benefits of vitamin supplementation and the potential participation of unidentified thrombosis mediators independently of homocysteine levels.[1,3,8,10,13] However, some authors have speculated about the benefits from such treatment. Weiss et al. suggested that folic acid supplementation reduces the risk of thrombosis by promoting nitric oxide biosynthesis independently of the homocysteine level.[1] In this case, no recurrence of thrombosis was observed during vitamin B12 and folic acid supplementation.

In conclusion, studies of the intrinsic relationship between homocysteine, vitamin B12 and venous thrombosis remain necessary. In particular, studies of hyperhomocysteinemia in patients with unexplained venous thrombosis should be conducted systematically, with the intent to identify the etiology and provide prophylactic interventions for secondary VTE. Finally, the absence of anemia and macrocytosis as signs of vitamin B12 or of folic acid deficiency should not discourage studies on hyperhomocysteinemia.

Conflicts of interest

The authors declare no conflicts of interest.

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