Scope
Volume 16 Number 02 June 2026

Deep Vein Thrombosis of the Lower Limb on Hyperhomocysteinemia Secondary to Biermer's Disease

R. Bouagaga[1], Z. Khammar[1], R. Berrady[1], A. El Maghraoui[2]
[1]Laboratory of Human Pathology, Biomedicine and Environment, Faculty of Medicine, Pharmacy and Dentistry of Fez, Sidi Mohammed Ben Abdellah University. (Morocco).
[2]Laboratory: Processes, Materials and Environment (LPME), Sciences and Technology Faculty, Sidi Mohammed Ben Abdellah University. P. O. Box 2202 Fez (Morocco).

Correspondence Author : **R. Bouagaga**

Abstract: Venous thrombosis mainly poses a problem of etiological investigation, some clinical and/or biological elements can guide this research. We report a case of deep venous thrombosis of the lower limb complicated by a pulmonary embolism, with a slight macrocytic anemia, which suggested hyperhomocysteinemia, secondary to Biermer's disease (chronic vitamin B12 deficiency). Effective anticoagulation associated Long-term vitamin B12 replacement therapy has prevented the occurrence of thrombotic recurrence.

Keywords: Thrombosis, macrocytosis, secondary hyperhomocysteinemia, vitamin B12 deficiency, Biermer's disease

Introduction

Venous thromboembolic disease (VTE) is characterized by the formation of a blood clot or thrombus that obstructs a vein and blocks blood flow [1]. It includes two clinical entities: deep vein thrombosis (DVT) and pulmonary embolism (PE), which in 90% of cases is secondary to DVT of the lower limbs [2,3]. It is a frequent and multifactorial pathology [4], which often poses a problem during the etiological investigation, particularly in young subjects [5]. Recent years have seen the recognition of a good number of factors favoring a state of thrombophilia, constitutional or acquired [6]. Through our observation we recall the implication of hyperhomocysteinemia secondary to B12 deficiency in thromboembolic disease.

Clinical Case

A 48-year-old patient was hospitalized in the department for the management of left sural thrombophlebitis. Her medical history was without any notable particularity. The

physical examination on admission found an asthenic patient, with a swelling of the left calf that was hot and painful, and a Homans sign that was positive. The rest of the somatic examination was without detectable abnormality. An ultrasound Doppler confirmed the diagnosis of thrombosis of the left posterior tibial vein. On the biological level, there was an inflammatory syndrome with a C-reactive protein at 35.7 mg/l.

The blood count showed white blood cells 8600/mm³, hemoglobin 11.2g/dl with macrocytosis 109fl and platelets 156000/mm³. The prothrombin rate was 87% with an activated partial thromboplastin time of 32 seconds for a control at 30 seconds. Creatinine was 6.22mg/l. The patient was put on heparin.

An etiological assessment was carried out, Behçet's disease was ruled out on clinical criteria (absence of bipolar aphthosis, uveitis, arthralgia and skin lesions), as well as lupus disease (absence of suggestive signs and antinuclear antibodies) and antiphospholipid syndrome (absence of miscarriages, and antiphospholipid antibodies). There was no nephrotic syndrome (normal albuminemia with negative 24-hour proteinuria), nor tumor cause (cervical-thoraco-abdomino-pelvic CT scan, mammography-breast ultrasound, cervical-uterine smear). Moreover, the CT scan performed as part of the etiological investigation revealed bilateral pulmonary embolism (Figure 1). The thrombophilia assessment showed hyperhomocysteinemia at 52.19 µmol/l (protein C, protein and antithrombin III levels were normal, as well as factor V Leiden mutations and factor II mutation were absent). The existence of macrocytic anemia at 11.2g/dl led to a vitamin B12 dosage which was low at 80pg/ml (correct liver function test, normal TSH). Anti-intrinsic factor antibodies were positive and esophago-gastro-duodenal fibroscopy with fundic biopsy revealed atrophic gastritis with intestinal metaplasia associated with hyperplasia of neuroendocrine cells in favor of Biermer's disease.

The evolution of phlebitis under heparin, then oral anticoagulant was satisfactory, Vitamin B12 (subcutaneously) prescribed for life led to normalization of the blood count.

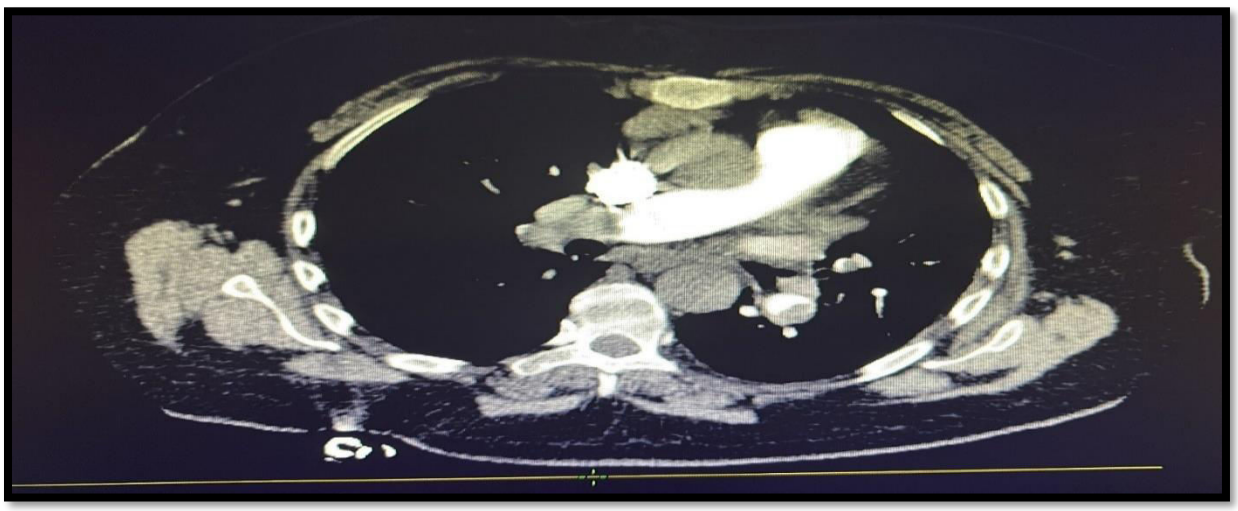

Figure 1: CT scan image showing bilateral pulmonary embolism

Discussion

Our reported observation concerns a case of Biermer's disease in a young female subject, diagnosed on the occasion of a mild macrocytic anemia (Figure 2)

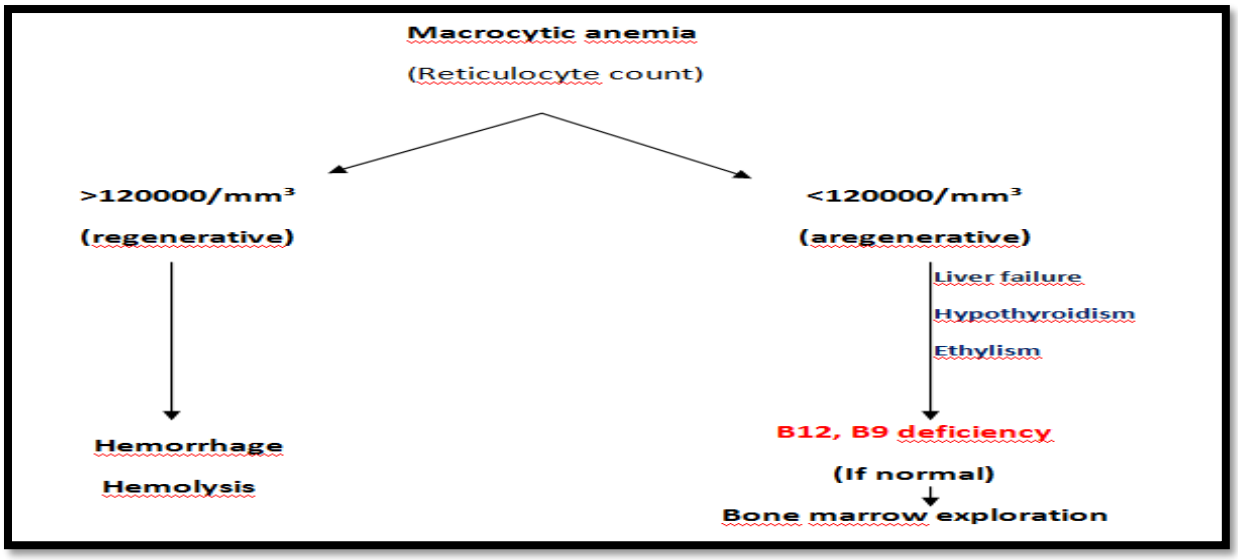

Figure 2: What to do when faced with macrocytic anemia

She was complicated by a DVT of the lower limb and pulmonary embolism. The mechanism invoked is hyperhomocysteinemia; this was confirmed by the biological assessment which found a significantly high level.

The association of even moderate hyperhomocysteinemia with an increased venous thrombotic risk is now well established [7,8]. Hyperhomocysteinemia can be classified according to its cause, prevalence and severity [9].

Table 1: Etiologies of hyperhomocysteinemia according to severity [9]

Etiology	Hyperhomocysteinemia moderate (12-30µmol/l)	Hyperhomocysteinemia Intermediate (31-100µmol/l)	Hyperhomocysteinemia severe (>100µmol/l)
Genetic abnormalities	-Heterozygous MTHFR mutation -Heterozygous CBS mutation -Transcobalamin polymorphism	-Vitamin B12 deficiency due to a genetic defect - Heterozygous MTHFR mutation	-Homozygous CBS mutation -Homozygous MTHFR mutation
Acquired abnormalities	-Nutritional deficiency in folate, vitamins B12, B6, choline, serine -High methionine intake -Pathologies: Renal failure Cancer Psoriasis Hypothyroidism Diabetes Drug addiction	-Nutritional deficiency in cofactors -Other pathologies -Treatment with drugs	-Nutritional deficiency in cofactors

The most severe cases (total homocysteinemia > 100 µmol/l) are due to a deficiency of the genes coding for cystathionine b-synthase. Moderate hyperhomocysteinemia is the most common form; it is linked to a mutation of the gene coding for key enzymes of homocysteine metabolism and/or an inadequate status of folates, vitamins B6 and B12 [10].

Biermer's disease, which is a chronic vitamin B12 deficiency, is one of the causes of hyperhomocysteinemia [11]. In vitamin B12 deficiency, the homocysteine level is on average 20 to 30 µmol/l (moderate hyperhomocysteinemia) [12].

Even moderate hyperhomocysteinemia increases the risk of thrombosis through complex mechanisms, involving: [9,13,14,15,16]

Endothelial dysfunction: Elevated homocysteine leads to endothelial damage, which promotes platelet activation and exposure of underlying collagen. This prompts thrombus formation due to platelet proliferation and aggregation, key elements of the thrombotic process.

Activation of the coagulation pathway: Hyperhomocysteinemia can also affect the coagulation cascade. It inhibits the expression and activity of thrombomodulin on the surface of endothelial cells which allows the activation of protein C (a powerful natural anticoagulant), and increases the activity of factor V and tissue factor, which promotes the formation of thrombin, an enzyme essential for clot formation.

Impairment of fibrinolysis: by decreasing the synthesis of tissue plasminogen activator (tPA).

Treatment of acquired hyperhomocysteinemia will depend on the cause and/or the vitamin deficiency identified, while treatment with folic acid, at a rate of 0.5 to 5 mg per day, combined or not with vitamin B12 (0.5 mg/day orally) or vitamin B6 (16 mg/day), appears relatively effective in the treatment of genetic methionine hyperhomocysteinemia [17,18].

In our observation, the therapeutic attitude was based on anticoagulant treatment with LMWH in the acute phase with a relay by oral anticoagulant, associated with vitamin B12 supplementation administered intramuscularly in the form of cyanocobalamin. The dosage of vitamin B12 administration was of 1000µg/day for 7 days, then 1000µg/week for 1 month. Treatment is continued indefinitely at a rate of one monthly intramuscular injection of 1000 µg. Monitoring by gastroduodenal endoscopy is recommended every 2 years in the absence of macroscopic lesions in the stomach.

Conclusion

The association between vitamin B12 deficiency, hyperhomocysteinemia and the occurrence and/or recurrence of thrombotic phenomena has already been reported in the literature [19]. Biermer's disease is a significant cause of acquired hyperhomocysteinemia, often underdiagnosed due to the frequency of atypical forms, observed at subclinical stages [12]. Early detection of Biermer's disease in patients with unexplained DVT allows specific management integrating effective anticoagulation and

treatment with long-term vitamin B12, aimed at preventing the occurrence of thromboembolic recurrence [5,12].

Conflicts of interest

The authors declare no conflict of interest.

References:

1. **Hong J, Lee JH, Lee JY, Lee JO, Choi WI, Ahn S, et al.** Seasonal variation in pulmonary embolism versus deep vein thrombosis incidence. Korean J Intern Med. 2020;35(3):682–691.
2. **Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al**. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2020;41(4):543–603.
3. **Pessinaba S, Atti YD, Baragou S, Pio M, Afassinou Y, Kpélafia M, et al.** Pulmonary embolism in Lomé: a retrospective study of 51 cases. Pan Afr Med J. 2017;27.
4. **Beckman MG, Hooper WC, Critchley SE, Ortel TL.** Venous thromboembolism: a public health concern. Am J Prev Med. 2010 Apr;38(4 Suppl): S495-501.
5. **A. Kharchafi*, Z. Oualim, T. Amezyane, F. Mahassin, D. Ghafir, V. Ohayon, MI Archane.** Biermer's disease and venous thrombosis. About two observations. Rev Med Interne 2002; 23: 563-6
6. **Alhassan S, Pelinescu A, Gandhi V, Naddour M, Singh AC, Bihler E.** Clinical Presentation and Risk Factors of Venous Thromboembolic Disease. Crit Care Nurs Q.Sept 2017;40(3):201-9.
7. **Den Heijer M, Koster T, Blom HJ, Bos GMJ, Briët E, Reitsma PH, et al**. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med 1996; 334:759-62
8. **Welch GN, Loscalzo J.** Homocysteine and athero-thrombosis. N Engl J Med 1998; 338:1042-50.
9. **J.-C. Guilland a, A. Favier b, G. Potier de Courcy c, P. Galan c, S. Hercberg c.** Hyperhomocysteinemia: cardiovascular risk factor or simple marker? 1. Fundamental data. Pathology Biology 51 (2003) 101–110
10. **Kang SS, Zhou J, Wong PWK, Kowalisyn J, Strokosch G.** Intermediate homocysteinemia: a thermolabile variant of methylenetetrahydrofolate reductase. Am J Hum Genet 1988; 43:414–21.
11. **Diop MM, Berthe A, Andrès E, Toure PS, Reimund JM, Sarr MM, Diousse P, Faye FA, Diop BM, Ka MM**. Biermer's anemia and its confusing presentations: an update, with a focus on black subjects. mt 2015; 21 (5): 340-6 doi:10.1684/met.2015.0510
12. **Angelica Loup-Leuciuc1, Pierre-Jean Loup2, Tommaso Lombardi3, Jacky Samson1.** Vitamin B12 deficiency (part 1): update. Med Buccale Chir Buccale 2011;17:211-224
13. **Hofman MA, Lalla E, Lu Y, Gleason MR, Wolf BM, Tanji N, et al.** Hyperhomocysteinemia enhances vascular inflammation and accelerates atherosclerosis in a murine model. J Clin Invest 2001; 107:675–83.

14. **McCully KS, Olszewski AJ, Vezeridis MP.** Homocysteine and lipid metabolism in atherogenesis: effect of the homocysteine thiolactonyl derivatives, thioretinaco and thioretinamide. Atherosclerosis 1990; 83:197–206.
15. **Harpel P, Zhang X, Borth W**. Homocysteine and hemostasis: pathogenic mechanisms predisposing to thrombosis. J Nutr 1996:1285S–9S
16. **Emsley A, Jeremy J, Gomes G, Angelini G, Planer F.** Investigation of the inhibitory effects of homocysteine and copper on nitric oxide-mediated relaxation of rat isolated aorta. Br J Pharmacol 1999; 126:1034–40
17. **Chasan-Taber L, Selhub J, Rosenberg IH, Malinow MR, Terry P, Tishler PV, et al.** A prospective study of folate and vitamin B6 and risk of myocardial infarction in US physicians.J Am Coll Nutr 1996; 15:136-43.
18. **R Clarke. Homocysteine Lowering Trialists' Collaboration.** Lowering blood homocysteine with folic acid-based supplements: metaanalysis of randomized trials. Br Med J 1998; 316:894-8
19. **Julien Pruvot.** Portal venous thrombosis due to profound vitamin B12 deficiency. 10.1684/sanmt.2023.191.