On the Association Between Recurrent Venous Thromboembolic Disease and Hyperhomocysteinemia

To the Editor: Pulmonary embolism is generally caused by the migration of a thrombus located in the deep venous territory of the lower limbs. It is highly prevalent and has high morbidity and mortality.[1,2] Recurrent venous thromboembolic disease (VTD) is a complex problem requiring an exhaustive multidisciplinary approach. The most common genetic risk factor for VTD affecting the Caucasian population is factor V Leiden, although new triggers are being discovered.[3] We present a case of VTD associated with hyperhomocysteinemia (HHC) that required a complex metabolic and hematologic workup.

The patient was a 57-year-old man who was an active smoker with no clinical or functional signs of chronic obstructive pulmonary disease. He reported a 3-day history of dyspnea and pleuritic chest pain in the left hemithorax, followed a few days later by pain in the right hemithorax. His clinical history included several recurring episodes of deep venous thrombosis and pulmonary thromboembolism 2 years before the present episode. He had been treated with oral anticoagulants, which he had stopped taking some months earlier. Examination showed the patient to be hemodynamically stable and cyanotic, breathless at rest, with a respiratory rate of 30 breaths/min. Heart sounds were normal; chest auscultation revealed a soft murmur in both hemithoraces, with coarse basilar rales on the right. The abdomen and lower limbs were normal. The most relevant laboratory finding was a leukocyte count of 12 720 cells/μL in the hemogram; blood biochemistry, ionogram, and coagulation factors were normal. Resting blood gas results were as follows: pH 7.44, PaO_2 40 mm Hg, $PaCO_2$ 36 mm Hg, bicarbonate 24 mEq/L, and SaO_2 70%. An electrocardiogram showed a sinus rhythm, with a heart rate of 120 beats/min and the presence of an S1Q3T3 pattern in leads II-III. A chest radiograph revealed shallow breathing, left basal pulmonary condensation, and a small pleural effusion. Computed tomography angiography showed multiple intravascular filling defects in the lobular branches of both lower lobes and peripheral pulmonary infarct in the lower left lobe, suggestive of a bilateral pulmonary thromboembolism (Figure). The Doppler ultrasound of the lower limbs was normal. The hypercoagulability study revealed an international normalized ratio of 0.99, prothrombin activity of 119%, thromboplastin time of 27 seconds, fibrinogen 430 mg/mL, plasminogen 120%, protein C 116%, protein S 111%, resistance to activated protein C 0.6 (normal), lupus anticoagulant 1.4 (normal), immunoglobulin (Ig) for anticardiolipin 8.6 IU/mL and IgM below 7.5 IU/mL, antithrombin III 89%, factor V Leiden 0.9, and normal factor II level. The blood homocysteine concentration was 16.3 μmol/L (normal, 0-15). The genetic study to determine the *C677T* methylenetetrahydrofolate reductase (MTHFR) polymorphism was positive, the patient being a heterozygous carrier. Sodium heparin (48 000 U/d) was administered and anticoagulation was achieved within the therapeutic interval. The patient progressed favorably and was discharged with oral warfarin and folic acid supplements.

The study of factors implicated in recurrent VTD is a fascinating area of medicine, and scientific research is gradually adding to currently known causes. These include HHC, a condition associated with genetic causes and with deficiencies of folic acid and vitamin B_{12}.[4] HHC has been considered a vascular risk factor (atherogenic and thrombogenic) ever since the studies by McCully in 1969 (mentioned in Fernández Miranda et al[5]), although much doubt currently surrounds this association. HHC is defined as a cause of VTD in adults, there being few studies on young people.[5,6] Some studies have tried to establish a relationship between the *C677T* MTHFR polymorphism and the risk of developing VTD, although results have been inconsistent.[1,5,6] The diagnosis in our patient, who had a history of recurrent VTD, was confirmed by the high level of homocysteine and the presence of the *C677T* MTHFR polymorphism, and both the response to treatment and the outcome were good. In young people, however, these abnormalities have not been established as a risk factor for recurrent VTD.

The recently published results of a meta-analysis involving different populations with VTD (including young patients) revealed a relationship between HHC and VTD.[6] However, attempts to analyze the relationship between VTD and the *C677T* MTHFR polymorphism have revealed it to be weak; therefore, the mutation cannot be shown to be the risk factor for developing VTD. More light has been shed by the results of a prospective study by Frederiksen et al (cited in Fernández Miranda et al[5] and Wald et al[6]) with 9238 patients followed for 23 years, which did not reveal a greater risk of VTD among the homozygous population with HHC.[5,6] Research currently under way might remove many doubts. Studies confirming that a reduction in homocysteine levels is associated with a fall in vascular morbidity and mortality are necessary.[4-6]

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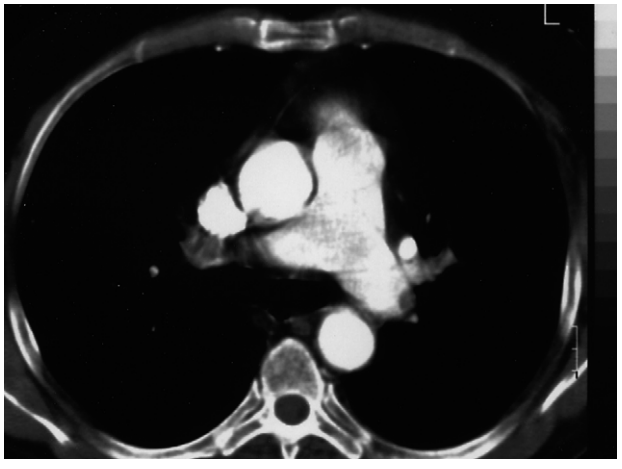
1. British Thoracic Society Standards of Care Committee. Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected pulmonary embolism. Thorax. 2003;58:470-84.
2. Cicero A, Jiménez D. Diagnóstico y tratamiento de la tromboembolia de pulmón. In: Mañas E, Pérez E, Jareño J, editors. Manual de actuación en patología respiratoria. Madrid: Ergón; 2004. p. 251-7.
3. Uresandi F, Blanquer J, Conget F, de Gregorio MA, Lobo JL, Otero R, et al. Guía para el diagnóstico, tratamiento y seguimiento del embolismo pulmonar. Arch Bronconeumol. 2004;40:580-94.
4. González AJ. Homocisteína y escasa ingestión de folatos: dos formas complementarias de deterioro. Med Clin (Barc). 2005;124:541-3.
5. Fernández Miranda C, Coto A, Martínez J, Gómez P. Efecto de la hiperhomocisteinemia y de la mutación metilentetrahidrofolato reductasa 677-T en el riesgo de tromboembolia venosa en adultos jóvenes. Med Clin (Barc). 2005;124:532-4.
6. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease; evidence on causality from a meta-analysis. BMJ. 2002;325:1202-6.



Computed tomography angiogram with a pulmonary embolism in a branch of the left lower lobe artery.