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LETTER TO THE EDITOR

Unexplained recurrent venous thrombosis in a patient with *MYH*9-related disease

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To the Editor

*MYH*9-related disease (*MYH*9-RD) comprises a spectrum of autosomal-dominant thrombocytopenias: May–Hegglin anomaly, Sebastian, Fechtner, and Epstein syndrome, all caused by mutations in *MYH*9, the gene for non-muscle myosin heavy chain IIA (NMMHC-IIA) [1]. Patients present since birth with macrothrombocytopenia and cytoplasmic aggregates of NMMHC-IIA in granulocytes recognizable by specific antibodies. These aggregates are often evident on May–Grünwald–Giemsa (MGG)-stained blood films as Döhle-like inclusions. Patients with *MYH*9-RD also present the risk of developing during lifetime the additional clinical features of glomerulonephritis, hearing loss and/or cataracts [2]. Here we report a patient with *MYH*9-RD who experienced idiopathic recurrent venous thromboembolism. The patient was a 40-year-old man with a history of epistaxis and bleeding gums since childhood. Thrombocytopenia was identified for the first time at age 23, when he presented with idiopathic left iliac and femoral vein thrombosis and multiple bilateral segmental defects in a perfusion lung scan. There was no family history of thrombosis. He was treated with heparin and then acenocumarol, which was discontinued because of thrombocytopenia. Four months later, he experienced recurrent proximal venous thrombosis in the contralateral leg, and received oral anticoagulants during 4 years. On follow-up, platelet counts ranged between 18 and 56×10^9/l and he was given prednisone with minor increases in platelet counts. Twelve years after initial presentation, he experienced thrombosis of the inferior vena cava and, 1 year later, calf vein thrombosis. Thrombophilia screening revealed normal protein C, protein S, antithrombin III and plasminogen levels, normal euglobulin lysis time and no activated protein C resistance. Tests for lupus anticoagulant were normal and IgG and IgM anticardiolipin, anti-β_2-glycoprotein I, antiphosphatidylserine and antiphosphatidylinositol antibodies were negative. Platelet GPIIIa genotype was HPA-1a/1a. Factor V Leiden and prothrombin 20210A polymorphisms were absent, while he was homozygous for methylenetetrahydrofolate reductase (MTHFR) 677T polymorphism. Homocysteine level by ELISA was 26.2 μmol/l (reference value <18.2 μmol/l). At age 36, urinanalysis revealed proteinuria and microhematuria and he subsequently developed nephrotic syndrome and end-stage renal failure. Homocysteine levels rose to 47.8 μmol/l. Hemodialysis was started and he experienced thrombosis of the radiocephalic arteriovenous fistulae. When macrothrombocytopenia was discovered in the patient's daughter,

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a diagnosis of inherited thrombocytopenia was considered for the first time, and the patient was referred to our institution. His platelet count by phase microscopy was 35×10^9/l and mean platelet volume (MPV) was 11.6 fl (reference values 6.5–10.5 fl). MGG-stained blood smears showed giant platelets and absence of Döhle-like inclusions in granulocytes. Audiometric examination revealed bilateral sensorineural hearing loss, while ophtalmological examination was normal. In the patient's affected daughter, platelet count was 70×10^9/l, MPV was 12.5 fl and urinanalysis was normal, whereas no abnormalities were found in the propositus' parents, three brothers and two sons. Immunofluorescence analysis on blood smears revealed cytoplasmic aggregates of NMMHC-IIA in polymorphonuclear granulocytes characteristic of *MYH*9-RD. Mutational screening of the *MYH*9 gene identified a G2105>A missense mutation resulting in the R702H substitution, which was previously described in several *MYH*9-RD pedigrees [2]. At age 40, the propositus presented with subarachnoid hemorrhage due to rupture of an intracranial aneurysm and died during endovascular treatment. The occurrence of a thrombotic diathesis in a patient with *MYH*9-RD and severe thrombocytopenia deserves some comments since such an association has never been reported. Thorough thrombophilia screening revealed that the patient was homozygous for the MTHFR677T polymorphism and had elevated homocysteine levels. Hyperhomocysteinemia predisposes to thrombosis by producing a complex damage of endothelial cells [3]. However, although hyperhomocysteinemia demonstrated a modest association with venous thrombosis [4], it does not increase the risk of deep-vein thrombosis among subjects under the age of 30 [5]. On this basis, it is unlikely that isolated mild hyperhomocysteinemia can justify by itself such a severe thrombotic disease in a young patient. Therefore, as no additional risk factors were detected, we have to consider the possibility that the *MYH*9 mutation, on its own or in cooperation with hyperhomocysteinemia, contributed to the thrombotic predisposition, although the potential underlying mechanisms remain speculative. Although the role of NMMHC-IIA in endothelial cells is almost completely unknown, recent evidence indicated that it is the main myosin isoform expressed in these cells [6], and suggested that it is involved in intracellular signaling [7]. On this basis, we can hypothesize that *MYH*9 mutation might induce endothelial cell dysfunction, further favouring thrombus formation. Alternatively, abnormality of platelet NMMHC-IIA could result in platelet hyperreactivity, although this phenomenon has never been reported in *MYH*9-RD patients. Long-term follow-up of large series of patients with *MYH*9-RD may identify additional patients with a concomitant thrombotic diathesis, and help to clarify whether this was a fortuitous association in our patient or a link between these two conditions exists.

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