ABSTRACT
Idiopathic hypereosinophilic syndrome is a rare condition characterized by extremely high peripheral blood eosinophil counts. Patients with idiopathic hypereosinophilic syndrome are at increased risk for thrombosis. The coexistence of idiopathic hypereosinophilic syndrome with other thrombotic disease is rare. We present an additional case of idiopathic hypereosinophilic syndrome and factor V Leiden mutation, which lead to deep vein thrombosis.

Case Report. A 29-year-old male patient presented with pain and swelling in the left leg that had started 2 weeks earlier and was increasing since then. He indicated that he had experienced a similar condition 8 years ago that yielded a diagnosis of deep vein thrombosis (DVT) and HES. He had used prednisolone 1 mg/kg initially with a subsequent tapering to a lower dose, for 6 months and an additional oral anticoagulant medication. Physical examination of the patient revealed hepatomegaly (2 cm), a left leg diameter of 43 cm and a right leg diameter of 38 cm and a positive Homan sign on the left side. Routine hematologic examination results were as follows: hemoglobin 14.7 g/dl [normal range (NR) 13.6-17.2 g/dl], white blood cell count 18.6 ×10⁹/l (NR 4-10 × 10⁹/l), absolute eosinophil count 10.8 × 10⁹/l (NR 0-0.5 × 10⁹/l), platelets 139 × 10⁹/l (NR 150-400 × 10⁹/l) and eosinophilia in the differential. Bone marrow aspiration was performed,
and a hypercellular bone marrow with a 10/1 ratio of myeloid/erythroid cells and 52% of eosinophilic cells was determined in the microscopic examination (Figure 1). Cytogenetic analysis revealed a 46;XY karyotype. Philadelphia chromosome was negative by banding prothrombin time, activated partial thromboplastin

IgM, IgE, vitamin B12, folate and tumor markers were in normal ranges. All biochemical tests were normal except for aspartate transaminase (AST), which was 67 U/l (normal range: 10-37 U/l) and alanine aminotransferase (ALT), which was 214 U/l (normal range: 10-37 U/l). The hepatitis B surface antigen and hepatitis C virus antibody were negative. The patient did not accept the suggestion of liver biopsy to elucidate the increase in liver enzymes. No parasite trophozoites or cysts were detected in 3 consecutive stool analysis. Cervical, thoracic and abdominopelvic tomographic examination were normal except for borderline hepatomegaly. Venous Doppler ultrasonographic examination of the left leg revealed thrombotic occlusion of the femoral vein. Scintigraphic examination markedly demonstrated segmental hotspots and collaterals of left leg. (Figure 2). The patient was diagnosed with HES and recurrent DVT. Subcutaneous (SC) low molecular weight heparin (LMWH) and hydroxyurea 500 mg/12 hour were initiated. Oral anticoagulant therapy (coumarin) was added on the 7th day of treatment. The LMWH was discontinued when the international normalization ratio (INR) was 2.4. Evaluation of the patient on the third month of coumarin treatment revealed that edema on the left leg had disappeared, Homan sign had become negative, the absolute eosinophile count was 1.1x10^9/l, and other hematologic parameters were normal. On the sixth month, 2 weeks after the discontinuation of coumarin treatment, protein C, protein S, antithrombin III levels were normal, Leiden mutation was heterozygote positive. Analysis of FV Leiden mutation in family members revealed that heterozygous FV Leiden mutation was present in the mother and her son.

Discussion. Idiopathic HES is a heterogenous disease characterized by the overproduction of eosinophils. Hypereosinophilic syndrome is diagnosed in patients with an eosinophile count of >1.5 x 10^9/l, and end organ damage and no explicable cause for eosinophilia.2,4 Cerebral, cardiac, pulmonary and portal vein thrombosis may develop in addition to organ destruction, in the course of HES. It is well known that ECP released from eosinophil plays an important role in the development of a thrombus and that eosinophils cause a tendency for thrombosis by direct injury to the vessel walls. However, the development of DVT in the veins of the extremities during the course of idiopathic HES is rare.1 Heterozygous FV Leiden mutation was detected in addition to idiopathic HES in our case. Factor V Leiden mutation is among the most important risk factors for venous thrombosis. The FV Leiden mutation occurs due to a point mutation on the factor V gene. According to this mutation, adenine is substituted for guanine in the nucleotide glutamine is substituted for arginin located in position 506 (Arg506Gln). Factor V cannot be cleaved by activated protein C, due to the FVL G1691A and FV is inactivated 10 fold slower than normal. Thus, the amount of FV eligible for the use by prothrombinase complex increases. This in turn causes an increase in thrombosis risk.
in the procoagulant activity of thrombin; namely, a hypercoagulable condition.\textsuperscript{3,6} While the prevalence of FV Leiden mutation is high in Southern Europe, it is 0.45-2.2\% in the US population.\textsuperscript{7,8} Prevalence and Sweden.\textsuperscript{9} The prevalence in Turkey is 4.7-10.2\% with geographical differences.\textsuperscript{10,11} On the other hand, this mutation is infrequent in South Africa, China and Japan.\textsuperscript{7}

While venous thrombosis risk increases 3-7-fold in heterozygous FV Leiden mutant persons, the risk is even higher in individuals with homozygous FV Leiden mutation.\textsuperscript{3,12} In a study by Rosendaal et al\textsuperscript{13} that include 471 patients with DVT and 474 control cases, while 18\% of the patient group had heterozygous and 1.5\% homozygous FV Leiden mutations, mutation was detected in 3\% of control cases.\textsuperscript{13} Although heterozygous FV Leiden mutation without any additional conditions causes a mild hypercoagulable condition, prothrombotic coagulation disorders may sometimes accompany this mutation. These additional risk factors, either hereditary such as homozygous methyltetrahydrofolate gene mutation, or acquired such as anti-phospholipid antibodies, hyperhomosisteinemia, physical inactivity, malignant or hormonal (oral contraceptives).\textsuperscript{14} Moreover, concomitant liver disease, pregnancy, operations, and trauma increase the risk of thrombosis in individuals with FV Leiden mutation.\textsuperscript{15} The presence of idiopathic HES may have contributed to the prothrombotic effect of heterozygous FV Leiden mutation in our case. Two patients with concomitant idiopathic HES and FV Leiden mutation have been reported in the literature. One of the cases reported deep vein thrombosis in their patients,\textsuperscript{1} whereas other case reported to have acute coronary syndrome along with recurrent cerebral stroke.\textsuperscript{16}

In conclusion, investigation of thrombophilia in cases with idiopathic HES with recurrent thromboemboli will be appropriate.

References


to activated protein C as an additional genetic risk factor in Blood 1995; 85: 3518-3523.
