CLINICAL REPORT

Recurrent Leg Ulcers in a Young Man with Hyperhomocysteinemia, Factor V Leiden and Impaired Fibrinolysis

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We present a young male patient referred to our hospital with leg ulcers on both legs that were more than 3 years refractory to standard treatment with compression therapy. By thrombophilia screening factor V Leiden mutation, hyperhomocysteinemia and evidence for impaired fibrinolysis were found. Treatment with folate acid in combination with long-term oral anticoagulant therapy was added to non-elastic compression therapy. The leg ulcers showed slow improvement and complete healing within 3 years. During a 6-year follow-up period neither new thrombo-embolic events occurred nor recurrence of ulcerations.

This case suggests a potential synergistic pathogenic role of factor V Leiden, hyperhomocysteinemia and impaired fibrinolysis in the development of postthrombotic syndrome and its sequelae. We postulate that increased formation of thrombi in the microcirculation of the skin in combination with ambulatory venous hypertension due to recurrent deep venous thrombosis might explain our observation.

Key words: microcirculation; bandages; thrombophilia; anticoagulants.

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Venous leg ulcers affect 0.5% to 2% of the general population (1), and 50% of patients with leg ulcers have a history of deep venous thrombosis (DVT). A common (22.8–60% after 2 years), and often disabling, consequence of DVT is post-thrombotic syndrome, with symptoms ranging from mild oedema to incapacitating swelling with pain and ulceration (3, 4). Post-thrombotic syndrome is strongly associated with ipsilateral recurrent DVT (4). Known risk factors for DVT include a number of inherited defects of coagulation (5). Some of these inherited defects are rare, but factor V Leiden and hyperhomocysteinemia are found quite frequently. Among European populations, factor V Leiden is currently the most common, known genetic defect causing thrombosis (5). Hyperhomocysteinemia may be caused by genetic factors or by acquired factors, such as deficiency of vitamin B6, B12 and folic acid (6).

When the action of both factors is exerted simultaneously, not just the additive but also synergistic effects may be seen (7, 8). In 70% of carriers of the factor V Leiden mutation, the occurrence of DVT is associated with a precipitating condition, most commonly pregnancy and surgery (5).

In this report, we present the case of a young man referred to us with a 3 year history of recurrent leg ulcers based on severe post-thrombotic syndrome following several episodes of DVT associated with factor V Leiden, hyperhomocysteinemia and impaired fibrinolysis.
CASE REPORT
A 24-year-old male was referred to our hospital because of long-standing ulcerations of the lower leg. He was known with Legg-Perthes disease when he was 7 years of age and had 3 documented episodes of proximal spontaneous DVT of both legs. The first spontaneous thrombotic event occurred in his left leg when he was 19 years old. Documentation of DVT was done by duplex sonography. After 3 months, anticoagulant therapy was stopped, and a few months later he developed DVT in his right leg, documented with duplex sonography. At 21 years of age he developed a third spontaneous DVT in his left leg and anticoagulant therapy for 6 months was re-started. Soon after anticoagulant therapy was stopped, he developed a severe post-thrombotic syndrome with bilateral leg ulcers. Phlebography at this time showed a residual thrombus in the left and right femoral vein. At the time of referral to our clinic he had had ulcerations for more than 3 years. He was treated with high-pressure compression therapy only and did not have oral anticoagulant therapy. There was no evidence of any underlying acquired disorder. The family history was negative for venous thromboembolism; his mother was known to have had an unexplained recurrent abortion.

On presentation at our hospital, this tall man with normal body proportions (height 197 cm; weight 88 kg) had bilateral ulcers with some debris at the medial malleolar regions on both legs. There were signs of white atrophy and extensive pigmentation in the lower legs, including lipodermatosclerosis (Fig. 1). There was no venous varicosity visible. The dorsal pedis and posterior tibial pulses were palpable on both legs.

Colour-coded duplex sonography showed venous reflux of the superficial femoral vein and popliteal veins; the groin area revealed several superficial collaterals. Ascending phlebography indicated residual signs of an old thrombus in the left and right femoral vein (Fig. 2). Retrograde filling of the venous system in both legs; left and right long saphenous veins showed no filling. Functional investigations with photoplethysmography showed a venous refill time that had decreased to 10 sec (normal 25 sec) and air-plethysmography showed an increased venous filling index (left leg 8.9 ml/sec and right 14.3 ml/sec; normal value < 2 ml/sec) and diminished ejection fraction (left leg 38.7% and right 34.5%; normal value > 60%).

Extensive thrombophilia studies revealed that the patient was heterozygous for the factor V Leiden mutation. In the presence of normal values for folic acid, vitamin B<sub>6</sub> and vitamin B<sub>12</sub>, we found an abnormal fasting homocysteine level (20.2 μmol/l, normal value < 18 μmol/l) and an increased homocysteine concentration 6 h after an oral intake of 100 mg methionine/kg body weight (64.4 μmol/l, normal < 56.3 μmol/l). A control methionine loading test after 3 months and after 4 years using folic acid was normal. His basal plasminogen activator inhibitor type 1 (PAI-1) activity was slightly increased (28 AU/ml, normal < 20 AU/ml) in several measurements in blood samples taken between 9 a.m. and 10 a.m. after an overnight fast. A venous occlusion test was performed in order to estimate his fibrinolytic response. Upon venous occlusion, no decrease of his PAI activity was found, suggesting impaired fibrinolysis also to be present.

The leg ulcers were treated with local petrolatum-gauze and a firm non-elastic compression bandage. Oral anticoagulant therapy was restarted (in principle, life-long), and folic acid 5 mg once a day added. The patient’s leg ulcers slowly improved, with complete healing after 3 years. There have been no recurrent thromboembolic events since the start of treatment in our hospital.

DISCUSSION
Clinical presentation of post-thrombotic syndrome is a rare complication before the age of 30. The presence of factor V Leiden, hyperhomocysteinemia and impaired fibrinolysis suggests a potential synergistic role in the development of recurrent venous thrombosis and venous difficult-to-treat leg ulcers. In our patient with documented deep and superficial insufficiency, the only known effective ambulant treatment is high-pressure compression therapy (9). It is of interest to note that our patient had been given adequate compression therapy for several years without clinical improvement. The slow, but complete, healing of the ulcers obtained by re-starting oral anticoagulants and introducing folic acid supplementation, suggests that the abnormalities found in the thrombophilia investigations might contribute to non-healing of the ulcers.

In a previous study it was shown that, compared to matched controls, the factor V Leiden mutation is found significantly more often in patients with venous leg ulcers (23% compared with 7.5%; p = 0.03) (10). It has also been proposed that impaired fibrinolysis may contribute to an increased thrombotic tendency. Microthrombi have also been found in the skin of patients with chronic venous insufficiency (11). This altered microcirculation can be the cause of the skin ulceration. The protein C pathway is especially important in the microcirculation of the skin (12, 13). Oral anticoagulant therapy is therefore a treatment option. Controversial data are known on the use of aspirin (14). Another interesting aspect of this case is the Legg-Perthes disease, which is also a thrombotic disorder with characteristic thrombotic venous occlusion of the femur leading to venous hypertension and osteonecrosis of the femur head. In the study by Glueck et al. (15), factor V Leiden is seen in 75% of patients with Legg-Perthes disease.

We recommend screening for both APC resistance.
and hyperhomocysteinemia in young people with symptomatic venous thrombosis or venous leg ulcers.

REFERENCES