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Letter to the Editor

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Running title: Livedo vasculopathy with MTHFR C677T homozygosity
Dear Editor,

Livedo vasculopathy (LV) is a chronic skin disease of unknown etiology. Treatment results are usually unsatisfactory. Here, we report a case of LV with methylenetetrahydrofolate reductase (MTHFR) C677T homozygosity. To the best of our knowledge, this is the first Japanese case of the MTHFR 677TT genotype with successful treatment based on the possible underlying pathophysiology.

A 19-year-old woman presented with more than a 10 year history of violaceous lesions on her lower legs. She had been diagnosed with livedo racemosa by a local dermatologist, but no treatment was given. Previously, she presented twice to our hospital for worsening of the condition, which later resolved spontaneously. In March 2009, she presented again because of the development of skin ulcers. Her family history was unremarkable. She smoked five to ten cigarettes a day and drank alcohol for the past four years. Physical examination revealed livedo and violaceous macules with petechiae and pigmentation on her lower legs (Fig. 1). Irregularly-shaped, shallow and deep ulcers with whitish atrophic scars were observed around the lateral malleolus bilaterally. Microscopic examination of a biopsy of violaceous macule revealed deposition of hyalinized fibrin in the vascular lumens in the upper and mid dermis with mild perivascular lymphocytic infiltration (Fig. 2a, b). These findings suggested a
diagnosis of LV.

Laboratory investigations including a complete blood cell count, serum immunoglobulin levels, glucose levels, complement levels, antinuclear antibody, antineutrophil cytoplasmic antibodies, and hepatitis B and C serology were negative or within normal limits. Coagulation profile and screening tests for thrombogenic factors including antithrombin III levels, antigen/activity levels of protein C and protein S, lupus anticoagulant, anticardiolipin antibody, anti β2-glycoprotein I antibody, phosphatidylserine-dependent anti-prothrombin antibody, cryoglobulins, and cryofibrinogen were negative or within the normal range. By PCR-RFLP analysis using genomic DNA from white blood cells, we found that she was homozygous for MTHFR C677T. Serum folate (4.0 ng/ml, normal range 3.6–12.9 ng/ml) and plasma homocysteine (7.8 nmol/ml, normal 3.7–13.5 nmol/ml) levels were within normal limits.

Initial treatment with sarpogrelate hydrochloride (300 mg per day) and tocopherol nicotinate (300 mg per day) was not effective. Dapsone (25 mg per day) was initiated and her skin ulcers gradually improved and completely healed for several months. However, 5 months later, painful skin ulcers recurred on her lower legs. Although dapsone was effective for the pain, ulceration progressed around the malleolus
bilaterally. After smoking cessation and supplementation with folic acid (5mg per day) and vitamin B12 (1500µg per day), the skin ulcers healed rapidly within 2 weeks with the improvement of other skin symptoms.

LV is characterized by livedo racemosa, recurrent painful skin ulcers, and atrophie blanche on the lower extremities. Etiologically, LV is considered to be a procoagulable state, and various systemic thrombogenic factors including genetic hypercoagulability risks—such as factor V Leiden, prothrombin gene mutations and MTHFR polymorphism—have been described. While the former two gene mutations are the well-known risk factors of thrombosis in Caucasians, they have not been detected in Japanese patients. On the other hand, MTHFR C677T homozygosity is distributed worldwide with a frequency estimated to be about 10% in the Japanese population. To the best of our knowledge, our patient is the first Japanese case of LV with the MTHFR 677TT genotype.

MTHFR catalyzes the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which remethylates homocysteine to methionine. Homozygous MTHFR 677TT decreases the enzyme activity to as low as 30% of normal, resulting in mild hyperhomocysteinemia, which induces hypercoagulation by oxidative damage and endoplasmic reticulum stress to endothelial cells. Folic acid is essential
for the homocysteine remethylation, and a low serum folate level is associated with hyperhomocysteinemia. In our patient, serum folate level was marginally decreased without apparent hyperhomocysteinemia. Serum folate is also decreased by low dietary intake, alcohol consumption, renal dysfunction and anti-folate drugs such as methotrexate. Smoking also reduces serum folate concentration by interfering with its absorption. Individuals with MTHFR 677TT genotype, especially smokers, are recommended to increase folate intake to maintain adequate plasma homocysteine and serum folate levels. In our case, livedo racemosa and skin ulcers developed in a smoker; smoking may play a role in LV, especially for patients with MTHFR 677TT genotype. It has been speculated that the occurrence of LV and hyperhomocysteinemia in a patient was related to a ‘double hit’ of MTHFR C677T polymorphism and smoking. MTHFR 677TT genotype is just one risk factor for thrombocytosis, so we consider more investigation for another thrombocytic factors about our patient.

LV is often recalcitrant to treatment. These include anticoagulation with warfarin or heparin; anti-platelet agents such as aspirin, dipyridamole, and pentoxifylline; thrombolysis with tissue plasminogen activator; and other therapies such as dapsone, hyperbaric oxygen, and intravenous immunoglobulin. Supplementation with folic acid is recommended for MTHFR 677TT, regardless of the plasma homocysteine level.
Vitamin B6 and vitamin B12—essential cofactors in homocysteine metabolism—are often given together with folic acid. Our patient responded well to oral folic acid and vitamin B12 supplementation.

In conclusion, our patient with LV associated with MTHFR 677TT genotype showed clinical improvement with folic acid supplementation and smoking cessation. Further investigation into the pathophysiology of LV, including MTHFR polymorphisms, may lead to more effective treatment for LV.
References


FIGURE LEGENDS

**Fig 1.** Spotted to reticular-shaped violaceous macules with skin ulcers on the lower legs bilaterally.

**Fig 2.** (a) Histopathology showed mild perivascular lymphocyte infiltration in the upper dermis (hematoxylin-eosin, original magnification × 100). (b) Fibrinous material occluded the lumens of dermal vessels (hematoxylin-eosin, original magnification × 400).