

SHORT COMMUNICATION

Recalcitrant Livedoid Vasculopathy Associated with Hyperhomocysteinaemia Responding to Folic Acid and Vitamins B6/B12 Supplementation

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Accepted: Mar 17, 2016; Epub ahead of print Mar 22, 2016

Livedoid vasculopathy (LV) is a rare skin disease affecting especially the calves, ankles and dorsum of the feet, and usually presenting with painful, purpuric macules/papules and small ulcerations evolving into livedoid brownish pigmentation and stellate scars (“atrophie blanche”) with surrounding punctate telangiectasias; a history of livedo reticularis may also be present (1, 2). Histologically, microthromboses and segmental hyalinization of the subendothelial intima of blood vessels of the middle/lower dermis are seen. LV is considered to be an occlusive vasculopathy due to a procoagulant state (1, 2), including protein C deficiency, factor V Leiden mutation, prothrombin gene mutation, increased levels of plasminogen activator inhibitor-1 or lipoprotein(a), antithrombin deficiency, and hyperhomocysteinaemia (3, 4). Although several treatments have been used in LV, mainly including antiplatelet/anticoagulant agents, fibrinolytic/vasodilating medications and anti-inflammatory agent, the condition remains difficult to manage (1, 2).

We report here 2 cases of LV associated with hyperhomocysteinaemia, which responded dramatically to folic acid and vitamin B6/B12 supplementation despite being refractory to several other therapies.

CASE REPORTS

Case 1. A 41-year-old man with numerous extremely painful stellate ulcers over a brownish background located on the legs and dorsal aspect of the feet (Fig. 1a), which had been present for approximately 3 months. Histological examination revealed fibrin, thrombi and necrosis of the dermal vessel walls, leading to a diagnosis of LV. Autoantibodies and routine parameters (including vitamins B6 and B12 levels and folic acid concentration) were within normal ranges. The patient was treated with oral steroid (methylprednisolone, 0.5 mg/kg daily) and acetylsalicylic acid, 100 mg daily, but the lesions continued to worsen after 3 weeks of therapy; therefore, we

Fig. 1. (a) Numerous stellate ulcers over a brownish background located on the legs and dorsal aspect of the feet in Case 1; (b) resolution of the ulcerations after 7 weeks following the introduction of vitamins B6/B12 and folic acid supplementation. (c) Several atrophic stellate scars, purpuric macules/papules, brownish pigmentation, and roundish/irregular ulcerations on the legs in case 2; (d) resolution of the ulcerations after 2 months of treatment as in (b).



decided to add pentoxifylline, 600 mg twice daily. However, after further 2 weeks we noticed only minimal amelioration of the ulcers and no improvement in pain. In the meantime, we received the results from blood tests, which showed an elevated homocysteine level (19.4 $\mu\text{mol/l}$) and heterozygous methylenetetrahydrofolate reductase (MTHFR) C677T mutation. Consequently, we decided to suspend the steroid and acetylsalicylic acid and start oral folic acid and vitamins B6/B12 supplementation (0.5 mg folic acid, 4.2 mg vitamin B6 and 5 μg vitamin B12 per day), with normalization of homocysteine level and resolution of the lesions (Fig. 1b) and pain after 7 weeks; there was neither clinical recurrence nor increase in homocysteine serum concentration after 3 months of follow-up.

Case 2. A 55-year-old woman with a 1-year history of intensely painful ulcerations affecting her lower extremities. Some months before coming to us, she was clinically diagnosed as having vasculitis and treated with a 2-month course of oral methylprednisolone (0.5 mg/kg daily), with only little improvement. When presenting at our clinic she was taking pentoxifylline (600 mg twice daily) for 3 months, with minimal effects on the lesions. On physical examination, several roundish/irregular ulcerations, having a diameter ranging from few millimetres to 3 cm, were visible on the legs and dorsal aspect of the feet; moreover, some atrophic stellate scars, purpuric macules/papules and brownish pigmentation were also evident (Fig. 1c). Histology displayed dermal vessel thrombosis consistent with LV. Testing for hypercoagulation factors revealed high homocysteine level (18.2 $\mu\text{mol/l}$) associated with heterozygous MTHFR C677T mutation; autoantibodies and routine parameters (including vitamins B6 and B12 levels and folic acid concentration) were within normal ranges. However, we decided to administer oral folic acid and vitamins B6/B12 supplementation (0.5 mg folic acid, 4.2 mg vitamin B6 and 5 μg vitamin B12

per day), which led to complete resolution of the lesions (Fig. 1d) and pain after 2 months, simultaneously to the normalization of homocysteine level. During the subsequent 2-month follow-up period, the patient retained the results achieved and homocysteine serum concentration remained within normal limits.

DISCUSSION

Homocysteine is a sulfhydryl-containing amino acid deriving from the demethylation of dietary methionine. Having high serum levels of homocysteine is considered to be a systemic prothrombotic condition, as this amino acid (and its metabolites) may be associated with endothelial toxicity (3). Both inherited and non-hereditary factors may affect its serum concentration; including mutations in genes encoding enzymes involved in its metabolism (cystathione- β -synthase, MTHFR and methionine synthase) and several acquired diseases/conditions (nutritional deficiencies, renal failure, use of folic acid and vitamin B6 antagonists, cardiovascular diseases and peripheral arterial occlusive disease) (3, 4). The normal homocysteine serum level is considered to be 5–15 $\mu\text{mol/l}$ (3).

Besides the well-known link between hyperhomocysteinaemia and increased risk for atherosclerosis and venous thrombosis, there is growing evidence supporting the possible role of this amino acid in several skin diseases, including LV (3–7). In particular, Gibson et al. (6) observed significantly higher homocysteine concentration in subjects with LV compared with a control group (8.7 ± 3.1 vs. 7.0 ± 2.9 $\mu\text{mol/l}$), although the values were still within the normal range. More recently, serum homocysteine levels exceeding the normal limit of 15 $\mu\text{mol/l}$ have been found to correlate with LV in 2 studies, thus confirming a possible role of hyperhomocysteinaemia in the pathogenesis of this condition (3, 4). In the case reported by Meiss et al. (3), high homocysteine concentration was related to a combination of acquired causes, i.e. chronic renal failure/vitamins B6 and B12 deficiency, while in the report by Ray et al. (4) it was apparently associated with neither genetic factors nor acquired conditions. Interestingly, in the former case, lesions started to improve concurrent with homocysteine serum level normalization after 2 months of therapy with vitamins B6/B12 and folic acid supplementation plus heparin and pentoxifylline, thereby emphasizing the importance of reducing elevated homocysteine concentration in the healing process of LV (3). On the other hand, in the case reported by Ray et al. (4), administration of folic acid together with oral prednisolone, pentoxifylline and low-dose aspirin did not lead to any improvement after 12 weeks of treatment, but the lesions healed following several sessions of hyperbaric oxygen therapy (it was not possible to assess possible correlations between disease activity and homocysteine serum concentration in this case).

In our study, both patients with LV had hyperhomocysteinaemia due to a genetic factor, i.e. MTHFR C677T mutation. MTHFR catalyses the conversion of

5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominant circulatory form of folate and the methyl-group donor in the B12-dependent remethylation of homocysteine to methionine (8, 9). C677T is the most common polymorphism of this enzyme (prevalence in the Italian population of approximately 20% and 40% in homozygous and heterozygous state, respectively) (10) and gives rise to a thermolabile variant of MTHFR predisposing to high homocysteine levels, especially in case of folate-deficient subjects (8, 9). Treatment of patients with such a mutation is the same as for those presenting high homocysteine levels because of acquired factors, i.e. with folic acid and vitamins B6/B12 supplementation (9). Its effects depend on the fact that homocysteine can be remethylated back to methionine or can be metabolized to cysteine (7–10).

Such a therapy resulted in a dramatic improvement in the lesions and pain in both our patients previously resistant to treatment, and clinical amelioration went hand in hand with reduction of homocysteine levels. These findings confirm the previously hypothesized role of homocysteine in the pathogenesis of LV, and imply a necessity to investigate the homocysteine serum concentration (and underlying causes) in patients with this disease, especially if they are resistant to other therapies.

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