

Leg ulcers due to hyperhomocysteinemia

D. S. Krupa Shankar, Syed Akhib

Department of Dermatology, Manipal Hospital, Bangalore, Karnataka, India.

Address for correspondence: Dr. Krupa Shankar DS, Department of Dermatology, Manipal Hospital, 98 Rustom Bagh, Airport Road, Bangalore-560 017, Karnataka, India. E-mail: dermakrupa@yahoo.com

ABSTRACT

Chronic leg ulcers are rare in young adults and generally indicate a vascular cause. We report a case of a 26-year-old man with leg ulcers of eight months duration. Doppler study indicated venous incompetence and a postphlebotic limb. However, as the distribution and number of ulcers was not consistent with stasis alone and no features of collagen vascular disease were noted, a hyperviscosity state was considered and confirmed with significantly elevated homocysteine level in the serum. Administration of vitamins B1, B2, B6 and B12, trimethyl-glycine, mecobalamine, folic acid and povidone iodine dressings with culture-directed antibiotic therapy led to a satisfactory healing of ulcers over a period of one month. Hyperhomocysteinemia must be considered in the differential diagnosis of leg ulcers in young individuals.

Key Words: Hyperhomocysteinemia, Hyperviscosity syndrome

INTRODUCTION

Hyperhomocysteinemia is a disorder of methionine metabolism and its metabolites (homocysteine, homocysteine-cysteine complex and others). The accumulation of homocysteine and its metabolites is caused by disruption of any of the three interrelated pathways of methionine metabolism. Deficiency in the cystathionine B-synthase (CBS) enzyme, defective methylcobalamin synthesis or abnormality in methylene tetrahydrofolate reductase leads to accumulation of homocysteine in blood.

CASE REPORT

A 26-year-old businessman presented with multiple episodes of ulcerations over the left leg during the last 14 months. After the first episode 14 months back

he was in remission for six months. The ulcers began on the dorsum of the left foot, medial malleoli-medial aspect of the knee and showed purulent discharge at all times. He was treated by a dermatologist with topical betamethasone and topical beclomethasone dipropionate, clotrimazole, neomycin and oral antibiotics. He had a Doppler study carried out at the age of 19 years and was diagnosed to have deep vein thrombosis and treated with acenocoumarol for one year.

On examination, the patient was obese. He presented with multiple varicosities, discoloration and cutaneous ulcers with surrounding induration on the left lower limb. There were 13 ulcers of which the biggest ulcer measured 3 x 8 cm in diameter with pale granulation, yellowish slough, greyish edge, a halo of erythema and induration [Figure 1]. Similar

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lesions were seen on the medial malleoli, shin and multiple ulcers on the lateral aspect of the left foot [Figure 2]. His systemic examination was unremarkable. There was no family history of diabetes mellitus, hypertension, atopy or stroke. He was a nonsmoker and nonalcoholic.

Keeping in mind the known causes of leg ulcers we went on to investigate him with a duplex color Doppler, which demonstrated venous incompetence and postphlebotic sequelae in the lower limb. Stasis per se seemed inadequate to account for the number and distribution of ulcers, hence a hyperviscosity syndrome was considered and the following investigations were done. Investigations showed anti-cardiolipin IgA: 3.866 apl (10), anti-cardiolipin IgM: 1.269 mpl (7), anti-cardiolipin IgG: 1.018 gpl (10), anti-thrombin III function 92% (80-100%), lupus anti-coagulant: 29 seconds (29), protein S activity 123.6% (65-140%) and T3 T4 TSH was within normal range. Protein C activity 68.2% (70-130%) was marginally but not significantly low. Electrocardiogram (ECG) was normal. Random blood sugar was 179 mg/dl (70-150), random urine sugar (0.5%) suggestive of stress diabetes or insulin resistance. Lipid profile showed total cholesterol 222 mg/dl (<200), triglycerides 251 mg/dl (<200), HDL cholesterol (Direct) 29 mg/dl (35-55), LDL cholesterol 143 mg/dl (<130), VLDL Cholesterol 50 mg/dl (10-40), Total cholesterol: HDL cholesterol ratio 7.65:1 (<6.0).

Culture from the ulcer grew *Staphylococcus aureus* and

Pseudomonas aeruginosa that were sensitive to a few antibiotics, of which ciprofloxacin 1g once daily for 10 days was chosen for treatment. The plasma homocysteine level was >50 (normal range 0-17) and hence a diagnosis of homocysteinemia was made. He received trimethyl glycine 500 mg, mecobalamine 500 mcg, folic acid 1 mg, pyridoxine hydrochloride 10 mg, ciprofloxacin and injections of vitamin B3, B12, vitamin C, niacinamide, acenocoumarol and dextropropoxyphen to relieve his pain. Povidone iodine dressings and collagen Type III dressings were done twice a week.

The ulcer on the medial aspect of the knee healed after four weeks with some atrophy and hyperpigmentation [Figure 1a]. At the time of ulceration some areas with erythema and overlying suppuration, erosions healed up without breaking down to ulcer. The ulcer in the region of medial malleoli had healed significantly at the end of six weeks. The multiple ulcers on the lateral aspect of the left foot had healed satisfactorily [Figure 2a]. The patient remains well one and a half years later.

DISCUSSION

Homocysteine is a sulfur-containing metabolite of methionine and hyperhomocysteinemia is a risk factor for atherosclerosis and venous thrombosis.^[1] It can be caused by genetic disorders affecting the trans-sulfuration or remethylation pathways of homocysteine metabolism, folic acid deficiency,



Figure 1: Cutaneous ulcers on the medial aspect of left knee



Figure 2: Healing ulcers after 4 weeks of treatment

vitamin B12 deficiency, renal failure, hypothyroidism, increasing age and smoking.^[2]

Hyperhomocysteinemia is a biochemical disorder resulting from deficiency of cystathionine-beta-synthase. The metabolic effects include increased platelet aggregation, toxic damage to endothelial surfaces^[3] and altered anti-thrombin III activity leading to thromboembolic phenomenon. The systemic effects are as follows:

- a) CVS: Myocardial infarction;^[4] hypertension; stroke;^[4] blindness, renal, portal or pulmonary embolism, deep vein thrombosis.
- b) Ocular: Ectopia lentis, myopia, retinal detachment
- c) Skeletal: Marfanoid habitus, osteopenia
- d) Skin: Malar flush, livedoid vasculitis,^[5] canities
- e) CNS: Mental retardation, seizures and stroke.^[6]

Hyperhomocysteinemia is generally recognized as an independent risk factor for coronary, cerebral and peripheral atherosclerosis. There has recently been renewed interest in homocysteine metabolism because hyperhomocysteinemia has been associated with occlusive arterial disease and neural tube defects. Deficiency of the enzyme 5, 10-methylenetetrahydrofolate reductase results in hyperhomocysteinemia and a wide variety of neurological and vascular symptoms. Molecular genetic analysis of the enzyme has led to the identification of nine rare mutations associated with a severe deficiency phenotype as well as one common mutation (found in 35 to 40% of alleles in the general population) that is proposed as a risk factor in some forms of cardiovascular disease and in neural defects.^[3]

Folic acid acts by participating in the synthesis of DNA, RNA and proteins. It is necessary for DNA repair, replication maintaining integrity of genome.^[7] Complications of hyperhomocysteinemia are inflammatory bowel disease, cerebral thrombosis, acute myocardial infarction, venous thrombosis and atherosclerosis. The associated disorders of hyperhomocysteinemia are thromboembolism, pulmonary embolism, schizophrenia, Parkinson's disease, stroke, diabetes mellitus, osteoporosis, scoliosis, kyphosis, spina bifida, lens dislocation, glaucoma and myopia. Strategies for the treatment

of CBS deficiency include increasing residual enzyme activity by giving pyridoxine in those patients with vitamin responsive variants, reducing the load on the affected pathway with a low methionine diet and supplementing the diet with cysteine and giving betaine in order to utilize alternative pathways to remove homocysteine.^[8]

All patients with chronic multiple leg ulcers with features suggestive of other vascular phenomena such as deep vein thrombosis, venous ulcer, stasis dermatitis, ischemic heart disease, retinal artery occlusion, claudication and Raynaud's phenomenon should have plasma homocysteine level measured immaterial of the age of the patient. It should also be considered in patients in whom basic investigations for the common causes of leg ulcers are not conclusive. Given the low cost of investigation and the easy prevention with folic acid, plasma homocysteine must be measured in every patient with chronic leg ulcers as it may be a contributory and correctable if not a primary cause of chronic leg ulcers.

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