Palmar plantar pustulosis responding to high-dose folic acid plus vitamins B6 and B12

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INTRODUCTION
This report shows a positive therapeutic effect of high-dose folic acid plus vitamins B6 and B12 on a patient with palmar plantar pustulosis. Improvement was likely through modulation of homocysteine (Hcy) and nitric oxide (NO) synthase metabolic pathways, and by inhibition of NF-kappa-B.

CASE REPORT
The subject of this report signed a consent approved by the Wayne State Institutional Review Board for retrospective case review and publication.

A 56-year-old African American woman with no previous skin conditions presented with a 2-month history of blistering on both hands and feet. Her medical history was significant for hypertension and osteoarthritis, which were managed by triamterene/hydrochlorothiazide, atenolol, acetaminophen/codeine, and cyclobenzaprine. The patient had no known allergies. She was not taking any vitamins, was a smoker, and did not drink alcoholic beverages.

On physical examination, there were multiple bilateral erythematous lesions with yellow scales and pustules on her palms (Fig 1) and soles that did not respond to previous treatments of hydrocortisone 1% cream. In addition, she had nail pitting and some splinter hemorrhages. Clobetasol 0.05% cream was prescribed for the initial diagnosis of psoriasiform dermatitis but the patient only had mild response to the treatment.

Later, she developed more papules and pustules on the palms and plantar surfaces, and scalp involvement began. Fungal culture from the scalp produced negative findings. The patient was then given a diagnosis of palmoplantar pustulosis and scalp dermatitis. We offered her clobetasol 0.05% ointment and ammonium lactate 12%, but her pustular lesions persisted, coalescing into larger lesions on her palmoplantar surfaces. Her vitamin B12 was within the normal limit, as was her plasma Hcy level (9.2 μmol/L, normal levels 3.2-10.7 μmol/L). We decided to begin methotrexate (5 mg per week) and folic acid (1 mg daily), with the plan of increasing the methotrexate dosage to 10 mg if her blood work was still within normal limits at her 2-week follow-up. At the same time, we recommended the patient use fluocinonide 0.05% cream to the affected areas.

Because of unforeseen logistic reasons, the patient was unable to obtain the methotrexate. She was then placed on daily folic acid (6 mg), vitamin B6 and psoriasis and 5-7 mg daily folic acid plus B6 and B12 alone may improve psoriasis but adding 5 mg acid plus B6 and B12 to adalimumab cannot in general be recommended. Annual Meeting of the American Academy of Dermatology, Denver, CO, March 21-24, 2014.

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Abbreviations used:
eNOS: endothelial nitric oxide synthase
Hcy: homocysteine
NO: nitric oxide
VEGF: vascular endothelial growth factor

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(100 mg), and vitamin B12 (1 mg) because of past success with such doses in patients with psoriasis. At the 2-week follow-up visit, the patient notified us of a significant improvement.

After the significant improvement of her symptoms, the patient continued with daily folic acid, vitamin B6, vitamin B12, and as-needed fluocinonide and ammonium lactate. By her 3-month follow-up visit the pustular lesions on her scalp, palms (Fig 2), and plantar surfaces were gone. Interestingly, while on the same oral regimen, 1 year later she was only found to have small thin dyschromic plaques on the plantar heel of her right foot without any pustules.

**DISCUSSION**

The amino acid Hcy is derived from methionine. Methionine is converted to S-adenosylmethionine. S-adenosylmethionine is the major biological methyl donor required for the formation of proteins, nucleic acids, epinephrine, melatonin, phosphatidylcholine, and creatinine. These reactions are catalyzed by various methyltransferases to form S-adenosyl-Hcy. S-adenosyl-Hcy is converted by S-adenosyl-Hcy hydrolase to simultaneously produce Hcy and adenosine.

Dietary folic acid forms 5-methyltetrahydrofolate by the vitamin B2-dependent enzyme 5,10-methylene tetrahydrofolate reductase. Hcy levels can be reduced by conversion to methionine by remethylation using methionine synthase with vitamin B12 as a cofactor and 5-methylhydrofolate as a methyl donor, or degraded to cysteine by transsulfuration using vitamin B6.

Neutrophils are essential for histopathologic diagnosis of psoriasis and for pustulosis palmaris and plantaris. Hcy increases neutrophil activity. Hyperhomocysteinemic subjects were found to have elevated levels of epithelial neutrophil-activating peptide, a regulator of polymorphonuclear white blood cell or neutrophil chemotaxis and CXC chemokines (the neutrophil activator interleukin-8/CXC chemokine ligand 8). Hcy increases superoxide anion release by neutrophils to the extracellular medium. Hcy also increases intracellular hydrogen peroxide production by neutrophil migration and adhesion to human endothelial cells, which promotes endothelial dysfunction from decreased availability and activity of NO.

In 2 studies, psoriasis patients’ plasma Hcy levels correlated directly with Psoriasis Area and Severity Index score and, when studied, Hcy levels inversely correlated with folic acid levels. Improved blood vessel cell function measured by flow-mediated dilatation correlates closely with the reduction in free plasma Hcy regardless of folic acid and vitamin B12 levels. However, with very high folic acid intake (5 mg/d, but not 400 µg/d) folic acid also improves flow-mediated vasodilation. Flow-mediated vasodilation is regulated by endothelial NO release. Endothelial NO synthase (eNOS) synthesizes NO. High-dose folic acid creates dimeric anti-inflammatory (coupled) activity. Meta-analysis identifies inducible NO synthase as a susceptibility locus for psoriasis. Etanercept-cleared psoriasis skin has 87% less inducible NO synthase. High-dose folic acid can reduce inducible NO synthase.

CARD-14 mutations are associated with palmar plantar psoriasis through activation usually of NF-kappa-B. CARD-14 is found on epidermal keratinocytes...
keratinocytes and dermal cells. Anti-inflammatory doses of folic acid reduce NF-kappa-B. Inhibition of NF-kappa-B is a mechanism for control of psoriasis. Based on the background material behind our use of the 3 B vitamins including high-dose folic acid, the only unexpected outcome in this case was the development of a small dyschromic plantar plaque without recurrent pustules with continued use of high-dose folic acid, and vitamins B6 and B12 seen at 1 year after initiation of this therapy.

More study is needed as shown elsewhere. Some patients with psoriasis who were already taking adalimumab experienced flare with the 3 B vitamins. Helicobacter pylori presence may strongly inhibit folic acid absorption, increasing Hcy. More likely if folic acid doses are absorbed that are not high enough to create dimeric eNOS, proinflammatory monomeric eNOS could be made or not opposed especially if eNOS is not stabilized with letpin. Psoriasis can be a disorder with elevated leptin. Psoriasis can be a disorder with elevated Hcy. More likely if folic acid dosing is increased and absorption is adequate.

2. Reducing Hcy with B vitamins therefore might reduce expression of vascular endothelial growth factor (VEGF). Hcy also reduces expression of vascular endothelial growth factor A, VEGF, and vascular growth factor receptor 2. Reducing Hcy with B vitamins therefore might sometimes increase VEGF, which is another possible reason for psoriasis-like disorders to flare.

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