The Use of B Vitamins for Cutaneous Ulcerations Mimicking Pyoderma Gangrenosum in Patients With MTHFR Polymorphism

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Background: Methylenetetrahydrofolate reductase (MTHFR) polymorphisms are associated with thrombophilia and vasculopathy that may result in cutaneous ulceration. Pyoderma gangrenosum (PG) is a clinical diagnosis that may be made following exclusion of alternate causes of ulceration, including vascular inflammatory or occlusive disease, infection, and malignant neoplasm.

Observations: We describe 2 patients with MTHFR polymorphisms discovered during hypercoagulable evaluation for cutaneous ulcerations on the lower extremities. Both patients showed a rapid improvement following treatment with oral vitamin supplementation and local wound care. One patient developed several subsequent ulcers when he decided to discontinue his therapy, and following reinitiation of therapy, the new ulcerations healed. The treatment was tolerated well without any adverse effects.

Conclusions: MTHFR polymorphisms should be part of a comprehensive laboratory evaluation during hypercoagulable workup. Vitamin supplementation with folic acid (B9), pyridoxine hydrochloride (B6), and cyanocobalamin (B12) may result in healing of cutaneous ulcerations in some patients with MTHFR mutations.

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Cutaneous ulcerations and chronic wounds are a relatively common health problem and are associated with substantial morbidity. Diverse causes of ulcerations include infection, malignant neoplasm, vasculopathy, vasculitis, venous stasis, collagen vascular disease, diabetes, trauma, and medications. Pyoderma gangrenosum (PG) is an ulcerative cutaneous process of uncertain cause, and a diagnosis is considered after a thorough medical history, physical examination, and laboratory evaluation excludes alternative causes of ulceration.

Homocysteine and folic acid metabolism may play a substantial role in clotting homeostasis. Deep venous thrombosis and arterial occlusive disease risk may be increased in patients with mutations in homocystine metabolism. Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folic acid and homocystine metabolism. Genetic polymorphisms may lead to decreased enzymatic activity of this pathway and increased risk of vascular occlusion secondary to a hypercoagulable state.

We describe herein 2 patients with cutaneous ulcerations clinically resembling PG who had dramatic clinical improvement following initiation of B vitamin treatment. The first patient was treated with vitamin B<sub>6</sub> (folic acid), pyridoxine hydrochloride (vitamin B<sub>6</sub>), and cyanocobalamin (vitamin B<sub>12</sub>) therapy, and the second, with folic acid as monotherapy. Both patients had heterozygous MTHFR mutations.

Case 1

A 33-year-old man presented with a 6-week history of bilateral lower extremity ulcerations that occurred following minor trauma. He was otherwise presumed to be healthy, but on review of systems, he reported that he had experienced a several-month history of foul-smelling, watery to semiformed bowel movements 3 to 5 times per day. He had no history of thrombophlebitis. He was not taking any prescription or over-the-counter medications. His mother had 2 miscarriages, but there was no confirmed personal or family history of a clotting disorder.

Physical examination revealed multiple purulent ulcerations with violaceous, scalloped, undermined borders (Figure 1A). There was mild lower extremity edema. The pulses in his legs were normal. The remainder of his physical examination findings were normal.

A 6-mm punch biopsy specimen from the periphery of an ulcer revealed vascular hyperplasia, focal vascular fibrin deposition, erythrocyte extravasation, and a mixed...
dermal inflammatory infiltrate. A skin bacterial culture grew *Escherichia coli* and *Acinetobacter lwoffii*. Findings from viral, mycobacterial, and fungal cultures were negative. Laboratory evaluation revealed a heterozygous A1298C mutation of *MTHFR* (GenBank U09806) and a serum homocysteine level at the upper limit of normal, 1.26 mg/L (reference range, 0.4-1.4 mg/L). Analysis of *MTHFR* mutation was performed as part of a thorough investigation to exclude any underlying cause of cutaneous ulceration: PG is a diagnosis of exclusion. The patient’s hemoglobin concentration was 7.9 g/dL (reference range, 13.9-17.1 g/dL) with a microcytic mean corpuscular volume of 64.9 fL (reference range, 82.1-97.7 fL) and a total iron level of 7 µg/dL (reference range, 29-105 µg/dL), consistent with iron-deficiency anemia. (To convert homocysteine to micromoles per liter, multiply by 7.397; to convert hemoglobin to grams per liter, multiply by 10; to convert iron to micromoles per liter, multiply by 0.179.) A urinalysis and assays of the following showed negative or normal results: beta-2 glycoprotein-1 antibody, antistreptolysin O titer, cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA), perinuclear ANCA (p-ANCA), cryoglobulins, cryofibrinogens, cryoprecipitates, antinuclear antibodies (ANA), anticardiolipin antibodies, lupus anticoagulants, factor V Leiden mutation, antithrombin III level, prothrombin 20210A mutation, hepatitis A, B, and C, urine protein electrophoresis, serum protein electrophoresis, and rheumatoid factor. A chest radiograph was also normal. Antibodies against tissue transglutaminase, endomysium, and gliadens were not evaluated. An esophagogastroduodenoscopy revealed villous blunting consistent with celiac sprue. A colonoscopy found no evidence of inflammatory bowel disease.

The patient was diagnosed with vasculopathic ulcers secondary to a heterozygous *MTHFR* defect aggravated by a malabsorption state. In addition to culture-directed antibiotics and local wound care, the patient began treatment with oral folic acid, 1 mg, twice daily; vitamin B6, 100 mg/d; and vitamin B12, 1000 µg/d, along with a gluten-free diet. His ulcerations were 30% improved at 4 weeks and 95% healed at his 5-month follow-up (Figure 1B). There were no adverse effects from the treatment reported.

**CASE 2**

A 12-year-old boy presented with an 18-month history of painful nodules and ulcerations on the lower legs. A skin biopsy specimen taken by the referring dermatologist tested negative for an infectious or neoplastic process, which was interpreted as being consistent with pyoderma gangrenosum. His medical history was significant for hypothyroidism, and his only medication was levothyroxine. Review of his systems was otherwise negative. Therapy with dapsone, 25 mg/d, was initiated and led to improvement. He subsequently discontinued treatment with the medication and presented with recurrent ulcerations.

Physical examination during the initial referral encounter demonstrated a 3-cm, scaly, erythematous plaque on the right tibia, and a 1-cm ulceration with a violaceous border and adjacent atrophic scar on the right posterior leg. The left leg demonstrated similar areas of atrophy and scar formation.

A complete blood cell count and assays of the following led to negative or normal results: complete metabolic panel, ANA, c-ANCA, p-ANCA, serum protein electrophoresis, rheumatoid factor, antiphospholipid antibodies, hepatitis C antibody, alpha-1-antitrypsin level, and cryoglobulin level A chest radiograph was also nega-
The qualitative cryofibrinogen finding was positive, and the C-reactive protein level was 30.0 mg/L (reference range, 0-4.9 mg/L). (To convert C-reactive protein to nanomoles per liter, multiply by 9.524.) The patient refused a repeated biopsy. Dapsone therapy was reinitiated at 100 mg/d, and tacrolimus ointment was applied to the affected areas twice daily. At follow-up, the patient had self-discontinued the dapsone treatment owing to headaches. He subsequently developed new nodules after a streptococcal infection. The patient was treated with indomethacin for possible erythema nodosum, but he self-discontinued this therapy as well.

He was lost to follow-up for 3 years until age 15 years, when he presented with new, tender ulcerations on his lower legs. Repeated laboratory evaluation demonstrated 2 heterozygous mutations of the MTHFR gene (C677T and A1298C). Treatment with folic acid, 5 mg/d, led to nearly complete healing after 3 weeks with no new lesions. The patient self-discontinued his folic acid treatment owing to diarrhea. Treatment with folic acid, 1 mg, twice daily; vitamin B6, 100 mg/d; and vitamin B12, 1000 µg/d, was reinitiated, which again resulted in complete healing within 3 months (Figure 2B).

**COMMENT**

Methylenetetrahydrofolate reductase is an enzyme catalyzing the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which in turn functions to provide a carbon group for the conversion of homocysteine to methionine (Figure 3). This metabolic pathway relies on folic acid, vitamin B12, and vitamin B6 as cofactors for various enzymes. Polymorphisms of the MTHFR gene lead to decreased enzymatic activity and may result in a hypercoagulable state. In addition, a deficiency of cofactors can also disrupt the pathway and may potentiate the hypercoagulable state in the setting of MTHFR mutations.

The most common MTHFR polymorphism is a point mutation (C→T substitution at nucleotide 677) resulting in an enzyme with 50% less activity. MTHFR mutations and hyperhomocysteinemia may increase the risk of deep-vein thrombosis and arterial occlusive disease. Theoretically, the same mechanism could lead to cutaneous ulceration. Several studies have linked the C677T polymorphism to increased cardiovascular risk, particularly when folic acid status was impaired. The A1298C mutation decreases MTHFR activity resulting in variable effects on homocysteine and folic acid status, and evidence suggests that the mutation may become clinically apparent under severe folic acid depletion.

Our first patient had a heterozygous A1298C mutation of the MTHFR gene, a relatively common mutation with an allele frequency of approximately 33%. He also had celiac sprue leading to malabsorption of nutrients such as iron, folic acid, and B vitamins. Lack of cofactors combined with a decreased baseline activity of MTHFR predisposed our patient to form ulcerations secondary to a small-vessel vasculopathy. Mild chronic venous stasis and bacterial wound contamination likely contributed to the ulcerations. However, dramatic improvement was noted after supplementation with folic acid, 1 mg, twice daily; vitamin B12, 1000 µg/d; and vitamin B6, 100 mg/d.

The second patient demonstrated remarkable improvement of PG-like ulcerations when using daily folic acid supplementation and developed new lesions when treatment was stopped. Those lesions subsequently healed with reinitiation of oral folic acid therapy at 5 mg/d. Both patients were lost to follow-up after their ulcerations had

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**Figure 3.** Biochemical pathway showing role of methylenetetrahydrofolate reductase in folic acid, homocysteine, and methionine metabolism.
improved. They were encouraged at each visit to continue supplementation therapy indefinitely.

Other cases of MTHFR mutations and cutaneous ulcerations have been described in the literature. Some of the cases are summarized in Table B. Cutaneous ulcerations misdiagnosed as PG are not uncommon, and our 2 patients highlight the importance of a thorough investigation prior to diagnosing a patient as having PG. In both of our cases, vasculopathy secondary to B vitamin deficiency and MTHFR mutations was likely the responsible underlying cause. As new discoveries are made, we will be able to direct therapy to specific causes in cases that were previously diagnosed as PG.

The present report should emphasize the importance of understanding that PG is a diagnosis of exclusion. The exact pathologic link between vascular occlusion and homocysteine metabolism is unclear and may be due to direct damage to the endothelium, proliferation of smooth muscle within the vessel, increases in clotting factors, or decreases in anti-thrombotic factors. Our report adds to the growing amount of literature raising the questions and prompting further investigation to determine if MTHFR polymorphisms and/or hyperhomocysteinemia contribute to the pathogenesis of vascular occlusion, including cutaneous small-vessel occlusive disease. It also suggests that vitamin supplementation, a relatively benign intervention, may improve cutaneous ulcerations associated with altered homocysteine metabolism.

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Table. Reported Cases of Recurrent Ulcerations Associated With MTHFR Mutations and/or Hyperhomocysteinemia

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Sex/Age, y</th>
<th>Clinical Presentation</th>
<th>Laboratory Abnormalities</th>
<th>Treatment and Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rampf et al</td>
<td>F/42</td>
<td>Recurrent multiple ulcerations of ankles and feet; livedoid racemosa; atrophie blanche</td>
<td>Homozygous mutation of MTHFR gene at codon 677; hyperhomocysteinemia</td>
<td>Rapid healing with folic acid, vitamin B12, low-molecular-weight heparin, and topical antiseptics</td>
</tr>
<tr>
<td>Browning and Callen</td>
<td>M/50</td>
<td>Recurrent cutaneous ulcerations on medial malleoli and calves</td>
<td>Hyperhomocysteinemia; cryofibrinogenemia; MTHFR mutation not evaluated</td>
<td>Unresponsive to aspirin, digipridamone, hydroxychloroquine and prednisone; partial response to stanozolol; dramatic improvement with warfarin</td>
</tr>
<tr>
<td>Cardoso et al</td>
<td>F/31</td>
<td>Recurrent ulcerations of ankles and feet</td>
<td>Homozygous C677T MTHFR mutation; normal serum homocysteine</td>
<td>Healed with methylprednisolone and enoxaparin</td>
</tr>
<tr>
<td>Nucera et al</td>
<td>M/19</td>
<td>Multiple cutaneous ulcerations</td>
<td>Heterozygous C677T and A1298C mutation; anti-beta-2-glycoprotein antibodies, antithrombin antibodies, hyperhomocysteinemia, DiGeorge syndrome</td>
<td>No discussion of therapy for cutaneous ulcerations</td>
</tr>
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REFERENCES