CASE REPORT

Successful treatment of hydroxyurea-associated panniculitis and vasculitis with low-dose methotrexate

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Key words: hydroxyurea; methotrexate; panniculitis; vasculitis.

INTRODUCTION

Hydroxyurea is a standard treatment for myeloproliferative disorders because of its cytoreductive effects on all bone marrow cell lines.1 As a hydroxylated derivative of urea, it inhibits DNA synthesis by inactivating ribonucleotide diphosphate reductase.2 Hydroxyurea is generally well tolerated.2 However, a variety of cutaneous side effects including leg ulcers, dermatomyositis, and hyperpigmentations have been described.3-5 Here we present a rare case of concomitant medium-vessel vasculitis and panniculitis associated with hydroxyurea therapy successfully treated with low-dose methotrexate.

CASE REPORT

An 80-year-old man presented with new-onset multiple painful nodules and plaques on his lower extremities and back in September 2011. His medical history is significant for coronary artery disease, type 2 diabetes, dyslipidemia, and hypertension. In addition, he had polycythemia vera treated with 750 mg/d of hydroxyurea since April 2011. Other medications include pravastatin, glyburide, amlodipine, lisinopril, esomeprazole, carvedilol, oxybutynin, and furosemide. He received multiple courses of oral antibiotics from a primary care physician with no significant improvement.

Physical examination found multiple 5- to 15-cm erythematous indurated plaques and subcutaneous nodules on his left dorsal foot, right thigh, and left lower back (Fig 1). These lesions were warm and tender to touch. Biopsy was performed on the back for both hematoxylin-eosin and tissue culture. Tissue cultures for bacteria, fungus, and acid-fast were negative. Histology results showed deep dermal and subcutaneous infiltrate. The septae of the subcutaneous fat were markedly thickened and contained an inflammatory cell infiltrate composed of lymphocytes, histiocytes, and numerous eosinophils. The septal infiltrate spilled into the lobules. There were inflammatory cells infiltrating the wall of some of the medium-sized vessels causing luminal obliteration (Fig 2, A-C). Laboratory tests found antinuclear antibodies at 1:40 and C-reactive protein at 28.1 (<8.0 mg/L). Results were negative for perinuclear antineutrophil cytoplasmic antibodies and cytoplasmic antineutrophil cytoplasmic antibodies.

Based on history, clinical presentation, and pathology findings, we suspected that the concomitant cutaneous vasculitis and panniculitis could be induced by long-term hydroxyurea therapy. Because of the patient’s age and comorbidity, his hematologist recommended against suspending hydroxyurea therapy. For treatment, the patient received 40 mg/d of prednisone for 2 weeks followed by a slow taper, which significantly improved the lesions. However, the painful indurated plaques and subcutaneous nodule would reoccur whenever the dose of prednisone decreased to less than 20 mg daily. To avoid side effects of long-term oral corticosteroids, we started the patient on 7.5 mg of methotrexate weekly with 1 mg of folic acid. Within 3 weeks, there were significant improvements in pain, erythema, and the size of plaque and nodules. The patient tolerated the medication well. The cutaneous findings of vasculitis and panniculitis completely resolved with only residual postinflam-

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Funding sources: None.

Conflicts of interest: None declared.

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JAAD Case Reports 2017;3:422-4.

2352-5126

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http://dx.doi.org/10.1016/j.jdcr.2017.06.009

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matory hyperpigmentation after 2 months of low-dose methotrexate (Fig 3). The dose of methotrexate was decreased gradually to 2.5 mg/wk with good control of his cutaneous reaction while he continued to take hydroxyurea. Since then, the patient experienced 2 episodes of flare associated with an increased dose of hydroxyurea. During both flare ups, the tender indurated plaques and nodules reoccurred about 3 months after the increased dose of hydroxyurea. Both episodes were successfully treated with a small increase in methotrexate dose back to 5 mg weekly with complete resolution in 6 to 8 weeks. This finding strongly suggests that hydroxyurea is the underlying cause of the concomitant cutaneous vasculitis and panniculitis. The patient has been on low-dose methotrexate.
methotrexate for 5 years with no reported side effects, and the postinflammatory hyperpigmentation nearly resolved (Fig 3).

**DISCUSSION**

Hydroxyurea therapy could evoke a wide range of adverse cutaneous reactions. Although poorly understood, long-term therapy causes cutaneous changes in up to 5% of patients. Most commonly reported manifestations include painful ulcers particularly in the malleolar area, dermatomyositis-like eruption, hyperpigmentation, melanonychia, xerosis, alopecia, palmoplantar keratoderma, and facial and acral erythema. Patients are also at higher risk of both squamous cell and basal cell carcinomas.

Two cases of leukocytoclastic vasculitis have been described associated with leg ulcers. Also a recent case report described coexisting leukocytoclastic vasculitis and acral keratosis in a patient during treatment of essential thrombocytemia with hydroxyurea. Only one case of noninfectious panniculitis has been reported in an 81-year-old woman after 8 years of hydroxyurea therapy for myeloproliferative disorders. In all cases, patients had to discontinue hydroxyurea use because of the severity of the cutaneous reaction.

The underlying mechanisms of hydroxyurea-induced cutaneous reactions are poorly understood. Hydroxyurea-induced inhibition of DNA synthesis, macrocytosis, and platelet dysregulations were thought to cause direct tissue damage including death of keratinocytes, microthrombus formation, and impaired tissue repair. Discontinuation of hydroxyurea was thought to be the only effective treatment for debilitating cutaneous reaction. Systemic corticosteroids could provide temporary relief but are not safe for long-term therapy. This finding could pose significant challenge to the treatment of myeloproliferative disorders.

To the best of our knowledge, this is the first case reported of concomitant vasculitis and panniculitis associated with hydroxyurea. Both vasculitis and panniculitis are rare cutaneous reactions that are only reported separately in few patients. This is the first time we saw medium-sized vessel vasculitis and sepal and lobular panniculitis in a patient related to hydroxyurea. More interestingly, the hydroxyurea-induced vasculitis and panniculitis in our patient has been successfully treated with very low-dose methotrexate (2.5-5 mg/wk) with no reported side effects. As a folic acid antagonist, methotrexate inhibits the conversion of dihydrofolate to tetrahydrofolate, which causes an increase in adenosine, subsequently diminishing inflammatory cell activity. Here we show that low-dose methotrexate could be a safe and effective treatment for hydroxyurea-induced vasculitis and panniculitis.

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