CASE STUDY

Malleolar Ulceration Induced by Hydroxyurea Therapy for Chronic Eosinophilia

Justin R. Bryant, DO, MBA, CWSP^{a,*}, Peter Andrade, DO^b, Raymond T. Hajjar, DO^a, Christopher R. Lumley, DO^a, Kongkrit Chaiyasate, MD^c

^aBeaumont – Farmington Hills Plastic Surgery Fellowship, Farmington Hills, MI, USA

^bDetroit Medical Center Sinai Grace Hospital Plastic Surgery Fellowship, Detroit, MI, USA; and

^cBeaumont – Royal Oak Plastic & Reconstructive Surgery, Royal Oak, MI, USA

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Abstract A 59-year-old African American female presented to a plastic surgery office in consultation for a very painful non-healing wound of her right lateral malleolus. An incisional biopsy was performed and ultimately a diagnosis of hydroxyurea-induced ulcer was concluded. Descriptions of this entity are rare in the surgical and wound care professional literature. This diagnosis does appear in the hematology/oncology literature; however, these practitioners may not be the first to examine a patient with the development of such an ulcer. This article presents the pathophysiology and clinical presentation of hydroxyurea-induced ulceration as well as the characteristics of hydroxyurea-induced ulceration in addition to the case study.

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Case Report

A 59-year-old African American female presented to a plastic surgery office in consultation for an extremely painful non-healing wound of her right lateral malleolus. She reported initially noticing a burning sensation over her right ankle while bathing three weeks prior and noticed a scratch on the ankle that she believes was from her husband's toenail. Over the next few days she developed ankle edema with pain and subsequent difficulty with ambulation. She visited the Emergency Department (ED) on three separate occasions due to progressive pain, edema, and erythema and was noted to have edema and skin

erythema but no skin ulceration. On each occasion she was diagnosed with cellulitis and treated with topical and oral antibiotics. The patient was not found to have leukocytosis on any of her prior ED visits. Multiple ankle radiographs had been performed at the time of her ED visits, all demonstrating only mild soft tissue swelling over the lateral malleolus. A venous duplex performed in the ED was negative for DVT.

At the time of her follow-up appointment with Infectious Disease an open necrotic wound with periwound hyperpigmentation and disproportionate pain was noted on exam, precipitating an urgent plastic surgery consult for biopsy and debridement. At the time of the plastic surgery consultation, the patient was found to have pitting edema of the right ankle and foot surrounding a 6 × 4 cm full thickness ulcer covered by eschar [Figure] with pain out of proportion to her examination. No other dermatologic abnormalities were found on examination. She was admitted

* Corresponding author. Beaumont – Farmington Hills Plastic & Reconstructive Surgery Fellowship, 3110 Telegraph Rd #280, Bingham Farms, MI 48025, USA. Fax: +1 248 208 1750.

E-mail address: justinRbryant@gmail.com

Figure Hydroxyurea induced lateral malleolar ulcer.

to the hospital for pain control, biopsy, and debridement. Consultations were obtained from hematology/oncology, rheumatology, and infectious disease. She was not found to have leukocytosis at the time of admission. An incisional biopsy including the wound border was performed under anesthesia due to the severity of the patient's pain.

Medical history revealed that the patient had a history of chronic anemia and persistent eosinophilia for which she was prescribed 500 mg hydroxyurea once daily. She was also on chronic prednisone for asthma. She denied prior history of similar wounds or known history of peripheral vascular disease. She did have a remote history of nicotine addiction but had ceased smoking 20 years prior. The patient also reported a history of deep venous thrombosis (DVT) one-year prior for which she had been followed by a hematologist.

Histopathologic examination demonstrated dermal necrosis with underlying intravascular fibrin thrombi in areas of dermal ischemia. There was sparse perivascular and interstitial neutrophilic infiltrate. No evidence of active vasculitis was seen. Characteristics of atrophie blanche were also noted. The overall pathologic impression was of a thrombotic vasculopathy. The specimen was negative for fungal and bacterial elements. Wound cultures grew *Pseudomonas aeruginosa*, which was deemed representative of superficial wound colonization.

The underlying etiology of her ulceration was initially diagnosed as acute thrombotic vasculopathy. Further

inpatient workup of the thrombotic vasculopathy was not possible, as the patient desired to be discharged. At the time of discharge from the hospital, the patient was continued on her preadmission hydroxyurea and prednisone by the hematology/oncology team with planned follow up with the plastic surgery team. The patient later developed a much smaller wound similar in appearance over the lateral malleolus of the contralateral lower extremity. At a subsequent follow-up with the patient's regular hematologist a diagnosis of hydroxyurea-induced ulceration was made and the use of hydroxyurea therapy was halted.

Local wound care was undertaken to facilitate healthy granulation tissue at the wound base. The patient progressed well with local wound care and underwent a split thickness skin grafting of the original lateral malleolar wound 3 months after initial presentation. The contralateral malleolar wound was small and progressed well with local wound care, achieving closure by secondary intention.

Hydroxyurea Pharmacology and Therapy

Hydroxyurea is an antimetabolite cytotoxic drug that inhibits the enzyme ribonucleotide reductase.¹ Inhibition of this enzyme prevents the conversion of ribonucleotides to deoxyribonucleotides and thus inhibits DNA synthesis. As deoxyribonucleotide pools are depleted, cells are arrested in the G1-S interface of the cell cycle. The inhibition of DNA synthesis ultimately results in DNA repair inhibition and cell death. Hydroxyurea has also been demonstrated to affect erythrocyte and neutrophil endothelial adhesion, decreasing vaso-occlusive events in hemoglobinopathies and chronic myeloproliferative disorders.¹

Hydroxyurea is administered orally or intravenously and has been used in the treatment of hematologic and myeloproliferative disorders, HIV, psoriasis, and in the treatment of sickle cell disease. Effects as a myelosuppressive agent have led to its use in the treatment of polycythemia, thrombocytosis, and as a drug of choice in myeloproliferative neoplasms.² The use of hydroxyurea in the treatment of sickle cell disease and thalassemia is affected by its ability to induce fetal hemoglobin production. In the case of sickle cell disease and chronic myeloproliferative disorders, hydroxyurea treatment may be continued indefinitely.

Dermatologic Side Effects

Common dermatologic adverse reactions of hydroxyurea therapy [Table 1] include skin erythema and hyperpigmentation, nail changes including hyperpigmentation, xerosis, photosensitization, alopecia, skin atrophy, palmar/plantar keratoderma, lichen planus, and dermatomyositis like eruptions.²⁻⁴ Less common dermatologic sequelae

Table 1 Dermatologic Side Effects of Hydroxyurea Therapy.	
Common	Less Common
Erythema	Lower extremity ulceration
Hyperpigmentation	Oral ulceration
Nail changes including hyperpigmentation	Squamous metaplasia
Xerosis	Non-melanocytic skin cancer
Photosensitization	
Alopecia	
Skin atrophy	
Palmar/plantar keratoderma	
Lichen planus	
Dermatomyositis like eruptions	

[Table 1] of long-term hydroxyurea therapy include lower extremity ulceration, oral ulceration,⁵ and the development of squamous metaplasia and non-melanocytic skin cancer.⁶ Lower extremity ulcerations have been estimated to occur in 9% of patients undergoing long term (average 5 years) hydroxyurea therapy.² Thus it has been recommended that frequent dermatologic follow-up be a part of the course in any patient receiving hydroxyurea therapy.⁴

Ulcer Presentation and Characterization

Ulcers associated with hydroxyurea therapy are most commonly reported to arise on or near the malleoli but have also been reported to occur on the calf, foot, lower leg, toes, hands, and arms and may be solitary or multiple in number.^{2,4} These ulcers are almost invariably reported as being extremely painful upon presentation, frequently described as pain out of proportion to examination. This disproportionate pain may initially cause concern for necrotizing soft tissue infection or pyoderma gangrenosum, but a thorough history and close examination of the wound provides differentiating features [Table 2].

The development of ulcerations may be preceded by complaints of painful localized cutaneous erythema, pigmentation, irritation, or cutaneous eruption. The patient may or may not recall an associated mechanical trauma, as

the trauma may only be minor.^{2,3} The wound itself is typically described as well defined with elevated or slightly undermined borders surrounding a fibrinous or necrotic appearing central base.³ The periwound is typically described as erythematous, fibrotic, or containing atrophie blanche. Concomitant presence of any of the aforementioned hydroxyurea-associated cutaneous side effects may also aid in the diagnosis. Although no specific histopathologic features have been outlined, commonly reported findings exist [Table 3].^{2,7}

Mechanism of Ulceration

Though the exact mechanism of ulceration resulting from long term hydroxyurea therapy has not been elucidated, common theories exist. Through its inhibition of DNA synthesis, hydroxyurea has been proposed to inhibit basal keratinocyte turnover in the skin.² This inhibition may cause reduced collagen production as well as thinning and atrophy of the epidermis. A minor trauma may be accused as the inciting event to skin barrier breakdown with patients commonly reporting only a possible minor trauma prior to ulcer formation.

The myelosuppressive effects of hydroxyurea, which make it useful in hematologic disorders, may also result in macroerythrocytosis.^{2,4} The resultant red blood cells may have difficulty traversing dermal microcirculatory vessels and thus impair flow. Ensuant dermal hypoxia may precipitate skin barrier breakdown and ulcer formation.

Treatment

Treatment of hydroxyurea-induced ulcerations consists of altering the dose either by decreasing dosage, increasing dosage interval, or by cessation of hydroxyurea therapy.² Alterations in dosage or cessation of hydroxyurea therapy is crucial for wound healing, and without this change other wound care efforts may be futile. A multitude of adjunctive and modern wound care modalities have been utilized with closure ultimately achieved by either skin grafting or secondary intention.

Table 2 Characteristics and Features of Hydroxyurea Induced Ulcers.		
History	Wound	Periwound
May or may not reveal minor preceding trauma	Pain out of proportion to examination	Erythematous
Painful	Well defined with elevated or slightly undermined borders	Fibrotic
Localized cutaneous erythema, pigmentation, irritation, or cutaneous eruption	Fibrinous or necrotic appearing central base	Atrophie blanche
Possible concomitant presentation of other HU associated dermatologic effects	Large variation in size, but progressive enlargement	

Table 3 Commonly Reported Histopathology in Hydroxyurea Induced Ulcers.

- Epidermal atrophy, dermal atrophy or fibrosis
- Scar tissue without vascular lesions
- Perivascular lymphocytic infiltration and swelling of vessel walls without vasculitis
- Atrophie blanche

Discussion/Conclusions

In the case presented here the patient presented with an extremely painful ulcer on of the lateral malleolus of unknown etiology. Pathologic findings initially led to a diagnosis of acute vasculopathy but follow up was with a hematologist who made the etiologic diagnosis. The majority of cases of hydroxyurea-induced lower extremity ulcers appear predominantly in the hematology/oncology and dermatology literature. This entity appears to be better known in the field of hematology/oncology as evidenced in the appearance of publications in hematology/oncology literature and anecdotally by the hematologist's diagnosis and familiarity with the wound presented in this case report. The importance of dermatologic monitoring of patients undergoing hydroxyurea therapy cannot be understated.

Conflict of interest

There are no conflicts of interest from any of the authors to disclose. No financial support was provided for the preparation of this article.

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