Hydroxyurea-Associated Dermatomyositis-like Eruption Demonstrating Abnormal Epidermal p53 Expression

A Potential Premalignant Manifestation of Chronic Hydroxyurea and UV Radiation Exposure

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Background: Chronic hydroxyurea therapy is associated with numerous cutaneous adverse effects. While hydroxyurea-associated nonmelanoma skin cancers are known to be associated with significant morbidity and occasional mortality, to date, dermatomyositis-like eruption has been considered a benign entity, other than its ability to mimic true dermatomyositis leading to inappropriate immunosuppression. More recently, hydroxyurea-associated squamous dysplasia has been characterized as a premalignant precursor to hydroxyurea-associated nonmelanoma skin cancers and shown to manifest abnormal p53 expression.

Observations: An elderly woman receiving chronic hydroxyurea therapy for myelodysplasia developed a dermatomyositis-like eruption that was misdiagnosed as true dermatomyositis, leading to continuation of hydroxyurea. Years later she developed severe hydroxyurea-associated nonmelanoma skin cancers resulting in discontinuation of hydroxyurea, poor control of her myelodysplasia, and death. Re-evaluation with immunohistochemical analysis of tissue from her original dermatomyositis-like eruption revealed focal confluent nuclear expression of p53 along the lower layers of the epidermis, suggestive of a premalignant state.

Conclusions: We suggest that dermatomyositis-like eruption and hydroxyurea-associated squamous dysplasia represent similar clinical manifestations of a common underlying chronic phototoxic process involving aberrant keratinocyte p53 expression mediated by hydroxyurea's antimitabolite properties and UV radiation exposure. Accordingly, we suggest that dermatomyositis-like eruption, previously considered a benign entity, may represent a premalignant precursor of hydroxyurea-associated nonmelanoma skin cancers warranting discontinuation of hydroxyurea therapy.

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Hydroxyurea (HU) is an antimitabolite that inhibits DNA synthesis via ribonucleotide reductase resulting in S-phase arrest of mitosis leading to apoptosis. Most commonly used in treating hematologic and oncologic conditions, HU has also been used to treat hypereosinophilic syndrome and refractory psoriasis.1,2

Cutaneous and/or mucosal adverse effects occur in 10% to 35% of patients receiving chronic HU therapy, most commonly facial erythema, hyperpigmentation, ichthyosis, alopecia, stomatitis, atrophy, acral erythema, palmoplantar keratoderma, leukocytoclastic vasculitis, melenonychia, and leg ulcers.3–9 More rarely, a dermatomyositis-like eruption (DM-LE), aggressive HU-associated nonmelanoma skin cancers (HU-NMSC), or the recently described HU-associated squamous dysplasia (HUSD) may develop.

We report a patient in whom chronic HU therapy resulted in a dermatomyositis-like eruption. Years later, she developed HU-associated nonmelanoma skin cancers, prompting the discontinuation of HU therapy and subsequent progression of her myelodysplasia resulting in death. We discuss herein the clinical, histologic, and mechanistic similarities among DM-LE, HUSD, and HU-NMSC and propose that DM-LE and HUSD are similar clinical presentations of a common underlying chronic phototoxic process involving HU and UV radiation (UVR)-induced damage, thus imparting significance to DM-LE as a potential premalignant clinical mani-

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An 82-year-old woman was referred to our dermatology clinic for evaluation and management of dermatomyositis. Four years earlier, she developed a violaceous, scaly cutaneous eruption on her dorsal hands, which was evaluated by an internist, hematologist-oncologist, rheumatologist, and outside dermatologist. Physical examination revealed mild muscle weakness and a cutaneous eruption suggestive of Gottron papules, which on histologic evaluation revealed mild interface dermatitis, epidermal atrophy, and effacement of the rete ridges (Figure 1). Clinical-pathologic correlation culminated in a diagnosis of dermatomyositis. Creatine kinase level and erythrocyte sedimentation rate were normal and antinuclear antibodies were undetectable. Laboratory evaluation revealed a rheumatoid factor of 29.8 IU/mL (reference range, 0-20 IU/mL), an aldolase level of 10 U/L (reference range, <8 U/L), and a polyclonal gamma globulin level increase of 1.85 g/dL (reference range, 0.74-1.7 g/dL). The cutaneous eruption on her hands progressively worsened despite 1 year of treatment with hydroxychloroquine sulfate, 200 mg by mouth twice daily, a 6-month course of azathioprine, 50 mg orally per day, and intermittent oral prednisone tapers.

At the time of our initial evaluation she was treating her hands with mupirocin, 2%, ointment and clobetasol propionate, 0.05%, cream. She denied muscle weakness, photosensitivity, or dysphagia. She complained of pain from ulcerations on her hands, generalized dry skin, and a chronic painful ulcer on her right ankle. Her medical history was notable for myelodysplastic syndrome diagnosed 15 years earlier, chronic renal insufficiency, deep vein thrombosis, dermatomyositis, squamous cell carcinoma (SCC) in situ of the dorsal right index finger 3 years earlier, stroke, and multiple episodes of pneumonia leaving her oxygen dependent. Medications included HU, metoprolol tartrate, triamterene, hydrochlorothiazide, warfarin sodium, paroxetine mesylate, colestipol, lanosprazole, allopurinol sodium, multivitamins, and radioactive phosphorus on 2 occasions.

Physical examination revealed Fitzpatrick skin type II, a 4-cm ulcerated, indurated plaque overlying the right third and fourth metacarpophalangeal joints (Figure 2), and scaly erythematosus plaques on the left thumb and second finger (Figure 3). There were erythematosus scaly papules and plaques overlying her proximal and distal interphalangeal joints bilaterally, with a relative sparing of the intervening skin. Periungual erythema was ob-
served; however, there were no tortuous nail fold telangiectasias and her cuticles appeared normal. Confluent erythema of her nose and cheeks, generalized xerosis, and poikiloderma of habitually exposed areas were noted. A 1-cm sharply demarcated, tender ulcer with yellow fibrinoid membrane and surrounding atrophy overlay her right lateral malleolus (Figure 4). There was no scalp involvement, heliotrope eruption, shawl sign, muscle weakness, or lymphadenopathy. Biopsies from the left thumb and the right dorsal hand revealed invasive SCC (Figure 5).

Further review of the case prompted by the aggressive nature of the patient’s SCCs revealed the diagnoses: chronic HU-induced SCCs, leg ulcer, xerosis, and poikiloderma. Her initial presentation 4 years earlier is consistent with HU-induced DM-LE rather than true dermatomyositis. Immunohistochemical analysis of her DM-LE (tissue samples were obtained at the time of cutaneous eruption onset 4 years earlier and depicted in Figure 1) revealed focal p53 expression in a confluent nuclear pattern along the lower levels of the epidermis (Figure 6).

We recommended diligent photoprotection and collaborated with her hematologist to discontinue her HU therapy in favor of anagrelide hydrochloride for continued treatment of her myelodysplasia. The patient was referred to a hand surgeon who recommended bilateral hand amputation, which the patient declined, opting instead for tumor debulking; clear margins were unobtainable. Despite discontinuation of HU therapy and applying imiquimod, 5%, cream daily, her SCCs continued to progress over the next 3 months. She declined further treatment, choosing palliative care only, and died 5 months later from complications of her myelodysplastic syndrome.

**COMMENT**

Chronic HU therapy has been associated with an interface dermatitis, initially reported in 1975 by Kennedy et al as a lichen planus-like eruption and later characterized as DM-LE by Senet et al in 1995 because of its ability to mimic cutaneous manifestations of true dermatomyositis both clinically and histologically. This condition, also referred to as dermatomyositis-like lesions, pseudo-dermatomyositis, HU dermopathy, and Gottron-like papules, presents as scaly erythematous patches, papules, and plaques of the dorsal hands, similar to those developed by our patient that led to her misdiagnosis of dermatomyositis. Ulceration occurs rarely and nail fold telangiectases have been noted. Dermatomyositis-like eruption is not associated with myopathy or malignancy and only rarely is associated with low-titer antinuclear antibodies. Histologic analysis, which reveals interface dermatitis with minimal inflammation, vacuolar alteration of the basal keratinocytes with dyskeratotic keratinocytes, incontinence of melanin pigment, vascular ectasia, and rarely the presence of mucin, does not aid in differentiating DM-LE from true dermatomyositis, for which clinical correlation is required. Vassallo et al observed DM-LE in 7 of 158 patients (4.4%) with chronic myelogenous leukemia receiving HU therapy for 7 to 120 months (mean, 30 months). Daoud et al observed DM-LE onset after 55 to 79 months (mean, 61 months) in 6 patients, and Senet et al observed DM-LE...
onset in 6 patients 24 to 120 months (mean, 60 months) after starting HU therapy. Dermatomyositis-like eruption has been reported to resolve within 10 days to 18 months after discontinuation of HU therapy but frequently recurs on rechallenge; however, atrophy, if present, tends to persist.\textsuperscript{3,4,11,12,15,16} To date, DM-LE has been described as benign and does not warrant discontinuation of HU therapy, with the significance of DM-LE being limited to its ability to mimic true dermatomyositis leading to inappropriate immunosuppression.\textsuperscript{3,4,15,16}

The association between long-term HU therapy and development of numerous, often aggressive, cutaneous carcinomas is well documented in the literature.\textsuperscript{17-24} Squamous cell carcinomas are most commonly associated, although actinic keratoses and basal cell carcinomas occasionally occur.\textsuperscript{17-19} These HU-NMSCs typically present with an abrupt onset after a variable latency period (range, 2-13 years; mean, 6.5 years) in patients with no history of cutaneous malignancy.\textsuperscript{3,17-20} Hydroxyurea-associated NMSCs occur most commonly in photodistributed sites (with oral involvement reported rarely) in patients with Fitzpatrick skin types I and II and in older patients with higher cumulative exposures of UVR.\textsuperscript{3} These cancers are typically refractory to treatment and result in significant morbidity and occasionally mortality.\textsuperscript{23,24} Strict photoprotection and aggressive surgical intervention are indicated; however, eradication of these tumors is rare without HU therapy discontinuation, after which some tumors have been observed to develop up to 4 years after HU therapy discontinuation.\textsuperscript{21} Rechallenge is typically associated with tumor recurrence and HU-NMSC have been observed to develop up to 4 years after HU therapy discontinuation, necessitating long-term surveillance.\textsuperscript{17,20} Chemoprevention with oral retinoids, strict photoprotection, and aggressive surgical therapy are indicated if HU therapy must be continued.\textsuperscript{17}

Sanchez-Palacios and Guitart\textsuperscript{17} recently proposed the term hydroxyurea-associated squamous dysplasia when they described 2 patients with extensive precancerous conditions associated with long-term HU therapy who later developed HU-NMSC. They described HUSD as photodistributed confluent patches of erythema and xerosis, which may mimic, but is distinct from, a photodermatitis or DM-LE. Histologic evaluation of HUSD reveals varying levels of nuclear atypia, disarray of keratinocytes, vacuolization of basal cells, acantholysis, and occasional squamous matization of the basal layer, similar to histologic features observed in DM-LE. They identified diffuse p53 expression along the lower layers of the epidermis in one patient and proposed that HUSD is a premalignant precursor to HU-NMSC. They reviewed the similarities between HUSD and DM-LE and suggested that some cases previously reported as DM-LE or HU dermatomyositis may instead represent HUSD.

The etiologies of DM-LE, HU-NMSC, and HUSD are not fully elucidated; however, they appear to share similar mechanisms involving direct effects of both HU and UVR. While HU itself is mutagenic via nitroxide-induced oxidative stress and its chronic anti-metabolite effect on the basal layer, it also inhibits normal nucleotide excision repair of both HU and UVR-induced DNA damage.\textsuperscript{10,12,16,22} Simultaneously, HU-induced cutaneous atrophy potentiates the magnitude of UVR induced-DNA damage. Sanchez-Palacios and Guitart\textsuperscript{17} provide an excellent review of the synergistic interaction of HU and UVR resulting in the development of p53 dominant clones, loss of p53-dependent repair of DNA damage, and growth of cutaneous carcinomas. In sum, HU appears to act synergistically with UVR to eventuate in the development aberrant p53 clones and ultimately HU-NMSC.

Up to 75% of actinic keratoses and over 90% of all cutaneous SCCs contain distinctive UVR-induced p53 mutations.\textsuperscript{25-27} Jonasen et al\textsuperscript{28} showed that p53-mutated keratinocytes are present in normal skin as well as sun-exposed skin, but mutant clones were both larger and more numerous in the sun-exposed skin. Backvall et al\textsuperscript{29} demonstrated p53 mutant clones to be significantly more numerous and larger in normal skin surrounding SCCs compared with normal skin surrounding benign nevi and basal cell carcinomas. Sanchez-Palacios and Guitart\textsuperscript{17} identified diffuse p53 expression along the lower layers of the epidermis in one patient with HUSD and concluded that HUSD represents a premalignant precursor of HU-NMSC distinct from DM-LE.

Our patient presented with clinical and histologic findings mimicking true dermatomyositis, and on re-evaluation these findings are most consistent with DM-LE. Re-evaluation of her cutaneous biopsy specimen, obtained at the time of initial skin eruption onset 4 years prior to her development of HU-NMSC, demonstrated focal epidermal staining of p53 in a confluent nuclear pattern (Figure 6). Ours is the first report, to our knowledge, evaluating p53 expression in DM-LE, and the pattern identified is similar, although more focal, to that described in HUSD, an entity recently characterized and suggested to be a precursor to HU-NMSC. Dermatomyositis-like eruption is typically reported earlier in the course of HU therapy (mean, 53 months) than HU-NMSC (mean, 75 months), which lends temporal support of DM-LE as a forerunner of HU-NMSC. The timing of development of HUSD is not well characterized; HUSD has been reported in only 2 patients,\textsuperscript{17} diagnosed after 9 and 11 years of HU therapy. However, the date of HUSD onset was not documented.

Considering the parallels in clinical presentation, histologic features, proposed etiologies, and p53 expression patterns, we propose that DM-LE and HUSD represent similar clinical manifestations of a common underlying chronic phototoxic process characterized by the development and expansion of mutant p53 clones mediated by the synergistic actions of HU therapy and UVR (Table).\textsuperscript{3,11,16,17} The extent of clinical overlap between DM-LE and HUSD is evidenced by the suggestion by Sanchez-Palacios and Guitart\textsuperscript{17} that many cases of HUSD may have been previously misdiagnosed as DM-LE. In fact, some may consider DM-LE and HUSD to be the same process, while others may choose to separate the 2 entities owing to the subtly different clinical presentations (DM-LE mimicking true dermatomyositis and HUSD manifesting precancerous actinic damage); this is likely a case of “lumpers” vs “splitters.” Nonetheless, while HUSD is likely a more appropriate term for these overlapping conditions because it more adequately describes the underlying process, DM-LE has been engrained in the medical literature throughout the past 30 years as a benign entity, while HUSD, considered premalignant, has only recently been described in 2 patients.
Regardless of the terminology chosen, our identification of abnormal p53 expression in DM-LE warrants consideration of DM-LE as a potentially premalignant precursor to HU-NMSC, supporting consideration of a change in the clinical significance attributed to DM-LE. Previously void of any prognostic significance, the development of DM-LE should be considered to represent underlying keratinocyte cellular atypia, thus identifying patients at increased risk of developing HUSD and HU-NMSC and warranting discontinuation of HU therapy. The ability of DM-LE to mimic true dermatomyositis is also noteworthy, since inappropriate immunosuppressive therapy might hasten progression toward HU-NMSC.

As our patient was inappropriately treated with low-dose azathioprine (6-month course of azathioprine, 50 mg orally per day) and intermittent prednisone tapers, we cannot entirely exclude a potential role of this iatrogenic immunosuppression in the development of her cutaneous carcinomas. However, as her cutaneous carcinomas developed and progressed years after her short period of iatrogenic immunosuppression, we believe that the chronic phototoxic effects of HU therapy were the primary stimulus in the development of her cutaneous carcinomas.

In addition, because this observation is only a single case evaluation of p53 expression in DM-LE, adding to the single case reported of aberrant p53 expression in HUSD, more extensive investigations of p53 mutations in DM-LE, HUSD, and HU-NMSC, while difficult to perform owing to the rarity of the conditions, should prove enlightening and help clarify the relationship between these entities. In the meantime, we suggest a heightened level of scrutiny when encountering cases of DM-LE.

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Table. Characteristics of Dermatomyositis-like Eruption (DM-LE), Hydroxyurea (HU)-Associated Squamous Dysplasia (HUSD), and HU-Associated Nonmelanoma Skin Cancer (HU-NMSC)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DM-LE</th>
<th>HUSD</th>
<th>HU-NMSC</th>
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<tbody>
<tr>
<td>Clinical presentation</td>
<td>Scaly erythematous patches, papules, and plaques of the dorsal hands</td>
<td>Photo-distributed confluent patches of erythema and xerosis</td>
<td>Numerous, often aggressive, cutaneous carcinomas, frequently presenting with an abrupt onset after a variable latency period</td>
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<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Histologic features</td>
<td>Interface dermatitis with minimal inflammation, vacuolar alteration of the basal keratinocytes with dyskeratotic keratinocytes, hypergranulosis or hypergranulosis, incontinence of melanin pigment, vascular ectasia, and rarely the presence of mucin</td>
<td>Varying levels of nuclear atypia, disarray of keratinocytes, vacuolization of basal keratinocytes, acantholysis, and occasional squamatization of the basal layer keratinocytes</td>
<td>Photo distributed Varying proportions of relatively normal and anaplastic squamous cells according to level of differentiation</td>
</tr>
<tr>
<td>Proposed etiology</td>
<td>Chronic cumulative cytologic damage to the basal layer via HU-derived free radical nitroxide intermediates and inhibition of DNA synthesis and repair</td>
<td>UVR-induced DNA damage, compounded by HU-mediated damage from free radical nitroxide intermediates and inhibition of DNA synthesis and nucleotide excision repair; HU-induced cutaneous atrophy potentiates the magnitude of UV radiation–induced DNA damage</td>
<td>UVR-induced DNA damage, compounded by HU-mediated damage from free radical nitroxide intermediates and inhibition of DNA synthesis and nucleotide excision repair; HU-induced cutaneous atrophy potentiates the magnitude of UVR-induced DNA damage</td>
</tr>
<tr>
<td>p53 Pattern</td>
<td>Focal p53 expression along the lower layers of the epidermis (current case)</td>
<td>Diffuse p53 expression along the lower layers of the epidermis (1 case)</td>
<td>More than 90% of cutaneous squamous cell carcinomas contain distinctive UVR-induced p53 mutations</td>
</tr>
<tr>
<td>Prevalence</td>
<td>7 of 158 patients (4.4%)</td>
<td>Unknown; reported only in 2 patients</td>
<td>7 of 184 patients (3.8%)</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>59.1 y</td>
<td>67.5 y (2 cases) at time of diagnosis; age at HUSD onset unknown</td>
<td>66 y</td>
</tr>
<tr>
<td>HU exposure (mean)</td>
<td>49.4 mo (34 cases)</td>
<td>Diagnosed in 2 patients after 9 and 11 y of HU therapy; however, time of onset was not reported</td>
<td>Abrupt onset after latency period averaging 79 mo (27 cases)</td>
</tr>
<tr>
<td>Change on HU therapy discontinuation</td>
<td>Resolves within 10 d to 180 mo; atrophy, if present, tends to persist</td>
<td>Unknown</td>
<td>Can experience some degree of improvement on HU therapy discontinuation</td>
</tr>
</tbody>
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Abbreviation: UVR, UV radiation.
Analysis and interpretation of data: Kalajian, Cely, Malone, Burruss, and Callen. Drafting of the manuscript: Kalajian and Cely. Critical revision of the manuscript for important intellectual content: Kalajian, Malone, Burruss, and Callen. Administrative, technical, and material support: Kalajian. Study supervision: Malone, Burruss, and Callen.

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