A patient case highlighting the myriad of cutaneous adverse effects of prolonged use of hydroxyurea

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Abstract

Background: Hydroxyurea is an antimetabolite primarily used to treat myeloproliferative disorders, and chronic treatment is associated with many cutaneous adverse effects ranging in severity from ichthyosis to aggressive nonmelanoma skin cancer. **Case Presentation:** We report a 67-year-old man with a history of polycythemia vera who was referred for management of progressively worsening dorsal hand lesions. The patient presented with hyperpigmentation, ichthyosis, plantar keratoderma, dermatomyositis-like eruptions, two squamous cell carcinomas, and actinic keratoses. The adverse reactions observed were acknowledged to be related to chronic hydroxyurea use. The patient underwent Mohs excision of the squamous cell carcinomas and the hydroxyurea was promptly discontinued; subsequent cutaneous improvement of the dermatomyositis-like lesions ensued. Another clinically suspicious aggressive squamous cell carcinoma was suspected and the patient was referred to the plastic surgery department for complete excision because of the size of the lesion. The patient remains on periodic dermatology follow up. **Conclusions:** We report a case that exemplifies the cutaneous adverse effects of chronic hydroxyurea therapy. Although many cases improve after drug discontinuation, strict photoprotection and ongoing surveillance are indicated given the recently proposed premalignant potential of dermatomyositis-like eruptions and the aggressive nature of hydroxyurea-induced nonmelanoma skin cancer.

Keywords: hydroxyurea, dermatomyositis, dermatomyositis-like eruption, drug-induced dermatomyositis, squamous cell carcinoma, nonmelanoma skin cancer

Introduction

Hydroxyurea (HU) is an antimetabolite commonly used to treat neoplastic myeloproliferative disorders, HIV, sickle cell disease, and even refractory psoriasis, metastatic melanoma, and hypereosinophilic syndrome. HU works by halting DNA synthesis by inhibiting ribonucleotide reductase, as well as inhibiting DNA repair. In addition to systemic effects, chronic use is associated with cutaneous adverse effects. These include facial erythema, hyperpigmentation, ichthyosis, alopecia, stomatitis, atrophy, acral erythema, palmoplantar keratoderma, leukocytoclastic vasculitis, melanonychia, leg ulcers, dermatomyositis-like eruption (DM-LE), recently proposed HU-associated squamous dysplasia (HUSD), actinic keratoses, and HU-associated nonmelanoma skin cancers (HU-NMSC).

We report a patient with polycythemia vera in whom chronic HU therapy resulted in ichthyosis, plantar keratoderma, hyperpigmentation, DM-LE, actinic keratoses, and HU-NMSC.

Case Synopsis

A 67-year-old man with a history of polycythemia vera (PV) was referred for management of progressively worsening dorsal hand lesions that had appeared 4 years earlier. His PV had been treated with HU for 15 years at a daily dose of 1000 mg alternating

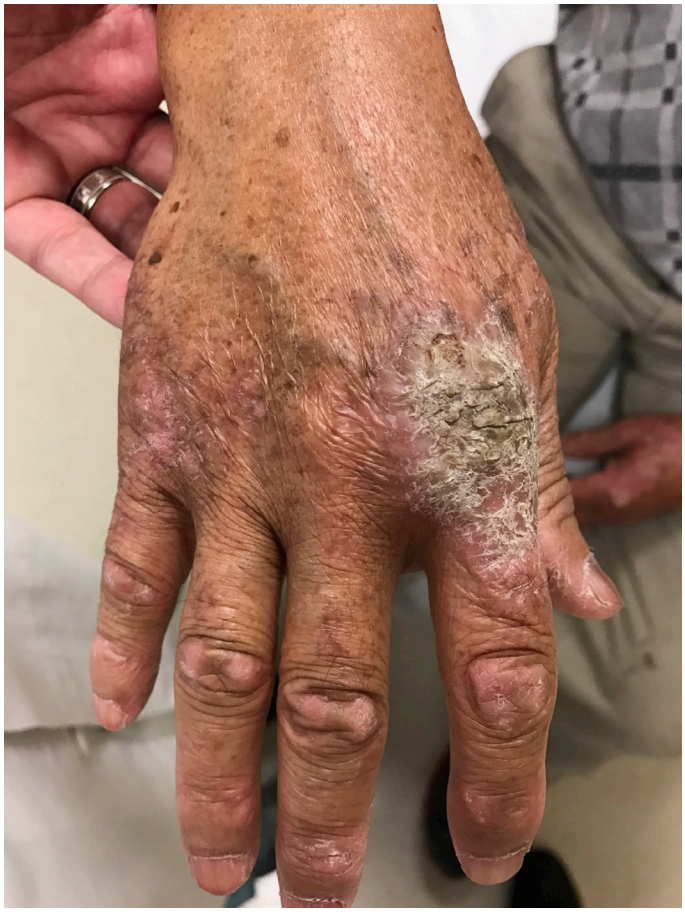

Figure 1. *Second right dorsal metacarpophalangeal joint with* **3.***5 x* **3.***0 cm hyperkeratotic plaque.*

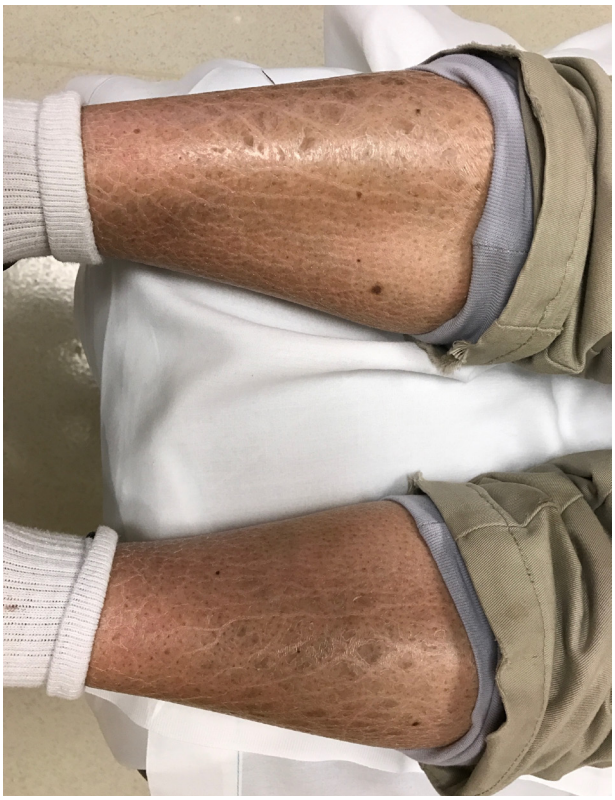

Figure 3. *Bilateral anterior lower extremities. Ichthyosiform lesions present as plate-like scaling.*

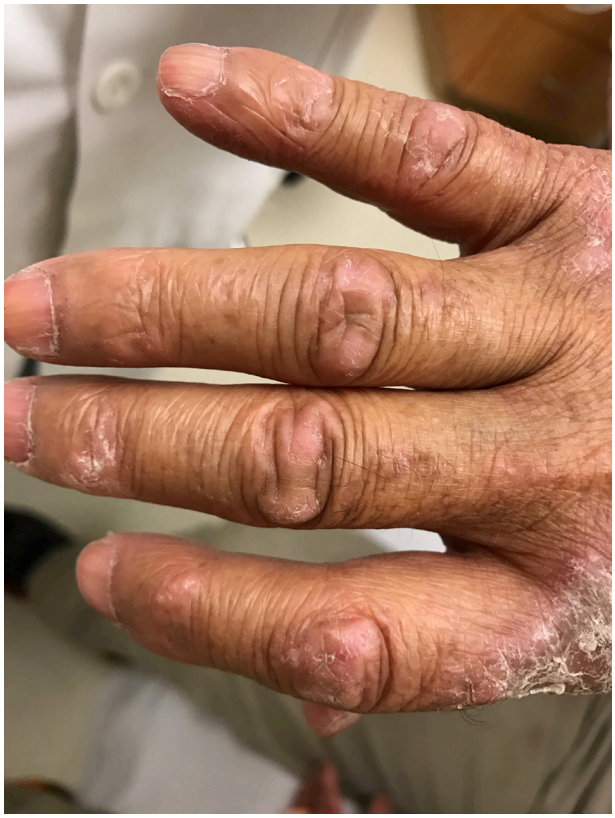

Figure 2. *Dorsal proximal interphalangeal joints. All digits displayed dermatomyositis-like hypopigmented pink papules (Gottron's papules).*

with 1500 mg, as well as phlebotomy every other month for hematocrit of greater than 45%. He also complained of a several year history of brown and tan spots distributed over his head, trunk, and extremities that worsened with sun exposure. A couple of years prior, he was found to have the JAK2 mutation, which is found in 95% of patients with PV and seen in other myeloproliferative neoplasms. The patient also had a history of coronary artery disease. Other medications included aspirin, atorvastatin, carvedilol, levothyroxine, multivitamins, magnesium, omeprazole, spironolactone, and tamsulosin. He denied a personal or family history of both skin cancer and ichthyosis vulgaris.

Physical examination revealed extensive photodamage, atrophy, and dermatoheliosis on the dorsal hands and posterior forearms. A violaceous hyperkeratotic papule was noted on his right helix, as well as a hyperkeratotic horn on the right lateral canthus and a 3.5 x 3 cm hyperkeratotic plaque on his 2nd right metacarpophalangeal joint (**Figure 1**). Hypopigmented pink papules covered the proximal interphalangeal joints of all digits (**Figure 2**). Plate-

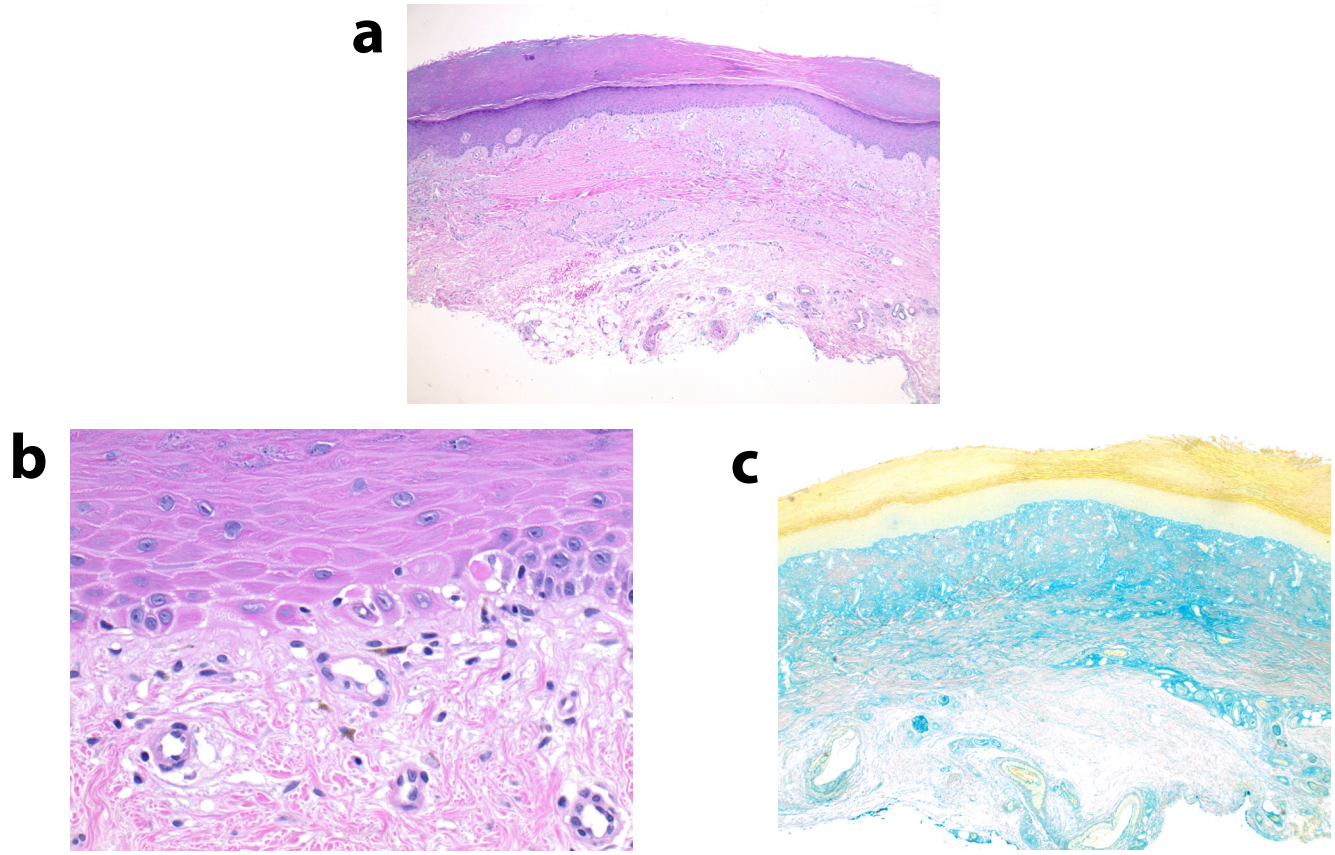

Figure 4. *Biopsy of the right fifth proximal interphalangeal joint lesion. A) Low power view showing marked orthohyperkeratosis, increase in dermal mucin and subtle vacuolar interface dermatitis, H&E, 2%. B) Higher magnification showing vacuolar interface changes with dermal pigment incontinence, H&E, 40%. C) Low power view of colloidal iron stain showing marked increase in dermal mucin, 2%.*

like scaling was noted on the anterior lower legs and forearms (**Figure 3**). There was no clinical evidence of heliotrope rash or nail changes. The patient described a progressive multi-year history of transient muscle soreness, weakness, and loss of muscle mass, but had never seen a rheumatologist.

Biopsies were performed on the right helix, right lateral canthus, and the right fifth proximal interphalangeal joint lesions. A complete blood count with differential showed a macrocytic, normochromic anemia (mean corpuscular volume 104.2 fL, hemoglobin, 14.5 g/dL). Many dyspoietic changes were consistent with hydroxyurea use. Creatine kinase was normal at 39 units/L.

Histopathological examination of the right helix and right lateral canthus lesions showed superficially invasive squamous cell carcinomas (SCC). The biopsy of the right first metacarpophalangeal joint showed broadly transected cutaneous horns with trichilemmal differentiation. Although nonspecific, these might represent a broad based actinic keratosis-like lesion. Histopathological examination of the right fifth proximal interphalangeal joint lesion showed sparse lymphoid infiltrate with rare necrotic keratinocytes, which can be seen in DM or a DM-LE (Figures 4A-C). Staining for p53 was not performed.

History and Histopathology correlated with the diagnoses of HU-induced DM-LE and HU-NMSC. The patient also displayed many other cutaneous adverse effects associated with chronic hydroxyurea, such as hyperpigmentation, ichthyosis, and plantar keratoderma. A few days after this visit, HU was discontinued and the patient underwent Mohs excision for the SCCs.

On return to the dermatology clinic three weeks later, the patient noted improvement of the rash on his dorsal hands. The lesion on his right second metacarpophalangeal joint had become thicker and punch biopsy revealed a hypertrophic actinic keratosis. The patient declined our recommendation to biopsy

a new lesion on the left second metacarpophalangeal joint. The patient was prescribed 5-fluorouracil (5-FU) cream to be used twice daily until follow up in one month.

One month later, the patient continued to note significant improvement in both the lesions on his dorsal hands and anterior legs. However, the patient reported the hypertrophic actinic keratosis on his right metacarpophalangeal joint had continued to progress in size and thickness despite consistent application of 5-FU cream. Our clinical suspicion was that the lesion was actually an SCC; partial biopsies only encompass one particular area of an entire lesion and may not be representative of the true underlying cause. Therefore, considering the lack of response to 5-FU and the size of the lesion, the patient was referred to the plastic surgery department for complete excision. The patient is scheduled to see a rheumatology consultant to further evaluate possible muscle involvement. The patient remains on periodic follow-up in dermatology.

Case Discussion

Cutaneous adverse reactions have been reported in 10% to 35% of patients on chronic HU therapy [1]. Our patient presented with many of the cutaneous adverse effects associated with long-term HU use, ranging from the more common ichthyosiform lesions, hyperpigmentation, and plantar keratoderma, to the less common dorsal hand DM-like changes and SCCs [1]. Other cutaneous manifestations of chronic HU therapy include facial erythema, atrophy, alopecia, stomatitis, acral erythema, leukocytoclastic vasculitis, melonychia, and leg ulcers [1-7].

It can be difficult to distinguish drug-induced DM from classic DM because the clinical presentation and histopathology are similar. A review of 70 reported cases of drug-induced DM by Seidler et al. found 76% of cases had pathognomonic skin findings for DM defined by presence of heliotrope rash, Gottron papules, or both [10]. However, classic DM has a female preponderance of 2:1 and drug-induced DM seems to affect males and females equally [10]. In contrast to classic DM being mostly associated with adenocarcinoma, drug-induced DM has been associated with many non-adenocarcinoma malignancies including chronic myelogenous leukemia, acute lymphocytic leukemia, follicular lymphoma, and melanoma [10]. Similar to classic DM, drug-induced (non-hydroxyurea) DM is associated with muscle weakness. However, HU-induced DM is rarely associated with muscle weakness, which we saw in this patient [10]. Unlike classic DM, drug-induced DM is very rarely associated with low-titer antinuclear antibodies [2,8-10]. Although DM antibodies were not drawn on this patient, the normal creatine kinase level and the improvement of his DM-like lesions with discontinuation of the HU seems to suggest this was drug-induced [2, 10]. The distinction between classic and drug-induced DM is important because inappropriate immunosuppressive therapy might hasten progression toward NMSC.

It is important to note that drug-induced DM can be divided into hydroxyurea-induced DM and non-hydroxyurea DM owing to different features of these subgroups; hydroxyurea may be associated with a distinctive dermopathy [10]. Since DM-like lesions can be caused by drugs other than HU such as NSAIDS, anti-infectious agents, D-penicillamine, and HMG-CoA reductase inhibitors, it is important to determine the culpable agent [10]. Seidler et al. showed that HU was the most common inciting agent (51% of cases). In addition, HU-induced DM-like lesions had a longer time of onset compared to the non-HU group (2 versus 60 months) and the HU group was older than the non-HU group (61 versus 50 years). The HU group was associated with other cutaneous signs of HU therapy and the HU group was not associated with myositis [10]. These findings are mostly consistent with what was seen in our patient, who was 67 years old, had an especially long time of onset (about 10 years), and displayed other cutaneous signs of HU therapy (ichthyosis, hyperpigmentation, palmoplantar keratoderma). However, he did report muscle weakness. Although DM-LE was once thought to be a benign entity, Kalajian et al. recently proposed it might actually be a potential premalignant precursor to HU-NMSC owing to their identification of abnormal p53 expression in DM-LE [19].

Chronic HU therapy is associated with NMSC, most commonly SCCs [11-18]. Sanchez-Palacios and Guitart explain how HU and ultraviolet radiation synergistically promote NMSC formation via

development of aberrant p53 clones [11, 19]. As in our patient, HU-NMSCs often appear suddenly in sun-exposed areas of lighter skinned older patients after a latency period of 2-13 years (mean 6.5 years) and are generally seen in those without prior history of skin cancer [11-15]. Our patient did not display the findings of squamous dysplasia with photo-distributed confluent patches of erythema and xerosis at the time of his dermatology clinic visits, but he noted some erythema prior to emergence of the hyperkeratotic plaques [11]. Strict photoprotection, aggressive surgical intervention, and HU discontinuation are indicated because these aggressive skin cancers are often refractory to treatment and associated with significant morbidity and sometimes mortality [17, 18]. It is necessary to maintain long-term surveillance as HU-NMSC can develop up to 4 years after discontinuing HU [11, 13]. If HU must be continued, strict photoprotection, chemoprevention with oral retinoids, and aggressive surgical therapy are indicated [11].

Conclusion

When evaluating patients with DM-LE, it is important to consider drugs as the possible etiology. HU is the most common cause of drug-induced DM. Although many cases improve after drug discontinuation, strict photoprotection and ongoing surveillance are indicated given the recently proposed premalignant potential of DM-LE and the aggressive nature of HU-induced NMSC.

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