Report

Hydroxyurea-induced dermatomyositis: true amyopathic dermatomyositis or dermatomyositis-like eruption?

Ahmad Nofal, MD, and Eman Salah El-Din, MSc

Department of Dermatology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Correspondence
Dr Ahmad Nofal, MD
Department of Dermatology
Faculty of Medicine
Zagazig University
Zagazig 11356
Egypt
E-mail: ahmadnofal5@hotmail.com

Funding sources: None.
Conflict of interest: None.

Abstract

Background Hydroxyurea-induced dermatomyositis is a rare adverse reaction of long-term hydroxyurea therapy. It has been reported under different names; however, the exact classification and nomenclature of this eruption have been the subject of much debate, and a more precise term is still awaiting. Herein, we review the different aspects of this reaction and suggest a new term that might help to minimize the confusion about its nomenclature.

Materials and methods We describe a 68-year-old woman who had been on long-term hydroxyurea therapy for the treatment of chronic myeloid leukemia for nine years. She presented with typical dermatomyositis-like lesions and many of the other mucocutaneous adverse effects of hydroxyurea.

Results Skin examination revealed typical Gottron’s papules on the dorsa of the hands, atrophy, xerosis, acquired ichthyosis, photosensitivity, cutaneous, oral and nail hyperpigmentation, acral erythema, palmoplantar keratoderma, actinic keratoses, and leg ulcers. There was no clinical or laboratory evidence of proximal muscle weakness. Cessation of hydroxyurea was associated with remarkable improvement of the skin lesions.

Conclusion Hydroxyurea-induced dermatomyositis is a rare drug-induced dermatomyositis characterized by skin lesions identical to classic dermatomyositis without clinical or laboratory evidence of myositis. We propose that the term hydroxyurea-induced amyopathic dermatomyositis that adequately describes the findings reported in this subset of patients would be more precise and specific.

Introduction

Hydroxyurea is a chemotherapeutic agent commonly used for the treatment of myeloproliferative disorders such as chronic myeloid leukemia, polycythemia vera, and essential thrombocytosis, less frequently for sickle cell anemia and rarely for severe recalcitrant psoriasis. It acts by inhibition of DNA synthesis through inactivation of ribonucleotide diphosphate reductase.

Major adverse reactions of hydroxyurea therapy include non-dermatological effects, such as bone marrow suppression, gastrointestinal symptoms, hepatotoxicity, and teratogenesis. On the other hand, cutaneous reactions are not infrequent and occur in 10–35% of patients who are subjected to long-term therapy. Skin eruptions include xerosis, acquired ichthyosis, acral erythema, hyperpigmentation, alopecia, photosensitivity, skin atrophy, fixed drug eruption, palmar-plantar keratoderma, allergic vasculitis, and, less commonly, dermatomyositis-like eruptions, nail abnormalities, oral ulceration and pigmentation, leg ulcers, actinic keratoses, and squamous cell carcinoma. These lesions have a typical clinical presentation and course, do not respond to conventional therapies, particularly leg ulcers, and characteristically resolve spontaneously when hydroxyurea is withdrawn. These observations should raise the suspicion of the drug as the causal agent and mean that clinicians, particularly dermatologists, should be aware of the adverse drug reactions associated with the long-term use of hydroxyurea to avoid any delay in diagnosis, unnecessary investigations, and exhaustive therapies.

Hydroxyurea-induced dermatomyositis has been reported under different names, including dermatomyositis-like eruption or lesions, hydroxyurea dermopathy, Gottron-like papules, pseudo-dermatomyositis, and skin lesions simulating chronic dermatomyositis. However, confusion continues regarding the nomenclature of this eruption, and a more precise term is still awaiting.

Herein, we describe a case presenting with dermatomyositis-like lesions along with many of the other mucocutaneous adverse effects of long-term hydroxyurea therapy, reviewing its different aspects and proposing a new term that might minimize the confusion about this entity.
Case report

A 68-year-old woman was referred to our dermatology clinic from the hematology unit of the oncology department to evaluate an eruption on the dorsa of her hands and resistant heel ulcers. The patient had received oral hydroxyurea 1–1.5 g/d for treatment of chronic myeloid leukemia that had been diagnosed nine years previously. Her condition started three years previously with a gradual onset of non-pruritic erythematous rash on the dorsa of the hands, followed within six months by discoloration of the nails and tongue. One year ago, the patient complained of extremely disabling painful ulcers that interfered with walking and did not respond to many conventional therapies. There was no history of muscle weakness, dysphagia, or joint pain. General examination was unremarkable, and no other concurrent diseases, or drugs that could induce dermatomyositis were detected.

Skin examination of the dorsa of the hands revealed atrophy, telangiectasia, and scaly erythematous papules and plaques on the dorsa of the metacarpophalangeal and interphalangeal joints. The lesions were indistinguishable from Gottron’s papules, pathognomonic lesions of classic dermatomyositis (Fig. 1). Examination of the face demonstrated photosensitivity, hyperpigmentation and actinic keratosis (Fig. 2). Dark brown pigmentation was observed in the tongue and nails, particularly toenails (Fig. 3). Examination of the palms and soles revealed palmoplantar keratoderma (Fig. 4). Bilateral, well-defined, and symmetrical large shallow ulcers were evident on both heels (Fig. 5). Xerosis, acquired ichthyosis, and poikiloderma of the upper back and legs were also demonstrated.

There was no clinical evidence of proximal muscle weakness. Laboratory tests revealed normal levels of lactate dehydrogenase, aldolase, and creatine phosphokinase. Antinuclear antibody test was negative, and other routine laboratory tests were within normal limits. Histopathology of a skin biopsy specimen showed slight

Figure 1 Typical Gottron’s papules

Figure 2 Photosensitivity, actinic keratosis and hyperpigmentation

Figure 3 Palmoplantar keratoderma. (a) Palmar keratoderma. (b) Plantar keratoderma and heel ulcer
epidermal atrophy with hyperkeratosis, vacuolar degeneration in the basal layer, and mononuclear perivascular inflammatory infiltrate in the upper and mid-dermis (Fig. 6). Based on clinicopathological correlation, hydroxyurea was suspected as the cause of the dermatomyositis-like lesions as well as other presenting lesions. As a consequence, hydroxyurea was stopped and replaced by busulfan. The cutaneous lesions, particularly the refractory leg ulcers, gradually improved over the next three months and completely disappeared within six months; however, the atrophic changes persisted without change despite withdrawal.

Discussion

Our patient presented with many of the mucocutaneous adverse effects associated with long-term hydroxyurea therapy. These include xerosis, acquired ichthyosis, atrophy, cutaneous photosensitivity, oral and nail hyperpigmentation, acral erythema, palmoplantar keratoderma, dermatomyositis-like eruption, actinic keratoses, and leg

Figure 4 Dark brown pigmentation. (a) Tongue. (b) Toenails

Figure 5 Large well-defined painful ulcer. (a) Before withdrawal of hydroxyurea. (b) Healing ulcer 2 months after withdrawal of hydroxyurea

Figure 6 Hyperkeratosis, epidermal atrophy, vacuolar degeneration of basal cell layer and mononuclear perivascular inflammatory infiltrate (H&E ×200)
ulcers. This unique constellation of findings in the same patient has not, to our knowledge, been reported in the literature (Table 1). The clinical course of these side effects was benign, except for leg ulceration.

Dermatomyositis is a rare connective tissue disorder primarily affecting skin and skeletal muscles. Although the etiology of dermatomyositis remains unknown, a small number of cases (about 75) have been implicated to be caused by drugs, with hydroxyurea as the most widely documented agent (in about 50% of cases), mostly in the context of treating chronic myeloid leukemia.14,15

According to previously proposed criteria,16,17 amyo-pathic dermatomyositis, also known as dermatomyositis sine myositis, was defined as a subset of dermatomyositis characterized by biopsy-confirmed hallmark cutaneous manifestations of classic dermatomyositis occurring for six months or longer with no clinical evidence of proximal muscle weakness and no serum muscle enzyme abnormalities. Because it had met all the previously mentioned criteria necessary for the diagnosis of amyo-pathic dermatomyositis, we consider that our patient and similar reported cases could be designated as drug-induced amyo-pathic dermatomyositis (Table 2).

Using the World Health Organization categories of “certain,” “probable,” and “possible” for causality assessment, Seidler and Gottlieb14 have proposed a classification system composed of four criteria to assess the causality of a drug in the onset of dermatomyositis.

<table>
<thead>
<tr>
<th>Table 1 Mucocutaneous adverse effects of hydroxyurea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse effect</strong></td>
</tr>
<tr>
<td>Skin lesions</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hair</td>
</tr>
<tr>
<td>Nails</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mucous membranes</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Table 2 Diagnostic criteria of hydroxyurea-induced amyo-pathic dermatomyositis

1. Presence of hallmark cutaneous manifestations of classic dermatomyositis
2. Histopathological features consistent with the diagnosis of dermatomyositis
3. Absence of clinical or laboratory evidence of proximal muscle weakness for 6 months or longer after onset of the skin lesions
4. Level of causal relationship: possible, probable or certain

According to this classification system, the causality of hydroxyurea in the onset of dermatomyositis in our case was considered as probable because it had met the first three criteria (Table 3).

The typical clinical picture of hydroxyurea-induced dermatomyositis is characterized by scaly erythematous papules and/or plaques on the dorsa of the interphalangeal and metacarpophalangeal joints, associated with atrophic and telangiectatic changes similar to those seen in patients with classic dermatomyositis but without any muscular involvement. Pruritic erythematous patches can also develop on the extremities and dorsa of the feet, and poikilodermia may be rarely present in photosensitive areas. The face may be involved, with edema and heliotrope erythema in some cases.1,7,18 The severity of clinical manifestations is mild to moderate in most of the patients and seems to correlate with the duration of the drug intake rather than with the evolution of the hematological malignancy.3,7

Histopathological examination of the classic skin lesions typically reveals hyperkeratosis, epidermal atrophy, vacuolar degeneration of the basal cell layer, and a moderate dermal mononuclear perivascular inflammatory infiltrate.7 Variable histological features include dyskeratotic cells, lichenoid tissue reactions, dermal mucin deposition, cytoid bodies in the papillary dermis, dermal telangiectases and dermal elastosis.1,7,8,19 Although non-specific, the histopathological findings described in hydroxyurea-induced dermatomyositis are identical to those demonstrated in classic dermatomyositis.18 Labora-

Table 3 Causality assessment of hydroxyurea-induced amyo-pathic dermatomyositis

1. A plausible time relationship to drug administration
2. No other concurrent diseases or drugs that could induce dermatomyositis
3. Remarkable improvement of the skin lesions after withdrawal
4. Reappearance of the skin lesions upon rechallenge

*Levels of causal relationship: possible = 1; probable = 1 + 2 + 3; certain = 1 + 2 + 3 + 4.
tory findings usually demonstrate negative antinuclear antibody and normal serum aldolase or creatine phosphokinase, electromyography, muscle biopsy, and MRI.\(^8,11,12\)

Although hydroxyurea-induced dermatomyositis usually occurs after prolonged intake (2–10 years) of continuous hydroxyurea therapy, there is no definite time after which the drug could be excluded as a cause of dermatomyositis.\(^3\)

Hydroxyurea-induced dermatomyositis is easily differentiated from classic dermatomyositis by absence of proximal muscle weakness and by means of normal muscle enzymes and electromyography. However, it cannot be differentiated from the amyopathic form of dermatomyositis.\(^18\) Dermatomyositis has also been reported to be caused by other drugs, such as penicillamine, lovastatin and simvastatin, BCG vaccination, tegafur, phenytoin, phenylbutazone, and tumor necrosis factor (TNF)-inhibitors.\(^1,3,14,20\) Hydroxyurea-induced dermatomyositis differs, both in the clinical and laboratory parameters, from those induced by the non-hydroxyurea drugs. The hydroxyurea group usually occurs in older patients, has a longer time from drug administration to onset of the disease (60 months vs. 2 months), has no muscular weakness (0 vs. 80%), shows more pathognomonic skin lesions of dermatomyositis (80 vs. 70%), is associated with less antinuclear antibody positivity (16 vs. 54%), and needs no systemic immunosuppressive therapy when compared with the non-hydroxyurea group.\(^3,14\)

The pathophysiology of hydroxyurea-induced dermatomyositis and other adverse effects remains unknown. The latency of onset, slow progression, and subsequent healing after cessation of hydroxyurea suggest that the underlying mechanism may be a chronic cumulative cytological damage on the basal layer of the epidermis due to inhibition of DNA synthesis and repair. These effects could be, in turn, responsible for the histopathological changes, including vacular degeneration of the basal cells, epidermal atrophy, and colloid bodies.\(^1,7,9,11\) Immunological alterations, as suspected from the high titers of antinuclear antibodies reported in some patients, have also been proposed to have a role in the evolution of hydroxyurea mucocutaneous side effects, including dermatomyositis.\(^22\)

In addition, hydroxyurea acts as a mediator of the inflammatory changes through indirect stimulation of the local production of interleukin 1 and 8 and granulocyte-monocyte colony-stimulating factor.\(^4\)

Kirby and Rogers\(^\text{53}\) have postulated that the almost exclusive occurrence of this eruption in hematological malignancies suggests that they may have a central role in its pathogenesis. Pittelkow and Gibson\(^\text{24}\) have also proposed that certain “co-morbidity factors” in myeloproliferative disorders may explain the preferential appearance of this eruption in these disorders. On the other hand, the strict evolution of dermatomyositis-like lesions after prolonged hydroxyurea intake,\(^7\) not parallel to the evolution of malignancy, the absence of dermatomyositis in patients with chronic myeloid leukemia not receiving hydroxyurea, the long duration of the malignancy before onset of dermatomyositis, the almost association of paraneoplastic dermatomyositis with adenocarcinomas, and the improvement of the skin lesions after hydroxyurea withdrawal\(^7,14\) could exclude the consideration of these cases of hydroxyurea-induced dermatomyositis as a paraneoplastic phenomenon.

Although the course of hydroxyurea-induced dermatomyositis has been considered benign, and the severity of clinical manifestations does not tend to worsen despite continuation of hydroxyurea,\(^18\) discontinuation of therapy is advisable to improve the clinical manifestations,\(^5,5\) particularly in cases associated with resistant leg ulcers, as was the case in our patient. Similarly, Kalajian \textit{et al.}\(^26\) have suggested that dermatomyositis-like eruption may represent a premalignant precursor of hydroxyurea-associated non-melanoma skin cancers warranting discontinuation of hydroxyurea therapy.

Therapy other than drug withdrawal is not usually required to control this adverse reaction of hydroxyurea. In most patients, clinical manifestations improve within 1–12 months following the discontinuation of hydroxyurea therapy without recurrence.\(^1,7\) Some authors, however, have reported that if the symptoms are severe or the lesions persist beyond one month after drug discontinuation, photoprotection, topical corticosteroids, and oral antimarials can be initiated.\(^14\) Systemic steroids have never been used to control this entity and are generally controversial in the treatment of amyopathic forms of dermatomyositis, including that caused by hydroxyurea.\(^1,7,27\)

Despite the continuous reports of hydroxyurea-induced dermatomyositis, there is still a confusion regarding the nomenclature of this entity. Daoud \textit{et al.}\(^8\) have described this condition in six patients and termed it hydroxyurea-induced dermopathy. In agreement with them, Kirby \textit{et al.}\(^18\) have suggested that this delayed adverse drug reaction is not dermatomyositis and that hydroxyurea-induced dermopathy is the preferred term to avoid any confusion with dermatomyositis. We think that this term is inaccurate and nonspecific, because the described lesions were typical of Gottron’s papules, pathognomonic lesions of dermatomyositis, and not lichenoid eruption as they mentioned, giving a false impression that hydroxyurea-induced dermatomyositis and hydroxyurea-induced dermopathy are different entities.

Varma and Lanigan\(^29\) have proposed that the descriptive term dermatomyositis-like eruption would clearly be valid to this eruption as it describes the characteristic cutaneous features usually observed in patients with classic...
dermatomyositis. Several authors have previously referred to the same condition as “dermatomyositis-like,” 
“pseudo-dermatomyositis”11,12 and “simulating chronic dermatomyositis”13 to reflect this clinical similarity.

On the contrary, Yoshida et al.10 have considered that the terms pseudo-dermatomyositis and dermatomyositis-like eruptions are rather confusing as they seem to include the miscellaneous eruptions in dermatomyositis rather than just Gottron’s papules, and may suggest an association with the systemic symptoms of dermatomyositis. They proposed that the term Gottron-like papules would be more precise and specific because Gottron-like papules are considered to be the most characteristic eruption induced by hydroxyurea without implying any of the other changes found in dermatomyositis. In fact, this was not the case in most of the reported cases, including the presented one, which showed many of the other characteristic dermatological features of dermatomyositis, such as heliotrope erythema, malar erythema, poikilodema in a photosensitive distribution, violaceous erythema on the extensor surfaces, and periungual and cuticular changes.14,18,30,31

Although the term dermatomyositis-like lesion or eruption or Gottron-like papules5,7,10 emphasizes that the major clinical complaint of the affected patients was the skin disease rather than the muscle weakness, it seems inappropriate to describe these cases by the term “-like” or “pseudo-” because they present by skin lesions identical with the pathognomonic lesions of classic dermatomyositis and there is a subtype, amyopathic dermatomyositis, that could include them.32 In addition, the term dermatomyositis-like eruption or pseudo-dermatomyositis may divert the attention away from or trivialize the significance of an important subset of patients with drug-induced amyopathic dermatomyositis who may be at risk of interstitial lung disease and/or delayed onset of classic dermatomyositis.14,17,30

So, we propose that the term hydroxyurea-induced amyopathic dermatomyositis might be more appropriate and specific because it precisely describes the findings reported in this subset of patients; namely skin lesions identical with classic dermatomyositis without the clinical or laboratory evidence of myositis, thus fulfilling the proposed diagnostic criteria of amyopathic dermatomyositis17 without any difference between the spontaneous or idiopathic cases and those induced by drugs. In support of the newly proposed term, Senet et al.7 have reported that it is tempting to consider hydroxyurea-induced dermatomyositis as similar to dermatomyositis sine myositis, and Rocamora et al.18 have also considered that amyopathic dermatomyositis is clinically indistinguishable from hydroxyurea-induced dermatomyositis. Going with the same concept, Dourmishev and Dourmishev33 have proposed that the clinical manifestations of drug-induced dermatomyositis may be presented in three subgroups, including those with only skin features of amyopathic dermatomyositis, and that hydroxyurea-induced dermatomyositis-like eruption represents a clinical example of drug-induced amyopathic dermatomyositis. Also, in accordance with our view, Flores-Suárez et al.34 have reported a case of drug-induced amyopathic dermatomyositis after fibrate therapy for hypertriglyceridemia, and Inhoff et al.35 in their article entitled “Simvastatin-induced amyopathic dermatomyositis,” have concluded that statins should be added to a list of drugs that, like hydroxyurea and D-penicillamine, are capable of eliciting amyopathic dermatomyositis.

Conclusion
Drug-induced dermatomyositis is a relatively rare subset of dermatomyositis that can be induced by different medications, with hydroxyurea as the most commonly implicated. The nomenclature used to describe hydroxyurea-induced dermatomyositis remains controversial, and we suggest that the proposed term hydroxyurea-induced amyopathic dermatomyositis could minimize the confusion, help to define the place, and might optimize the management of this rare but important drug reaction.

Acknowledgment
We would like to thank Dr. Arige Amir Dessouky, Assistant Lecturer, Histology and Cell Biology Department, Faculty of Medicine, Zagazig University, for her sincere work in imaging the histopathological photos.

References


This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.