Hydroxyurea Induced Dermatomyositis-Like Eruption and Melanonychia

Worakamol Tharnkratoke MD, Nataya Voravutinon MD.
Institute of Dermatology, Department of Medical Services, Ministry of Public Health, Bangkok, Thailand.

ABSTRACT:
Hydroxyurea is utilized to treat myeloproliferative disorders, including essential thrombocythemia, polycythemia vera, and chronic myeloid leukemia. The most common adverse effects are hematological issues, gastrointestinal symptoms, and anorexia, while dermatological side effects are rare. We present a patient who developed a dermatomyositis-like eruption and melanonychia, induced by hydroxyurea, after receiving the drug for the treatment of essential thrombocytosis.
Key words: Dermatomyositis-like eruption, Melanonychia, Hydroxyurea

Introduction

Dermatomyositis is an idiopathic inflammatory myopathy that typically presents with inflammation of the skin and skeletal muscles. However, amyopathic forms progress without laboratory abnormalities or muscle weakness. Although the exact cause is generally unknown, certain forms can be induced by medications[1-3].

Drug induce dermatomyositis-like eruption presents with symmetrical, photodistributed erythematous scaly plaques (such as Gottron papules, heliotrope sign, shawl sign, V-neck sign, and Gottron sign), resembling the presentation of idiopathic dermatomyositis. Hydroxyurea, a chemotherapeutic agent, is most frequently associated with this condition[4].

Case report

A 50-year-old Thai woman, diagnosed with essential thrombocytosis, had been treated with hydroxyurea 1500 mg per day for 20 years. She presented with localized erythematous papules and plaques on the dorsum of her hands. The lesions had gradually developed over the past year, followed by nail discoloration 6 months later (Figure 1A, 1B, 2). She had no history of myalgia, dyspnea, dysphagia, or joint pain. A general examination revealed no signs of proximal muscle weakness, muscle tenderness, or dysphagia.

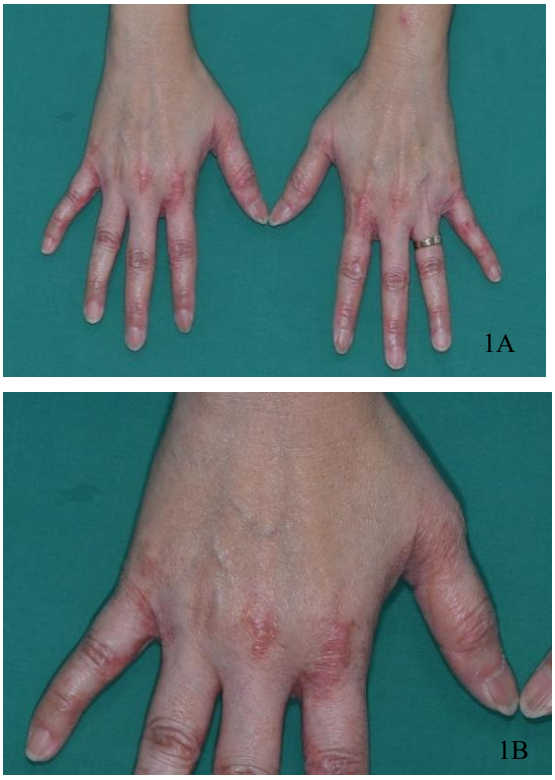

Figure 1A, 1B Gottron's papules and longitudinal melanonychia on both sides of fingernails

Correspondence Author: Nataya Voravutinon MD., Email: v_nataya@yahoo.com

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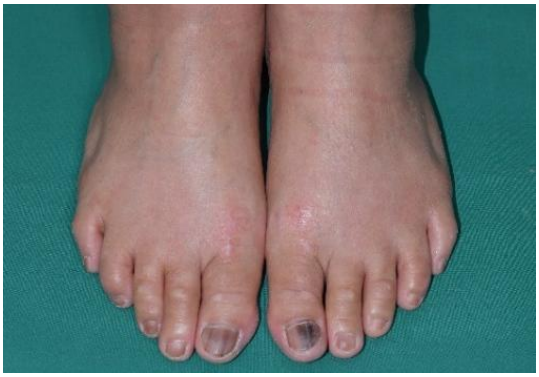

Figure 2 Longitudinal melanonychia on both sides of toenails

A dermatological examination showed scaly erythematous papules and plaques on the metacarpophalangeal joints of both hands. Multiple longitudinal hyperpigmented bands were observed on the toenails of both big toes (Figure 2). Laboratory tests for myositis-specific antibodies (anti-TIF1, anti-Mi, anti-MDA5, anti-NXP2, anti-SAE1, anti-KU, anti-PM-Scl-100, anti-PM-Scl-75, anti-Jo1, anti-SRP, anti-PL7, anti-PL12, anti-U1RNP) were negative. Antinuclear antibodies were negative. Serum aldolase and serum creatine phosphokinase levels were within normal limits. Histopathologic examination of the erythematous papule on the dorsum of the hand reveals hyperkeratosis, parakeratosis, and sparse inflammatory cell infiltration in the papillary dermis, which are considered nonspecific findings. Histopathologic examination of melanonychia from the toenail displays slight hyperplasia of the epidermal rete ridges of nail matrix. Neither melanocyte nor hypermelanization is seen, sparse superficial perivascular infiltration of lymphocytes, and no malignant component is found. The finding suggests reactive nail pigmentation. (Figure 3, 4)

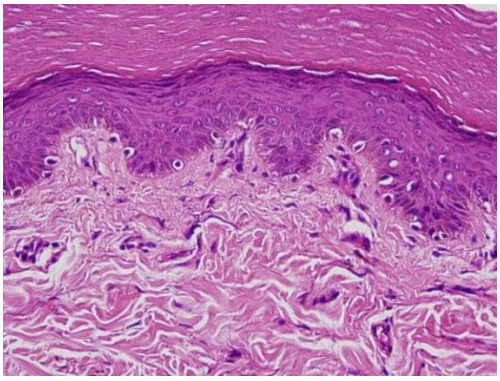

Figure 3 Hyperkeratosis, parakeratosis, and sparse inflammatory cell infiltrates in papillary dermis

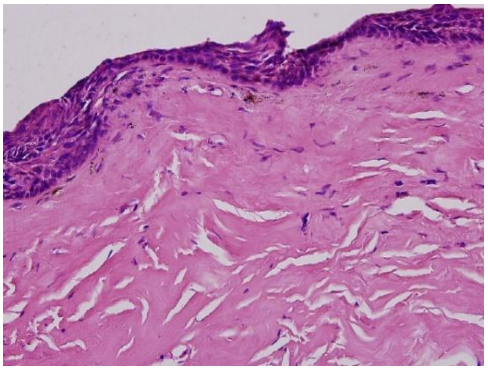

Figure 4 Slight hyperplasia of the epidermal rete ridges of nail matrix, mild superficial perivascular infiltration of lymphocytes, no malignant component is found

We suspect that the rash is a pathognomonic sign of dermatomyositis, specifically Gottron's papules, which have been reported to occur in hydroxyurea-induced dermatomyositis-like eruptions. Therefore, we recommend that the patient stop taking the medication and consult the hematologist to consider alternative treatment options for essential thrombocytosis. A workup for malignancy includes mammogram, ultrasound abdomen, chest X-ray, and PAP smear, which revealed no abnormalities. The hematologist discontinued hydroxyurea and switched her treatment to anagrelide. The eruption on the dorsum of her

hands partially improved after one month, but the melanonychia remained unchanged (Figure 5, 6). After adjusting to anagrelide, the patient experienced palpitations, so the hematologist decided to discontinue anagrelide and resume hydroxyurea, which caused a recurrence of the lesions. The resolution of the lesions after discontinuing the drug and the worsening after taking hydroxyurea support the conclusion that the drug played a significant role in her condition.

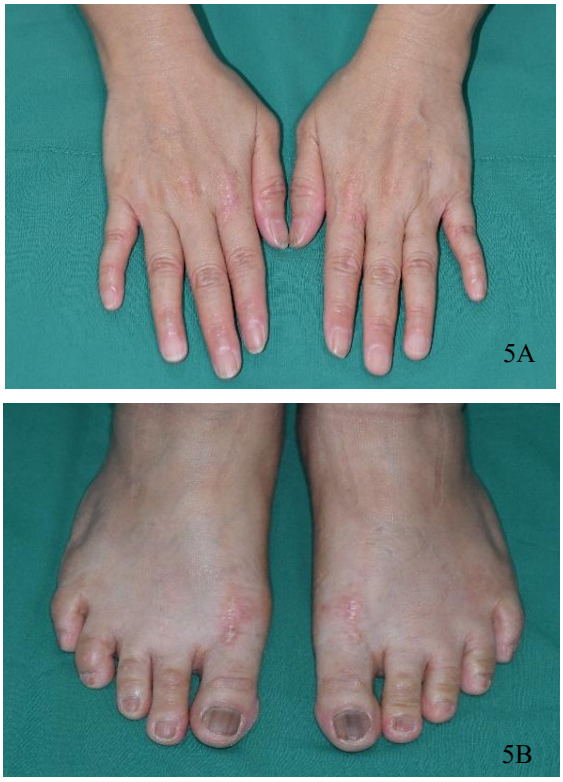

Figure 5A, 5B After withdrawal of the hydroxyurea for 1 month there was partial improvement of Gottron's papules, but the melanonychia remained unchanged

Discussion

Classic dermatomyositis (CDM) is an idiopathic inflammatory myopathy characterized by progressive, symmetric muscle weakness and distinctive skin manifestations. In contrast, drug-induced dermatomyositis-like eruption arises as an adverse reaction to certain medications, such as hydroxyurea, statins, and penicillamine. Muscle involvement is a hallmark of CDM, presenting with proximal muscle weakness and elevated muscle enzymes. In contrast, drug-induced dermatomyositis-like eruptions often present without significant muscle involvement; for instance, hydroxyurea-induced dermatomyositis-like eruptions frequently lack clinical or laboratory evidence of myositis.

Autoantibodies are commonly associated with CDM. In drug-induced dermatomyositis-like eruption, these autoantibodies are typically absent, and antinuclear antibody (ANA) tests may be negative or only weakly positive.

There is a well-established association between CDM and an increased risk of malignancy, with studies indicating a prevalence of around 20%. In contrast, drug-induced dermatomyositis-like eruption does not exhibit a direct association with malignancy.

Hydroxyurea primarily works by inhibiting the enzyme ribonucleotide reductase, which is crucial for the conversion of ribonucleotides to deoxyribonucleotides. This inhibition leads to a decrease in DNA synthesis. The most common adverse effects are hematological (myelosuppression), gastrointestinal symptoms (stomatitis, nausea, vomiting, diarrhea, and constipation), and anorexia. Dermatological side effects include hyperpigmentation (skin and mucosal), nail hyperpigmentation, photosensitivity, lower extremity ulcers, vasculitis, dermatomyositis-like eruptions and non-melanoma skin cancer including actinic keratosis and squamous cell carcinoma[5-7].

Drug-induced dermatomyositis-like eruptions are rare, with hydroxyurea being the most common culprit. Other drugs associated with this condition include statins, TNF inhibitors, immune checkpoint inhibitors, and penicillamine. Clinical manifestations of drug-

induced dermatomyositis include Gottron papules, periorbital erythema (heliotrope sign), shawl sign, V-neck sign, Gottron sign[7].

The underlying pathophysiology of this condition, along with its other adverse effects, remains uncertain. In cases of dermatomyositis-like eruptions induced by hydroxyurea, the improvement of skin lesions after discontinuation of the drug suggests that prolonged cumulative cytological damage to the epidermal basal layer might play a role.

Histologically, drug-induced dermatomyositis-like eruptions cannot be distinguished from classic dermatomyositis. The findings consist of interface dermatitis with vacuolar changes in basal layer of epidermis, epidermal thinning, pigment incontinence and interstitial mucin deposition within the dermis. The inflammatory infiltrate in the dermis is typically lymphocytic and can range from sparse to moderate in density. Therefore, the presence of only a sparse lymphocytic infiltrate does not rule out this condition. In fact, some cases have reported mild basilar vacuolization accompanied by a sparse dermal perivascular lymphocytic infiltrate and a mild increase in dermal mucin. [10] In some cases, atypical keratinocytes and p53 expression in the basal layer of the epidermis are observed. Some authors suggest that this condition should be considered premalignant, with a risk of progression to cutaneous squamous cell carcinoma, which necessitates long-term follow-up and withdrawal of the offending drug[3, 8].

The differences between hydroxyurea induced dermatomyositis like eruption and other drugs induced dermatomyositis like eruption are shown in Table 1[7].

	Hydroxyurea	**Other drugs**
Median age at diagnosis (year)	61 years	50 years
Underlying malignancy (%)	69 %	17 %
Median time from start of drug to onset of symptoms (month)	60 months	2 months
Clinical presentation **- Muscular weakness/myositis (%)**	0 %	79 %
- Pathognomonic finding of DM: Gottron's papules, heliotrope rash (%)	80 %	70 %
Positive ANA titer (%)	16 %	54 %
Treatment	Cessation of drug	Cessation of drug ± immunosuppressive drug

One of the challenges in diagnosis is differentiating drug-induced dermatomyositis-like eruption from paraneoplastic dermatomyositis, as both conditions often lack muscle involvement. The timing of symptom onset can help distinguish paraneoplastic dermatomyositis, as it often develops within the first two years following a cancer diagnosis and is more likely to appear within the first seven months, whereas drug-induced dermatomyositis like-eruption usually appears within the first five years of treatment[3,7]. Additionally, hydroxyurea-induced dermatomyositis like-eruption is often associated with palmoplantar hyperkeratosis or skin ulcerations, which can contribute to the diagnosis[9]. For myositis-specific antibodies, the presence of anti-TIF1-γ or anti-NXP-2 should prompt an evaluation for underlying malignancy.

Treatment for CDM often involves immunosuppressive therapies. The primary

treatment of drug-induced dermatomyositis-like eruption is discontinuing the medication that caused the dermatomyositis-like eruption. For hydroxyurea, stopping the drug alone is usually sufficient, and immunosuppressive therapy is typically not required. However, for other medications or if lesions persist for more than a month after discontinuation, corticosteroids (both topical and systemic) or disease-modifying antirheumatic drugs (DMARDs) may be considered[7-9].

Prognosis in CDM varies based on factors such as malignancy presence and treatment response. In drug-induced dermatomyositis-like eruption, the outlook is generally favorable, with symptoms often resolving after stopping the causative medication. The time to resolution of drug-induced dermatomyositis-like eruptions after discontinuing the offending medication varies depending on the specific drug involved and individual patient factors. In many cases, symptoms begin to improve within weeks after stopping the medication. In patients who develop a dermatomyositis-like eruption from hydroxyurea, improvement is observed within the first 10 days to several months. However, in cases with skin atrophy, the condition may persist even after discontinuing the medication. In a review by Seidler and Gottlieb reported that 56.3% of patients with drug-induced dermatomyositis-like eruptions experienced complete clearance of symptoms within the first two months following drug discontinuation. By the end of the first year, 87.5% of these cases exhibited complete symptom clearance[7].

In hydroxyurea-induced dermatomyositis-like eruption, given the potential for delayed resolution and the risk of associated conditions, such as squamous cell carcinoma, regular follow-up is advised. Periodic follow-up after discontinuation is recommended to ensure complete resolution and early detection of complications[8]. In other drug-induced cases, the follow-up period should be individualized based on patient response, the severity of symptoms, and the presence of any complications. Regular dermatologic assessments are crucial to ensure complete resolution and to address any persistent or emerging issues.

Hydroxyurea-induced nail abnormalities include brittle nails, onychodystrophy, onycholysis, and melanonychia. Its mechanism is possibly related to intermittent high doses of hydroxyurea. Other drugs known to induce melanonychia include bleomycin, 5-fluorouracil, busulfan, cyclophosphamide, doxorubicin, and daunorubicin[11]. The onset of hydroxyurea-induced melanonychia varies among patients. While it typically develops after several months of therapy, cases have been reported with onset as early as 4 weeks and as late as 5 years after initiating treatment. The prevalence of melanonychia in patients treated with hydroxyurea is estimated to be around 4%. This incidence appears to increase with age and is more common in females, as well as in Black and Hispanic patients. Hydroxyurea-induced melanonychia can present in various patterns, including longitudinal bands, transverse bands, and diffuse hyperpigmentation. Longitudinal banding is the most commonly reported pattern. In contrast, other medications, particularly certain chemotherapeutic agents like doxorubicin and cyclophosphamide, are more frequently associated with transverse melanonychia[12,13,14]. Melanonychia induced by hydroxyurea is generally a benign condition and primarily a cosmetic concern. In most cases, specific treatment is not necessary, especially if the pigmentation does not cause significant distress to the patient. However, if there is a suspicion of malignancy (e.g., abrupt onset after middle age, rapid growth, involvement of a single nail), further evaluation, including possible biopsy, may be considered[15]. Upon discontinuation of hydroxyurea, nail pigmentation often improves or completely resolves. The fading of pigmentation may be gradual, occurring over several weeks to

months, as the nail grows out and is replaced by new, unpigmented nail material. It's important to note that not all patients can discontinue hydroxyurea due to its therapeutic necessity, and in such cases, the pigmentation may persist[12].

This case highlights hydroxyurea-induced dermatomyositis-like eruption and melanonychia as rare but noteworthy dermatologic adverse effects in patients undergoing long-term treatment with hydroxyurea. The diagnosis was supported by the presence of characteristic Gottron's papules, histopathologic features, and temporal correlation with hydroxyurea administration and withdrawal. Unlike classic dermatomyositis, the absence of muscle involvement and autoantibodies, along with symptom resolution upon drug discontinuation, supported a drug-induced etiology. Additionally, melanonychia appeared to be a benign, cosmetic manifestation. This case underlines the importance of recognizing cutaneous signs of drug adverse effects, timely cessation of the offending agent, and the need for multidisciplinary management and long-term dermatologic follow-up to monitor for recurrence or potential malignant transformation.

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