Hydroxyurea-induced hyperpigmentation with iron deposition

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Abstract

Hydroxyurea is a chemotherapeutic agent that is used in the treatment of various hematological diseases including chronic myelogenous leukemia, polycythemia vera, and sickle cell anemia. Hydroxyurea is also used to treat psoriasis. Drug-induced hyperpigmentation is a known cutaneous side effect of hydroxyurea along with xerosis, dermal ulcers, and dermatomyositis-like eruptions. Hyperpigmentation has been observed in the oral mucosa, nails, and in a generalized or a diffuse pattern. The mechanism of hyperpigmentation related to hydroxyurea is believed to be correlated with increased melanin. Classically, clinical types of diffuse hyperpigmentation owing to iron deposition in the dermis have been associated with minocycline and not with hydroxyurea. We report a novel case in which hydroxyurea hyperpigmentation is associated with iron deposition.

Keywords: hydroxyurea, drug-induced hyperpigmentation, hyperpigmentation, iron deposition

Introduction

Hydroxyurea is a chemotherapeutic agent used in the treatment of various hematological diseases, most commonly chronic myelogenous leukemia, polycythemia vera, and sickle cell anemia [1]. It is also used to treat psoriasis [2]. Hydroxyurea blocks DNA synthesis and cellular division by inhibiting ribonucleoside reductase [3]. Numerous cutaneous side effects have been observed with hydroxyurea administration including xerosis, dermal ulcers, dermatomyositis-like eruptions, and hyperpigmentation [4]. Hyperpigmentation has been observed in the oral mucosa, nails, and in a diffuse pattern [1, 3]. Diffuse hyperpigmentation related to hydroxyurea is thought to be correlated with increased melanin [5]. We report a novel case in which hydroxyurea hyperpigmentation exhibited iron deposition.

Case Synopsis

A 75-year-old man with a history of myelodysplastic syndrome presented to the dermatology clinic with a one-year history of progressive darkening of his lower legs. The patient denied a history of trauma and other associated symptoms including pruritus and pain. There had been no preceding edema or hyperpigmentation. He had been taking hydroxyurea for several weeks prior to the onset of the hyperpigmentation. Other medications included garlic tablets, levothyroxine, "Liver Defense" tablets,

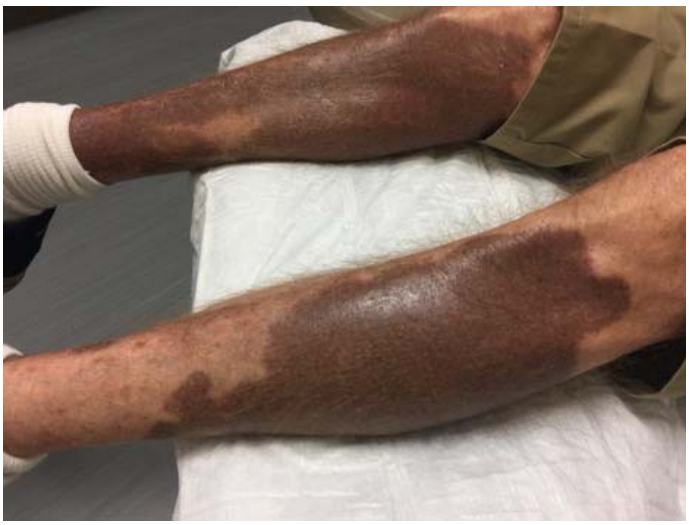

Figure 1. *Drug-induced hyperpigmentation. Well-demarcated violaceous to hyperpigmented confluent patches on bilateral distal lower extremities.*

multivitamin tablets, NutriFeron immunity supplement, Vitamin B complex, Vitamin D3, and Vitamin E.

Physical examination revealed well-demarcated violaceous to hyperpigmented confluent patches on his distal lower extremities bilaterally (**Figure 1**). There was no pigment deposition in the nails or the mucosa. The conditions in the differential diagnosis included ecchymosis, hydroxyurea-induced hyperpigmentation, and angiosarcoma.

A punch biopsy from the right lateral shin showed a slightly atrophic epidermis with increased number of venules throughout the dermis and extension into the subcutaneous tissue. Extravasated erythrocytes from venules and small capillaries were seen with yellow-brown pigment. Perls stain was positive, whereas Fontana-Masson was negative, which is consistent with hemosiderin (**Figure 2**). Scanning Electron Microscopy/Energy Dispersive x-ray Spectroscopy (SEM/EDS) analysis of the pigment deposits was consistent with endogenous iron deposition (**Figure 3**). The patient's final diagnosis was hydroxyurea-induced hyperpigmentation related to dermal iron deposition.

The patient was continued on hydroxyurea given its benefit in managing his myelodysplastic syndrome. At follow up, the patient reported the eruption had continued to remain asymptomatic and had not spread further.

Case Discussion

Drug-induced hyperpigmentation (DIH) is a known cutaneous side effect of hydroxyurea. Sites of DIH involvement include the oral mucosa, the nail plates, and a generalized or diffuse cutaneous pattern [1, 3]. Involvement of the nail plates can involve the entire nail plate or present as longitudinal or transverse bands [1]. The incidence of hydroxyurea-induced hyperpigmentation has been reported to be as high as 50 % [6]. Drug-induced hyperpigmentation has been seen as early as 7 weeks to several years after initiating hydroxyurea treatment [7].

The clinical types of DIH can be classified as:
Type I: black-blue pigmentation in pre-existing scars

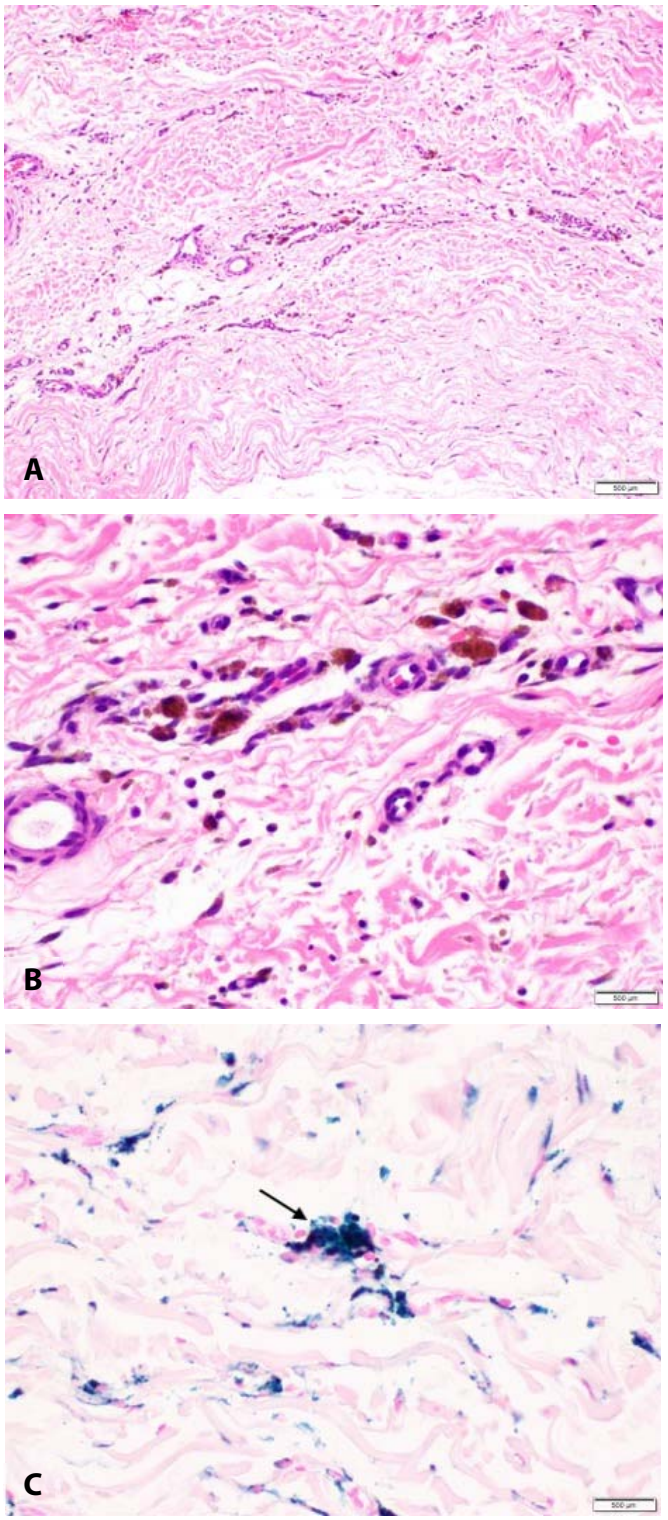

Figure 2. *Drug-induced hyperpigmentation. A punch biopsy from a pigmented area on the right lateral shin showed an increased number of venules throughout the dermis extending into the subcutaneous tissue along with extravasated erythrocytes and yellow-brown pigment, and a positive Perls stain for iron (see arrow). H&E* ***A)*** *100×,* ***B)*** *400×;* ***C)*** *Perls stain 400×.*

Type II: blue-grey pigmentation on shins and forearms

Type III: diffuse muddy-brown discoloration in sun-exposed areas

These clinical types have been classically reported with minocycline DIH. Drug-induced hyperpigmentation clinical types I and II are associated with iron deposition in the dermis [8]. Analysis of cutaneous minocycline pigmentation has shown high levels of iron chelated to a minocycline metabolite that is stored within the lysosomes of macrophages [9].

Our patient's DIH was consistent with a type II pattern. Similar to minocycline type II DIH in which the shins are the most commonly involved area and histologically the pigment is often found perivascularly, this patient presented with lower extremity involvement including the shins and the histopathology showed the pigment was located in the perivascular region [10]. Furthermore, we conclusively demonstrated iron deposition within the dermis. Therefore, using the minocycline-associated pigment analogy, a proposed pathogenesis of a subset of hydroxyurea DIH could

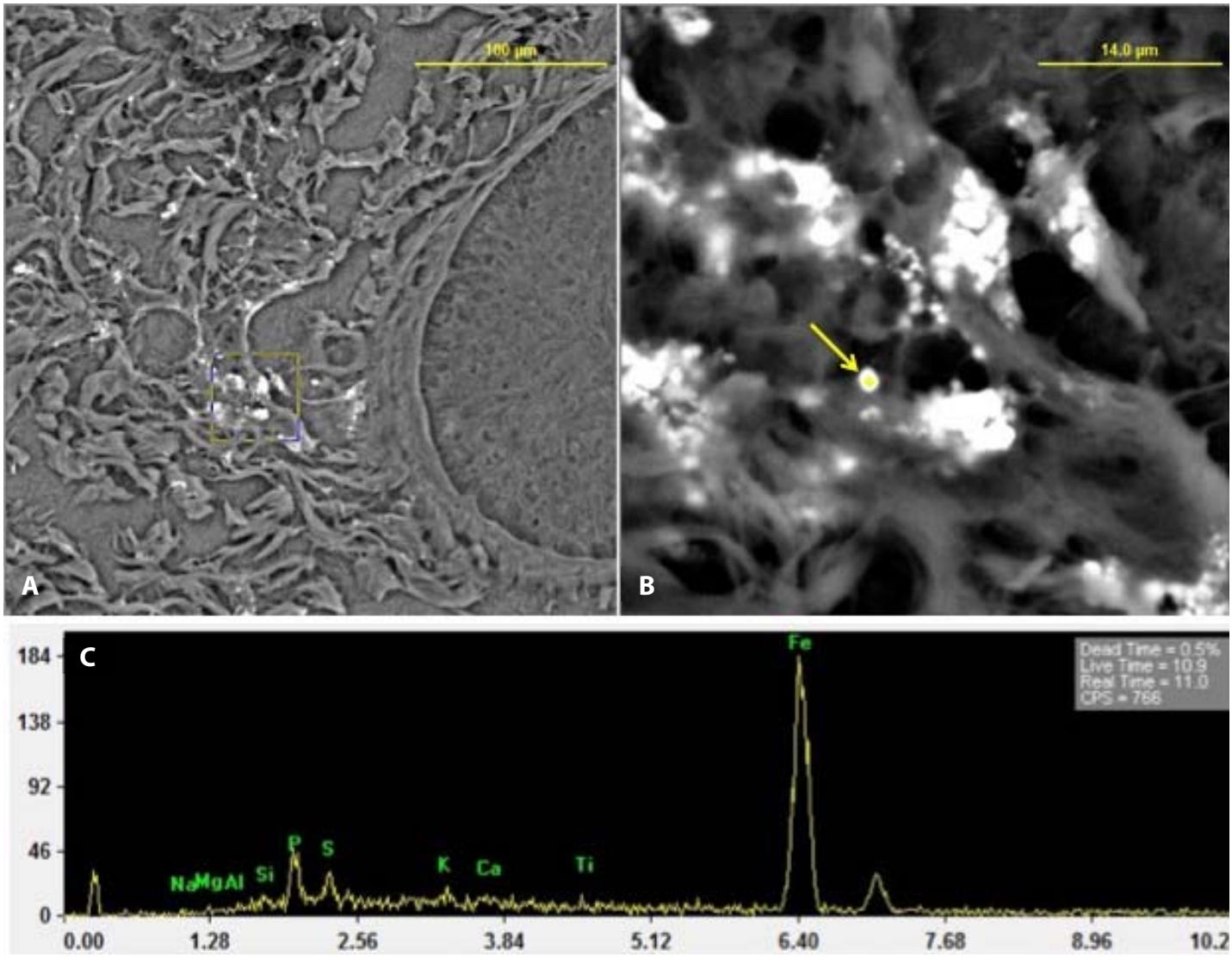

Figure 3. ***A)*** *Scanning electron microscopic low magnification backscatter electron image of the deep dermis showing brighter inorganic particles with higher density than the underlying tissue.* ***B)*** *Higher magnification of the boxed area in (A) with particle analyzed (yellow arrow).* ***C)*** *Energy dispersive X-ray spectroscopic image of the particle showing composition of hemosiderin (Fe, P and S). No unusual minerals or metals were observed.*

be postulated as hydroxyurea or its metabolite forming a complex with iron. However, this possible hypothesis is limited by the lack of a control biopsy from normal appearing skin. More cases and further studies would be needed to prove this proposed mechanism.

Conclusion

This case report demonstrates that hydroxyurea or its metabolite can possibly form a complex with iron in hydroxyurea-induced hyperpigmentation. The biopsy from the patient's shin showed a negative Fontana-Masson stain, but SEM/EDS analysis was consistent with iron deposition. Furthermore, histopathology showed that the pigment was located in the perivascular region similar to minocycline type II DIH. The proposed mechanism of hydroxyurea or its metabolite forming a complex with iron will require further studies.

Potential conflicts of interest

The authors declare no conflicts of interest.

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