CASE REPORT

Iatrogenic Dyschromia: A Preliminary Report on 6 Cases on The Clinical, Dermoscopy and Histopathology Findings

Julius G. Gatmaitan, MD[1*], Jolene Kristine G. Gatmaitan-Dumlao, MD[2], Johannes F. Dayrit, MD[3]

[1]Gatmaitan Medical & Skin Center, Skines Aesthetic & Laser Center
[2]Baguio General Hospital, Notre Dame De Chartres Hospital
[3]De La Salle Medical & Health Sciences Institute & Research Institute for Tropical Medicine

Address of corresponding author:
Gatmaitan Medical & Skin Center, Skines Aesthetic & Laser Aesthetic, Philipines
Email:
juliusggatmaitan@gmail.com

Abstract

In the Philippines and other Asian countries, "bleaching creams" containing various concentrations and mixtures of hydroquinone, steroids and retinoids are often used without regulation. With immediate improvement, most patients lack follow-up and continue to self-medicate without knowing the complications of long- term use. Iatrogenic dyschromia refers to skin color alteration induced by medical treatment or inadvertently by physicians. To the best of our knowledge, the clinical and histopathologic characteristics have not been fully elucidated yet.

We have identified 6 females with Fitzpatrick skin phototype IV with mottled pigmentation on the forehead, nose and cheeks initially diagnosed as exogenous ochronosis. Dermoscopy revealed intervening white and light brown areas, visible follicular openings and extensive network of vessels. Histopathology showed basal cell layer hyperpigmentation of the epidermis. The dermis revealed telangiectasias, solar elastosis and focal degeneration of collagen fibers. Masson's trichrome revealed thinning of collagen bundles. Melan-A stain revealed melanocytopenia.

The dermatologist should be able to recognize iatrogenic dyschromias as they differ from melasma and ochronosis in clinical, histopathologic and dermoscopy findings. Continuous application of skin lightening agents without sun protection is most likely the major predisposing factor in the development of this condition. A larger study is warranted to fully define this condition.

Keywords:

iatrogenic dyschromia, facial hyperpigmentation, hypermelanoses, hypomelanoses

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In the Philippines and other Asian countries, "bleaching creams" containing various concentrations and mixtures of hydroquinone, topical corticosteroids and retinoids are being prescribed or used often without regulation (Republic of the Philippines Department of Health, 1999). The pursuit of fairer skin in the Philippines is rampant due to social pressures. The desire to have fairer and lighter skin dates back to the Philippines having an extensive history of colonial occupations. The colonizers may have instilled the idea of social hierarchy based on skin color and lighter skin means higher social status. However, this desire for a "fairer" or "whiter" skin had health repercussions physically and psychologically (Singson, 2017). With immediate improvement in the condition, most patients lack follow-up and continue to self-medicate without knowing the complications of long-term use. Iatrogenic dyschromia refers to alteration in skin color induced by medical treatment or inadvertently by physicians. In an unpublished manuscript done by one of the authors in Cavite Philippines where 82 female patients were diagnosed with facial hyperpigmentation, 57/82 (70%) had melasma, 10/82 (12%) had iatrogenic dyschromia, 7/82 (9%) had exogenous ochronosis and 7/82 (9%) had post-inflammatory hyperpigmentation based on dermoscopy findings (Dayrit, 2021). The term "iatrogenic dyschromia" has been used to describe the mottled pigmentation observed after repeated pigment laser procedures. The condition has been mentioned in very few case reports but the clinical, dermoscopic and histopathologic features have not been fully elucidated yet (Passeron & Ortonne, 1998). "Dyschromatoses" involve both hyper-pigmented and hypopigmented macules. Topical medication induced dyschromia refers to the iatrogenic hyperpigmentation and hypopigmentation due to the excessive use of unregulated and banned by FDA topical lightening agents containing steroids, mercury, hydroquinone and hydroquinone-derivatives (Passeron & Ortonne, 1998). This condition is clinically characterized by mottled pigmentation on malar areas . Although the clinical diagnosis of such condition is straightforward based on the chronic use of lightening agents and based on its distribution and age of onset, sometimes it can be mistaken for other pigmentary disorders such as melasma or exogenous ochronosis. The authors aim to characterize for the first time the dermoscopic and histopa-

Age in years	Gender	Name of individual components with concentration	Duration of use(in months)	Frequency of use
44	F	Tretinoin 0.025%, Hydroquinone 2%	12	Regular
56	F	Tretinoin 0.05%, Hydroquinone 2%, Clobetasolpropionate cream	24	Intermittent
52	F	Hydroquinone 2%, Tretinoin 0.025%	12	Intermittent
53	F	Hydroquinone 4%, Clobetasol propionate cream	12	Regular
49	F	Clobetasol propionate cream, Niacinamide, Tretinoin0.025% cream, Hydroquinone 2%	10	Intermittent
39	F	Hydroquinone 2%, Tretinoin 0.025%, Vitamin C	12	Regular

Table 1: Summary of Patients

thological features of iatrogenic dyschromia and be able to differentiate it from melasma and ochronosis in terms of clinical, histopathologic and dermoscopy findings.

Case Presentation

A total of 6 patients were included in this case series. All of them are females with Fitzpatrick skin phototype IV, with mean age of 48.8 ± 5.8 years old. 1 out of 6 (16.67%) had a history of oral contraceptive use. Number of pregnancies ranges from no child to 4 children with 5 out of 6 (83.33%) had more than one pregnancy All patients complained of mottled pigmentation on the malar areas and had a history of application of over-the-counter topical lightening agents that contains hydroquinone, tretinoin and other actives including clobetasol propionate cream, niacinamide cream and Vitamin C (Table 1) with intermittent use of sunscreen. Details regarding the SPF and type of sunscreen (physical, chemical or mixed) were unavailable. No pre-existing medical conditions for all of the patients were noted based on their clinical history. No aesthetic treatments were performed in any of the patients before they used the lightening agents. These patients applied the combination topical lightening agents for a mean duration of 13.7 ± 4.7 months.

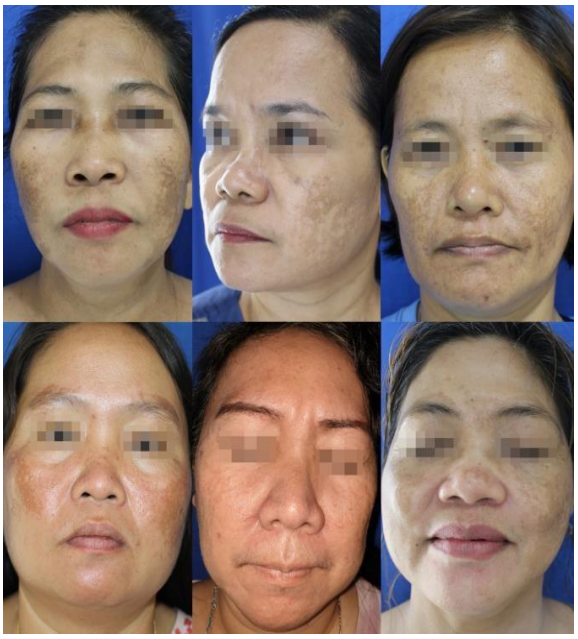

Figure 1: Mottled pigmentation on the forehead, nose and cheeks on all 6 patients.

Dermoscopic evaluation was performed using the features and common findings in dermoscopy of pigmentary disorders by Khopkar and Barti (2018). In all cases, the authors used a manual polarized light device (Dermlite DL2x10; 3Gen, San Juan Capistrano, CA). Dermoscopic findings for all cases include intervening light brown areas with areas of exaggerated pseudonetwork and whitish area containing uniform pigment network and feathery margins and, extensive network of vessels and visible follicular opening in all instances (6/6; 100.0%). The whitish areas show similarities to the depigmented macules and patches of vitiligo but with absence of follicular repigmentation (Figure 2).

4- mm skin punch biopsy was performed on all cases. On histopathology, apoptotic melanocytes (Figure 3a) and sunburn cells (Figure 3b) observed in 6/6 of the cases. The dermis showed loosely arranged and fragmented collagen fibers, as well as dilated blood vessels (Figure 4a). Solar elastosis and pigment- laden macrophages were prominent (Figure 4b). Serial sections were performed,

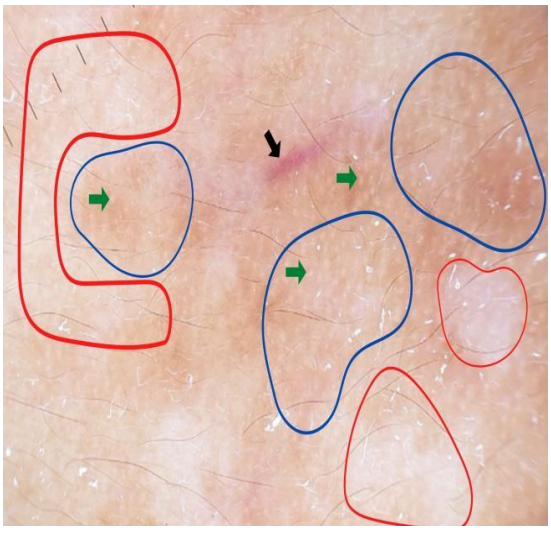

Figure 2: Representative photos of the dermoscopy of iatrogenic dyschromia. Intervening light brown areas with areas of exaggerated pseudonetwork (blue outline) and whitish area containing uniform pigment network and feathery margins (red outline), extensive network of vessels (black arrow) and visible follicular opening (green arrow).

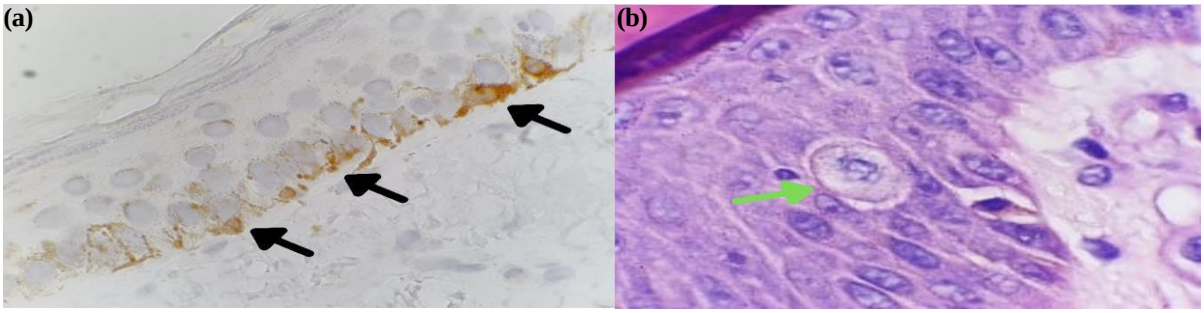

Figure 3: Melan-A shows deformed and apoptotic melanocytes in the basal cell layer (black arrow). H&E shows a sunburn cell (green arrow), and apoptotic (a. Melan-A, 1000x (OIO); b. H&E, 1000x (OIO))

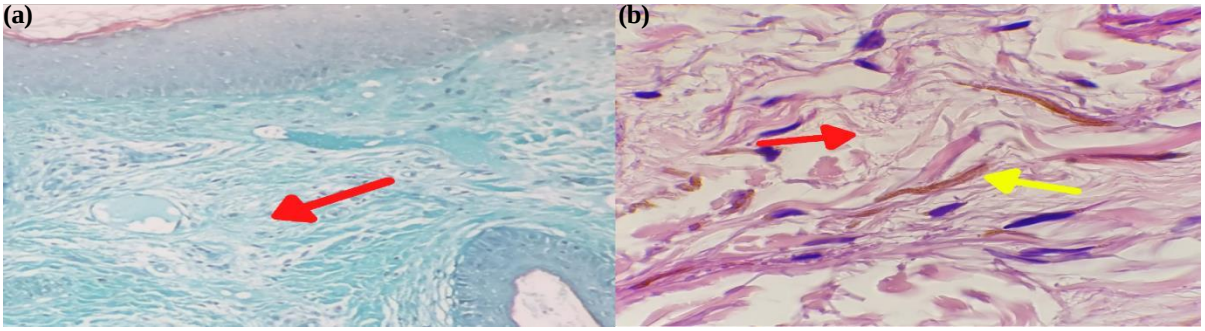

Figure 4: The dermis reveals (a) loosely arranged and fragmented collagen fibers (red arrow) and dilated blood vessels (Masson's Trichrome, 100x) and (b) pigment-laden macrophages (yellow arrow) and prominent solar elastosis (red arrow) (H&E, 400x)

and ochre bodies were not identified in all of the specimens. All 6 cases presented with the same histopathologic findings in the dermis.

Management And Outcome

Iatrogenic dyschromia is a condition caused by the excessive use of unregulated and banned by FDA topical lightening agents containing steroids, mercury, hydroquinone and hydroquinone-derivatives. A multi-disciplinary approach which includes discontinuation of the offending agent, adequate skin care, topical and/or systemic therapy as well as physical modalities.

In approaching patients with iatrogenic dyschromia, patient education is very essential. Chronicity of the disease and its long-term treatment. Proper selection of therapeutic agents and laser treatments which would not aggravate their current condition is also necessary.

In our patients, laser treatments with at least 2 sessions of 1064 Nd:Yag laser and Co2 laser was combined with mild cleanser, lightweight moisturizer containing 2ppm of medical grade epidermal growth factor, sunscreen and low dose oral isotretinoin with marginal improvement.

Discussion

Melasma, iatrogenic dyschromia and exogenous ochronosis manifest clinically with light brown to hyperpigmented macules and patches. The authors believe that these diseases belong to a spectrum based on the published studies on their clinical manifestation, dermoscopy and histopathological features. There is an urgent need to fully understand and properly define these skin conditions to prevent significant worsening of pigmentation and psychological distress afflicted with these skin conditions. Due to the striking and overlapping similarities between these conditions clinically, the use of dermoscopy may aid in differentiating these spectrums.

Iatrogenic dyschromia pathogenesis remains to be enigmatic but can be attributed to the excessive use of unregulated and banned by FDA topical lightening agents containing steroids, mercury, hydroquinone and hydroquinone-derivatives.

In this case series, the group investigated the dermoscopic and histopathological correlation of iatrogenic dyschromia in order to differentiate it from recalcitrant melasma and exogenous ochronosis. For the dermoscopic findings, our group found the appearance of intervening light brown areas with areas of exaggerated pseudonetwork and whitish area containing uniform and faint pigment network and feathery margins along with extensive network of vessels and visible follicular opening in the dermoscopy of all the six cases. Some of the white areas show similarities to the depigmented areas observed in vitiligo but with the absence of follicular repigmentation. The appearance of these dermoscopic features altogether has not been fully described in published studies.

It is important to note that facial skin is devoid of rete ridges and characterized by closely follicular infundibula. The diffuse pigmentation of the epidermis or the papillary dermis in facial skin is what we term as pseudonetwork of the face (Malvehy et al., 2006). Histopathologically, it corresponds to the pigmented cells located in the epidermis and dermo-epidermal junction interrupted by follicular openings. (Yélamos et al., 2019).

In our study, the findings of the whitish areas containing uniform pigment network and feathery margins similar with nevus depigmentosus (Vinay & Ankad, 2021) may be attributed to the prolonged application of lightening agents such as hydroquinone [tyrosinase inhibition], retinoids, [downregulation of tyrosinase and increased epidermal turnover], niacinamide [inhibition of melanosome transfer] and corticosteroids [nonselective inhibition of melanogenesis] (Grimes et al., 2019). These whitish areas correspond to reduced melanin in the epidermal keratinocytes while the faint and uniform reticular pigment network correspond to the melanin remaining in the melanocytes. Dermoscopic pattern in melasma shows diffuse brown reticular pigmentation with sparing of follicular openings producing an exaggerated pseudonetwork pattern and prominent vessels. On histopathology, the findings of brown reticular pigmentation on dermoscopy corresponds to increased melanin in the epidermis & increased free melanin in the dermis. The presence of prominent vessels or telangiectasias correspond to increased vascularity histopathologically (Khopkar, 2018). Dermo-scopy criteria of exogenous ochronosis on the other hand shows blue-gray amorphous areas obliterating the follicular openings. These blue-gray amorphous areas correspond to the brownish-yellow (ochre) banana-shaped fibers in the papillary dermis (Khunger, 2013).

The extensive network of vessels found in all 6 cases in our study are similar to the findings of Khopkar et al. They described the presence of prominent vessels or telangiectasias in melasma may have been due to topical steroid abuse which correspond to increased vascularity histopatho-logically. Furthermore, taking into consideration that topical treatments containing retinoids and steroids may induce telangiectasias, a study by Kim et al demonstrated through immuno-histological evaluation by factor VIIIa - related antigen that increased numbers of enlarged blood vessels are found in melasma (E. H. Kim et al., 2007). The number of vessels is directly correlated to the degree of pigmentation and can be attributed to the fact that the presence of deoxyhemoglobin contributes to the color of the skin (Stamatas & Kollias, 2004).

The anatomy of the facial skin is different than the rest of the body because it has a flattened dermo- epidermal junction interrupted by numerous adnexal openings. In the dermoscopy of iatrogenic dyschromia, visible follicular openings were observed in all of our cases. This is similar to findings in Melasma by Niti Khunger et al, where there is sparing of the follicular openings. In contradistinction with Exogenous ochronosis where in amorphous and globular structures obliterate the hair follicle openings as described

by Khunger et al in their study (Khunger, 2013).

To visualize the amount of collagen fibers in all of our cases, a Masson's trichrome stain was requested and revealed degeneration of collagen fibers. This study is similar with the findings of Nan-Hyung et al in which they evaluated eleven female melasma patients with CDH11 upregulation. The hyperpigmented skin and the adjacent normally pigmented skin were biopsied and sent for Masson's trichrome. Their results revealed that areas from the paired hyperpigmented and normally pigmented dermis showed a decreased collagen level but an increased elastotic material content in the hyperpigmented dermis in Verhoeff Van Gieson (N. H. Kim et al., 2016). This result is in contradistinction with exogenous ochronosis where in there is appearance of a green contour surrounding the brown-black materials in between the collagenous fibers (Gönül et al., 2006).

To determine the characteristic of melanocytes, Melan-A stain was requested. Our study revealed presence of injured melanocytes and apoptotic sunburn cells. In a study by Caelen and Cerroni, Melan- a is a more sensitive marker for intraepidermal melanocytes of normal skin than S-100 or HMB-45. This stain can also be sensitive in keratinocytes and other non-melanocytic cells damaged by an inflammatory process (el Shabrawi-Caelen et al., 2004).

The dermatologist should be able to recognize iatrogenic dyschromias as they differ from melasma and ochronosis in terms of clinical, histopathologic and dermoscopy findings. Continuous application of skin lightening agents without sun protection is most likely the major predisposing factor in the development of this condition. The authors believe that iatrogenic dyschromia is now very prevalent among women of skin of color but most of those who are affected are hesitant to seek professional consultation. A larger study is further recommended to fully define this skin condition.

Being able to differentiate these conditions clinically, dermoscopically and histopatho-logically will have a huge impact on the treatment and prognosis of patients. Facial hyper-pigmentation remains to be a very difficult condition to treat be it Melasma, Iatrogenic dyschromia or Exogenous ochronosis. To provide the improved outcome for our patients afflicted with these conditions, early differentiation and prompt diagnosis by a dermatologist is essential.

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