Fırat Tıp Dergisi/Firat Med J 2017; 22(3): 143-145

Case Report

Oral Isotretinoin Induced Pigmentation Disorder: A Case Report

Betül DEMİR[1,a], Demet ÇİÇEK[1], Leyla BİLİK[1], Ebru GÜLER AYDOĞDU[2], Hakan ARTAŞ[3], Nida DEMİRPOLAT[4], Can ERGİN[5]

[1]*University of Firat School of Medicine, Dermatology Department, Elazig, Türkiye*
[2]*Elazig Education and Research Hospital, Clinic of Dermatology, Elazig, Türkiye*
[3]*University of Firat School of Medicine, Department of Radiology, Elazig, Türkiye*
[4]*University of Firat School of Medicine, Department of Otolaryngology, Elazig, Türkiye*
[5]*Diskapi Yildirim Beyazit Education and Research Hospital, Clinic of Dermatology, Ankara, Türkiye*

ABSTRACT

Hyperpigmentation, which develops secondary to drugs, is generally due to the accumulation of the drugs on the skin. Isotretinoin is synthetic derivative of vitamin A and it is the 13-cis retinoic acid form of a retinoid. A 20-year-old female patient presented to the dermatology outpatient clinic with complaints of brown stains on the nose. The medical history also revealed that the patient had been using isotretinoin 30 mg/day for the last six months for acne and no other oral or topical drug use was present. Her dermatological examination revealed that a gray macule of 1x1 cm was present in the left nasal wing. The dermatoscopic examination of the lesion revealed thin, gray, pigmented structures in particular, surrounding the follicular openings. The absence of pigmentation defects due to systemic isotretinoin use in the literature review has led us to present the current case.
Keywords: *Drug Eruption, Isotretinoin, Pigmentation Disorder.*

ÖZET

Oral İsotretinoinin Tetiklediği Pigmentasyon Bozukluğu: Olgu Sunumu

İlaçlarla gelişen hiperpigmentasyonlar genellikle ilacın deride birikimine bağlıdır. İsotretinoin A vitamininin sentetik derivesidir ve retinoidlerin 13-cis retinoik asit formudur. Yirmi yaşında kadın hasta burunda kahverengi leke şikayeti ile dermatoloji polikliniğine başvurdu. Hastanın hikayesinden son altı aydır akne tedavisi için 30 mg/gün isotretinoin kullandığı, beraberinde başka oral veya topikal bir ilaç kullanmadığı öğrenildi. Dermatolojik muayenesinde sol burun kanadında 1x1 cm çaplı gri renkte makül mevcuttu. Lezyonun dermatoskopik muayenesinde sol burun kanadında özellikle foliküler açıklıkların etrafını saran ince, gri renkte pigmente yapılar görüldü. Literatürde oral isotretinoin kullanımına bağlı gelişen pigmentasyon bozukluğuna rastlamamış olmamız bizi bu olguyu sunmaya teşvik etmiştir.
Anahtar Sözcükler: *İlaç Erupsiyonu, İsotretinoin, Pigmentasyon Bozukluğu.*

Isotretinoin is synthetic derivative of vitamin A and it is the 13-cis retinoic acid form of a retinoid. It is recommended in severe forms of acne and in patients who demonstrate the psychological effects of acne. Oral isotretinoin shows its effect by suppressing the activity of the sebaceous glands, the growth of *Propionibacterium acnes* and inflammation in the treatment of acne vulgaris. Its daily dose is 0.5-1mg/kg, and cumulative dose is 100-150 mg/kg (1, 2). Isotretinoin has several mucocutaneous and systemic side effects. In addition to its side effects such as decreased sebum production, thinning of stratum corneum, drying of skin and mucosa, cheilitis, nasal hemorrhage, xerophthalmia, blepharoconjunctivitis, pruritus, photosensitivity, telogen alopecia, *Staphylococcus aureus* skin infections, dermatitis, nail fragility, paronychia, and periungual pyogenic granuloma, its adverse effects on the musculoskeletal system, gastrointestinal system, central nervous system, eyes, ears, thyroid, and kidneys have been defined. Rarely seen eruptions such as urticaria, polymorph erythema, and pityriasis rosea-like lesions have also been reported (2). Hyperpigmentation, which develops secondary to drugs, is generally due to the accumulation of the drugs on the skin. In the literature, pigmentation changes depending on minocycline, chloroquine, amiodarone, clofazimine, zidovudine, imipramine, chemotherapeutic agents, and heavy metals such as gold, silver, and arsenic have been defined (3). The absence of pigmentation defects due to systemic isotretinoin use in the literature review has led us to present the current case.

CASE REPORT

A 20-year-old female patient was admitted to dermatology polyclinic with the complaints of nasal stain. The patient's history revealed that the macule began as a brown-gray color lesion 3.5 months ago and there was no redness or pruritus prior to the development of the lesion and there had been no change in the color of the stain over time. It was recorded that she had not experienced previous trauma or enlargement in the nose, and she has had dribble-like hemorrhage.

[a]Yazışma Adresi: University of Firat School of Medicine, Dermatology Department, Elazig, Türkiye
Tel: 0424 233 3555 e-mail: drbkaraca@yahoo.com
Geliş Tarihi/Received: 17.04.2016 Kabul Tarihi/Accepted: 30.06.2016

The medical history also revealed that the patient had been using isotretinoin 30 mg/day for the last six months and no other oral or topical drug use was present. On the dermatological examination of the patient, while there was no hyperpigmentation on the right nasal wing (Figure 1a), there was a gray macule of 1x1 cm in diameter in the left nasal wing (Figure 1b). There was hyperemia in left conjunctiva, rugae and desquamation in the lips, xerosis in the bilateral lower and upper extremities, and erythematous plaque of 1x1 cm in diameter in medial part of right leg that was covered with squam.

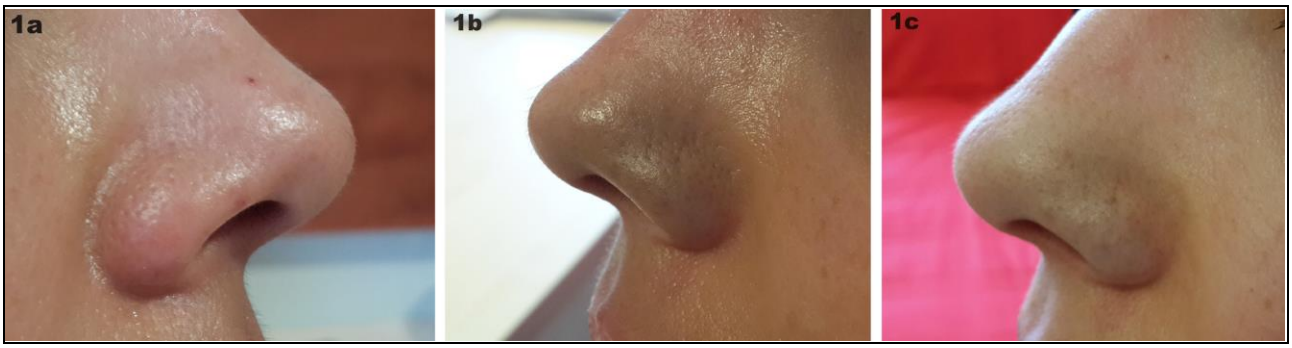

Figure 1. *Clinical appearance of nasal wings* ***1a.*** *Right nasal wing (normal),* ***1b.*** *Gray-colored macule of 1x1 cm in diameter in the left nasal wing,* ***1c.*** *Light, gray-colored macule of 1x1 cm in diameter in the left nasal wing two months after cessation of the drug.*

The physical examination of nails and mucosa was normal. The dermatoscopic examination of the lesion revealed a normal pseudonetwork structure (Figure 2a), brown unstructured areas in right nasal wing, and thin, gray, pigmented structures in particular, surrounding the follicular openings, in addition to the pseudonetwork structure in left nasal wing, (Figure 2b). Punch biopsy was not taken as the localization of the lesion brought esthetic concerns. The patient was recommended for consultation with the department of otolaryngology, as it was thought that the nasal mucosa could have been affected and it was reported that there was no hyperpigmentation or vascular pathology in the nasal vestibule and nasal mucosa on her endoscopic examination. On laboratory examination, no pathological finding was detected in complete blood count and blood chemistry.

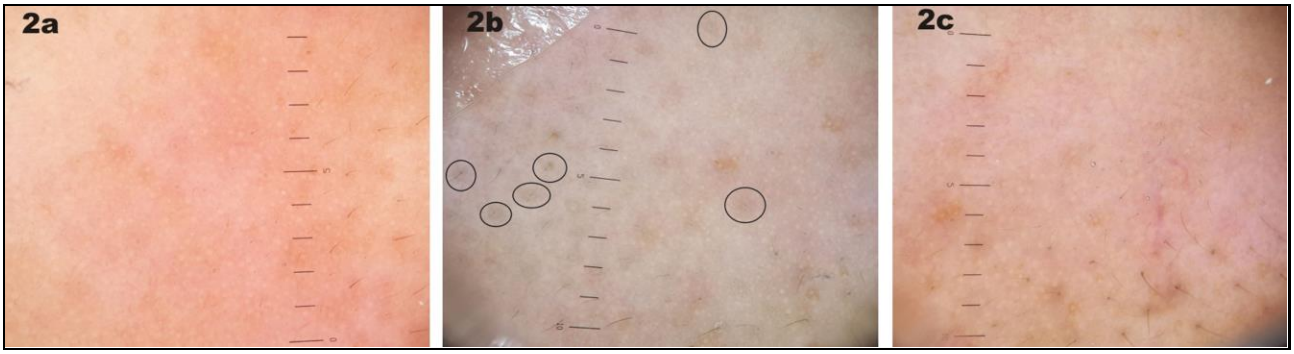

Figure 2. *Dermatoscopic image of nasal wings* ***2a.*** *Normal pseudonetwork structure in the right nasal wing,* ***2b.*** *Pseudonetwork structure in the left nasal wing; especially thin, gray-colored pigmentation particularly prominent around the follicular openings (shown within a circle),* ***2c****. The pseudonetwork structure in the left nasal wing two months after the cessation of drug therapy.*

On bilateral superficial ultrasonography and doppler examination of the nasal wings, it was reported that in the subcutaneous tissue thickness measurements of the nasal wing that was performed symmetrically on the right lateral side, the right nasal wing was 3.9 mm (Figure 3a) and the left nasal wing was 5.6 mm in line with the edema 5.6 mm (Figure 3b). It was reported that no asymmetry was observed in vascularity of both nasal wings.

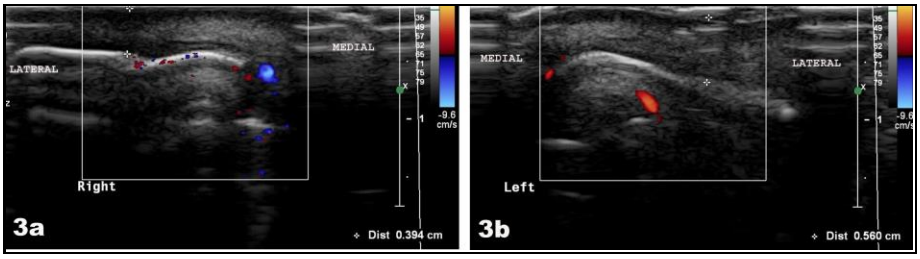

Figure 3. *Subcutaneous tissue thickness measurement of the nasal wings under bilateral superficial ultrasonography and doppler examination* ***3a.*** *Tissue thickness measurement of the right nasal wing was 3.9 mm,* ***3b.*** *Tissue thickness measurement of the left nasal wing was 5.6 mm.*

DISCUSSION

Drug-induced hyperpigmentation is the cause of 10-20% of all acquired hyperpigmentation cases and it occurs through various mechanisms. These mechanisms are explained as melanin storage, nonspecific cutaneous inflammation, sunlight, accumulation of the triggering agent, accumulation of specific pigments of the drug, or iron accumulation due to the injury of the dermal vessels caused by the drug. Melanin accumulation is particularly observed in dermal macrophages rather than the basal layer of epidermis. This melanin accumulation could develop because of excessive melanin production due to melanocyte stimulation by the drug, a response to a drug-associated nonspecific cutaneous inflammation without a true photosensitivity reaction, or the disturbance of melanin excretion from the macrophages due to formation of a stable complex between the drug and melanin. Another pigmentation mechanism is the accumulation of the drug alone, separately from melanin, as free granules distributed between extracellular matrix proteins or as foreign bodies within the dermal macrophages that could not be eliminated (4). Clinically hyperpigmented macules can be observed on the skin, mucosa and nails in drug-related hyperpigmentation. Hyperpigmentation can be localized or generalized (5). The current patient had a localized hyperpigmented lesion only in the left nasal wing. No hyperpigmented lesion was observed in the oral or genital mucosa or the nails of the patient. Histopathological findings in drug-related hyperpigmentation vary. Colored particles accumulated in the dermal macrophages can be observed. Dermal macrophages can be found around the blood vessels and skin appendages (4). As we could not obtain biopsy due to cosmetic concerns, we could not provide precise information about the mechanism of hyperpigmentation caused by isotretinoin. Retinoic acids demonstrate their activities, such as epidermal cell growth and differentiation in skin, and their activities in sebaceous glands with tissue specific receptors (6). Especially isotretinoin has receptors in human sebaceous glands and this is a precursor drug in the sebaceous glands. It has been reported that it is activated by undergoing selective intracellular isomerization (1). The affinity of isotretinoin to pilosebaceous unit is obvious. We did not perform histopathological examination; however, the dermoscopic examination of the lesion revealed a gray-colored pigmentation change, which was especially prominent around the follicles. These findings were quite similar to the dermoscopic images that were presented in studies examining drug accumulations. Therefore, we assumed that the present case might be hyperpigmentation that developed due to isotretinoin usage. In the study of Mishra et al., pigment structures around the follicles were shown to be more prominent in dermoscopic images of the exogenous ochronosis cases caused by topically administered hydroquinone (7). Direct penetration of a topically administered drug to the skin can cause dense pigment accumulation. However, pale colored pigmentation around the follicles in the dermoscopy of the current case could be the result of systemic drug use. On the other hand, it has been reported that the retinoic acid concentrations in the dermis are lower than the subcutaneous tissue (6). Thus, when the factors such as the presence of more systemic drugs in the subcutaneous tissue compared to the dermis and localization of the lesion in nose are considered, it is obvious to detect pale-colored pigmentation in the dermoscopy.

Oral isotretinoin therapy was terminated and the patient was followed-up. The patient was reevaluated clinically and dermoscopically on her follow-up at the second month. It was observed that there was paleness in the color of a pigmented macular lesion in the left nose (Figure 1c). In the dermoscopic examination, in addition to the pseudonetwork structure, the gray-colored, pigmented structures had decreased (Figure 2c).

In conclusion, clinicians should consider that isotretinoin, which is used in the treatment of acne, could have a hyperpigmentation effect with an unknown mechanism, in addition to the numerous known side effects.

Acknowledgments: Thank you to the NOVA translation company for language translation.

This study has been presented in the DOD Dermatology Meeting held at Eskisehir /Turkey in 3-6 September 2015, numbered PS-06.

REFERENCES

1. Zouboulis CC. Retinoids-which dermatological indications will benefit in the near future? Skin Pharmacol Appl Skin Physiol 2001; 14: 303-15.
2. Brito F, Sant'Anna IP, Galindo JC, Rosendo LH, Santos JB. Evaluation of clinical adverse effects and laboratory alterations in patients with acne vulgaris treated with oral isotretinoin. An Bras Dermatol 2010; 85: 331-37.
3. Odom RB, James WD, Berger TG. Andrew's Disease of the Skin Clinical Dermatology, 9th ed. Philadelphia: WB Saunders Company, 2000, 95-145.
4. Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. Am J Clin Dermatol 2001; 2: 253-62.
5. Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. J Am Acad Dermatol 1999; 40: 367-98.
6. Orfanos CE, Zouboulis CC, Almond-Roesler B, Geilen CC. Current use and future potential role of retinoids in dermatology. Drugs 1997; 53: 358-88.
7. Mishra SN, Dhurat RS, Deshpande DJ, Nayak CS. Diagnostic utility of dermatoscopy in hydroquinone-induced exogenous ochronosis. Int J Dermatol 2013; 52: 413-7.