

# Amiodarone-Induced Skin Hyperpigmentation: Case Report

## Amiodarona Bağlı Deride Hiperpigmentasyon

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**ABSTRACT** Amiodarone (amiodarone hydrochloride) is an anti-arrhythmic drug that has been currently used in the treatment of supraventricular and ventricular tachyarrhythmias. Long-term amiodarone treatment can cause numerous side effects such as pulmonary fibrosis, pneumonitis, hepatotoxicity, neuropathy, myopathy and thyroid gland dysfunction. In addition, it can have dermatological side effects as well. Amiodarone-induced photosensitivity is seen approximately in 57-75% of the patients. Amiodarone-induced blue-grey skin discoloration following sunlight exposure is seen in 2-5% of the patients. Herein, we discuss a 61-year-old male presenting with amiodarone-induced skin hyperpigmentation, in the light of literature.

**Key Words:** Amiodarone; hyperpigmentation; adverse effects

**ÖZET** Amiodaron (amiodaron hidroklorid) günümüzde supraventriküler ve ventriküler taşiaritmilerde kullanılan bir ilaçtır. Uzun süreli amiodaron tedavisinin çok sayıda yan etkiye yol açtığı kabul edilmektedir ki, bunların en şiddetlileri arasında pulmoner fibrozis ve pnömoni, hepatotoksisite, nöropati, miyopati ve tiroid fonksiyon bozukluğu yer almaktadır. Ayrıca, dermatolojik yan etkiler de ortaya çıkarmaktadır. Güneş ışığına karşı aşırı hassasiyet %57-75 gibi yüksek bir oranda görülürken, güneşe maruz kalan deri alanlarında mavi-gri renk değişikliği %2-5 gibi daha düşük bir oranda gelişmektedir. Burada 61 yaşındaki bir erkek hastada amiodaron kullanımına bağlı ortaya çıkan deri hiperpigmentasyonu sunulmakta ve literatürler ışığında gözden geçirilmektedir.

**Anahtar Kelimeler:** Amiodarone; hiperpigmentasyon; istenmeyen etkiler

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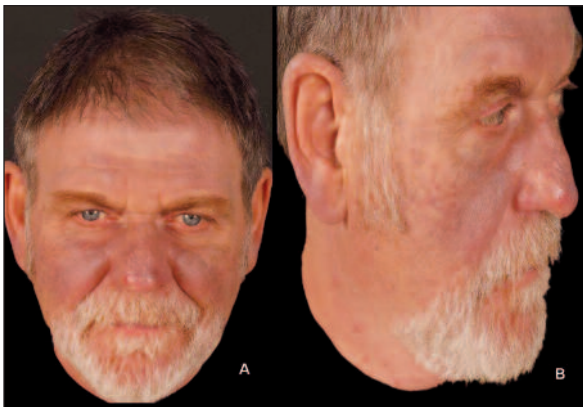
Amiodarone hydrochloride is an anti-arrhythmic drug that has been currently used in the treatment of supraventricular and ventricular tachyarrhythmias since 1970.<sup>1</sup> It is stored primarily in lungs, liver, spleen and adipose tissue following its absorption from the gastrointestinal system. Toxic effects are observed particularly in lungs, eyes, gastrointestinal system, liver, thyroid gland and central nervous system. It can cause corneal accumulation, liver dysfunction, hyperthyroidism, hypothyroidism, hyperpigmentation, bone marrow suppression and peripheral neuropathy.<sup>2</sup>

Amiodarone-induced dermatological side effects are seen in approximately 15% of the patients. Amiodarone-induced photosensitivity is seen in

approximately 57-75% of patients. Amiodarone-induced blue-grey skin discoloration following sunlight exposure is seen in 2-5% of patients. Herein, due to its rarity, we report a 61-year-old male patient presenting with amiodarone-induced skin hyperpigmentation.

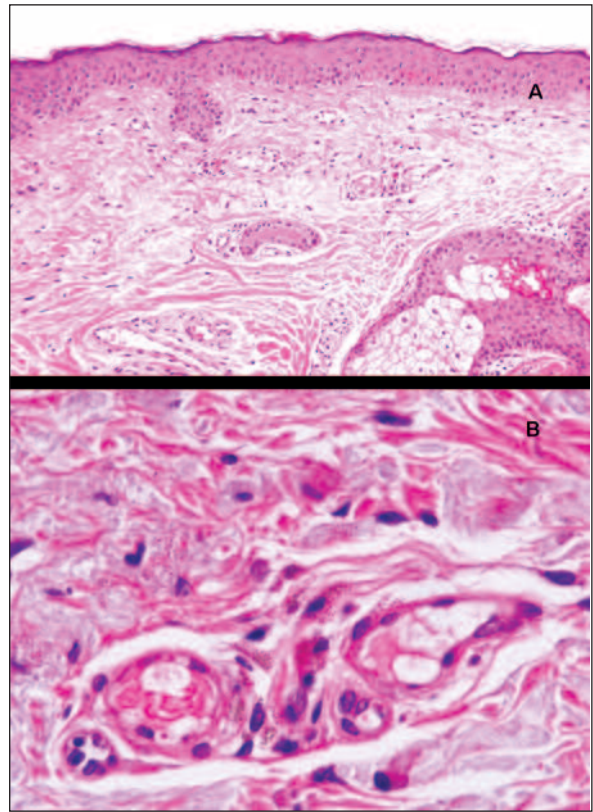
## CASE REPORT

A 61-year-old male with Fitzpatrick skin phototype II presented with slowly progressive, asymptomatic skin hyperpigmentation of sun-exposed areas which started at November 2011. His medical history was remarkable for arrhythmia. He had no known history of drug allergies. For more than 4 years, he had been treated with amiodarone at a dose of 2x 200 mg tablets per day. The cumulative dose was around 576 g over 48 months. The systemic examination findings were normal, except for varicose veins on both legs. The dermatologic examination showed blue-grayish discoloration on maxillary area, forehead, nose, ears and on all over the face (Figure 1A, B). The echocardiography showed left ventricular hypertrophy. A punch biopsy was taken from a pigmented area of the face. The biopsy specimen demonstrated orthokeratosis and numerous macrophages accumulated around superficial dermal vessels in the upper dermis (Figure 2A, B). The cytoplasm of these cells showed brown-pigmented round inclusions that stained positive by Fontana-Masson special staining (Figure 3A, B). There was no increase in melanin con-



**FIGURE 1:** Blue-gray hyperpigmentation of the forehead, cheeks, nose and malar regions (A) and ears (B).

(See color figure at <http://tipbilimleri.turkiyeklinikleri.com/>)



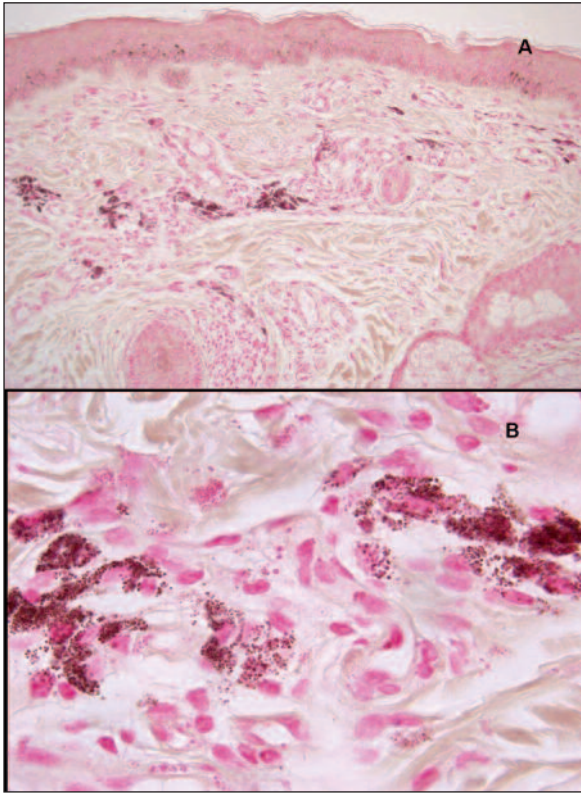
**FIGURE 2:** Numerous macrophages surrounding superficial blood vessels (A) (HE, x100). Upper and mid-dermal deposits of brown granular pigment distributed perivascularly and in the cytoplasm of dermal macrophages (B) (HE, x1000).

(See color figure at <http://tipbilimleri.turkiyeklinikleri.com/>)

tent in the keratinocytes (Fontana-Masson staining). Immunohistochemical staining for Melan A and S 100 was negative. The PAS special staining was negative for fungal elements. The patient was diagnosed with amiodarone-induced hyperpigmentation based on the clinical and histopathological findings. Then, amiodarone was discontinued and he was referred to cardiology department for a medication change. Q-switched Nd:YAG laser treatment was administered to accelerate the recovery process. Informed consent was taken from the patient before the publication.

## DISCUSSION

Amiodarone (2-butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride) is an anti-arrhythmic agent, is frequently used nowadays for the treatment of some



**FIGURE 3:** Brown granular pigment deposits stained positive with Fontana-Masson (original magnification x 100) (A). Brown deposits Fontana-Masson x1000 (B).

(See color figure at <http://tipbilimleri.turkiyeklinikleri.com/>)

arrhythmias such as ventricular arrhythmia, paroxysmal supraventricular tachycardia, atrial fibrillation, atrial flutter.<sup>3</sup> However, it can cause several side effects due to its high iodine concentration. Therefore, its use is limited.<sup>3</sup>

Amiodarone can cause several dermatological side effects including angioedema, alopecia, iododerma, leukocytoclastic vasculitis, linear IgA dermatosis, lupus erythematosus, pseudoporphyria, psoriasis vulgaris, Stevens-Johnson syndrome and urticaria.<sup>4</sup> The most common amiodarone induced side effect is photosensitivity. This side effect may disappear within 1-3 days after discontinuation of amiodarone, or it may last up 4-12 months. Amiodarone induced photosensitivity occurs after exposure to ultraviolet (UV) A rays. Under the regimens commonly used, photosensitivity can be expected to occur after 4 months of continuous treatment and a minimal cumulative dose of 40 g.<sup>5,6</sup> Amio-

darone induced hyperpigmentation occurs after an average of 20 months of continuous treatment and a minimal cumulative dose of 160 g.<sup>5</sup> The cumulative dose of our patient was 576 g and the period of drug use was over 48 months.

Amiodarone-induced skin hyperpigmentation is more frequently seen in patients with Fitzpatrick skin type I and II. Our patient's skin type was determined as Fitzpatrick II. Blue-grey discoloration is determined clinically on sun-exposed areas.

The exact mechanism of amiodarone-induced skin discoloration is still unclear. Wiper et al. stated that it might be a drug-induced lipidosis, a photosensitivity reaction to UVA and or may be leukocytoclastic vasculitis.<sup>7</sup> On the other hand, the results of Ammouy et al. clearly demonstrated that amiodarone-induced skin hyperpigmentation was related to drug deposition.<sup>8</sup> This pigmentation can be explained by the Tyndall effect, in which dermal pigment; melanin, iron, or another pigment, is perceived as blue, gray or blue-gray.<sup>7,8</sup>

Amiodarone-induced hyperpigmentation is a seldom-encountered side effect that should be considered during differential diagnosis of diseases involving hyperpigmentation of the face, such as argyria, hydrargyria, chrysiasis, hemochromatosis, arsenic melanosis, Berloque dermatitis, melasma, poikiloderma of Civatte, Riehl's melanosis and nevus of Ota.<sup>4</sup> Differential diagnosis of facial hyperpigmentation is summarized in Table 1. The treatment is discontinuation of amiodarone, however the pigmentation may continue more than 2 years. In the literature, limited numbers of patients were successfully treated with laser.<sup>8-10</sup>

Other medications, including phenothiazine, antimalarial drugs, bleomycin, heavy metals, clofazimine, methotrexate, cyclophosphamide, apomorphine, imipramine and tetracycline, can also cause hyperpigmentation.<sup>4</sup>

Consequently, although facial hyperpigmentation can occur as a result of several diseases, a careful and detailed medication history should be obtained to detect drug-induced facial hyperpigmentation, such as the one caused by amiodarone.

**TABLE 1:** Differential diagnosis of facial hyperpigmentation.

Disease	Characteristics
Argyria (silver)	Occurs in persons exposed to silver salts and clinically appears as a slate-gray pigmentation on sun-exposed areas of the skin, especially the forehead and nose. Conventional histology shows silver granules in the dermis particularly evident near the basal layer of sweat glands.
Lichen Planus Pigmentosus	Asymptomatic (sometimes itchy), diffuse (less frequently reticular, blotchy, or perifollicular) hyperpigmented dark-brown to slate-grey macules present mostly over exposed areas and flexures.
Exogenous ochronosis	Complication of hydroquinone develops after prolonged use of high concentrations in dark-skinned patients. It presents with diffuse pigmentation in the hydroquinone treated photo-exposed areas namely cheeks, forehead and temporal and periorbital skin with less frequent involvement of nasal, peribuccal, and chin areas.
Hemochromatosis	One of the most common genetic errors of metabolism and is characterized by a diffuse cutaneous slate-gray pigmentation in light-exposed areas. The onset of the disease generally occurs during the fourth or fifth decade of life. Men are more commonly affected than women.
Melasma	Irregular, light brown to gray-brown macules with increased activity and numbers of melanocytes with sparse or absent inflammation.
Civatte-Poikiloderma	Characterized by the presence of reddish-brown reticulate pigmentation, telangiectasia and atrophy in irregular, symmetrical patches on the convexities of cheeks and the sides of the neck, sparing the area under the chin. It occurs predominantly in middle-aged women.
Riehl's melanosis	Probably a pigmented contact dermatitis to antigens present in cosmetics and textiles. Spotty brown-gray facial pigmentation with lymphohistiocytic infiltrate in the upper dermis. Patients may show positive patch test to cosmetics or their ingredients.
Discoid lupus erythematosus	Erythematous lesions with vacuolar degeneration of the basal cell layer and marked melanin deposits in the upper dermis following basal cell damage; atrophy of the epidermis; hyperkeratosis; follicular plugging.
Erythema dyschromicum perstans	Slate-gray to violet or blue macules with perivascular lymphohistiocytic infiltrate; pigment incontinence and immune-associated antigen expression in keratinocytes.
Nevus of Ota	Represents aborted embryonic migration of melanocytes from neural crest to epidermis. It is characterized by speckled or mottled coalescing blue-grey pigmentation of the area supplied by ophthalmic and maxillary divisions of trigeminal nerve. It is usually unilateral (90%). In addition to skin, pigmentation of nevus may involve oral mucosa and the eye.

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