Facial pigmentation associated with amiodarone

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Amiodarone is one of the most commonly used drugs for treatment of cardiac arrhythmia. Several undesirable effects are associated with its long-term use. This report describes the case of a 71-year-old female patient, with a diagnosis of cardiac arrhythmia, who presented with a stigmatizing blue-gray facial pigmentation and altered serum values of thyroid hormones associated with the intake of amiodarone. The patient was referred to her cardiologist. The aim of this report is to increase clinicians’ awareness about the potential adverse effects of this drug.

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Amiodarone is a drug taken for the treatment of the heart condition, cardiac arrhythmia.1,2 However, several adverse effects have been reported in patients taking amiodarone.3,4 Two of the collateral effects of amiodarone—which are rarely seen, and mainly reported in elderly patients—are skin photosensitivity and blue-gray facial pigmentation.3,4 The authors present a case report of a patient who developed extremely bluish facial pigmentation and thyroid dysfunction during the use of amiodarone for the treatment of cardiac arrhythmia. Emphasis was given on the diagnosis process, as well as to the differential diagnoses of this drug-related complication.

Case report

A 71-year-old woman was referred to the Oral Diagnosis Clinic, Piracicaba Dental School, State University of Campinas, Brazil, with the chief complaint of a nodule on the hard palate that had been present for approximately 7 years. The patient had a medical background of hypertension and cardiac arrhythmia, which had been treated with amiodarone over the last 3 years. The patient recounted that she took 400 mg daily in the first 15 months, and 200 mg daily thereafter. Head and neck physical examination revealed a distinct blue-gray pigmentation of the mid- and upper-thirds of the face, especially in the nose, zygomatic, and frontal regions (Fig. 1). According to the patient, this had had been noticeable for the last 18 months; when asked about the facial pigmentation, the patient reported that she was diagnosed with rosacea by her dermatologist, who treated her with tetracycline and sunblock lotion. She had been in treatment for 9 months without improvement. Intraorally, a pedunculated nodule was observed on the hard palate, which presented a superficial area of bluish pigmentation (Fig. 2). Discreet areas of denture-related stomatitis were also noticed.

Laboratory blood tests showed altered hepatic and thyroid functions, with abnormal values for aminotransferase, T4, and TSH: AST/TGO = 38 U/L (ref. <31 U/L); T4 = 2.66 ng/dL (ref. 0.75 to 1.80 ng/dL); and TSH = 0.012 UIU/mL (ref. 0.350 to 5.500 UIU/mL).

After examination, and with the provisional diagnosis of facial pigmentation associated with amiodarone, a skin biopsy was performed on the zygomatic region. H & E stain revealed an orthokeratinized stratified epithelium covering the dermis with evident signals of solar elastosis. A granular yellow-brownish pigmentation was observed inside histiocytes along the dermis, close to the blood vessels (Fig. 3).

Fig. 1. Extraoral photograph showing a blue-gray facial skin discoloration, affecting the upper and middle third of the face.

Fig. 2. Intraoral view showing a fibrous hyperplasia in the palate with a posterior pigmentation.
stains were also performed, and both were negative, excluding the possibility of melanin and hemosiderine pigments (Fig. 4 and 5). The palatal nodule was removed, and the microscopic examination confirmed the clinical hypothesis of fibrous hyperplasia. The pigmentation was observed inside the macrophages and scattered in the connective tissue. Perls stain was positive, being compatible with hemosiderine (Fig. 6). Finally, the patient was referred to her cardiologist with the diagnosis of facial skin pigmentation associated with amiodarone.

Discussion
Amiodarone is an iodine-rich medicament and one of the most effective and commonly used drugs available for treatment of cardiac arrhythmia.\textsuperscript{1-3} It has a high lipophilicity and a long plasma half-life. Amiodarone prolongs the cardiac repolarization by the sodium and calcium channel block and nonselective β-adrenergic inhibition.\textsuperscript{5} It has a variable (20%–80%) oral bioavailability and its hepatic metabolization results in mono-N-desethylamiodarone. The peak serum level of amiodarone, after oral dosage, is achieved within 3-7 hours.\textsuperscript{2} Amiodarone exhibits several adverse effects, such as corneal deposition; phototoxicity and skin pigmentation; thyroid damage; and hepatic, gastrointestinal, myopathic, or neurological complications.\textsuperscript{3,4,6-8} Drug interactions related to amiodarone also have been reported to cause diverse collateral effects.\textsuperscript{9} The majority of these effects are related to the duration of the treatment and drug dosage. Intraorally, hypersalivation, blue pigmentation of the oral mucosa, and bitter taste have also been described.\textsuperscript{10}

Adverse effects of the skin induced by amiodarone affect approximately 10% of patients, and is associated with a prolonged use of the drug (generally >1 year), a dosage of 200–800 mg daily, and/or sun exposure.\textsuperscript{3,4,6-7} The mechanism by which it causes skin pigmentation is still controversial, but several theories have been considered, including drug-induced lipiodosis, photosensitivity reaction to ultraviolet light, or leukocytoclastic vasculitis.\textsuperscript{11} Harris et al compared the dosage and plasma concentration of amiodarone and its metabolites in patients with and without photosensitivity, and they did not find any significant difference between the 2 groups.\textsuperscript{3} There are 2 types of skin reactions associated with amiodarone. The first and most common is photosensitivity, which is characterized by pruritis and erythema; the second is a slate-grey discoloration of the sun-exposed skin, affecting only 1%-3% of patients, with a predilection for males.\textsuperscript{3,7,12} The current case presents an asymptomatic facial pigmentation with a clinical appearance similar to other reports in the literature.\textsuperscript{5,12,13} This pigmentation was not observed on other parts of the body. Facial skin pigmentation can be stigmatizing, since it may persist for long periods, even after amiodarone treatment is discontinued. However, there have been reports that the pigmentation can disappear within 2-24 months after withdrawal of the drug.\textsuperscript{4,12} Corneal microdeposits, with no impairment to visual acuity, also have been reported, but the patient in this case did not show any visual alterations.\textsuperscript{3,7}

Skin biopsies typically show yellowish-brown or brown pigmented granules in macrophages of the dermis.\textsuperscript{7,13} Studies have established that these granules contain iron, sulphur, iodine, amiodarone, and desethylamiodarone. Amiodarone and its metabolites bind to lipofuscin in macrophages, and tend to concentrate in areas of highly sun-exposed skin.\textsuperscript{7} In addition, ultraviolet light induces amiodarone and its metabolites to bind to the blood vessel walls and the perivascular tissue, triggering an associated vasodilatation that increases the diffusion of these metabolites, resulting in chronic accumulation in the tissues.\textsuperscript{7} The incisional skin biopsy of the current case showed similar histopathological features to the previous published cases.
The pigmentation of the oral fibrous hyperplasia was not associated with the skin pigmentation, and represented a reactive pigmentation due to deposits of hemosiderine in the dermis, probably caused by the chronic trauma on the palate with the upper denture.

Thyroid hormone alterations found in the patient can be explained since amiodarone inhibits the reversion of T4 into T3, resulting in increased T4 and TSH levels, and decreased T3 levels in long-term users. Our patient presented normal T3 serum values, increased levels of T4, and decreased levels of TSH. The levels of aminotransferase were also altered (AST/TGO levels were increased and ALT/TGP levels were normal). Similar to complications reported in previous cases, these laboratory results indicate that the thyroid and hepatic function were altered due to the use of amiodarone.6,7,13 Because of these adverse effects, it has been suggested that the dosage of amiodarone has to be determined individually, according to the results of the patient’s follow-up.6 The patient returned once after the diagnosis, with no improvement in thyroid hormones levels, because the medication was not discontinued by the cardiologist.

The association between amiodarone-induced skin pigmentation and multiple basal cell carcinomas has been reported.14,15 The differential diagnoses include, but are not limited to, argyria, rosacea, and cutaneous lupus erythematosus. Argyria is manifested by a grey-bluish cutaneous pigmentation and is associated with the intake of drugs or other substances containing silver. Rosacea is a chronic skin condition with predominantly facial manifestations, and is characterized by erythema, flushing, pustules, and telangectasias. Cutaneous lupus erythematosus affects the face and other parts of the body and its diagnosis depends on a combination of clinical and laboratory findings.

Conclusion
The detection of early signals of photosensitivity, thyroid dysfunction, or other alterations associated with the use of amiodarone must be checked closely by physicians, geriatrists, dermatologists, dentists, and other health professionals who may see patients that receive this drug, in order to prevent more severe complications.

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