Amiodarone - induced skin pigmentation

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SUMMARY

In last year a few cases of blue-gray skin pigmentation in photo exposed areas (face and hands) were observed at our department. Because of a chronic myocardiopathy and arrhythmia, all these patients had taken amiodarone 200 mg daily over more than two years. Histopathololgic examination revealed upper and mid-dermal deposits of a yellow-black granular pigment distributed perivascularly in the cytoplasm of dermal macrophages. Special staining demonstrated that this pigment has the characteristics of lipofuscin. The small number of cases reported are probably due to the fact that this side effect of amiodarone is not so rare but frequently unrecognized.

Introduction

Amiodarone is a very effective antiarrhythmic drug, however sometimes associated with adverse effects involving several organs (pulmonary toxicity, hypothyroidism, and various neurologic side effects). Several types of pathologic cutaneous reactions have been reported, including allergic rash, photosensitivity, vasculitis and skin pigmentation. Photosensitivity is a side effect that occurs in 30% to 57% of patients on amiodarone and between 1% and 10% show cutaneous hyperpigmentation. Side effects associated with amiodarone use are generally well tolerated and reversible (1,2).

Case report

In lasts years three cases of blue-gray skin pigmentation in photo exposed areas (face and hands) were observed at our department. Because of chronic myocardiopathy and arrhythmia, all these patients had taken amiodarone 200 mg daily over more than two years.

Patients

Patient 1 (S. A.).

This man was born in 1929 and had ischemic myocardiopathy. Due to attacks of atrial fibrillation which remained unaffected by conventional antiarrythmic drugs he was in 1997 given Cordarone in a dose of 200 mg daily. Late in summer 1998, after having taken Cordarone for one year, he noticed a blue-grey discoloration of his face and extensor surfaces of the hands. In spite of this side effect, the patient continued with his medication and a slight worsening of the skin lesion was noticed. (Fig.1)

Patient 2 (D. R.).

The male patient was born in 1931. In 1994, after an acute myocardial infarction he experienced frequent attacks of atrial fibrillation with symptoms and signs of cardiac ischemia. He was given Cordarone 200 mg three times daily for a week, then a maintenance dose of 200

KEY WORDS

camiodarone, side effects, skin pigmentation

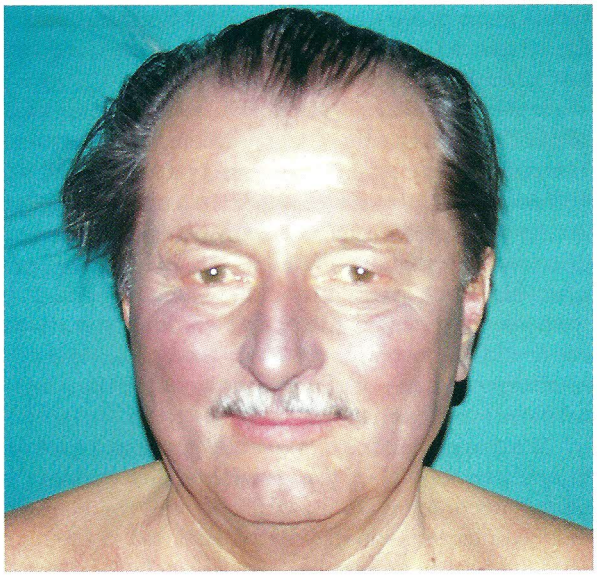


Figure 1. Patient 1. Greyish color of the face due to amiodarone tretment.

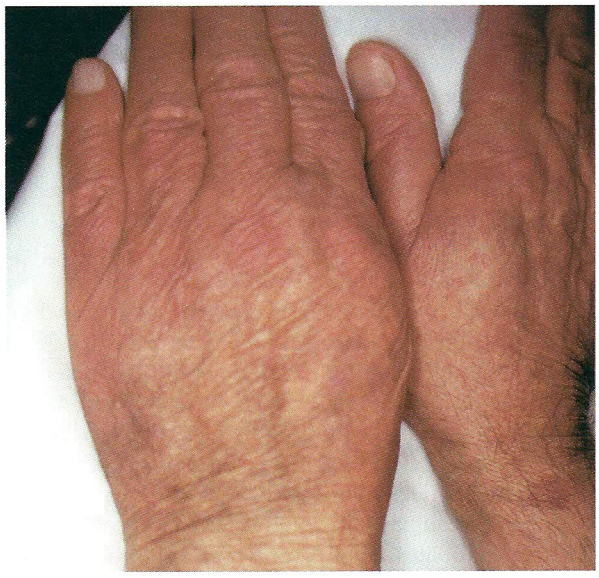


Figure 2. Patient 3. Brownish hyperpigmentation of the dorsa of the hand due to amiodarone treatment.

mg daily. Because of arterial hypertension, hyperlipidemia and peripheral vascular disease, his medical treatment also included enalapril, furosemid, simvastatin and acetylsalicylic acid. After having taken Cordarone for six years, he noticed inhomogeneous dirty discoloration of face and hands. In February 2001, his cardiologist noticed a worsening of skin discoloration and Cordarone treatment was discontinued.

Patient 3 (H. M.)

The female patient, born in 1939, started the therapy with Cordarone in 1999 in a dose of 200 mg two times daily for one week, thereafter 200 mg daily, because of an atrial fibrillation and myocadiopathy. During the autumn of 2001 she noticed increasing discoloration of her facial skin. Due to this side effect of Cordarone, the daily maintenance dose was decreased to 100 mg daily. (Fig.2).

Punch biopsies were taken from light-exposed pigmented areas of the preauricular regions. The tissue was examined by standard light microscopy using HE and special stain for lipofuscin. Histopathologic examination revealed upper and mid dermal deposits of yellow-black granular pigment distributed perivascularly and in the cytoplasm of dermal macrophages (Fig.3). Special staining demonstrated that this pigment has the characteristics of lipofuscin (Fig. 4). Electron microscopy revealed electron dense secondary lysosomes lying within dermal macrophages (3).

Figure 3. Patient 1. Histology, macrophages filled up with pigment granules. HE stain.

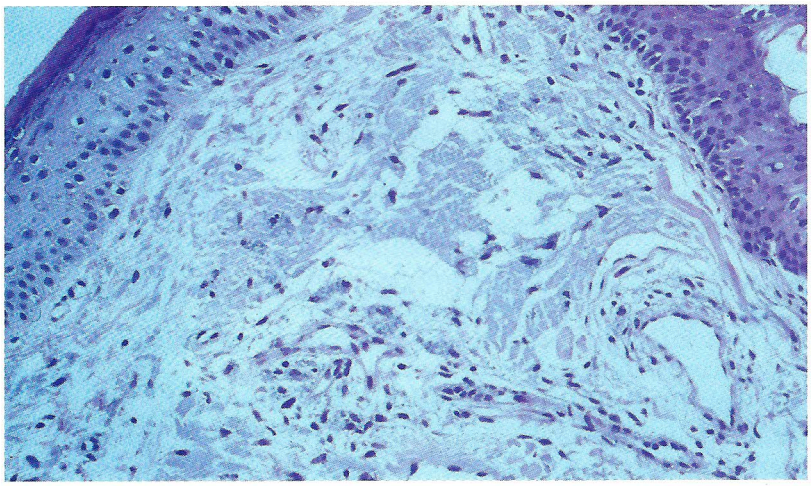
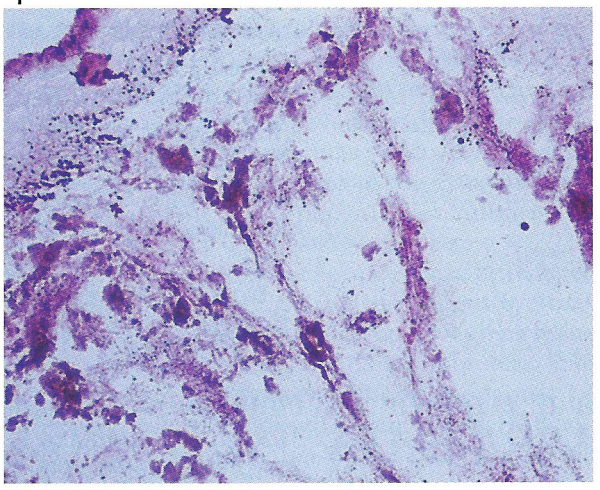


Figure 4. Patient 1. Histopathology, lipofuscin, special stain.



Discussion

Amiodarone is a highly effective antiarrhythmic drug from group III of the Vaughan-Williams classification. Amiodarone hydrochloride is a benzofuran derivate that has been credited with controlling 60% to 80% of cases of serious recurrent ventricular tachycardias and 80% to 100% of refractory supraventricular dysrhythmyas. The drug has a variable half-life, ranging from 18 to 45 days in some patients and accumulates in several body tissues, including fat and skin. Amiodarone skin pigmentation is caused by the UV-induced accumulation of lipofuscin in dermal macrophages, depending on both the daily dose and the duration of therapy (4). It is likely that UV exposure induces vasodilatation and increased diffusion of amiodarone and its metabolite desethylamiodarone in perivascular tissue, resulting in chronic accumulation of the drug and its metabolites. Amiodarone is an amphiphilic compound with nonpolar ring (hydrophobic) and hydrophilic side chain. Polar lipids (phospholipids derived from cellular membranes) are changed by forming complexes with the amiodarone. Lipofuscin in secondary lysosomes probably reflects phagocytosis by macrophages of degraded cell membranes bound to the lipid-soluble amiodarone. As these complexes are not enzymatically digestible, they accumulate within the lysosomes (5).

The precise mechanism of the photosensitivity is unknown, but suggests a nonimmunologic or "toxic" mechanism and a form of drug-induced lipidosis. It seems that a tissue threshold level for amiodarone exists, above which skin discoloration appears and below which it fades (6,7).

Some new studies suggest a novel pathogenetic aspect of amiodarone induced hyperpigmentation. Amiodarone and its metabolite desethylamiodarone in combination with UV radiation probably block melanosomal maturation, resulting in defective protection UV radiation. Absence of epidermal melanin and dermal accumulation of dark pigment results in a gray-blue color, as explained by the Tyndall effect (8,9). It would be interesting to investigate if an early presentation and an increased intensity of amiodarone induced skin pigmentation could serve for early detection of the target internal organ involvement.

The skin pigmentation is reversible but it may take up to one year for a complete resolution after the drug is discontinued. Although medically benign, amiodarone-induced pigmentation may be cosmetically disfiguring. The Q-switched ruby laser has been reported to be successful in treating amiodarone induced skin pigmentation (10).

Conclusion

In our opinion, skin pigmentations are not rare side effects of amiodarone. The small number of cases reported is probably due to the fact that this side effect of amiodarone remains frequently unrecognized.

The side effect seems to be rather benign and does not necessitate the discontinuance of the medication.

REFERENCES

1. Hilleman D, Miller MA, Parker R, Doering P, Pieper JA. Optimal management of amiodarone therapy: efficacy and side effects. Pharmacotherapy 1998; 18: 138-45.

2. Rappersberger K, Honigsman H, Ortel B, Tanew A, Konrad K, Wolff K. Photosensitivity and hyperpigmentation in amiodarone-treated patient: incidence, time course and recovery. J Invest Dermatol 1989; 93: 201-109.

3. Butany J, Downar E, Hanna W. Ultrastructural findings in patients on long-term amiodarone treatment. Lab Invest 1983; 48: 12A

4. Kounis NG, Frangides C, Papadaki PJ, Zavras GM, Goudevenos J. Dose-dependent appearance and disappearance of amiodarone-induced skin pigmentation. Clin Cardiol 1996; 19: 592-4.

5. Zachary CB, Slater DN, Holt DW, Storey GCA, Macdonald DM. The pathogenesis of amiodarone-induced pigmentation and photosensitivity. Br J Dermatol 1984; 110: 451- 6.

6. Ammann R, Braatthen LR. Amiodarone-Pigmentierung. Hautarzt 1996; 47 : 930-1.

7. Lullman H, Lullman-Rauch R, Wassermann O. Commentary: lipidosis induced by amphiphilc cationic drugs. In: Biochemical pharmacology. London: Pergamon Press, 1978; 1103-8. (Vol. 27)

8. Hass N, Schadendorf D, Hermes B, Henz BM. Hypomelanosis due to block of melanosomal maturation in amiodarone-induced hyperpigmentation. Arch Dermatol 2001; 137 (4).

9. Adams PC, Holt DW, Storey GCA, Morley AR, Callaghan J, Campbell. Amiodarone and its desethyl metabolite: tissue distribution and morphologic changes during long-term therapy. Pharmacology 1985; 72(5): 1064-75

10. Karrer S, Hohenleutner U, Szemies RM. Amiodarone-induced pigmentation resolves after treatment with the Q-switched ruby laser. Arch Dermatol 1999; 135 (3): 251-3.

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