Pseudocyanotic pigmentation of the skin induced by amiodarone: a light and electron microscopic study

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Summary: An unusual bluish discolouration of the nose was noticed in a woman 9 months after she had begun treatment with a coronary vasodilator, amiodarone hydrochloride. Cutaneous biopsies of the nose were obtained 6 and 9 months later for light and electron microscopic studies. In the dermis were histiocytes containing cytoplasmic yellow-brown granules with histochemical properties of melanin and lipofuscin. Ultrastructurally the granules appeared as lysosomal membrane-bound dense bodies similar to lipofuscin. Similar granules were observed at diascopy in both corneas. The pathogenesis is obscure. A storage disease involving the drug or its metabolites cannot be ruled out. Another possibility is that amiodarone accelerates the normal cellular autophagocytosis, resulting in increased production of lipofuscin, which then accumulates in lysosomes because of a deficiency in lipolytic enzymes.

Résumé: Neuf mois après le commencement d'un traitement continu au chlorhydrate d'amiodarone, un vasodilatateur coronarien, une femme a remarqué une coloration bleutée de son nez. Des biopsies furent pratiquées 6 et 9 mois plus tard pour étude au microscope optique et électronique. Il y avait dans le derme des amas d'histiocytes contenant des granules jaunâtres dont les caractéristiques histochimiques étaient celles de la mélanine et de la lipofuscine. En ultrastructure ces granules consistaient en des corps denses de nature lysosomiale et correspondaient à de la lipofuscine. On a également observé des granules semblables dans les deux cornées en diascopie. La pathogénie est inconnue. On ne peut exclure une maladie de surcharge du médicament ou ses métabolites. Il se pourrait également que l'amiodarone accélère les processus d'autophagocytose entraînant une formation exagérée de lipofuscine qui s'accumulerait dans les lysosomes par déficit possible en enzymes lipolytiques.

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Amiodarone hydrochloride, a coronary vasodilator, was introduced in Europe in 1964 and has been widely used, particularly in Belgium, France and the Netherlands, in the treatment of coronary insufficiency. In 1968 a Belgian ophthalmologist, François,[1] observed a peculiar yellow-brown granular pigmentation in the cornea of patients treated with amiodarone, and he called the condition "cornea verticillata". Subsequently other ophthalmologists reported identical findings in their patients.[2-4]

The first electron microscopic study of the pigment deposits in the cornea was that of Toussaint and Pohl[3] in 1969. They described numerous lysosomal inclusions, most probably lipofuscin, in the cytoplasm of the basal and intermediary cells of the cornea.

Barchewitz, Laurent and Jamaer[5] studied the histochemical properties of the pigment deposits in various organs of different animals after long-term administration of high doses of amiodarone, and showed that the pigment consisted mainly of melanin and, to a smaller extent, lipofuscin.

In 1971 a Belgian group[6] reported for the first time a grey-blue (pseudocyanotic) colouration of the face and the other areas of the skin exposed to light in three patients receiving amiodarone. At about the same time an increasing number of similar observations appeared in the European literature.[7-15] All the authors described yellow-brown granules in the cytoplasm of histiocytes in the dermis of the affected areas. Electron microscopic studies of the cutaneous pigment were done by Geerts[11] in 1971 and by Morand *et al*[12] and Vos *et al*[14] in 1972. Membrane-bound dense bodies, believed to be lipofuscin, were detected in the cytoplasm of dermal histiocytes. The pathogenesis of the condition is poorly understood.

In this paper we present the histochemical, histologic and electron microscopic findings in a case of pseudocyanotic pigmentation of the face in a patient treated with amiodarone hydrochloride. To our knowledge this is the first North American report of this condition.

Case report

A 54-year-old white woman presented to the dermatology clinic of l'Hôtel-Dieu Hospital with a 6-month history of a bluish discolouration of her nose.

The grey-blue pigmentation was limited to the lower half of the nose and the alae nasi. The perioral area and the wrinkles and folds of the face were spared, thus ruling out cyanosis. Diascopy revealed violet granules in the discoloured areas. The results of the remainder of the physical examination were normal and all laboratory data were within normal limits. An ophthalmologic examination, however, revealed small, brown granular deposits on the caruncles and at the peripheral margin of both corneas. Similar deposits were also present on the free margin of the right superior lid and on both inferior lids. The fundus was normal and there was no impairment of vision.

It was then learned that the patient had been taking amiodarone hydrochloride for coronary insufficiency while living in Europe. She had taken the drug for 15 months (August 1971 to November 1972) at a daily dose of 200 to 400 mg. She first noticed the bluish pigmentation after 9 months of this treatment. Six months later a skin biopsy of the nose was done and the medication discontinued. A second biopsy of the nose was obtained 3 months later for electron microscopic study. As of April 1974, 17 months after amiodarone was discontinued, the blue pigmentation had not disappeared.

Microscopic studies

Material and methods

Light microscopy: A cutaneous biopsy of the nose was obtained in November 1972 with a 2-mm punch. It was fixed in formalin 10%, embedded in paraffin and sections stained with hematoxylin-eosin and saffron (HES), periodic acid-Schiff reagent (PAS) for mucopolysaccharides, Turnbull blue for ferrous iron, Fontana's silver (8 and 18 hours) for melanin, and Ziehl-Neelsen acid-fast stain for lipoproteins. (Fontana's stain is not specific for melanin; lipofuscin can also reduce ammoniacal silver nitrate at 8 and 18 hours.)

Electron microscopy: The tissue from the second biopsy of the nose (February 1973) was fixed in ice-cold 4% glutaraldehyde solution in phosphate buffer at pH 7.3. After being washed overnight with phosphate buffer and a solution of 0.2 M sucrose the blocks were postfixed in ice-cold buffered 1% osmium tetroxide. The tissue was then dehydrated and embedded in Epon 812. Sections were cut on a Reichert OM U2 microtome (C. Reichert, American Optical Corporation, Buffalo, New York), stained with uranyl acetate and lead citrate and examined on a Zeiss EM 9A electron microscope (Carl Zeiss, Inc., Chicago) at 60 kV.

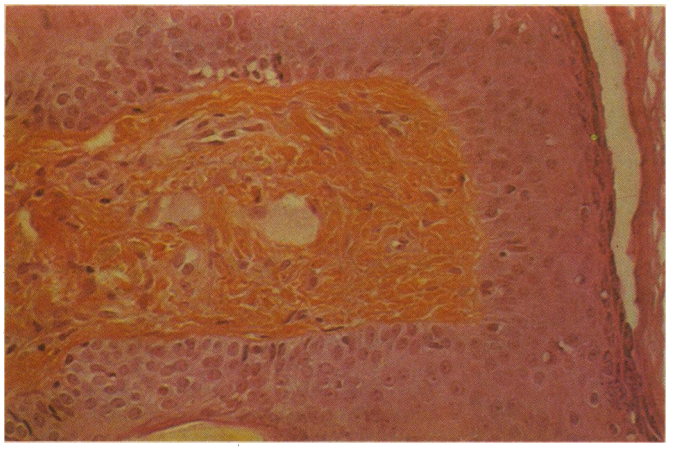

FIG. 1—Papillary dermis contains a few histiocytes with yellow-brown granules in cytoplasm (hematoxylin-eosin-saffron: enlarged 2½ times from x250).

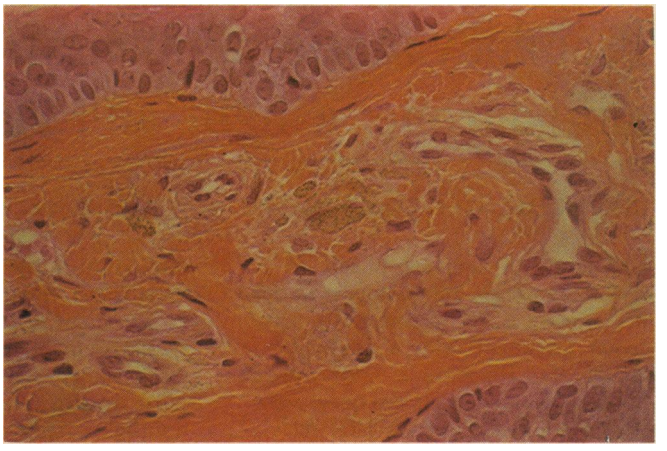

FIG. 2—High-power view of pigment-laden histiocytes in superficial dermis (hematoxylin-eosin-saffron; enlarged 2½ times from x400).

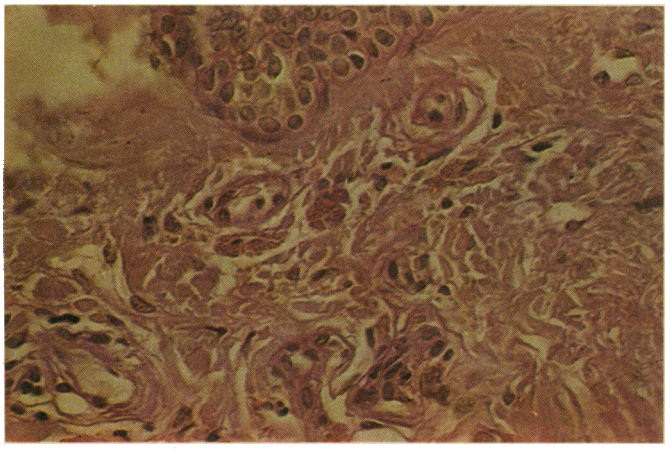

FIG. 3—Dermal histiocytes:. cytoplasmic pigment granules moderately positive for PAS stain (enlarged 2½ times from x250).

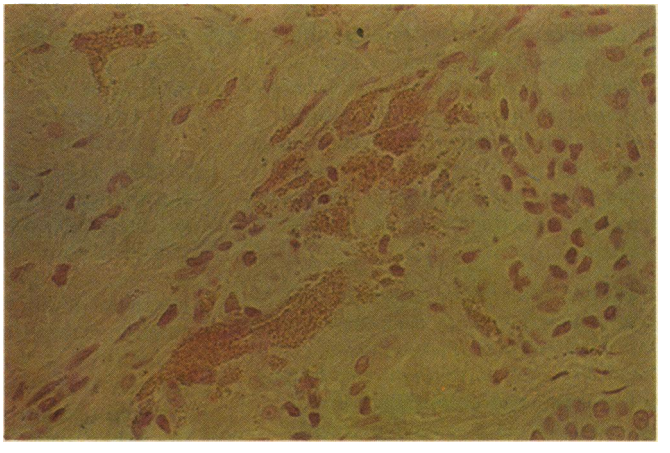

FIG. 4—Dermal histiocytes: cytoplasmic pigment granules negative for Turnbull blue stain (enlarged 2½ times from x250).

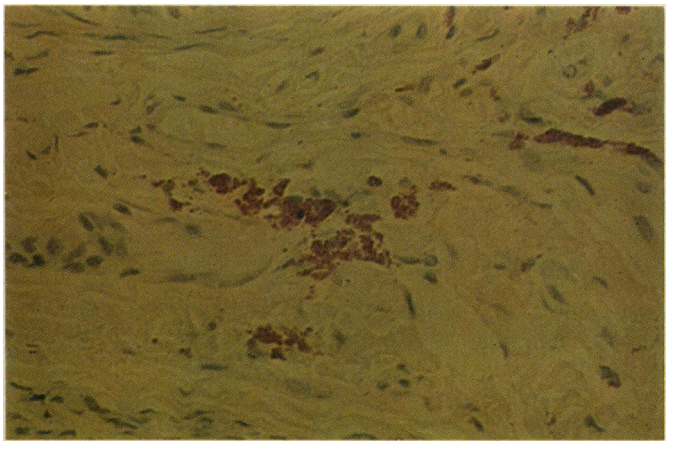

FIG. 5—Dermal histiocytes: cytoplasmic pigment granules strongly positive for Ziehl-Neelsen stain (enlarged 2½ times from x250).

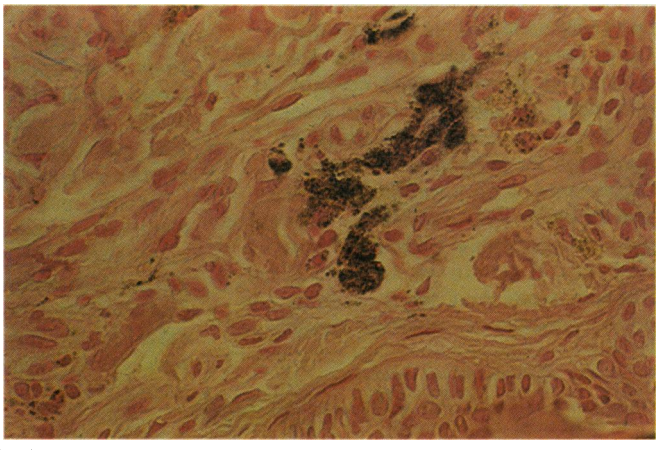

FIG. 6—Dermal histiocytes: cytoplasmic pigment granules strongly positive for Fontana's silver stain (18 hours) (enlarged 2½ times from x400).

Results

Light microscopic findings: The epidermis was normal. Sections stained with HES showed in the midportion of the dermis a small number of histiocytes with conspicuous aggregates of a finely granular yellow-brown pigment in their cytoplasm. These pigment-laden histiocytes were often located around capillaries. The inflammatory response was minimal (Figs. 1 and 2). The pigment was slightly to moderately positive for PAS (Fig. 3), negative for Turnbull blue (Fig. 4) and strongly positive for Ziehl-Neelsen (Fig. 5) and for both 8- and 18-hour Fontana's stain (Fig. 6).

Electron microscopic findings: The dermal histiocytes, scattered among bundles of collagen, were large, fusiform or roughly polygonal, and many had long cytoplasmic processes. The nuclei were elongated or spheroid and had a dense chromatin network. Within the abundant cytoplasm were numerous dense bodies (diameter, 250 to 2500 nm) composed of dense, slightly granular osmiophilic material within a single membrane (Fig. 7). Between the membrane and the electron-dense material a clear halo could sometimes be seen. Most of these dense bodies varied little in shape or content but occasionally the membrane-bound material was vacuolar and remnants of cytoplasmic organelles could be seen (Fig. 8). Pseudomyelinic figures were rarely observed. Other cytoplasmic organelles (mitochondria, free ribosomes, short profiles of rough endoplasmic reticulum) varied in number from cell to cell and did not show any distinct abnormalities.

Discussion

The reported frequency of corneal and dermal pigmentation associated with amiodarone therapy varies greatly, from very low[6,12] or low[7,9] to very high.[2,4] Babel and Stangos[4] found granular pigmentation of the cornea in 25 of 33 patients (76%), whereas Morand and colleagues[12] recorded only three cases in 45 patients (7%).

On the other hand, most authors agree on the direct relation of dosage and duration of amiodarone therapy with appearance of both corneal and cutaneous pigmentation. Long-term administration of moderately high doses — from 400 to 800 mg daily — seems necessary to produce the condition; the therapeutic dosage is about 400 mg daily. Here again controversy exists because pigmentation of the cornea has been discovered as early as the 13th[1] or 20th[2] day of therapy; in contrast, the granular deposits in the skin are usually observed later, from 6 to 39 months after onset of therapy.[6-9,11,12] In most cases the cutaneous lesions are preceded by a photosensitivity reaction on the areas of the skin exposed to light.[6-9,11-14]

Discontinuation of therapy seems to be followed by slow disappearance of the pigment granules from the cornea:[1-4] in all the patients of Facquet *et al*[2] the corneal granules had completely disappeared between 1 and 5 months after amiodarone therapy was stopped. In general the cutaneous bluish discolouration progressively fades after many months,[6,9,10,12] but it may persist for more than a year, as in our patient.

Results of histochemical and electron microscopic studies of the pigment granules in epithelial cells of the cornea and the cytoplasm of histiocytes in the dermis suggest that the pigment is a substance closely related to the lipofuscins.[3,6,10-15] All electron microscopic studies have shown highly osmiophilic dense bodies within a single membrane, which are probably lysosomal.[3,11,12,14] Geerts[11] obtained a positive acid phosphatase reaction and concluded that the pigment granules were lysosomes. He described in the cytoplasm of dermal histiocytes several types of lysosomal structures, from clear vesicles to myelinic figures, and dark, electron-dense bodies most probably representing different stages of lipofuscin accumulation. Our ultrastructural findings are in accord with those of Geerts,[11] Morand *et al*[12] and Vos *et al*[14]. We saw very few vacuolar or myelinic structures; most of the membrane-bound inclusions consisted of highly osmiophilic, electron-dense bodies of homogeneous or slightly granular appearance. These bodies could represent the end stage of lipofuscin accumulation since the biopsy for electron microscopy was obtained 18 months after the patient had begun amiodarone therapy; had the biopsy been taken earlier in the course of treatment, such vacuolar inclusions as those described by Geerts might have been seen.

How pigment is deposited in the epithelial cells of the cornea and in histiocytes of the dermis is poorly understood. This deposition is possibly the main feature of a storage disease due to accumulation of amiodarone or its metabolites in the tissue.[1,3,8,9] The molecule of amiodarone contains two atoms of iodine and in some patients receiving amiodarone the iodine content of the skin is increased.[11] Many authors have pointed out the analogy between amiodarone pigmentation and other drug-induced pigmentation disorders, such as those associated with chloroquine[16-19] and phenothiazine therapy,[20,21] in which pigment deposits may be observed in the cornea and in the skin. In the latter two conditions there appears to be a disorder in the metabolism of melanin. In amiodarone-related pigmentation the disorder does not seem to involve melanogenesis; the membrane-bound dense bodies are most likely lysosomal structures and the osmiophilic material is probably lipofuscin. Fréour and colleagues[10] have pointed out that the chemical composition of lipofuscins has nothing in common with that of amiodarone and it is probably not the drug itself

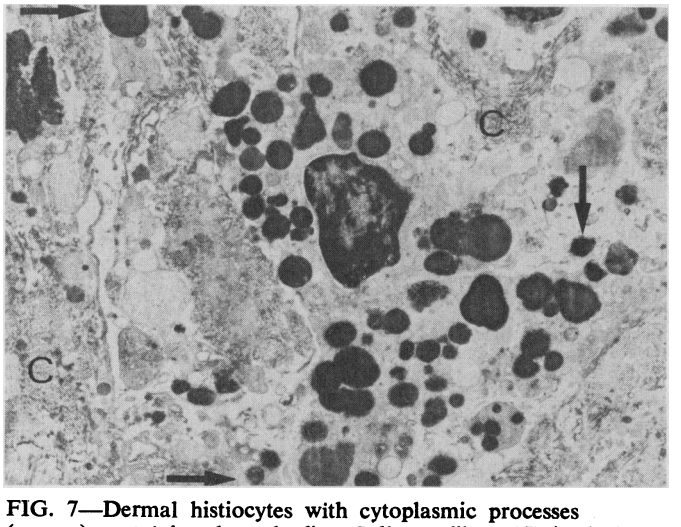

FIG. 7—Dermal histiocytes with cytoplasmic processes (arrows) containing dense bodies. Collagen fibers (C) (x3600).

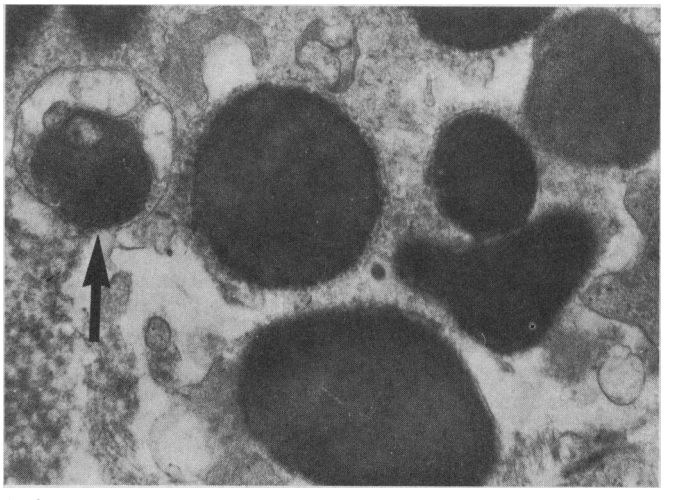

FIG. 8—Higher magnification of Fig. 7, showing dense bodies within single membrane. Most bodies are electron-dense (x18 000).

that accumulates in the histiocytes of the dermis. Possibly amiodarone accelerates the normal cellular autophagocytosis, with increased formation of wear and tear pigments (lipofuscins); moreover, these pigments could accumulate in lysosomes because of a deficiency in lipolytic enzymes.[10,11] This concept of an enzyme failure would relate amiodarone-induced pigmentation to such disorders as Fabry's disease, in which a deficiency in ceramide trihexosidase results in the accumulation of glycolipids in lysosomes in various tissues.[22,23]

This enzymatic deficiency would explain why the unusual corneal or skin pigmentation does not develop in all patients receiving amiodarone. This theory remains to be proved.

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ANNUAL MEETING, AMBULATORY PEDIATRICS ASSOCIATION. Royal York Hotel, Toronto. June 9-10, 1975. Information: Dr. George D. Comerci, Department of pediatrics, University of Arizona college of medicine, Tucson, AZ 85724, USA

PEDOAUDIOLOGY. Kingston. Symposium: June 9, 1975. Workshop: June 9-13 (basic course in school and public health settings; advanced course in audiology department of Kingston General Hospital). Sponsored by department of otolaryngology of Queen's University and The Sir James Whitney School and Regional Resource Centre for the Hearing Handicapped, Belleville, Ont. Information: Mrs. Mary Robinson, Department of audiology, Kingston General Hospital, Kingston, Ont. K7L 2V7

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