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Catecholamine-induced Cardiomyopathy in Multiple Endocrine Neoplasia*

A Histologic, Ultrastructural, and Biochemical Study

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A catecholamine-induced dilated cardiomyopathy is reported in a patient with multiple endocrine neoplasia, type 3. A histologic and ultrastructural study has been undertaken in cardiac biopsy samples, together with determination of myocardial Ca^{++} and cellular membrane fatty acids. Contraction band necrosis of cardiocytes with supercontraction of sarcomeres progressing to myofibrolysis and increased levels of myocardial Ca^{++} have been found as morphologic and biochemical abnormalities, respectively. No lipoperoxidation of cellular membranes or an α-adrenergic mediated reduction of coronary supply could be recognized in the study. We indicate a receptor-mediated intracellular Ca^{++} overload as the main abnormality responsible for myocardial impairment.

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LVED = left ventricular end-diastolic; LVEF = left ventricular ejection fraction; dw = dry weight

Cardiovascular manifestations of catecholamine overproduction, as occurs in pheochromocytoma, include hypertension, possibly with ST-segment deflection and T-wave inversion[1] and supraventricular or ventricular tachyarrhythmyas (or both). When this last condition occurs, the echocardiogram usually shows LV hypertrophy with normal LV function.[2] Occasionally, patients with pheochromocytoma present with manifestations of dilated cardiomyopathy,[3] which may be reversed when the tumor is removed.[4] The pathogenesis of this cardiomyopathy is poorly understood; there are only a few clinical reports in the literature, and no study exists which correlates morphologic and biochemical changes with myocardial clinical damage.

The pathogenesis of the damage induced by catecholamine overproduction may be enlightened by two basic recent achievements. First, catecholamines are known to exert a receptor-mediated effect on myocardiocytes, which triggers a phosphorylation cascade dependent on inositol metabolites.[5] Ultimately, two main cell functions are activated: (1) the opening of sarcolemma and sarcoplasmic reticulum Ca^{++} channels; and (2) an increase of peroxidative and lipoperoxidative metabolism.[6] Secondly, early irreversible myocardial injury, described in detail as contraction band necrosis with the electron microscope,[7] has been correlated with an impairment of cytosolic Ca^{++} homeostasis in various experimental models and in patients who died as a result of pheochromocytoma.[8] Both the opening of Ca^{++} channels and the lipoperoxidative damage of membranes may explain the impairment of cytosolic Ca^{++} homeostasis and then myocardial necrosis.

In this report, we have studied a patient with multiple endocrine neoplasia, type 3, presenting with a severe dilated cardiomyopathy associated with catecholamine overproduction. Histologic and ultrastructural observations, myocardial Ca^{++} measurement, and determination of the lipid pattern of cell membranes have been performed on biopsy samples and correlated with clinical features to ascertain the pathogenesis of the damage.

Case Report

A 33-year-old man was admitted because of dyspnea on effort. He had suffered since childhood with dilatation of the stomach, megacolon, and bilateral megaloureter. At the age of 18 years, he had undergone left hemithyroidectomy because of a tumor. In the previous two years, he had developed a moderate hypertension, which was controlled by diuretics and serum converting enzyme inhibitors. At the time of admission, physical examination revealed a tall, slender, and hypotonic patient with enlarged and nodular lips; multiple neuromatous nodules were present in the tongue and in the labial mucosa. Palpation of the neck revealed a thyroid lump localized on the right lobe. Cardiac auscultation revealed a gallop rhythm (120 beats per minute) unaccompanied by murmurs.

Blood pressure measured 160/110 mm Hg. The ECG showed sinus rhythm; there was left ventricular hypertrophy (SVI + RV5 = 85 mm) with strain (ST deflection and asymmetric negative T wave in leads D1, aVL, V_5, and V_6). The chest x-ray film revealed enlargement of the cardiac silhouette due to prominence of the left-sided chambers. A 2D echocardiogram showed mild dilatation of the left atrium (internal end-diastolic diameter, 44 mm) and remarkable dilatation of the left ventricle (LVED diameter, 68 mm) with diffuse reduction of LV contractility (LVEF, 0.30).

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Chemical analysis revealed mild renal failure (creatinine clearance, 45 ml/min), while levels of serum electrolytes, BUN, and creatininemia were in the normal range.

Analysis of the blood showed leukocytosis (16,980/cu mm), with 76 percent neutrophils and thrombocytosis (776,000/cu mm). A screening test for hypertension revealed an abnormal increase of urinary catecholamines (181 mg/24 h; normal, 5 to 60 mg/24 h), as well as vanillylmandelic acid (23.5 mg/24 h; normal, 2 to 7 mg/24 h), suggesting the presence of a pheochromocytoma. A CT scan confirmed the presence of a 4×4-cm mass on the right adrenal gland and a 6×4-cm mass on the left one.

The thyroid lump was investigated by needle biopsy, and a medullary carcinoma was diagnosed. Increased levels of carcinoembryonic antigen (118.8 ng/ml; normal, 0 to 5 ng/ml) and as calcitonin (3,800 pg/ml; normal, 0 to 100 pg/ml) were found in the serum. A total-body scan with dimethyl-mercapto-succinic acid failed to show metastatic localization.

Heart muscle impairment was investigated by cardiac catheterization and angiography. Increased LVED pressure (22 mm Hg) and pulmonary pressure (45/20 mm Hg) were found, with appreciable LV dilatation and hypokinesia. Both coronary arteries and cardiac valves were normal. Catheterization was followed by a LV endomyocardial biopsy, with the extraction of five fragments which were processed for histology and electron microscopy. Material was also made available for determination of myocardial Ca^{++} and cardiac cell membrane fatty acids, to be described later.

Due to the association in our patient of multiple mucosal neuromas of the gastrointestinal tract, together with medullary carcinoma of the thyroid and bilateral pheochromocytomas, the diagnosis of multiple endocrine neoplasia, type 3, was made, and the patient was submitted to surgery for removal of residual thyroid and of the adrenal glands. This intervention was well tolerated and was followed by administration of hormonal substituting therapy, specifically thyroxine (150 μg daily), hydrocortisone (50 mg daily), and fludrocortisone (0.2 mg daily).

The evolution of catecholamine-induced myocardial impairment was evaluated at 6, 12, and 16 months by ECGs and 2D echocardiograms. The last follow-up showed reduction of ECG criteria of LV hypertrophy (SV1 + RV5 = 65 mm) and of LV strain (mild hammocking of the ST segment in leads D1, aVL, and V_6). The 2D echocardiogram registered a reduced LVED diameter (from 68 to 60 mm), with partial recovery of LVEF (from 0.30 to 0.44).

Morphologic Study

At histology, hypertrophy with contraction band necrosis of myocardial fibers was evident (Fig 1). Only a few inflammatory cells were observed, localized around severely injured myocardiocytes and suggesting a reactive phenomenon to cell necrosis, rather than a primary myocarditic process. Widening of the interstitium was also present due to an increase of connective fibrous tissue, as well as some areas of fibrous replacement. Seven normal arterioles were included in our specimens; none of them had luminal reduction or thickening of the muscular coat, as is present in contracted walls.

At transmission electron microscopy, a complete study of divided endomyocardial biopsy samples was done. Myocardial cells showed varying degrees of disorganization, depending on the severity of the contracture. In particular, identifiable shortening of the sarcomeres (of which the maximum was up to half the length of a normally contracted sarcomere) (Fig 2), disappearance of M-lines, progressive disorganization of Z-lines, and final loss of vectorial filament organization were also seen (Fig 3).

FIGURE 1. Catecholamine-induced dilated cardiomyopathy in multiple endocrine neoplasia, type 3. Contraction band necrosis of myocardiocytes with foci of inflammatory reaction *(arrows)* are seen (hematoxylin-eosin, original magnification ×250).

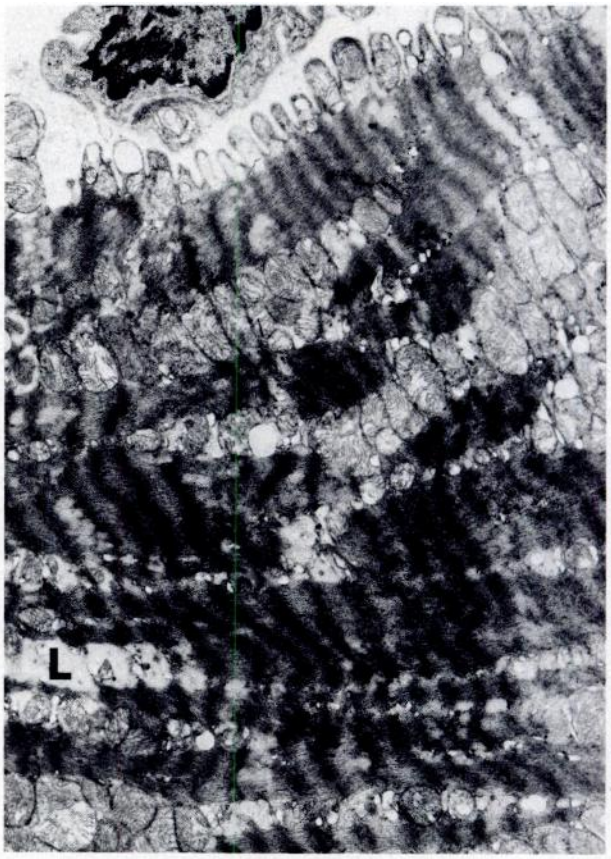

FIGURE 2. Supercontraction of sarcomeres associated with intracellular Ca^{++} overload and progressing focally to myofibrolysis (L).

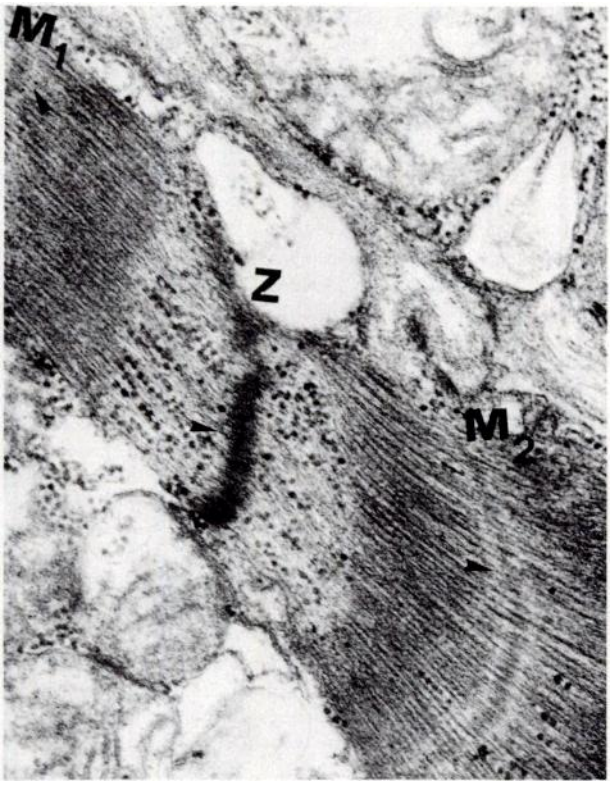

FIGURE 3. Detail of contraction bands that suggests mechanism of damage produced by supercontraction. Two hypercontracted hemisarcomeres delimited by arrows (Z-M1)(Z-M2) are shown. Between them, initial myofibrolysis is evident.

Comparative histologic and morphometric studies with three fragments of tetralogy of Fallot, drawn surgically from the right ventricular outflow, were undertaken. The histology of control samples showed moderately hypertrophied myocardial fibers, mostly in regular alignment. Their average thickening at the nuclear level and with magnification of 400× was 24.5μ, vs 60.9μ of myocardiocytes of the patient with multiple endocrine neoplasia. The interstitium and arterioles observed in control samples were unremarkable.

Biochemical Analysis

Myocardial Ca^{++} has been determined in a biopsy fragment of 1.8 mg w/w by atomic absorption spectrophotometry after overnight drying at 90°C, acid extraction (1N HNO_3), and addition of 1 percent $LaCl_3$. As a control, five samples of similar weight were taken during surgery for tetralogy of Fallot. The value of myocardial calcium observed in our patient (82 nM/mg dw) was higher than the second SD in the control group (mean ± SD = 39.8 ± 8/mg dw; 2nd SD = 52.1/mg dw).

Analysis of fatty acids of cardiac cell membranes has been obtained in 2.2 mg w/w biopsy sample by gas chromatography and compared with three surgical control samples from a patient with tetralogy of Fallot. This method included tissue homogenization, lipid extraction by chlorophormium-methanol (2:1), filtration, and transesterification by BF3. Fatty acids were not different in the sample from multiple endocrine neoplasia (stearate, 0.134 nmol/mg of protein; palmitate, 0.363 nmol/mg of protein) compared with controls (stearate, 0.140 ± 0.005 nmol/mg of protein; palmitate, 0.360 ± 0.010 nmol/mg of protein).

DISCUSSION

Bilateral pheochromocytomas have been observed in a patient with medullary thyroid carcinoma and mucosal neuromatosis of the tongue, stomach, and colon (megacolon), which is the typical configuration of multiple endocrine neoplasia, type 3.[9] The major cardiovascular feature was a catecholamine-induced dilated cardiomyopathy, which is rare and has not been previously described in multiple endocrine neoplasia, type 3. At light microscopy, myocardial biopsy samples showed hypertrophy, with contraction band necrosis of myocardiocytes and a moderate inflammatory reaction, mainly due to macrophages and fibroblasts (Fig 1). This pattern does not meet the morphologic criteria for myocarditis, as recently defined.[10] The increase of interstitial fibrous tissue as well as the areas of fibrous replacement suggest a reparative process, which also explains the incomplete recovery of cardiac function, even several months after tumor removal; however, a case of complete recovery has been recently reported,[4] indicating that the substitution of viable myocardium must have been less extensive; unfortunately, no morphologic studies were reported in this article.

The coronary network has been evaluated through coronary angiography and light microscopy of intramyocardial arterioles. Although a direct measurement of coronary blood flow was not obtained, we failed to document abnormalities of the main coronaries, as well as thickening of intimal and medial layers of intramyocardial arterioles. This seems in contrast with some animal studies which ascribe a major role to α-adrenergic mediated coronary constriction[11] in the pathogenesis of catecholamine cardiomyopathy.

In particular, such a long-term stimulation of the coronary smooth muscle should have induced in the intramural arterioles a hypertrophic reaction, which is totally lacking in our patient. This suggests that reduction in coronary blood flow may have a minor role, if any, in the pathogenesis of catecholamine-associated myocardial damage in man.

At electron microscopy, most of myocardiocytes showed all stages of supercontraction of sarcomeres (Fig 2 and 3), previously described in isolated myocardiocytes and induced by high cytosolic Ca^{++} levels.[7] Such changes are considered sequential events leading to irreversible disorganization and myocardial cell death, and many experimental evidences suggest that most of the steps are dependent on cytosolic Ca^{++} and energy supply, that are similar to that of the physiologic contraction. Determination of total calcium in biopsy tissue sample showed a net increase when compared with normal myocardium from surgical samples of tetralogy of Fallot. This further suggests a key role of Ca^{++} also in myocardiopathy associated with catecholamine overproduction; however, there is no agreement on what is the Ca^{++} dependent function that is responsible for cell disor-

ganization. Calcium may accumulate in mitochondria as fluffy, dense precipitates, impairing energy metabolism; but only occasionally are mitochondria disorganized or damaged. The Ca^{++} may activate lysosomes or neutral proteases, which may explain the injury of proteinaceous supramolecular structures, such as microfilaments, anchoring blocks, or membranes; however, in various experimental models, this has been shown to be a late event in the disorganizing sequence. Finally, Ca^{++} may trigger a strong activation of lipoperoxidative metabolism, giving rise to a diffuse membrane damage which further impairs the cytosolic Ca^{++} homeostasis. To test this possibility, we have studied the lipid pattern in membranes isolated from biopsy specimens from our patient and, as a control, from surgical samples from a patient with tetralogy of Fallot. We failed to find any difference between the two samples, indicating that lipoperoxidation also is of minor significance in the necrotic disorganization associated with catecholamine overproduction.

In conclusion multiple endocrine neoplasia, type 3, although very rare, can be accompanied by a catecholamine-induced dilated cardiomyopathy. This entity, at least partially reversible after removal of the pheochromocytoma, is characterized by contraction band necrosis of cardiocytes on histology and supercontraction of sarcomeres on electron microscopy. A receptor-mediated intracellular Ca^{++} overload seems to be the main biochemical abnormality responsible for myocardial impairment.

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