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Case report

Primary lipid cardiomyopathy

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Summary. In this communication, we describe an isolated, apparently congenital cardiomyopathy (CMP) characterized by the accumulation of stainable lipid in mitochondria of cardiomyocytes. This lesion, which we term primary lipid cardiomyopathy, has not been reported so far. The structural alteration was associated with progressive heart failure, leading to death at the age of 3 years, and with massive hypertrophy of myocardium. Lipid storage in heart muscle cells resulted in an impressive yellow to orange color of the myocardium. We suggest that this type of primary CMP may represent a new member within the group of mitochondrial CMPs. Possible pathogenic mechanisms are discussed.

Key words: Cardiomyopathy – Lipid myopathy – Congenital heart disease

Introduction

Myocardial involvement is observed with many congenital and/or hereditary disorders (Table 1). With the exception of well-defined inborn errors of metabolism, the pathogenesis of many congenital cardiomyopathies (CMPs) is still largely unknown, and this also holds true for the wide array of congenital myopathies associated with myocardial disease. One group of congenital muscle disorders is characterized by the accumulation of lipids within myocytes (lipid storage myopathies or lipid myopathies; Table 2). Lipid droplets in muscle cells are, e.g., found in carnitine deficiency (Engel and Angelini 1973). In this disorder, myocardial involvement may occur (Vandyke et al. 1975; Hart et al. 1978). One type of lipid storage myopathy was found to be associated with hypertrophic CMP (Matsuishi et al. 1985). In this communication we report on an unusual, apparently congenital and isolated CMP characterized by the accumulation of lipid in cardiomyocytes, without involvement of skeletal muscle. This lesion, which we term lipid cardiomyopathy, has not, to our knowledge, been previously described.

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Case report

The postnatal development of this boy was normal up to the age of 2 years, when dyspnoea was noted, and a CMP was diagnosed (not further specified). At the age of 3 years the child suddenly became paretic (flaccid) on the right half of the body. Chest X ray showed marked cardiomegaly, and echocardiography showed large left heart cavities with reduced motility of the ventricle. Brain scintigraphy displayed an occlusion of the left medial cerebral artery with leptomeningeal shunt circuit. Routine laboratory investigations were normal, apart from a microcytic anaemia. Under treatment with steroids, diuretics and digitalis ventricular function improved. 5 months later, however, the boy developed severe dyspnoea, cyanosis, metabolic acidosis, and shock. The patient expired 2 h after admission. An autopsy was performed.

No myopathic disorders are knwon in the family of the patient. However, it is reported that the paternal grandfather died of "heart attack" at the age of 35 years.

Materials and methods

For light microscopy tissue was fixed with 4% buffered neutral formalin and samples were routinely processed (stains used: haematoxylin-eosin, PAS, Elastica-Van Gieson, Gomori's silver, Masson's trichrome, alcaline Alcian Blue, Turnbull's). Formaline-fixed tissue was also processed for frozen sections stained with Oil Red 0 and Sudan Black. For electron microscopy, small samples were fixed with 2.5% glutaraldehyde in cacodylate buffer, dehydrated, and embedded in Epon and Spurr's low viscosity medium. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined in a Zeiss EM 10 TEM. The postmortem interval for the material used was 1 day and 21 h.

Table 1. Congenital disorders associated with CMP

A) Non-mitochondrial disorders	
Central core disease	Shy and Magee 1956
Nemaline myopathy	Meier et al. 1983
Multicore myopathy	Magliocco et al. 1989
Autophagic vacuolar myopathy	Hart et al. 1987
Inclusion body CMPs	Fardeau et al. 1978; Porte et al. 1980; Osborn and Goebel 1983
Muscular dystrophies and Friedreich's ataxia	
Myotonic dystrophy	Ludatscher et al. 1978
Mucolipidosis type II	Schultz et al. 1987
Heteroglycanoses with CMP	Holmes et al. 1960; Karpati et al. 1969
Defect of cardiac phosphorylase kinase	Eishi et al. 1985
Glycogenosis types II and III	
B) Mitochondrial disorders (for reviews, see Busch et al. 1981; DiMauro et al. 1985; Carafoli and Romani 1985; Engel and Banker 1986)	
1. Structural mitochondrial disorders	
Toroconial myopathy	Mackay et al. 1976
Oncocytic CMP syndrome	Zimmermann et al. 1982; Franciosi and Singh 1988
X-linked mitochondrial CMP	Neustein et al. 1979
Idiopathic mitochondrial CMP	Hug and Schubert 1970
Mitochondrial CMP and myopathy	Hübner and Grantzow 1983
2. Metabolic mitochondrial disorders	
Carnitine deficiency	Engel and Angelini 1973
Defect of long-chain acyl-CoA dehydrogenase	Hale et al. 1985
CMPs with defects of the electron transport chain	Rimoldi et al. 1982; Moreadith et al. 1984; Papadimitriou et al. 1984; Zeviani et al. 1985; Müller-Höcker et al. 1986
3. Mitochondrial multisystem disorders	
Kearns-Sayre syndrome	Kearns and Sayre 1958
CMP, myopathy, cataract	Sengers et al. 1975; Sieverding et al. 1988
Mitochondrial encephalomyopathy with cardiac involvement	Oldfors et al. 1987
X-linked mitochondrial disease	Barth et al. 1983
Mitochondrial myopathy and CMP with neurodegenerative features	Bogousslavsky et al. 1982
MELAS syndrome with cardiac ininvolvement	Ihara et al. 1989
MERRF with cardiac involvement	Lombes et al. 1989

Table 2. LIPID storage myopathies (LSM)*

A) Associated with a known metabolic defect		
LSM in carnitine deficiency	CMP	Engel and Angelini 1973
LSM in complex I deficiency		Koga et al. 1988
LSM in cytochrome c oxidase deficiency		Oldfors et al. 1989
LSM in short-chain acyl-CoA dehydrogenase deficiency		Turnbull et al. 1984
LSM in glutaric aciduria type II		
Group 1 (with malformations)		Goodman et al. 1983
Group 2 (with fatty change)	CMP?	Goodman et al. 1982
Group 3 (late onset)		Di Donato et al. 1986
B) Defect unknown		
Chanarin's disease		Chanarin et al. 1975
Systemic triglyceride storage disease with CMP	CMP	Ibayashi et al. 1988
LSM with ichthyosis		Miranda et al. 1979
Familial idiopathic LSM		Snyder et al. 1982
Autosomal dominant lipid neuromyopathy		Askanas et al. 1985
CMP with short stature and LSM	CMP	Sengers et al. 1976
LSM		Jerusalem et al. 1975
Multisystemic (type 3) LSM		Radom et al. 1987
Dystrophic lipid myopathy		Carroll et al. 1986
Familial lipid myopathy		Kuntzer et al. 1987
LSM with scoliosis		Nogami et al. 1983

* CMP: associated with cardiomyopathy

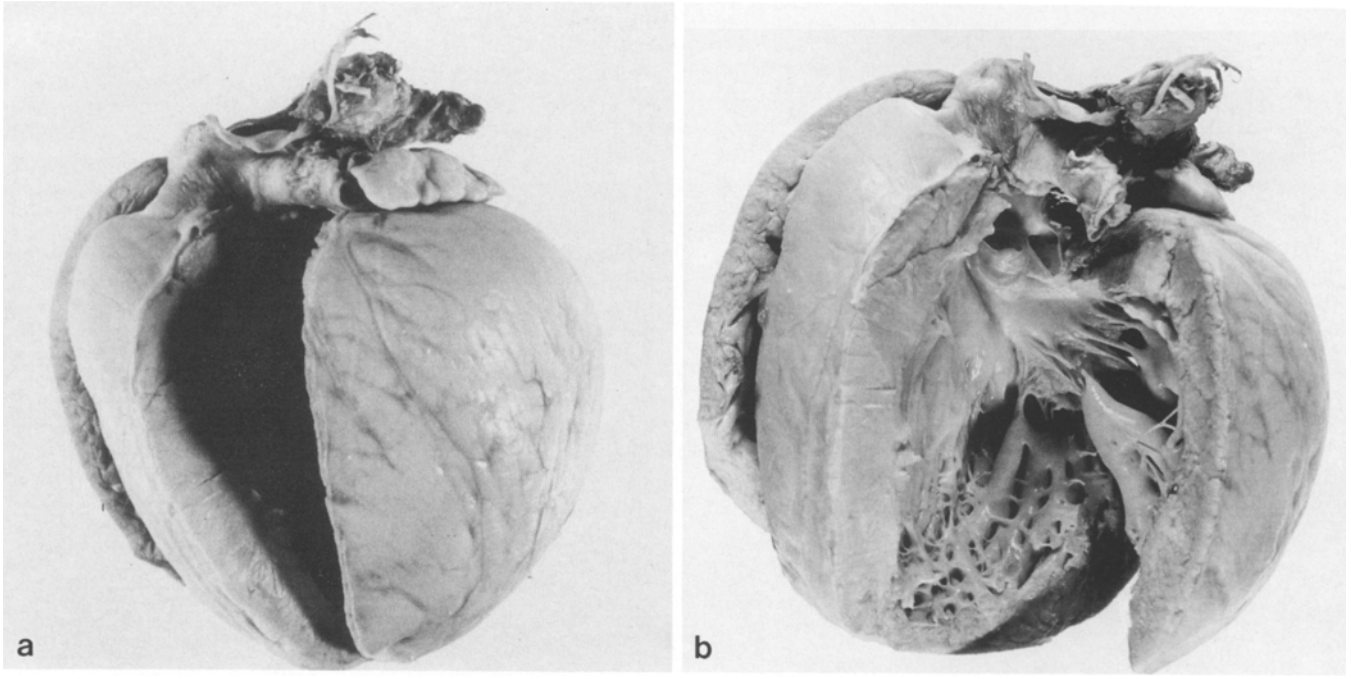

Fig. 1. a Anterolateral view of the left side of the heart. The left ventricle is opened close to the septum. There is massive hypertrophy of the left ventricle. In the fresh state, the heart displayed a yellow to orange color. **b** Part of the left ventricular wall has been turned out. Note the increased thickness of the wall and the prominent papillary muscles

Results

Gross findings

The main finding consisted of cardiomegaly (350 g) with an increased mass mainly of the left ventricle (left ventricular wall thickness: 15 mm; Fig. 1a and b). The valvular apparatus and the coronary vessels were normal. Interestingly, the myocardium exhibited a strongly yellow to orange color, slowly changing to a light yellow after long-standing fixation. After several weeks of fixation, the fixation fluid itself became yellowish and turbid, without microbial contamination, indicating the extraction of a hydrophobic substance. Additional organ findings consisted of acute pulmonary oedema, incipient pneumonia, and an old haemorrhage in the left frontotemporal leptomeninx. Skeletal muscles were not atrophic. Malformations were not seen.

Microscopy

On light microscopy cardiomyocytes contained polyploid nuclei as seen in hypertrophy and frequently showed cytoplasm with a granular structure and with numerous small vacuoles (Fig. 2). Many cytoplasmic lipid droplets were found in frozen sections of myocardium stained with Oil Red 0. Staining with Sudan Black and Alcian Blue gave negative results, whereas some of the granules were PAS positive. Stainable iron was not found, and there were neither infiltrates nor signs of fibrosis. Samples of skeletal muscles displayed a few atrophic fibers, but no myopathic changes. The brain showed no significant findings apart from an old leptomeningeal haemorrhage.

Notwithstanding the relatively long postmortem interval many cellular structures of cardiomyocytes could still be assessed electronmicroscopically. The major change consisted of numerous inclusions, already clearly visible at low magnification (Fig. 3). These spherical to pear-shaped bodies were associated with mitochondria and in contrast to typical cytoplasmic lipid droplets, they frequently contained a central zone of rather low electron density and an excentrically placed, crescent-like band of higher density (Fig. 4). At high resolution, part of the inclusions showed filamentous structures in their center, whereas the peripheral zone was more homogeneous. Mitochondrial cristae or parts thereof were never seen in these bodies, and paracristalline or tubular structures were not observed. However, even large inclusions were located within the mitochondrial profile. Cytoplasmic inclusions were not found at the ultrastructural level. Thus, it is reasonable to suggest that the mitochondrial bodies in fact correspond to the lipid inclusions seen with light microscopy.

Discussion

Clinically, this patient presented with severe heart failure, starting at the age of two years, leading to his death. This progressive disorder was due to an isolated CMP without associated functional or structural neuromuscular changes. Pathologically, this CMP is characterized

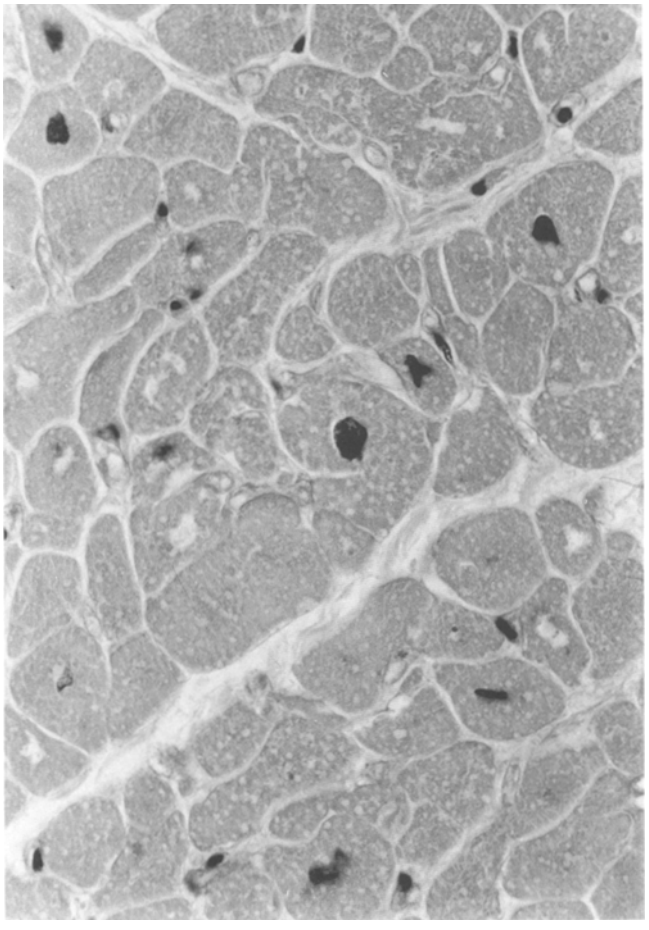

Fig. 2. Light microscopy of cross section of myocardium. Nuclei of myocytes are polyploid, typical for hypertrophic cells. The cytoplasm contains numerous small vacuoles (H and E stain)

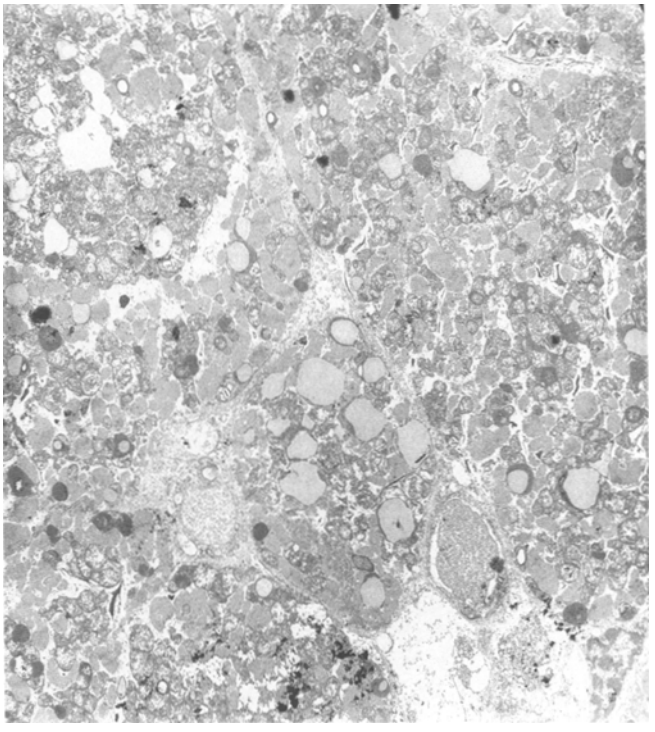

Fig. 3. Electron microscopy of cardiomyocytes. The cells contain numerous inclusions with a pale center and an electron-dense peripheral rim (5962:1)

by an impressive cardiomegaly, a striking yellow to orange color of the myocardium, numerous lipid droplets in the cardiomyocytes, and mitochondrial inclusions in these cells. As skeletal and visceral muscles were not involved, and the aetiology was not identified, we tentatively use the term primary lipid cardiomyopathy to describe this disorder.

Primary CMPs of infancy and childhood form a heterogeneous group. About a third may be attributed to defined metabolic disorders, and the remaining are regarded as primary non-obstructive CMPs, of which only a few have been adequately analyzed. Isolated and primary lipid cardiomyopathy has not yet been reported, as far as we know. In contrast, cardiac involvement has been described for myopathies associated with lipid deposition in cells of skeletal muscle (lipid myopathies, or lipid storage myopathies; Table 2). The different types of lipid myopathy with or without cardiac manifestations reported in the literature show that, where EM studies had been done, lipid deposits are located in the cytoplasm of myocytes, but not within organelles. In our patient, lipid-containing particles are structurally associated with a peculiar type of mitochondrial inclusion, thus relating this case to the large group of mitochondri-

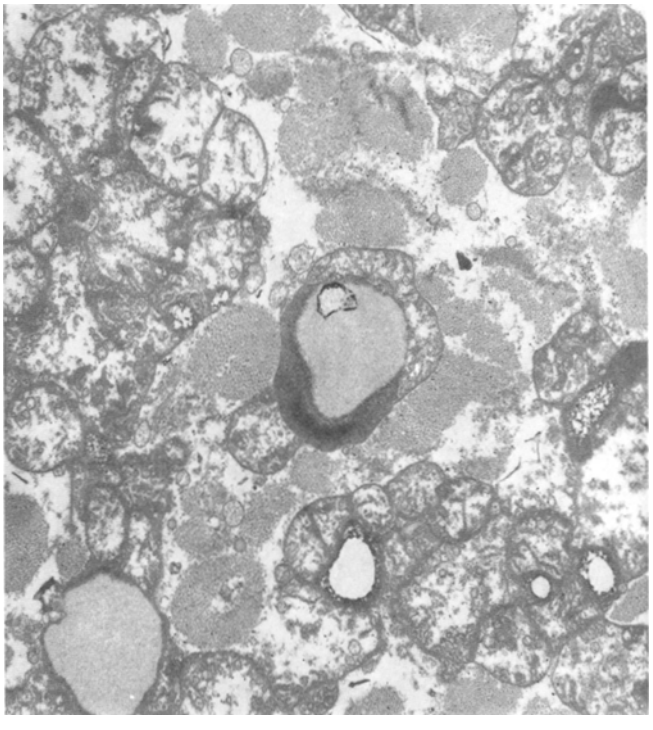

Fig. 4. Electron microscopy of a cardiomyocyte. It is seen that the pear-shaped inclusion visible in the center of the figure is associated with a mitochondrion. Note the excentrically placed, crescent-like dense part of the inclusion (16875:1)

al myopathies and mitochondrial CMPs (see Table 1). In fact, structural anomalies of myocardial mitochondria as an element of CMP have been observed and range from mitochondriosis (oncocytic or "histiocytic" CMP; Silver et al. 1980; Zimmermann et al. 1982; Franciosi and Singh 1988) to formation of giant mitochondria (Hug and Schubert 1970), and to a derangement of the inner mitochondrial compartment, in particular the cristae (Kearns and Sayre 1958; Lochner et al. 1981; Hübner and Grantzow 1983; Oldfors et al. 1987). The type of inclusion found in our patient does not correspond to organelle lesions seen in other mitochondrial CMPs, such as paracristalline structures, membrane whorls, or tubular transformation of cristae.

The development of lipid-containing inclusions in mitochondria, but not in the cytoplasmic matrix, is unusual. Cytoplasmic lipid droplets are seen in carnitine deficiency states, where long-chain acyl residues are not sufficiently transported into mitochondria, due to lack of the acyl transporter itself (carnitine) and accumulation of esterified fatty acids in the cytosol. Thus, intramitochondrial triglyceride deposits are not to be expected, and have not, in fact, been observed. Acyl residues entering the mitochondrial compartment via the carnitine pathway are metabolized through beta oxidation mediated by at least three acyl CoA dehydrogenases with overlapping affinities (Gregersen 1984). Defects of these enzymes have been described. A patient with deficiency of short-chain acyl CoA dehydrogenase and lipid myopathy has been reported, but she showed ultrastructurally normal mitochondria (Turnbull et al. 1984). Deficiency of the medium-chain acyl CoA dehydrogenase represents a life-threatening disorder with a phenotype similar to that of Reye's syndrome and associated with secondary carnitine deficiency (Roe et al. 1985; Allison et al. 1988). These two disorders and the multiple acyl CoA dehydrogenase defect (Rhead and Amendt 1984) do not fit the clinical and pathological findings in our patient. Mitochondrial anomalies, steatosis of the liver, muscular weakness and cardiomegaly have, however, been reported for the defect of long-chain acyl CoA dehydrogenase (Treem et al. 1986). Pathogenetically, this disease is characterized by a reduced beta oxidation of long chain fatty acids, intramitochondrial accumulation of potentially toxic intermediary products of acyl CoA, an increased omega oxidation, and secondary carnitine deficiency. It is claimed that incompletely metabolized acyl CoA residues may directly damage mitochondrial structures (Roe et al. 1985), and adeninnucleotide translocase, an enzyme important in the regulation of mitochondrial oxidative phosphorylation, may be inhibited by long-chain acyl CoA esters (Tager et al. 1983). Hallmarks of long-chain acyl CoA dehydrogenase deficiency, such as liver steatosis and myopathy, are not found in our patient. Nevertheless we suggest that this novel lipid CMP may be due to an isolated myocardial defect of mitochondrial fatty acid metabolism.

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