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Congenital "Histiocytoid" Cardiomyopathy: Evidence Suggesting a Developmental Disorder of the Purkinje Cell System of the Heart

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Summary. The so-called "histiocytoid cardiomyopathy" is an unusual cardiac disorder of infancy and childhood, characterized by the presence of numerous foamy, lipid-containing cells between the endocardium and the striated myocardial cells of the left ventricle and the interventricular septum. The disease usually affects females, the clinical picture being dominated by severe disturbances of conduction.

The original designations of the disorder stem from the morphological resemblance of the foamy cells to lipid-laden histiocytes. However, subsequent investigations have shown these cells to contain myofibrils interposed with Z lines. It has, therefore, been suspected that the leading cell population might be related to the myocardium.

Using a histochemical method for the demonstration of cholinesterase activity in the foamy cells, we present evidence that "histiocytoid" cardiomyopathy may in fact correspond to a maldevelopment of the Purkinje cell system of the heart.

Key words: Histiocytoid cardiomyopathy – Purkinje cells

"Histiocytoid cardiomyopathy" is a rare cardiac disorder of infancy and childhood, chiefly characterized by a peculiar change of subendocardial cells (Reid et al. 1968). The typical lesion consists of groups of large, foamy cells (so-called arachnocytes) between the endocardial lining and the striated muscle cells of ventricles and papillary muscles, giving the involved regions a macroscopically visible yellow tinge. Based on the observation that the leading cell population is rich in lipids, a number of terms have been proposed to designate this disorder: isolated cardiac lipoidosis (Ross and Belton 1968); infantile cardiomyopathy with histiocytoid reaction (Reid et al. 1968); focal lipid cardiomyopathy (Bove

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and Schwartz 1973); and infantile xanthomatous cardiomyopathy (Bruton et al. 1977). The typical cells are probably not of the histiocytic (macrophage) cell system, however, since they reveal myofibrils and Z lines, attesting a relationship to the cardiocyte population. No satisfactory interpretation of this unusual change has been made to date.

Based on electron microscopic findings, it has been suspected that the peculiar type of cardiomyopathy might result from a "diffuse lesion of specific (conducting) myocardium" (Amini et al. 1980). In this report we present histochemical and ultrastructural evidence suggesting that histiocytoid cardiomyopathy may in fact correspond to a maldevelopment of Purkinje fibers.

Case Report

(T.J., Female)

After an uneventful postnatal development, a routine paediatric examination at the age of 1 year revealed a slightly enlarged heart. It was, therefore, planned to perform a more detailled cardiological examination and to search for the cause of this undefined cardiomegaly which had not led to any clinical symptoms up to that time. However, before more information could be obtained, the infant suddenly and unexpectedly died without an obvious external cause. An autopsy was performed.

Material and Methods

For light microscopy, tissue samples were fixed in buffered, neutral formaldehyde (4%), dehydrated in graded alcohols, embedded in paraplast, and processed to sections stained with haematoxylin-eosin, PAS, Turnbull's iron, Van Gieson, Weigert's elastica and Gomori's silver. For lipid stains, frozen sections of fixed tissue were used.

For the histochemical assessment of cholinesterase activity, the direct thiocholine method, as modified by Karnovsky and Roots (1964) was used. Sections of fixed heart tissue containing foam cells and normal looking myocardium, and sections of normal skeletal muscle used as a control, were incubated at room temperature in a reaction mixture containing thiocholine iodide, copper sulfate and potassium ferricyanide at a pH of 5.5. After incubation, sections were rinsed in distilled water and mounted with glycerol-gelatine. In normal control tissue, enzyme activity is demonstrated in the form of a reddish to brown reaction product located in sublemmal cytoplasm.

For electron microscopy, fixed tissue samples were postfixed in osmium tetroxide, dehydrated in graded alcohols, and embedded in Spurr's low-viscosity medium. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with a Zeiss EM 10 transmission electron microscope.

Results

Gross Findings. The heart weighed 50 g (normal for this age: 49 g), but showed a slight left ventricular hypertrophy. The geometry of the large arteries and veins, and of the coronary vessels, was normal. Macroscopic examination revealed a peculiar yellowish discoloration of the endocardial surface of the left ventricle, including the papillary muscles and the papillary insertions of chordae tendineae. The findings in other organs were unconspicuous.

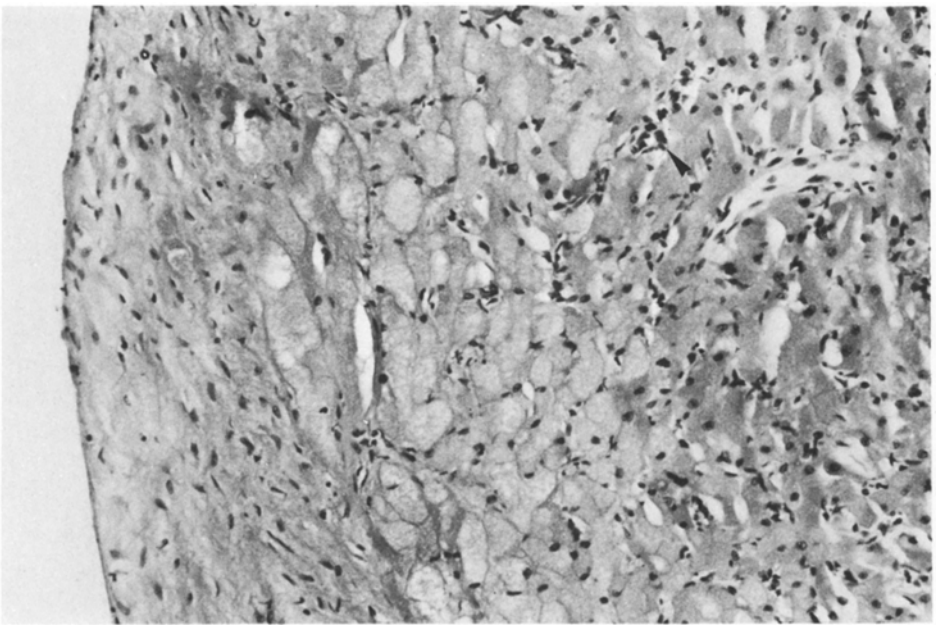

Fig. 1. Subendocardial part of the interventricular septum. Groups of large, foamy cells have accumulated between the thickened endocardium (*to the left*) and the working myocardium (*to the right*). The tissue is traversed by thin-walled vessels containing clusters of lymphocytes (*arrow*; haematoxylin-eosin stain, × 250)

Light Microscopy Findings. The macroscopically yellowish parts of the left ventricle consisted chiefly of band-like accumulations of large cells with sharply delineated borders, a foamy cytoplasm and small ovoid nuclei, located between a thickened fibrous endocardium and the striated myocardium (Fig. 1). In the papillary muscles, the foamy cells were, in part, intermingled with myocardiocytes, forming complex bundles (Fig. 2). However, the foamy cells were always clearly separated from working myocardium, transitional cell forms not being observed. At higher magnification, the large vesiculated cells exhibited a close spatial relationship to small blood and/or lymph vessels (Fig. 3). In all sections examined, the typical cells were topographically limited to subendocardial regions of the ventricular wall, interventricular septum and papillary muscles. Interestingly, typical normal Purkinje cells could not be discerned in regions containing foam cells. Dense clusters of large cells were also found at the crest of the membranous part of the ventriculo-atrial junction, a region traversed by the bundle of His. Small clusters of lymphoid round cells (probably mainly lymphocytes) were found in close proximity to foamy cells and to endothelial channels. The right ventricle and both atria were spared.

Histochemical Findings. In preparations stained with Sudan Black, large vesiculated cells presented numerous dark, small cytoplasmic granules (Fig. 4), completely lacking in striated myocardiocytes. Sections processed by the direct thiocholine method for activity of cholinesterase exhibited scattered foamy cells

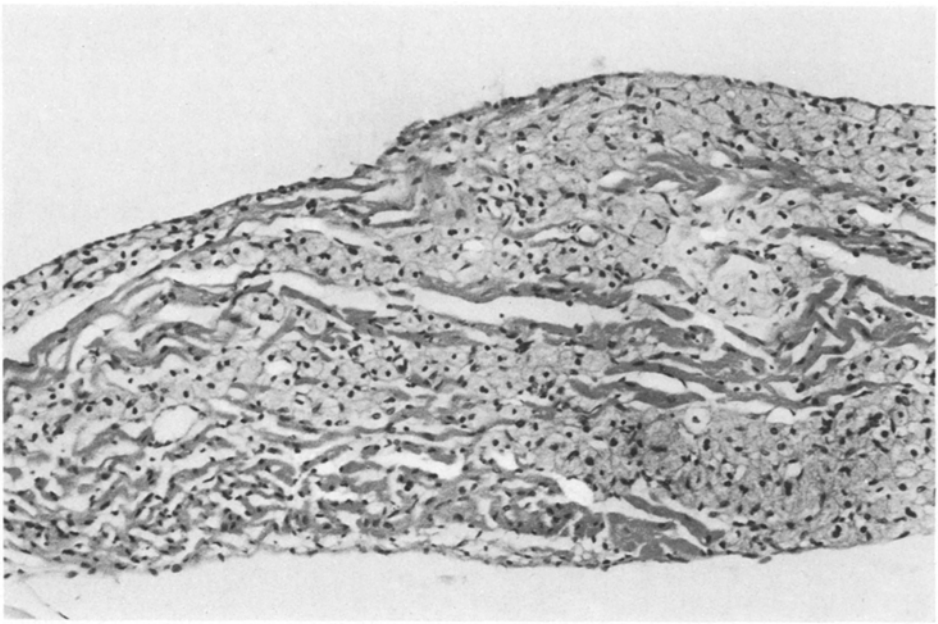

Fig. 2. Papillary muscle of left ventricle, showing myocardiocytes intermingled with groups and bundles of foamy cells (haematoxylin-eosin stain, ×180)

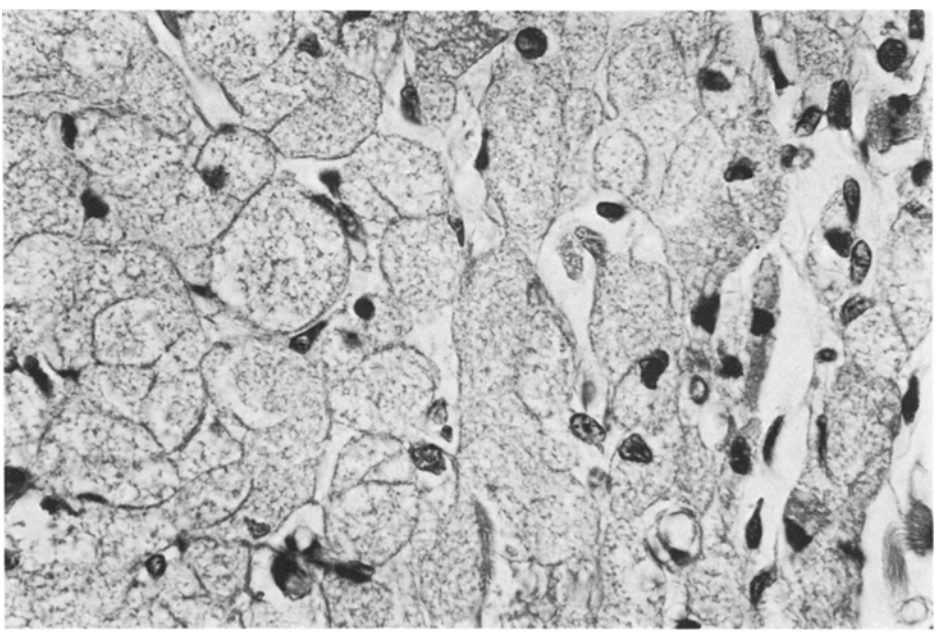

Fig. 3. Typical foamy cells at higher magnification. Note the close spatial relationship of the vesiculated cells to endothelium-lined channels (haematoxylin-eosin stain, ×400)

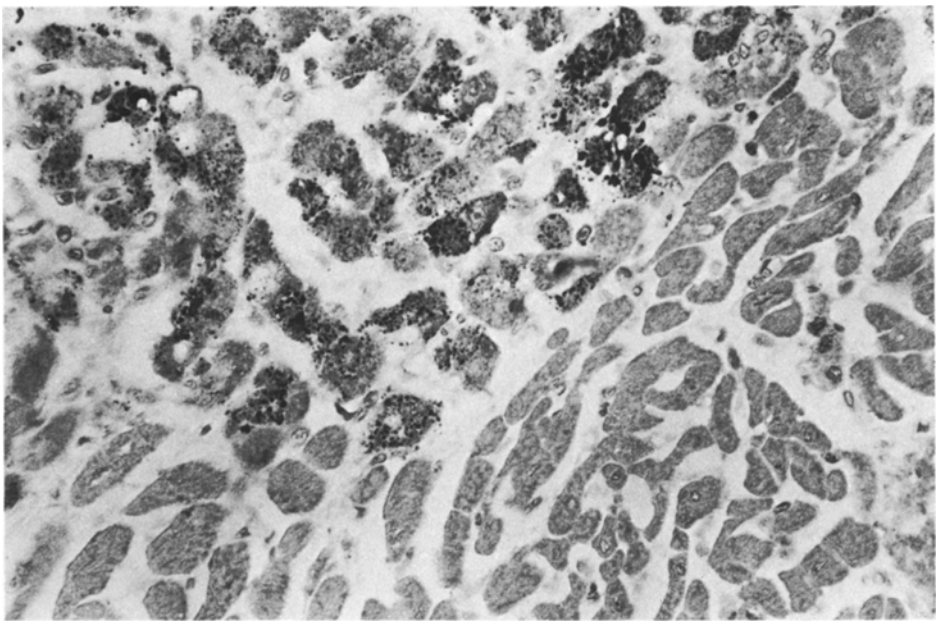

Fig. 4. In this lipid stain, the foamy cells exhibit numerous cytoplasmic grains or droplets. The cells of the working myocardium are free of visible lipids (Sudan Black, ×250)

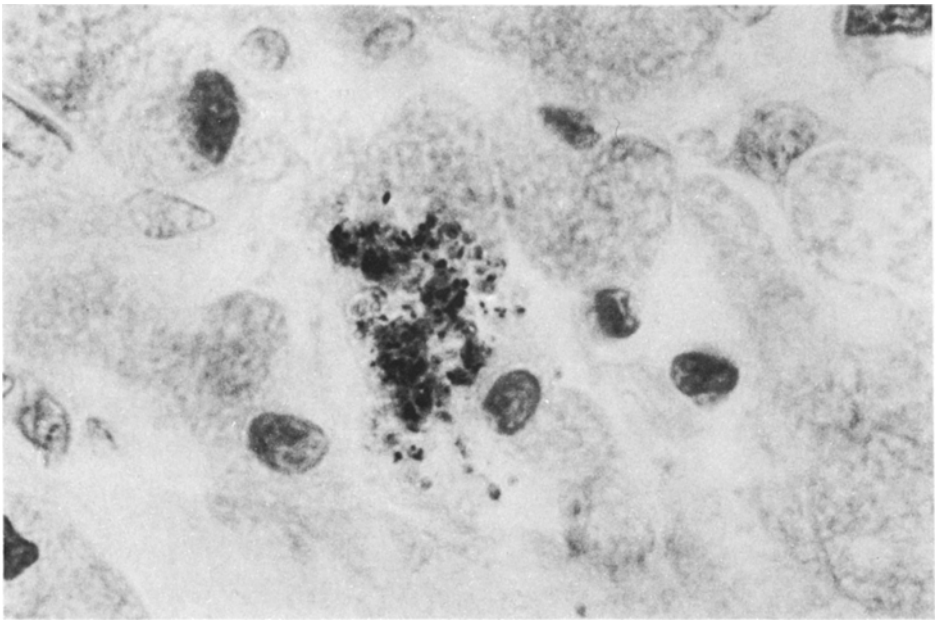

Fig. 5. Tissue section processed by the direct thiocholine method for the demonstration of cholinesterase activity. The two cells in the center of the figure exhibit a granular, cytoplasmic reaction product (×1,000)

with a spotty or granular, cytoplasmic brown reaction product, comparable to that found in normal skeletal muscle cells used as a control (Fig. 5). Only a fraction of "arachnocytes" presented this reaction, probably due to partial inactivation of cholinesterase by fixation. Myocardiocytes completely lacked this activity.

Electron Microscopy Findings. Typical cells showed abundant cytoplasm with numerous mitochondria of the crista type and empty vesicles probably resulting from extracted lipids. Many of these cells were directly adjacent to and in close contact with endothelial channels, and some of them contained small bundles of densely packed fibrils and hexagonal arrays, corresponding to incomplete or distorted sarcomeral structures. Some cells exhibited a coarse, electron dense cytoplasmic material, reminiscent of Z membrane-associated material, as has been demonstrated in former reports.

Discussion

The cardiac lesion discussed in this communication corresponds to the few cases of so-called "xanthomatous" or "histiocytoid" cardiomyopathy reported previously by other authors (Voth 1962; Reid et al. 1968; Ross and Belton 1968; MacMahon 1971; Haese et al. 1972; Kauffman et al. 1972; Bove and Schwartz 1973; Ferrans et al. 1976; Witzleben and Pinto 1978; Amini et al. 1980). The histochemical and ultrastructural findings obtained in our study suggest that this cardiopathy may result from a developmental disorder of the specific, conducting portions of myocardium, involving the bundle of His and the Purkinje fiber system.

So-called xanthomatous or histiocytoid cardiomyopathy, first described in 1962 as arachnocytosis of the myocardium (Voth 1962), is a rare, isolated heart disorder of hitherto unknown character, observed mainly in infants and children under two years of age. As in our case, the disease usually affects females, only three male patients having been reported so far (Ferrans et al. 1976; Amini et al. 1980). The clinical picture is dominated by severe disturbances of cardiac rhythm; we feel justified to suspect, although we have no electrocardiographic data, that the sudden unexpected death occurring in the patient described in this report was due to such a disorder. The main morphological lesion consists of groups of lipid-rich and large cells, found in the subendocardium of the ventricle and its papillary muscles. The vesicular structure of these cells, together with their content of lipid droplets, in some respect resembling lipid-laden, foamy macrophages or histiocytes, has formerly led to designations such as histiocytoid or xanthomatous cardio(myo)pathy (Reid et al. 1968; Mac Mahon 1971). However, subsequent ultrastructural investigations have shown the typical cells to contain myofibrils interposed with Z lines (Haese et al. 1972; Bove and Schwartz 1973; Ferrans et al. 1976; Bruton et al. 1977; Witzleben and Pinto 1978; Amini et al. 1980). Bundles of myofibrils and Z membrane-like bulky material in the large mitochondria-rich cells were also demonstrated in the present case. Therefore, the unusual cell population in question may bear a relationship to the myocardiocyte system itself. Based on this finding

and the subendocardial location of the cells it has been suspected that so-called "histiocytoid" cardiomyopathy may in fact result from a diffuse lesion of the specific myocardium (Amini et al. 1980). However, further evidence to support this notion is still lacking.

The ontogenetic development of the specialized conductive tissue of the heart has been studied in detail in recent years (for review: James 1970; Manasek 1970; Anderson et al. 1976; Nanot and Le Douarin 1977; Marino et al. 1979; Viragh and Challice 1980). In brief, the sinus node of the human heart is readily discernible by the 6th to 8th week of fetal development, containing P cells and transitional cells as the AV node, which migrated inward from an original (sub)epicardial location to finally lie deep within the heart. In contrast, the bundle of His and its branches develop at a later stage and lack the typical cellular heterogeneity of the two nodes, being almost exclusively composed of Purkinje cells or their precursors. There is strong embryological, morphological and functional evidence that the Purkinje cell system does not originate as a mere outgrowth of the AV node, but develops separately from the ventricular crest. Early Purkinje cells present a morphology quite different from cardiocytes of the working myocardium (V fibers), inasmuch as they show an abundant "clear" cytoplasm with numerous mitochondria and only scarce and peripherally situated myofibrils. The AV node and bundle of His are spatially separated for a longer time period, being united by the second month of gestation.

In the light of these findings, parallels can be seen between the developing Purkinje cell system and the peculiar cell population found in the cardiopathy under discussion. The foamy cells exhibit a structure which is very similar to that of immature Purkinje cells, both cell types containing a large cytoplasmic mass, numerous mitochondria, and only sparse myofibrils, not organized into typical and complete sarcomeres, and lacking intercalated discs. Sudanophilic lipids, found in our material, can also be demonstrated in the cells of the normal specific cardiac tissue (Robb and Kaylor 1948). A second point in favour of the afore – mentioned assumption is the typical distribution of arachnocytes within the heart. The cells are located in a subendocardial position along the ventricular and septal wall, the ventricular crest and the papillary muscles, sparing the atria and the interatrial septum. In the normal heart, this exactly corresponds to the location of the bundle of His and its branches, and of peripheral Purkinje cells. The lack of involvement of both cardiac nodes is well in line with the evidence of a separate ontogenetic derivation of the nodes on the one hand and the bundles on the other hand, as exemplified above. As a third point to raise are the results of our histochemical analysis. The functional difference between the specific tissue and working myocardium is represented by different patterns of enzyme activity (for review, see Schiebler and Doerr 1963). It has formerly been shown that the activity of acetylcholinesterase may be used as a histochemical discriminator of specific cardiac tissue and working myocardium: the enzyme is present in the cells of the former, and is lacking in the latter (Elias et al. 1980). We found a positive reaction for this enzyme activity in at least some of the typical cells, further indicating a possible relationship of these cells to Purkinje cells.

The accumulation of small lymphoid cells in close spatial relationship to subendocardial foamy cells may be suspected to have resulted from a local derangement of lymph circulation. The collections of foamy cells were traversed by many small endothelial channels reminiscent of lymph vessels. The latter have been demonstrated in the normal myocardium (Haagensen et al. 1972). The general direction of lymph flow is from the endocardium to the superficial myocardium. Lymphatic vessels lie adjacent to Purkinje fibers and communicate with myocardial lymph channels through anastomosing vessels. Thus, as signs of inflammatory change were lacking, we suggest that lymphocyte accumulation at this specific site may be caused by deficient cell transport from a deranged lymph vessel system, as seen for example, in lymphangiomas.

In conclusion, the findings obtained in this case of so-called "histiocytoid" cardiomyopathy lead to further evidence suggesting that the typical cell population found in this disorder may in fact be derived from Purkinje cells and/or their precursors. We theorize that the Purkinje cell system, but not the atrioventricular node, undergoes deranged development in this cardiopathy, resulting in the persistence of an embryonal (or fetal) state of differentiation. The leading clinical picture, dominated by a disorder of conductance, is in line with this assumption.

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