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Histiocytoid Cardiomyopathy: Case Report and Literature Review

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ABSTRACT: The sudden death of an infant may be due to a variety of causes. In such cases, complete autopsy with radiologic, gross, microscopic, and toxicologic examination is warranted. We present a case of a previously healthy 15-month-old girl with no known disease, who experienced witnessed cardiac arrest, ventricular fibrillation, and death. Complete postmortem examination revealed histiocytoid cardiomyopathy as the cause of death.

Histiocytoid cardiomyopathy is a rare infantile cardiac-muscle disorder characterized by the presence of enlarged, polygonal subendocardial myocytes which, by light microscopy, lack normal striations, and instead have granular, faintly eosinophilic cytoplasm. Ultrastructurally, the myocytes contain numerous mitochondria and markedly reduced numbers of myofibrils. Clinically, the disorder is characterized by cardiac arrhythmias and/or sudden death occurring in children under the age of two years. We discuss the differential diagnosis, proposed theories of etiology, and the pathology of this rare entity.

KEYWORDS: pathology and biology, histiocytoid cardiomyopathy, sudden death

Case Report

A previously healthy, developmentally normal, 15-month-old, black female suddenly collapsed while playing at home. Family members immediately initiated cardiopulmonary resuscitation and contacted the local Emergency Medical System (EMS). Arriving within minutes, EMS personnel found the child in ventricular fibrillation and twice attempted defibrillation unsuccessfully. Subsequent electrocardiographic monitoring revealed an idioventricular rhythm and eventually asystole. Advanced cardiac life support protocol was continued, and the child was transported to the local hospital's Emergency Department, where resuscitation efforts continued. Despite all resuscitative efforts, including the placement of a pacemaker, the child never resumed a functional cardiac rhythm or spontaneous respirations. All further medical intervention, including transport to a regional medical center, was unsuccessful. The child was pronounced dead four hours after the initial collapse.

Autopsy Findings

At autopsy, the well-developed, well-nourished, normal-appearing 15-month-old black female weighed 17 pounds. Evidence of emergency resuscitation and medical therapy

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included an endotracheal tube, a nasogastric tube, multiple intravenous catheters, a Foley catheter, multiple needle puncture wounds, and patterned circular defibrillator-pad markings. Thorough external, internal, and radiologic examination revealed no evidence of acute or remote injury.

Gross examination of the internal organs was unremarkable except for the heart, which weighed 76 g (normal for age/weight = 40 to 46 g [*1*]). The epicardium of the left ventricle and apex had a variegated pale gray to gray-white opaque appearance with irregular borders that merged with adjacent normal epicardium. Extending from the base to the apex, the subendocardium of the circumference of the left ventricle had a mottled tan-yellow "infiltrative" discoloration which varied from 0.3 to 0.6 cm in thickness (Fig. 1). The overall thickness of each ventricular wall was normal. The endocardium overlying the abnormal subendocardial discoloration was gray-yellow and opaque. The subepicardial left-ventricular myocardium, the right-ventricular myocardium, and both atria were red-brown, firm, and unremarkable. The remainder of the heart, including the coronary arteries, valves, and septa, was grossly unremarkable.

Microscopically, the noncardiac tissues were essentially unremarkable or nonspecific, with central hepatic congestion, multiple interstitial and parenchymal petechial hemorrhages of the thymus, slightly hyperplastic lymph nodes, and pulmonary interstitial and alveolar emphysema consistent with mechanical ventilation.

Within the heart, sheets of large round to polygonal myocytes with small, round to slightly irregular nuclei and abundant, granular, nonstriated, faintly eosinophilic cytoplasm were present in the subendocardial muscle of the right and left ventricles (Fig. 2). Clusters and bands of these cells were also found scattered within the subepicardium and deeper parts of the myocardium (Fig. 3), including the left atrial wall. Occasional cells contained areas of normal myocyte cytoplasm and histiocytoid cytoplasm, suggesting that the abnormal cells were altered myocytes (Fig. 4). The conduction system was not specifically examined. No other organ or tissue contained histiocytoid cells.

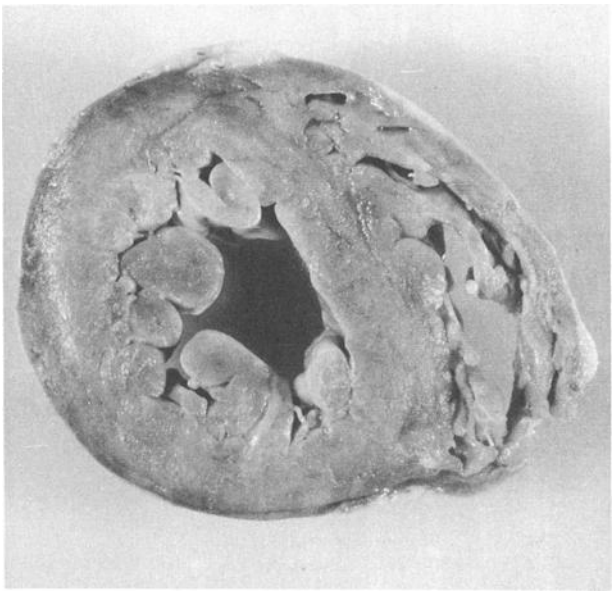

FIG. 1—*Cross-section through the left and right ventricles showing diffuse pale discoloration of the myocardium with relative sparing of the subepicardial regions. Also evident are markedly pale regions within the subendocardial myocardium.*

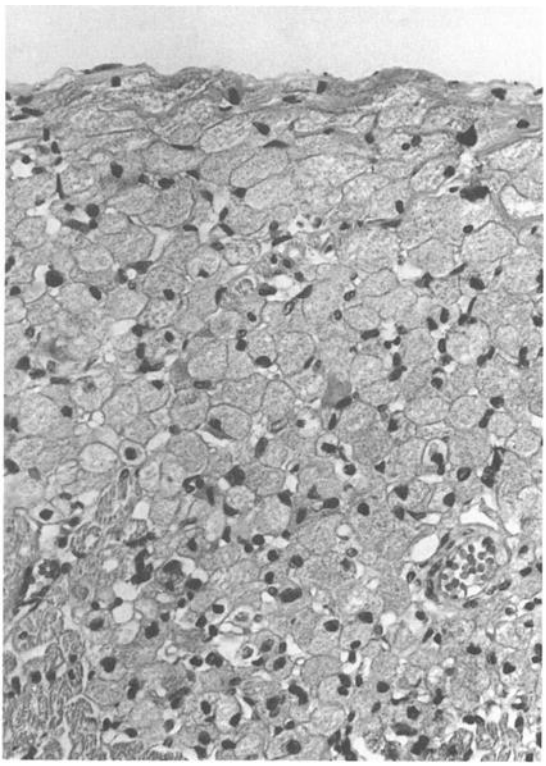

FIG. 2—*Medium-power view of subendocardial histiocytoid cells with abundant, pale, granular cytoplasm (hematoxylin and eosin, 200 ×).*

Ultrastructurally, the abnormal cells within the heart were determined to be myocytes with either absent or markedly decreased numbers of distorted myofibrils and great numbers of mitochondria (Fig. 5). Neither lipid nor glycogen appeared to be increased.

Based on these findings, the cause of death for this 15-month-old black female was histiocytoid cardiomyopathy, a rare but distinct idiopathic cardiac disorder.

Discussion

In 1962, Voth reported an entity that he called "arachnocytosis of the heart muscle" [*2*]. Since then, several reports of the same condition have been published and referred to by different names, including isolated cardiac lipidosis [*3*], xanthomatous cardiomyopathy [*4*], focal myocardial degeneration [*5*], idiopathic infantile cardiomyopathy [*6*], focal lipid cardiomyopathy [*7*], infantile cardiomyopathy with histiocytoid change [*8,9*], or reaction [*10*], multifocal Purkinje-cell tumors of the heart [*11,12*], histiocytoid cardiomyopathy [*13–16*], foamy myocardial transformation of infancy [*17,18*], infantile xanthomatous cardiomyopathy [*19,20*], oncocytic cardiomyopathy [*21,22*], and congenital histiocytoid cardiomyopathy [*23*]. We prefer the term histiocytoid cardiomyopathy (HC).

In addition to our case, we found 37 cases of HC in the medical literature [*2–24*]. The classic case is that of a child under age 2 presenting to an emergency department or physician's office with cardiac dysrhythmias/tachycardia [*2–14,17–19,21,22,24*]. Var-

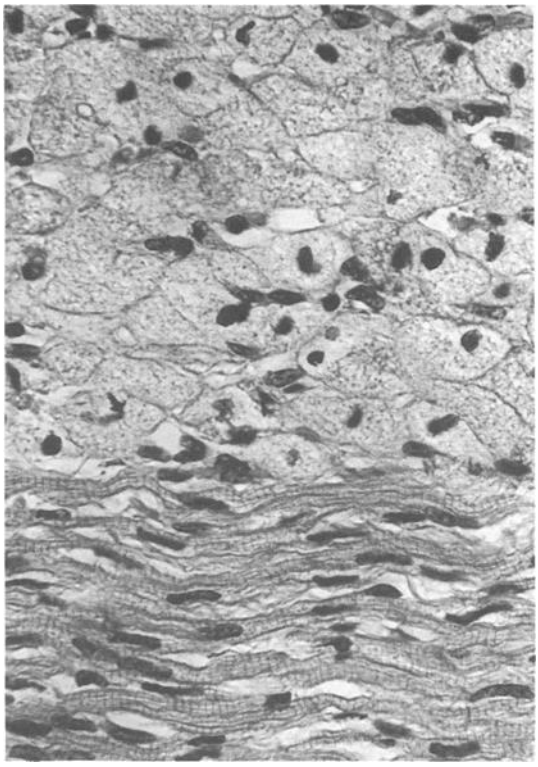

FIG. 3—*High-power view of histiocytoid cells adjacent to normal myocytes (hematoxylin and eosin, 400 ×).*

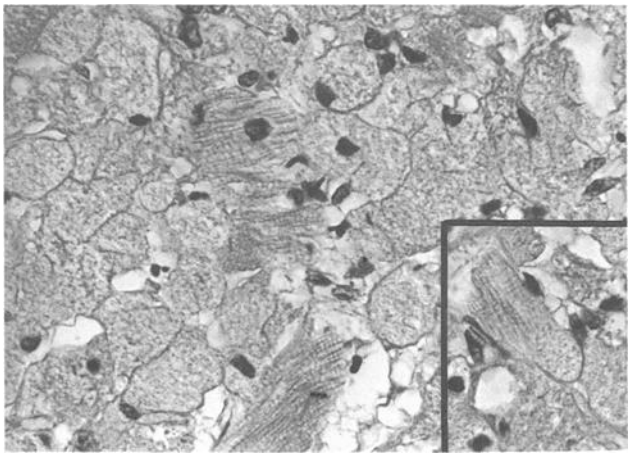

FIG. 4—*High-power view of histiocytoid cells and normal myofibers. Inset shows a cell containing myofibrils and histiocytoid cytoplasm (hematoxylin and eosin, 400 ×).*

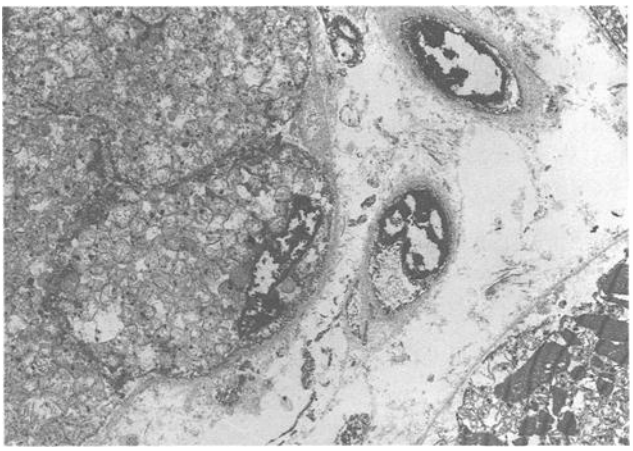

FIG. 5—*Electron micrograph showing two interstitial cells bounded by two myocytes. The myocyte in the upper left represents the typical histiocytoid cell, with virtually no myofibrils and a large number of mitochondria. The myocyte in the lower right has residual myofibrils and an increased number of mitochondria (6500 ×).*

ious rhythm disturbances have been reported, including atrial tachycardia [*6,7*], atrial flutter [*6*], atrial fibrillation [*19*], junctional tachycardia [*14,22*], supraventricular tachycardia [*5,6,21,22*], ventricular tachycardia [*6,22*], ventricular fibrillation [*9*], premature ventricular contractions [*5*], right bundle branch block [*5,6*], the Lown-Ganong-Levine syndrome [*12*], and the Wolff-Parkinson-White syndrome [*7,13,19,22*]. Of the 38 patients, 31 have been female [*2–11,13,15–24*]. Often, a nonspecific viral-like illness precedes or accompanies the cardiac disturbance [*2,3,5,8–11,15–19,22*]. This most often manifests itself as a gastrointestinal-type illness encompassing vomiting with or without diarrhea [*2,3,5,8,10,11,16–19*]. Others appear to have a respiratory-type illness [*8,9,22*]. Relatively well-defined viral illnesses, including chickenpox, measles, and roseola, occurred in some individuals [*8,18*]. Two children had recently received vaccinations, one diphtheria-pertussis-tetanus (DPT) [*7*] and one smallpox [*2*]. One child's mother had been exposed to rubella during her pregnancy [*21*]. Central nervous system and eye defects were present in three patients [*8,13,21*]. A history of toxin (insecticide) exposure was documented in only one case [*6*].

In all cases, the cardiac dysrhythmias prove to be the most important problem facing the patient and clinician. Despite aggressive treatment, the cardiac rhythm disturbances eventually become refractory to all non-surgical intervention. Death ensues within hours to months after initial presentation. Recently, surgical intervention has proven to be of potential benefit in some of these patients [*9,24*].

Although most patients are extensively evaluated prior to their deaths, sudden death may be the first manifestation of HC. Seven cases of HC-induced sudden death have been described [*10,15,17,18,20,23*], and a sudden infant death syndrome (SIDS)-like scenario has occurred [*20*].

Unfortunately for those individuals affected by HC, most diagnoses have been made at autopsy, even in cases extensively evaluated prior to death. When faced with a young child who is experiencing unremitting tachycardia, clinicians must approach the situation aggressively. The differential diagnosis in such a situation includes myocarditis, metabolic disturbances, endocardial fibroelastosis, cardiac tumors (especially rhabdomyomas), idiopathic causes, and HC [*7,9*]. When pharmacotherapy fails to alleviate the tachycardia,

placement of pacemaker wires may be attempted. As our case and another have demonstrated, however, external pacing, while perhaps temporarily beneficial, may not be successful in patients with HC [7]. Ultimately, surgical intervention with electrophysiologic mapping studies should be performed [9,24]. Excision of arrhythmogenic foci or possibly cardiac transplantation appear to be the only means by which infants with HC have a chance of survival. In four cases in which the infant was taken to surgery, a diagnosis of HC was made based on biopsy, and surgical excision of the abnormal cells was performed [9,24]. Three of the four patients were alive and doing well when the cases were submitted for publication (ranging up to >6 years post-surgery) [9,24].

The gross, microscopic, and ultrastructural findings in HC have been well-documented in the medical literature. Grossly, the hearts of children with HC are almost always enlarged [3,4,6–19,21–23]. The epicardium [4,7,10,21,22], myocardium [2–4,6–10,12, 13,15,18,19,21–23], endocardium [3,4,6,10,15,18,22], valves [3,15,21,22], and papillary muscles [15,22,23] may all have grossly evident abnormal tissue which is variously described from one report to another. In general, the lesions are typically sharply demarcated from the surrounding normal tissue, are opaque, white-yellow to yellow-tan, and tend to have a predilection for the subendocardium [3,4,6,7,10,13,15,18,21–23]. Any chamber may be involved [10,13], although ventricular-wall involvement appears to be most common [3,4,6,7,10,18,21–23]. The abnormal tissue may occur as multiple nodules [15,21,22], single or multiple distinct plaque-like thickenings [3,4,7,10,13,15,24], or a diffuse opaque discolored thickening involving virtually an entire chamber [6,18,21,22,24]. Occasionally, no appreciable abnormal tissue is identified grossly [5,11,14,17,18,20].

Microscopically, the hearts in each reported case of HC have collections of abnormal cells within the myocardium [2–24]. These cells are variously described by each author, but, in general, are characterized as large, polygonal to elongated cells with vacuolated to somewhat granular, pale and slightly eosinophilic cytoplasm, and small, hyperchromatic, round to angulated nuclei [2–24]. Characteristically, they are said to resemble histiocytes [6–10,13–16,23], Purkinje cells [11,12,23], xanthoma cells [4,19,20], oxyphil cells or oncocytes [7,21,22], and the granular cells of myoblastomas [7]. Rare intranuclear inclusions have been described within the HC cells [6,7]. Some authors report the presence of "transition forms," cells which appear to be intermediate between the classic HC cells and normal myocytes [8,22].

Special stains have been performed in most cases in order to better elucidate the origin and content of HC cells [2–8,10,12,13,17,18,21–23]. Stains for lipid and glycogen are, at best, variable from one case to another [2–8,10,12,13,17,18,21–23]. The most consistently positive stain appears to be Sudan Black B, which was reported as positive by all but one of those who used it [5–8,17,22,23]. Using immunohistochemical stains, Rossi et al. found that HC cells stain with myoglobin markers and are negative with histiocyte/macrophage markers [12].

Some reported cases of HC contain areas of myocardial necrosis near or within areas of HC cells [5–8,17]; most of these have associated inflammatory cells, including neutrophils and mononuclear cells [5–7,17]. Occasional cases contain focal clusters of chronic inflammatory cells (with no necrosis) in association with HC cells [8,10,21,23]. A small amount of fibroelastosis was reported by one author [10], while subendocardial sclerosis was evident in one case [22].

The abnormal collections of cells seem to occur in one of two general patterns, either as an isolated area within the myocardium [9,18,24], or as a relatively diffuse or multifocal process that may involve any or all portions of the heart, including the atrial and ventricular walls, the valves, and the papillary muscles [2,3,8,10,14,18,21,22,24]. HC cells are present within the conduction system in a majority of cases in which specific mention is made of the conduction system [3,4,6–8,10–14,19,21–23]. Accessory AV

pathways are described in three hearts, two of which had at least some accessory pathways composed of HC cells [*12,22*].

Electron-microscopic studies have been performed on many of the reported cases [*2,5–9,13–18,21–23*]. The consensus is that HC cells are enlarged distorted myocytes containing very few to no myofibrils and massive numbers of enlarged mitochondria [*5–9,13–18,21–23*]. Desmosomes, although decreased in number, are reported within HC cells [*7,8,17,22*]. Coarse, electron-dense cytoplasmic material suggestive of Z-bands is frequently encountered [*7,8,12,22,23*]. Intracytoplasmic lipid vacuoles, thought by some to result from degenerating mitochondria [*6,14*], are reported in several cases [*6,7,14,15,17,18,21*]. Evidence of mitochondrial abnormality includes the presence of various intramitochondrial densities [*7,8,18*], dilated or stacked mitochondrial cristae [*7,17,18*], and abnormalities of intramitochondrial membranes [*7*]. Clearly defined ultrastructural evidence of viral infection is lacking in HC cells [*6,7*]. While a few of the ultrastructural changes of HC may be attributed to ischemic or autolytic changes, the constellation of changes seems to be specific for HC [*13*].

In those cases in which antemortem and postmortem viral cultures are reported, all cultures have been negative [*5,17,21*]. The mother of one infant who died of HC had been in contact with rubella during her pregnancy [*21*]. In addition to the findings of HC, the infant had rubella-related eye and central nervous system (CNS) abnormalities but a nondiagnostic rubella hemagglutination titer [*21*]. Two other reported cases had CNS defects [*4,13*], while two had eye changes [*8,13*]. Two infants had recently received vaccinations, one DPT [*7*], the other smallpox [*2*]. One child had recently been diagnosed with roseola [*8*], while another had chickenpox [*8*].

Other pertinent studies have only rarely been reported in the literature. A heavy-metal screen was negative in one case [*5*]. In the only case in which biochemical studies were reported, a deficiency of reducible cytochrome b was found within, and limited to, heart mitochondria [*16*].

Occasional reports mention the presence of HC-like cells within various noncardiac tissues, including the thyroid and pituitary glands [*21,22*], major and minor salivary glands [*21*], and paratracheal mucous glands and the adrenal medulla [*22*].

Although the findings in HC are rather specific, care must be taken to differentiate HC from other conditions which may have similar features. Among those diseases in the differential diagnosis are the generalized lipidoses, particularly the xanthomatoses [*3*], and cardiac rhabdomyomas [*6,21*]. If light microscopy fails to allow differentiation from HC, electron microscopy should provide the capability to do so [*21*].

One early report considered HC to be an isolated lipidosis of the heart [*3*], while another considered it a disease of myocardial fibers and myocardial histiocytes [*4*]. Subsequent reports have firmly established that HC is a disorder of myocytes alone. It is generally agreed that the altered cells ultimately lead to cardiac dysrhythmias and/or cardiac failure rather than vice versa [*7,8,19*]. The anatomic findings of HC appear to represent the end result of cellular injury due to a degenerative process of myofibers [*6,13,18*]. The underlying cause of this degenerative process has been the subject of much discussion. Various theories of etiology have included toxin exposure [*7*], an acquired metabolic disorder [*7*], a congenital storage disorder confined to the heart [*3*], and a virus-induced process [*7,8,21*]. Some authors contend that the condition is a neoplastic process involving the Purkinje cell system [*11,12*]. Others suggest that the process is not neoplastic but is confined to the Purkinje cell system and involves some type of maldevelopment [*14,23*]. The strongest evidence for an acceptable explanation of this disease comes from the biochemical studies that have been performed. Bove and Schwartz were the first to suggest that HC resulted from a mitochondrial functional derangement [*7*]. Papadimitriou et al. have demonstrated that HC may well represent an inborn error of mitochondrial electron transport characterized as a deficiency of reducible

cytochrome b [*16*], the impairment of electron transport and energy production resulting in mitochondrial proliferation [*16*]. The authors of that study refer to several cases of skeletal muscle mitochondrial myopathies that display similar changes [*16*].

The female preponderance in this condition is unexplained. Whether HC is inborn or acquired remains unclear. Bruton et al. proposed a possible sex-linked dominant gene or new mutation as an underlying genetic defect responsible for HC [*13*]. An autosomal recessive gene was proposed by Suarez et al., but this does not adequately explain the female preponderance [*18*]. Papadimitriou et al. proposed a mutation in a mitochondrial gene as the genetic defect responsible for HC [*16*].

Conclusion

Histiocytoid cardiomyopathy is a rare condition that typically affects females under the age of 2 years. This disorder seems to represent an inborn or acquired metabolic derangement within the mitochondria of certain myocytes, possibly preferentially affecting the Purkinje cell system. The affected cells may occur in a single focus or, more commonly, as diffuse or multifocal areas within the heart. The abnormal myocytes often occur within or around various portions of the myocardial conduction system and cause progressively worsening dysrhythmias. Ultimately, the arrhythmias and subsequent heart failure cause death, except in rare instances when isolated foci of abnormal cells can be surgically excised. The condition typically presents itself with various nonspecific symptomatology, but sudden death may be the initial presentation of the disorder. Consequently, the authors alert the forensic community to be aware of this rare cardiac abnormality.

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