Infantile Cardiomyopathy with Histiocytoid Change in Cardiac Muscle Cells

Report of Six Patients

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SUMMARY Clinical and pathologic findings are presented in 14 patients (six newly reported, eight described previously), all children ranging in age from 6 months to 2 years, with a clinicopathologic syndrome termed "infantile cardiomyopathy with histiocytoid change in cardiac muscle cells." This syndrome is manifested clinically by severe, eventually fatal cardiac arrhythmias, and is characterized pathologically by cardiac hypertrophy and by a distinctive type of focal degeneration of the muscle cells, which lose their myofibrils, undergo marked mitochondrial hyperplasia, become rounded in shape and enlarged, and resemble histiocytes. Evidence is presented to support the conclusions that these manifestations are those of a cardiomyopathy, that cardiac hypertrophy precedes the onset of the clinical features, that the focal degeneration is likely to be a cause rather than a consequence of the arrhythmias, and that the latter developed only in the late stages of the disorder. The etiology of this cardiomyopathy remains unclear.

UNIQUE CARDIAC LESIONS have been described during the past twelve years under the various names of arachnoctosis of the heart muscle, isolated cardiac lipidoses, infantile cardiomyopathy with histiocytoid reaction, infantile xanthomatous cardiomyopathy, lipid histiocytosis, focal myocardial degeneration, idiopathic infantile cardiomyopathy, and focal lipid cardiomyopathy. These lesions are characterized morphologically by the presence in the heart of yellow nodules composed of histiocyte-like cells that are large, spherical and frequently rich in lipid droplets. These cells have been shown to be severely altered cardiac muscle cells that have lost their contractile elements. Lesions with the features just described have been reported in a total of eight patients, all of whom were children ranging in age from eight months to two years.

The purposes of this communication are: 1) to present clinical and pathologic observations on six new patients with the lesions described above, and to compare these findings with those in the eight previously reported patients with these lesions; 2) to describe ultrastructural studies of the hearts of two of these patients; 3) to compare the cardiac histopathologic changes in these patients and in 26 young patients (ranging in age from 2 days to 16 years) who developed myocardial necroses of various causes, and 4) to define, on the basis of these studies, what appears to be a distinct clinicopathologic syndrome.

Clinical Observations

Cardiac nodular lesions containing histiocyte-like muscle cells were found in six patients whose clinical and necropsy records were on file at the Division of Cardiovascular Pathology of the Armed Forces Institute of Pathology. The clinical and necropsy findings on these patients (four girls and two boys) are summarized in tables 1 and 2. Also given in these tables are corresponding data on the eight patients previously reported to have similar morphologic abnormalities. The average age of our six patients, 16 months (range 6 to 24), was similar to the 15 months (range 8.5 to 24 months) found in the other eight patients; the average age for the entire group was 15.5 months. Four of our six patients and all eight previously reported patients were girls.

The clinical feature common to the group of patients was the development of severe, eventually fatal disturbances of cardiac rhythm (table 1). Twelve (patients 2–8 and 10–14) of the 14 patients presented to the hospital with rapid arrhythmias. These arrhythmias were: supraventricular tachycardia in nine, specifically identified as paroxysmal atrial tachycardia in patients 8 and 14; ventricular tachycardia in two and runs of both ventricular and supraventricular tachycardia in one. Of the two remaining patients, one (1) presented with a brief period of cardiac arrest, and the other (9) died suddenly while playing at home. Of our six patients, four (2, 3, 4 and 5) were found to have supraventricular tachycardia on initial evaluation. This tachycardia was in excess of 200 beats/min, occurred with 1:1 atrioventricular conduction, and in three patients (2–4) it was associated with aberrant intraventricular conduction. Patient 1 developed a cardiac arrest while being admitted to the hospital for evaluation of vomiting of two days duration. This patient responded initially to resuscitative measures, but then developed recurrent bouts of supraventricular and ventricular tachycardia, ventricular fibrillation, and had terminal cardiac arrest on the third day of hospitalization. The initial arrhythmia in patient 6 probably was also a supraventricular tachycardia; the patient had a regular pulse with a rate of 300 beats/min (electrocardiograms were not made at that time). Of the eight previously reported patients, four (8, 10, 12, 14) had supraventricular tachycardia as the presenting arrhythmia (including 14, who had Wolff-Parkinson-White syndrome), two (11 and 13) had ventricular tachycardia, one (7) had runs of both ventricular and supraventricular tachycardia, and one (9) died suddenly.

Events which may have played a role in the pathogenesis of the arrhythmias varied considerably. Five (patients 1–4 and 6) of our six patients had had normal growth and
development. The other patient (5) was a premature child who also had grown normally, but had a corneal opacity and blindness in the left eye; this patient also had been found to have a soft systolic murmur at the lower left sternal border, but the cause of the murmur was not evident at necropsy. None of the other patients had previous evidence of any type of heart disease. Of our six patients, three (1, 4, and 5) first presented to the hospital with a complaint of vomiting, which in two patients (1 and 5) occurred as an isolated event and in one (4) in association with mild diarrhea; patient 2 had had roseola (with an apparently uneventful recovery) three weeks before the onset of the terminal illness, which began with cough and fever two days before admission, and patient 6 had developed chickenpox four days before having the arrhythmia; patient 3 had had an upper respiratory tract infection two weeks before admission. Of the eight patients previously reported, one (patient 10) had been seen at the hospital several times, during an unspecified period of time, for fever, diarrhea, bilateral otitis media, and pneumonia; on admission he had evidence of cerebral embolization. Two patients (7 and 14) had had recent vaccinations when arrhythmias first developed: patient 14 for diphtheria-pertussis-tetanus and for polio (this patient, however, also had Wolff-Parkinson-White syndrome), and patient 7 for smallpox; patients 8 and 11 presented with vomiting, and patients 9, 12, and 13 had been completely asymptomatic. The home of patient 13 had been fumigated with insecticides two days before onset of the illness. Of the 14 patients, only one had a sibling with heart disease: a sibling of patient 14 had multiple developmental anomalies including some form of congenital heart disease and had died at 16 months of age, but necropsy had not been performed. The clinical course in all patients who were hospitalized, including our six patients, was marked by recurrences of arrhythmias, which were refractory to vigorous treatment. These arrhythmias led to transient ventricular fibrillation or cardiac arrest, and eventually to cardiac arrest that was unresponsive to resuscitative measures.

Necropsy Observations

Compared to normal values for age, cardiac weights were increased in all ten patients in whom this information was available: in two patients (2 and 14) the cardiac weights were approximately twice normal, and in eight patients they exceeded the normal values by 35% or more. None of the 14 patients had abnormalities involving the pericardium or coronary arteries, or any congenital malformations of the heart or great vessels.

Grossly evident abnormalities in the hearts of the 14 patients consisted of: 1) mural thrombi (2 patients); 2) endocardial thickening (6 patients); 3) areas of yellow-white discoloration of myocardium (5 patients), and 4) small nodules on or near the cardiac valves (4 patients). Both the nodules on the valves and the areas of myocardial discoloration were composed of abnormal cardiac muscle cells that resembled histocytes. Histologic study (table 2) showed the incidence of the valvar changes to be higher than was suspected on gross examination. Mural thrombi were found in the right

TABLE 1. Infantile Cardiomyopathy with Histioctoid Change in Cardiac Muscle Cells: Clinical Findings in 14 Patients

<table>
<thead>
<tr>
<th>Pt no. (ref)</th>
<th>Age (mo)</th>
<th>Events preceding illness</th>
<th>Presenting complaint</th>
<th>Initial arrhythmia</th>
<th>Hospital course and sequence of arrhythmias</th>
<th>Duration of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15/F</td>
<td>Vomiting 2 days</td>
<td>CA and RA</td>
<td>CA</td>
<td>Resuscitated but developed VT, VF, ST, CA, ST, VF and CA</td>
<td>2 days</td>
</tr>
<tr>
<td>2</td>
<td>14/M</td>
<td>Roseola 3 weeks</td>
<td>Cough and fever</td>
<td>ST with AIVC</td>
<td>CA, NSR with first degree A-V block, VF, CA</td>
<td>2 days</td>
</tr>
<tr>
<td>3</td>
<td>19/F</td>
<td>URI 2 weeks</td>
<td>URI, rapid pulse</td>
<td>ST with RBBB</td>
<td>CHF, CA</td>
<td>6 days</td>
</tr>
<tr>
<td>4</td>
<td>15/F</td>
<td>Vomiting, mild</td>
<td>Vomiting and</td>
<td>ST with RBBB</td>
<td>AP ?, CA</td>
<td>1 day</td>
</tr>
<tr>
<td>5</td>
<td>6/F</td>
<td>Diarrhea 4 days</td>
<td>Cough, tachypnea,</td>
<td>ST</td>
<td>CA</td>
<td>1 day</td>
</tr>
<tr>
<td>6</td>
<td>24/M</td>
<td>Chickenpox 4 days</td>
<td>Rapid pulse</td>
<td>ST</td>
<td>CA, ST, NSR, CA</td>
<td>1 day</td>
</tr>
<tr>
<td>7</td>
<td>12/F</td>
<td>Smallpox vaccination 11 days</td>
<td>Rapid pulse</td>
<td>ST and ST</td>
<td>Bursts of VT and ST, CA</td>
<td>3 days</td>
</tr>
<tr>
<td>8</td>
<td>18/F</td>
<td>Vomiting 2 days</td>
<td>Rapid pulse</td>
<td>PAT</td>
<td>Recurrences of ST for 6 weeks, CA, recurrent ST for 2 weeks, CA</td>
<td>8 weeks</td>
</tr>
<tr>
<td>9</td>
<td>13/F</td>
<td>None</td>
<td>Sudden death</td>
<td>CA</td>
<td>Death from multiple systemic emboli and sepsis</td>
<td>3 days</td>
</tr>
<tr>
<td>10</td>
<td>16/F</td>
<td>Fever, diarrhea, BOM, P</td>
<td>Vomiting, drowsiness, left hemiplegia</td>
<td>ST</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>13/F</td>
<td>Vomiting</td>
<td>Rapid pulse, tachypnea</td>
<td>VT</td>
<td>Recurrent VF and VT; acute renal failure and CA</td>
<td>3 days</td>
</tr>
<tr>
<td>12</td>
<td>17/F</td>
<td>Vomiting</td>
<td>Rapid pulse,</td>
<td>ST</td>
<td>Recurrent ST and VT, VF</td>
<td>5 weeks</td>
</tr>
<tr>
<td>13</td>
<td>24/F</td>
<td>None</td>
<td>Loss of consciousness</td>
<td>VT</td>
<td>NSR, recurrent VT, ST, VF, CHF 6 weeks and death</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>8-12/F</td>
<td>ST at age 2 months,</td>
<td>Rapid pulse</td>
<td>PAT</td>
<td>VF, bradycardia, bigeminy, recurrent ST and VF; died of shock.</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 days after vac</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients 1-14 were available to necropsy: Abbreviations: AF = atrial fibrillation; AIVC = aberrant intraventricular conduction; A-V = atioventricular; BOM = bilateral otitis media; CA = cardiac arrest; CHF = congestive heart failure; DPT = diphtheria-pertussis-tetanus; F = female; M = male; No. number; NSR = normal sinus rhythm; Pt = patient; P = pneumonia; PAT = paroxysmal atrial tachycardia; RA = respiratory arrest; RBBB = right bundle branch block; ref = reference; ST = supraventricular tachycardia; URI = upper respiratory tract infection; VF = ventricular fibrillation; VT = ventricular tachycardia; WPW syndrome = Wolff-Parkinson-White syndrome.
ventricle of patient 1 and in the right atrium and left ventricle of patient 10. Both patients had pulmonary emboli. Patient 10 also had widespread systemic emboli; the thrombus in his right atrium was infected. Endocardial thickening involved the left ventricle in three patients (2, 3 and 13), the left ventricle and the left atrium in one (5), and unspecified sites in two (9 and 10). Slight thickening of the mitral valve was noted in two patients (5 and 13). The heart was grossly normal in patients 4 and 12, and not described in detail in patient 6. The heart was soft, flabby, and dilated in two patients (1 and 2), and showed areas of yellow-white discoloration in five patients (1, 5, 10, 11 and 14). The left ventricular subendocardium showed discoloration in all five patients; left ventricular subepicardial discoloration also was noted in two patients (11 and 14).

Small nodules on or near the cardiac valves were observed grossly in four patients (1, 5, 7, and 8). Patient 1 had a yellow nodule, 2 mm in diameter, on the atrial aspect of the mitral annulus, at the basal attachment of the posterior mitral leaflet (fig. 1A, B). Also present in endocardium of this patient was a larger (4 × 5 mm), multilobulated nodule that was adjacent to the membranous portion of the ventricular septum near the base of the noncoronary cusp of the aortic valve (fig. 1A). The heart of patient 5 had several

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### Table 2. Infantile Cardiomyopathy with Histiocytoid Change in Cardiac Muscle Cells: Necropsy Findings in 14 Patients

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Cardiac Wt. (N)</th>
<th>Mural thrombi</th>
<th>Endoc. fibr.</th>
<th>Card. necr.</th>
<th>Histiocytoid cells</th>
<th>Distribution in:</th>
<th>Reaction for</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inflam. cells</td>
<td>Myocardium</td>
<td>Valves</td>
<td>A-VCS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MV</td>
<td>±</td>
<td>+</td>
<td>Staph. tracheobronchitis; pulmonary embolus; anoxic encephalopathy</td>
</tr>
<tr>
<td>1</td>
<td>68(45)</td>
<td>RV</td>
<td>0</td>
<td>LV</td>
<td>0</td>
<td>LA, RA, LV, RV</td>
<td>MV</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>108(45)</td>
<td>0</td>
<td>LV</td>
<td>LV</td>
<td>0</td>
<td>LV</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>66(52)</td>
<td>0</td>
<td>LV</td>
<td>0</td>
<td>+</td>
<td>LV</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>75(52)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>LV, RV</td>
<td>0</td>
<td>near BH</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>0</td>
<td>LA, LV</td>
<td>0</td>
<td>+</td>
<td>LV, RV</td>
<td>MV, TV</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>LV</td>
<td>MV</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>RA</td>
<td>MV</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>80(52)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>?*</td>
<td>MV, base of AV</td>
<td>SAN</td>
</tr>
<tr>
<td>9</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>LV</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>65(48)</td>
<td>RA, LV§</td>
<td>+*</td>
<td>0†</td>
<td>+</td>
<td>RA, RV, LV</td>
<td>0</td>
<td>A-VN</td>
</tr>
<tr>
<td>11</td>
<td>65(44)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>LV, RV</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>55(48)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>LV, RV</td>
<td>LA, RA</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>76(56)</td>
<td>0</td>
<td>LV</td>
<td>LV</td>
<td>+</td>
<td>LA, LV</td>
<td>MV, base of AV</td>
<td>LBB</td>
</tr>
<tr>
<td>14</td>
<td>75(37)</td>
<td>0</td>
<td>0</td>
<td>LV, VS</td>
<td>+</td>
<td>LA, LV, RV</td>
<td>0</td>
<td>A-VN, BH, both BB</td>
</tr>
</tbody>
</table>

*Abbreviations: AV = aortic valve; A-VCS = atrioventricular conduction system; A-VN = atrioventricular node; BB = bundle branches; BH = bundle of His; Card. necr. = cardiac necrosis; Endoc. fibr. = endocardial fibrin; Inflam. cells = inflammatory cells; LA = left atrium; LBB = left bundle branch; LV = left ventricle; MV = mitral valve; N = normal cardiac weight, in grams, for age; PAS = periodic acid-Schiff reaction; RA = right atrium; RV = right ventricle; SAN = sinoatrial node; TV = tricuspid valve; VS = ventricular septum; Wt = weight in grams; ± = present; 0 = absent; — = information not available; *= variable from negative to slightly positive.

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*Exact site not specified.
†Myocardial degeneration present.
‡Near base of tricuspid valve.
§Septic thrombus.
yellow endocardial plaques and small nodules, 1 mm in diameter, below the annulus of the pulmonic valve and along the annulus of the tricuspid valve, as well as a 2 mm nodule on the mitral valve 5 mm above its closing margin; this patient had such severe, extensive yellow-white discoloration of left ventricular subendocardium that only a few, small focal areas retained their normal color. In contrast to this, gross cardiac lesions in patient 7 were limited to small nodules on the posterior leaflet of the mitral valve and in the right atrium, just above the septal leaflet of the tricuspid valve. The heart of patient 8 had a yellowish brown, lobulated, 4 mm nodule at the base of the mitral valve and several small, yellowish brown nodules on both surfaces of the anterior leaflet of the mitral valve and on the adjacent endocardium at the base of the septum, just reaching the base of the right coronary cusp of the aortic valve; no gross lesions were described in the myocardium of this patient. Nodules in parietal pericardium were not found in any of the 14 patients.

On histologic study (figs. 1-5), the characteristic finding in all the hearts was the presence of large (20 to 40 μ in diameter), rounded or oval-shaped cells with smooth borders, one or two nuclei that usually were deeply indented, and lightly eosinophilic cytoplasm with numerous, small (1-3 μ in diameter) vacuoles. These cells appeared particularly large because of the small diameters (5-8 μ) of the uninvolved heart muscle cells in these patients. Some of the large cells appeared to be isolated in the interstitium, either singly or in clusters that measured up to several mm (fig. 2A). These cells contained no myofibrils and resembled foamy or lipid-filled histiocytes (fig. 4A). Other cells, however, were in direct contact with unaltered cardiac muscle cells and with cells that appeared intermediate forms between normal cardiac muscle cells and the clear cells just described (figs. 2B and 5A). Appropriate staining procedures showed that the large, abnormal cells contained variable amounts of glycogen and lipofuscin. Frozen sections of heart tissue from five of our patients (1 and 3-6)

FIGURE 1. Gross and histologic views of nodules in valvular and mural endocardium of patient 1. A) Views of small nodule (indicated by 3 arrowheads) on posterior leaflet of mitral valve (PML) and of larger nodule (indicated by 5 arrowheads) adjacent to membranous portion of ventricular septum (MVS). LA = left atrium; PMP = posteromedial papillary muscle; AML = anterior leaflet of mitral valve. × 4. B) Higher magnification view of nodule shown in lower left of A. This nodule is located at junction between left atrial mural endocardium (LA) and the endocardium of the atrial side of the posterior leaflet of the mitral valve (PML). The chorda tendinea on the right extends from posteromedial papillary muscle to anterior mitral leaflet. × 10. C) Histologic section through left atrial wall (LA), posterior mitral leaflet (PML) and posterior wall of left ventricle (LV), showing thickening of leaflet. Hematoxylin-eosin, × 17. D) Higher magnification view of area within rectangle in C shows that valvular thickening is caused by masses of cells with finely vacuolated cytoplasm and no myofibrils. Hematoxylin-eosin, × 200.
were stained either with oil red O or Sudan black B. Study of these preparations disclosed numerous droplets of nonbirefringent lipid in many of the large, abnormal cells in patients 3, 4, and 6; lipid droplets in cells of this type were sparse in patient 5 and absent in patient 1.

The large, vacuolated cells were present in left ventricular myocardium in our six patients and in six (patients 9–14) of the eight previously reported patients; the distribution of these cells was not described in detail in the other two patients (7 and 8). In all 12 patients with left ventricular involvement these cells were found in subendocardial areas; masses of these cells also were observed in left ventricular subepicardium of patients 1, 2, 4, and 9–11. Selective involvement of left ventricular papillary muscles was not found in any patient. The right ventricle was involved in seven patients (1, 4, 5, 10–12, and 14); the right atrium, in four (1, 7, 10, and 12); the left atrium, in four (1, 12–14); various areas of the atrioventricular conduction system, in six (4, 8, 10, 11, 13, and 14), and the cardiac valves in six (1, 5–8, and 13). The morphology of the large, vacuolated cells was the same regardless of their location in the heart. In one patient (4) large masses of these cells were present in the atrioventricular ring near the bundle of His. In other patients (see table 2) the cells of the bundle of His and its branches were interspersed with large, vacuolated cells of the type described above. None of these patients, however, developed A-V block. The mitral valve was involved in six patients (1, 5–8, and 13) in the form of small nodules or strands of histiocytelike, vacuolated cells (figs. 1C and 1D) in the upper third of the leaflets (i.e., the third adjacent to the valvular ring). Clusters of these cells were found near the base of the tricuspid valve in patient 5 and near the base of the aortic valve in patients 8 and 13.

Myocardial necroses were observed in patients 1, 2, 12, 13, and 14. Patient 1 had microinfarcts, consisting of small areas of coagulation necrosis, in left ventricular subendocardium (fig. 3). Some, but not all, of these areas were adjacent to masses of the vacuolated cells. Patient 2 had small, patchy foci of myocytolysis, but not of coagulation necrosis, in left ventricular subendocardium. This myocytolysis was characterized by dissolution of the myofibrils, with formation of elongated cells that consisted of sarcomembrane sheaths and clear, empty, nonvacuolated cytoplasm. These cells were of the same size as uninvolved cardiac muscle cells and showed no tendency to assume spherical shapes. Patient 14 had sharply demarcated zones of acute ischemic necrosis in the inner and middle third of the left ventricular free wall, ventricular septum, and both atria. For the most part these microinfarcts were located in areas of previously unaltered myocardium, but occasionally also involved zones containing the large, vacuolated cells. Patient 13 was the only one in whom myocardial necrosis was limited to zones within the larger accumulations of large, histiocytelike cells in left ventricle.

Chronic inflammatory cells were found in six patients (3, 5, 10, 12–14). In patients 3 and 5 the inflammatory cells, mostly lymphocytes, were not associated with cardiac necrosis and were present both within and outside areas containing the large, clear cells. In patient 10 the inflammatory cells consisted of histiocytes and Anitschkow cells that were associated with the large, vacuolated cells. In patients 12–14 the inflammatory response was localized to areas of cardiac necrosis.

Extracardiac pathologic findings in the 14 patients are listed in table 2. In the majority of the patients they consisted of visceral organ changes that were attributable to hypotension, hypoxia, and congestive cardiac failure. In addition, patients 1, 2, 5, 7 and 9 had evidence of pulmonary infections; patients 4 and 9 had enlarged mesenteric lymph nodes, and patients 1 and 10 had embolic phenomena resulting from cardiac mural thrombi. Changes indicative of Reye's syndrome such as fatty degeneration of liver and kidneys were not described in any of the eight previously reported patients; these changes were specifically sought and not found in our six patients. Attempts to isolate viruses from various tissues and body fluids of patients 12 and 13 were unsuccessful.

Ultrastructural Studies

Ultrastructural studies, with emphasis on defining the features of the histiocytelike cells, were made of myocardium from patients 4 and 12. Tissues from patient 12

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**Figure 2. Nodules of histiocytelike cardiac muscle cells in left ventricle myocardium of patient 1.** A) Low magnification view showing nodules that surround a thin-walled blood vessel and are clearly demarcated from uninvolved muscle cells. Hematoxylin-eosin, × 100. B) High magnification view of edge of subendocardial nodule (note endocardium on right side) composed of vacuolated cells. In contrast to the nodule in A, this nodule is bordered by cells that have lost some of their contractile elements and appear transitional between normal and histiocytoid muscle cells. Compare with figures 5 and 6. Hematoxylin-eosin, × 400.
were fixed five hours after death by perfusion of the coronary arteries with glutaraldehyde. Preservation of structural detail in these tissues (figs. 4–7) was better than in tissues from patient 4, which were fixed by immersion eight hours after death. Nevertheless, the findings in both patients were the same, for which reason they are not described separately. A preliminary report of the ultrastructural findings in patient 12 has been presented by one of us (W.H.H.).

The histiocytoid-like cells (figs. 4B, 5B, and 6A) had smooth borders with no microvilli or surface projections. The plasma membranes of adjacent cells followed parallel courses, but without the interdigitations that are characteristic of intercellular junctions of normal human cardiac muscle cells. These areas of parallel membranes had desmosomes (figs. 4B, 5B, 6A and 7A), but not nexuses. Basal laminae were thin and inconspicuous. The nuclear membranes showed irregular indentations and convolutions. Nucleoli were small. The chromatin was in part margined and in part finely dispersed. The structure of the nuclei of these cells did not differ from that of the nuclei of unaltered cardiac muscle cells. No viral particles or inclusions were observed either in the nuclei or in the cytoplasm. Most of the cytoplasm was occupied by mitochondria. Compared to mitochondria of normal cardiac muscle cells, those in the histiocytoid-like cells were more concentrated (i.e., occupied a much greater than normal fraction of the total cell volume), exhibited greater variation in size, and had less densely packed and more vesicular-appearing cristae. Frequently they also contained intramitochondrial inclusions, of which three types were identified: 1) stacks of closely apposed, parallel, unusually dense cristae (fig. 6A); 2) intramitochondrial glycogen deposits (figs. 6A and 7B), similar to those found in cardiac muscle cells in other pathological conditions, and 3) rounded, dense inclusions (fig. 6B) that measured from 1,000 to 2,000 Å in diameter and resembled lipid droplets. Tubules of sarcoplasmic reticulum, T tubules, Golgi zones, and cisterns of rough-surfaced endoplasmic reticulum were not present in any of the histiocytoid-like cells, and lysosomes were rarely found. The numbers of lipid droplets, glycogen particles and lipofuscin granules varied considerably from one cell to another. In general, the cells in patient 4 contained much more lipid than those in patient 12.

Figure 3. Myocardial necrosis and histiocytoid change in left ventricular myocardium of patients 1 (A and B) and 3 (C). A) Thickened endocardium overlies a zone of myocardial necrosis and several foci of histiocytoid cells. Note the sparing of necrosis in the area adjacent to the blood vessel at bottom center. Hematoxylin-eosin, × 50. B) Higher magnification view of one of the foci of histiocytoid cells (shown at upper right in A) which is well demarcated from adjacent myocardium. These cells appear similar to those in the mitral valve (see fig. 1D). Only one of these cells (lower center) contains myofibrils. Hematoxylin-eosin, × 500. C) Frozen section showing variable numbers of fine lipid droplets in the large, abnormal cells, but not in endocardium (upper left) or normal-sized muscle cells (lower right). Sudan black B, × 250.
Glycogen particles, demonstrated selectively by the Thiéry method, were very abundant in some cells (fig. 7B). These particles, the lipid droplets, and the mitochondria appeared to cause the vacuolization observed in histologic sections. In patient 12, some cardiac muscle cells contained glycogen particles arranged into elongated strands.

Most of the histiocyte-like cells were totally devoid of myofibrils. Only occasionally a portion of a myofibril could be identified in the cytoplasm. Most cells, however, contained small patches of electron-dense material subjacent to their plasma membranes (figs. 4B, 6B, 6C, 7A and 7D). This material resembled that in normal Z bands; in some cells (fig. 7D) it was amorphous, while in others (figs. 6C and 7A) it formed well defined masses that had a periodic substructure and were associated with filaments that measured from 60 to 80 Å in diameter. The substructure of the latter masses was similar to that of the abnormal Z band material that has been described in cardiac and skeletal muscle cells in a variety of disease states (see reference 10 for review). The periphery of the histiocyte-like cells also contained clusters of ribosomes (figs. 6C and 7D), many of which were associated with the Z-band-like material, and a small meshwork of microtubules (fig. 7C) that measured 200 Å in diameter.

**Histopathologic Studies of Myocardial Necrosis in Infants and Children**

In order to evaluate the possibility that the lesions observed in our patients were a peculiar, age-related manifestation of myocardial damage and necrosis resulting from prolonged, severe cardiac arrhythmias in small children, we reviewed histologic sections of myocardium from a group of 26 infants and children who had been diagnosed at necropsy as having myocardial necrosis of various causes. Six of these patients were from two to nine days of age; six, from two to 20 weeks; three, from one to two years, and 11 from two to 16 years. The ages and diagnoses of these patients are listed in table 3. As expected from the wide variety of diseases, the nature and extent of the cardiac necroses in these patients varied considerably. In no instance, however, did we find large, foamy, histiocyte-like cardiac muscle cells such as those in the patients.
cytolysis appeared to proceed in ways comparable
described in the preceding sections of this communication. In these 26 patients both coagulation necrosis and myocytolysis appeared to proceed in ways comparable to those observed in the hearts of adults.

Discussion

This study documents the occurrence of a distinct clinicopathologic syndrome that develops in small children and is characterized by severe, recurrent, eventually fatal cardiac arrhythmias and by foci of severely altered cardiac muscle cells. These cells are enlarged and round-shaped, have a foamy cytoplasm, lack myofibrils, and resemble histiocytes. It is possible that these cardiac cellular alterations represent a peculiar form of myocytolysis occurring in small children as the result of prolonged, severe arrhythmias. Several findings, however, favor the concept that these arrhythmias are a consequence rather than a cause of the heart disease, and that the latter is a form of cardiomyopathy. These findings relate to the presence of cardiac hypertrophy and to the gross and microscopic features of the lesions in our six patients and in eight others previously reported. A patient reported in 1935 by Wegman and Egbert as having a rhabdomyoma may represent an additional case of this syndrome; because of incomplete anatomic information this patient has not been included in the present series.

All 14 patients had increased cardiac weights, often to a very considerable extent, even though most of these patients died within a few days after developing their terminal illnesses. Ten of the 14 patients died within three days of the onset of the arrhythmias; one survived for six days, and three lived for one to two months. Therefore, it would not seem possible that these patients could develop severe degrees of cardiac hypertrophy during such short periods of time (for example, the cardiac weights in patients 2 and 14, each of whom survived only for two days, were twice normal for age). Thus, cardiac hypertrophy must have developed in these patients well before the onset of the arrhythmias. We consider the small foci of myocardial necrosis, which were found in five patients, to be ischemic lesions resulting from prolonged arrhythmias and associated poor myocardial perfusion. The nature and distribution of these lesions are con-
sistent with this concept. The distribution of the large, foamy, histiocytoid-like cardiac muscle cells differed from that of the ischemic lesions. In particular, the presence of such cells in cardiac valves is most unlikely to result from ischemic damage to the cardiac muscle cells that normally are present in these structures.

The most convincing evidence that the histiocytoid-like cardiac muscle cells do not develop as a result of ischemia was provided by: 1) review of the histologic features of myocardial lesions occurring in 26 other infants and children with cardiac necroses from various causes, and 2) comparison of the ultrastructural findings in the present study and in studies of experimentally induced myocardial ischemia. Histiocytoid-like cardiac muscle cells were not found in any of the 26 patients with cardiac necroses of various types. Such cells have not been described in other morphologic studies of myocardial ischemia and necrosis or of cardiomyopathies in children. In fact, we are not aware of these histiocytoid-like cardiac muscle cells being described in any other condition. These histiocytoid-like cells do bear some resemblance to the large, clear cells in cardiac rhabdomyomas. The latter cells do have myofibrils arranged either radially or in narrow, peripheral zones parallel to the plasma membranes and their cytoplasm is clear rather than extensively vacuolated. Rhabdomyomas do not originate from, or invade, cardiac valves. As discussed below, rhabdomyoma cells also differ ultrastructurally from the histiocytoid-like cardiac muscle cells.

At the ultrastructural level, the histiocytoid-like cardiac muscle cells were characterized by: 1) increase in cellular size; 2) altered cell shape; 3) loss of myofibrils, sarcoplasmic reticulum, and T system; 4) marked increase in the fraction of the total cell volume occupied by mitochondria; 5) accumulation of variable amounts of glycogen and lipids; 6) partial or complete dissociation of intercellular junctions, and 7) preservation of nuclear structure. These features are similar to those described by Voth in patient 7 and by Bove and Schwartz in patient 13. In contrast, the ultrastructural features of myocardial ischemia (see references 24 and 25 for reviews) are: 1) intracellular swelling that is not accom-

**Figure 6.** Abnormalities of contractile elements in histiocytoid muscle cells from patient 12. A) Electron micrograph of small histiocytoid-like cell surrounded by cardiac muscle cells with normal contractile elements. Only one fragment of a myofibril (small arrowheads at upper right) remains in this cell, which is filled with closely packed mitochondria. Some of the mitochondria contain stacks of parallel cristae or glycogen deposits (large arrowheads). A desmosome (paired arrowheads at lower left) still connects this cell to an adjacent muscle cell. ×9,000. B) Peripheral region of a cell similar to that shown in figure 4B, showing a desmosome (paired arrowheads), a dense, lipid-like intramitochondrial inclusion (MI), masses of Z-band-like material (ZB), residual bodies (RB), and numerous clusters of ribosomes (R). ×20,000. C) High magnification view of periodic substructure of Z-band-like material in histiocytoid cell. Note thin filaments attached to the mass of Z-band-like material. ×62,000.
panned by change in cell shape from cylindrical to spherical; 2) early, severe mitochondrial damage, with formation of intramitochondrial flocculent precipitates or calcific deposits; 3) myofibrillar alterations that consist either of relaxation of sarcomeres and persistence of myofilaments for relatively long periods of time (coagulation necrosis) or hypercontraction and dissolution (myocytolysis); 4) glycogen depletion, and 5) rapid, progressive nuclear damage. These features differ from those of the histiocyte-like muscle cells in our patients. Cardiac rhabdomyoma cells have intercellular junctions, with desmosomes and nexuses, all along their periphery. These cells usually have few mitochondria and large amounts of glycogen; they contain clearly recognizable myofibrils as well as peculiar banded structures known as leptofibrils. Thus, rhabdomyoma cells also differ from the histiocyte-like cardiac muscle cells in our patients.

The histiocyte-like appearance of these cardiac muscle cells was due to the change in cellular shape, the loss of myofibrils, and the cytoplasmic vacuolization. Although it was pronounced in histologic preparations, this resemblance was not evident on ultrastructural study. Histiocytes are distinguishable by their markedly irregular surfaces, which have many protrusions and pocket-like flaps, and by their well developed Golgi zones, cisterns of endoplasmic reticulum and often prominent lysosomes and residual bodies. These features were not present in the histiocyte-like cardiac muscle cells. The change in the shapes of these cells appeared to be made possible by the loss of myofibrils and by the immaturity of the connective tissue framework that surrounds the cardiac muscle cells in very young children. We attribute the marked increase in cell size to cytoplasmic distension by both swelling and proliferation of mitochondria. We believe that mitochondrial swelling alone cannot account for the fact that these cells, which were enlarged to several times their normal size, were filled with mitochondria. Therefore, actual proliferation of mitochondria must have taken place. The network of microtubules in peripheral regions of these cells may have served to stabilize their shape. It is uncertain whether the accumulations of Z band material were due to reorganization of Z band material derived from lysed myofibrils or to new synthesis of Z band material. It was evident that these cells

FIGURE 7. Subcellular structures in histiocyte-like cardiac muscle cells. A) Desmosome with typical morphology is adjacent to mass of Z-band-like material. × 67,000. B) Intramitochondrial (arrowheads) and free cytoplasmic glycogen are visualized as dark particles in section stained according to method of Thiery. The nucleus and nucleolus are unstained. × 7,500. C) Microtubules (arrowheads) are close to cell surface. × 34,500. D) Small masses of Z-band-like material (arrowheads) are associated with clusters of ribosomes and are immediately subjacent to the plasma membrane. × 37,000.
had undergone extensive dissociation of their intercellular junctions, of which only a few desmosomes remained. The accumulation of glycogen and fat, both of which normally serve as sources of energy for contraction, may reflect the loss of contractile function in these cells. We do not consider that the deposition of either of these substances is a critical feature of this cardiomyopathy, even though the lipid deposition has attracted considerable attention. We found lipid deposition to be an inconstant feature of the histiocyte-like cells. The features just reviewed and the presence of intermediate forms of these cells indicate that the histiocyte-like cells are cardiac muscle cells that have assumed a very primitive type of morphology. Increased automaticity, with a pronounced tendency to produce ectopic cardiac rhythms, may be a consequence of this peculiar morphology.

The mitochondrial alterations are one of the most prominent morphologic features of this syndrome. Mitochondrial proliferation in cardiac muscle cells is not a phenomenon unique to the patients described in this report and in that of Bove and Schwartz. We also have observed this alteration in a small percentage of degenerated cardiac muscle cells from adult patients with severe cardiac hypertrophy due to hypertrophic cardiomyopathy (asymmetric septal hypertrophy, ASH) or to aortic valvular disease. Although in these patients mitochondrial proliferation is accompanied by myofibrillar loss, it is not associated with cellular enlargement or spherical cell shape and histiocyte-like appearance. It also has been our experience that degenerated cardiac muscle cells showing mitochondrial proliferation in adult patients do not form clusters or nodules. Some of the mitochondria in the histiocyte-like cells had glycogen deposits; others had either stacks of dense cristae or lipid-like inclusions. We consider the accumulation of glycogen to be related to increased permeability of the outer mitochondrial membranes (see reference 9 for review). The stacks of cristae may result from postmortem autolysis, and the significance of the lipid-like inclusions is unknown. We did not observe nuclear changes of the type found by Bove and Schwartz in their patient (14), although we have observed such changes in myocardium of patients receiving anthracycline drugs. We consider these changes to represent disruption and unraveling of nuclear chromatin and to differ clearly from those due to the presence of myxoviruses in nuclei. The presence of nodules of histiocytoid cells in cardiac valves is attributable to the fact that cardiac muscle cells are normal components of atrioventricular valves (see 30, 31 for review).

The studies of James on the remodeling of the bundle of His in newborn humans and the observations of Manasek on myocardial cell death in chick embryos are pertinent to a discussion of myocardial necrosis in infants, as these studies show that morphogenesis of the heart involves the death of certain cells. James found evidence of cell death in some areas of the atrioventricular conduction system, particularly in the left half of the bundle of His, and considered this change to be part of the normal postnatal resorptive degeneration that molds and shapes the bundle of His. The involved cells appeared pale and enlarged, resembling somewhat the abnormal cells described in this communication. The abnormal cells in our patients were not, however, components of the conduction system. No data are available on the ultrastructure of the cells described by James within the conduction system. In an electron microscopic study, Manasek showed that degeneration and death of cells also is a normal occurrence during the morphogenesis of embryonic chick ventricle (at seven days of incubation). Dying cells were extremely rare in developing ventricular trabeculae and did not show any specific distribution in the remainder of the ventricular wall. The dying cells described by Manasek were characterized by: loss of shape, with the cells becoming rounded; decrease in size to about 5 μ or less; dissociation of intercellular junctions; marked nuclear pyknosis; increase in the density of the cytoplasm, and presence of large amounts of glycogen. The end stage of this process was removal of the cells through phagocytosis by macrophages.

In contrast to the altered cells in our patients, the dying cells in chick embryos did not show an increase in size, large numbers of mitochondria, or an increase in the lucency of their cytoplasm. The cells in our patients did not show the increased cytoplasmic density, the nuclear pyknosis, or the topographical distribution of the cells in chick embryos. From these comparisons we conclude that the pathologic process in our patients differs morphologically from those described by James and Manasek.

We believe that the clinical and pathologic alterations discussed above are manifestations of a cardiomyopathy, the etiology of which is unclear. No evidence of a familial incidence was found in any of the patients, and exposure to toxic agents could be documented only in one patient. The changes observed are not suggestive of an inborn error of metabolism involving the heart. The possibility of a con-
genital defect involving the differentiation of certain groups of cardiac muscle cells cannot be excluded, although it is difficult to explain all of the features (particularly the hypertrophy) on the basis of such a defect. The peculiar sex distribution (12 girls and two boys) is unexplained.

In searching for possible causes of this disorder, it is of interest to note that several of the patients had prodromes characterized by illnesses that definitely were or could have been caused by viruses, while others had recently received vaccinations against viral diseases. Patients 1, 4, 5, 8, 10, 11, and 12 presented with vomiting; only in patient 4 was this associated with diarrhea; in the other patients the etiology of the vomiting was unclear, although it could have been related to the arrhythmia. Patient 3 had an upper respiratory tract infection, and patients 4 and 9 were found to have enlarged mesenteric lymph nodes. Whether these manifestations and the cardiac lesions and pulmonary infections found at necropsy were caused by viral infections or by some bizarre post-viral stage remains a matter of conjecture. Patient 2 had had roseola and patient 6, chickenpox. Patient 14 was the only one in whom the arrhythmias had an obvious cause; this patient had Wolff-Parkinson-White syndrome.

Although we cannot exclude the possibility that the cardiac lesions in our patients are those of a bizarre form of viral myocarditis, we are not aware of such lesions having been described in viral myocarditis. The association at the onset of the illness in some of our patients with exposure to viruses or viral products is reminiscent of that in Reye's syndrome, which also is frequently associated with viral infections and is characterized by encephalopathy and fatty degeneration of visceral organs, especially liver and kidneys.

In a study of the hearts of eight patients with Reye's syndrome, Brown and Madge observed increased cardiac weights, interstitial edema, focal hemorrhages, diffuse lipid deposition in muscle cells, and vacuolization and myocytolysis, but not necrosis; ultrastructural study also disclosed mitochondrial swelling and disruption. The clear differences between clinical and pathologic findings in Reye's syndrome and those in our patients, however, indicate that our patients did not have Reye's syndrome.

In conclusion, we should like to suggest the following possibilities: 1) that the cardiomyopathy in the subjects of this report represents a state of myocardial damage or degeneration related either to viral infection or to other unknown agents; 2) that small children are unusually susceptible to this damage (as they are to damage by viral infections of the heart); 3) that the peculiar distribution of the lesions, not only in the myocardium, but also in the valves, reflects the occurrence of multiple foci of involvement; 4) that this process eventually leads to cardiac hypertrophy and focal degeneration, and 5) that arrhythmias develop only in the terminal phase of the syndrome.

References

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