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Unexpected infant death attributable to cardiac tumor or cardiomyopathy

Immunohistochemical and electron microscopical findings in three cases

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Summary. The pathological findings, including immunohistochemical and electron microscopical findings, in three infants who died unexpectedly of cardiac tumor or cardiomyopathy are reported. The first was a 13-month-old boy with tuberous sclerosis and multiple rhabdomyomas of the heart, who presented with a postpartal cardiac murmur and moderate cardiomegaly. The further history was unknown. The rhabdomyoma nodules were composed of spider cells containing small amounts of desmin and myosin as well as isolated myofibrils. Microscopically small glioma nodules contained high amounts of GFAP. The second case, a boy 4 months of age, died of a large benign fibrous histiocytoma of the heart after an uneventful history. Tumor cells contained alpha-1-anti-chymotrypsin and lysozyme. The third case, a girl 2 months of age, died unexpectedly of histiocytoid cardiomyopathy. The affected cells contained fat droplets, glycogen granules, many leptomer myofibrils and small amounts of myosin and desmin.

Key words: Sudden unexpected infant death – Tuberous sclerosis and multiple rhabdomyomas – Histiocytoid cardiomyopathy – Cardiac tumors – Fibrous histiocytoma

Zusammenfassung: Wir berichten über drei unerwartete Kinds- bzw. Säuglingstodesfälle: Ein 13 Monate alter Junge starb unerwartet und ohne Krankheitszeichen. Er hatte nach der Geburt lediglich mäßige kardiale Symptome aufgewiesen. Im multiplen kardialen Rhabdomyomen wurden Arachnozyten nachgewiesen, die einzelne Myofibrillen und in geringem Umfang Myosin und Desmin enthielten. Eine tuberöse Sklerose wurde durch den Nachweis mikroskopisch kleiner GFAP positiver Gliome gesichert. Im Fall eines 4 Monate alten Jungen konnte durch den Nachweis von alpha-1-Anti-Chymotryp-

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sin und Lysozym ein großes benignes fibröses kardiales Histiozytom diagnostiziert werden. Bei einem 2 Monate alten Mädchen wurde eine histiozytoide Kardiomyopathie durch Nachweis leptomerer Fibrillen und geringer Mengen von Desmin und Myosin gesichert.

Schlüsselwörter: Unerwarteter Säuglings- und Kindstod – Multiple Rhabdomyome und tuberöse Sklerose – Fibröses Histiozytom – Histiozytoide Kardiomyopathie

Introduction

Cardiac tumors and cardiomyopathies are rare causes of sudden unexpected infant death.

In autopsy studies, the frequency of primary cardiac tumors is reported to be far below 1% in all age groups [3, 16]. In contrast, metastatic heart tumors are 6–40 times more frequent [3, 16]. In adults, benign cardiac tumors such as myxomas, lipomas, papillary fibroelastomas, rhabdomyomas and fibromas have been reported in declining order of frequency [3, 16]. In infants, the incidence of primary cardiac tumors is much lower. However, rhabdomyomas, teratomas, fibromas, hemangiomas and mesotheliomas have been observed in declining order of frequency [3, 16].

Primary cardiomyopathies are common in all age groups, decreasing in frequency from congestive to hypertrophic and restricted cardiomyopathies [8]. Histiocytoid cardiomyopathies in infants have only been reported in a small number of cases [1, 5, 6, 11, 13, 14, 15, 17–23, 27, 29, 30].

We describe the morphological findings in three infants who died unexpectedly of cardiac tumors or cardiomyopathy: multiple rhabdomyomas in a case of tuberous sclerosis; a fibrous histiocytoma; and a histiocytoid cardiomyopathy.

Materials and methods

Tissues obtained at autopsy were fixed in 5% neutral formalin and embedded in paraplast by standard protocol. Sections were stained with H&E and Elastica van Gieson (EvG).

For immunohistochemistry, sections were glued to the slides with an aqueous dilution of Pritt (Henkel, Düsseldorf, FRG) and dried for 1 day at 45°C. Tissue sections were incubated with the following commercially available primary antibodies diluted in 5% bovine albumin in phosphate-buffered saline, pH 7.6 (PBSA): GFAP (1:2000), S-100 (1:2000), desmin (1:100), vimentin (1:200), alpha-1-anti-chymotrypsin (1:5000), myosin (1:500) and lysozyme (1:1000). Antigen-antibody complexes were visualized by the peroxidase-antiperoxidase (PAP) reaction for polyclonal antibodies and by avidin biotin complex (ABC) for monoclonal antibodies. Final visualization was achieved by reaction with 3′, 3-diaminobenzidine. Sections were counterstained with hematoxylin. Negative controls were obtained by omission of the primary antibody. All solvents and materials used were of analytical purity.

Antibodies against desmin, glial fibrillary acid protein (GFAP), acidic protein S 100, alpha-1-anti-chymotrypsin and lysozyme were purchased from Dakopatts (Hamburg, FRG), antibodies against vimentin from Boehringer (Mannheim, FRG) and antibodies against myosin from Dianova (Hamburg, FRG). The PAP staining kit was purchased from Dakopatts and the ABC staining kit, from Vecta (Burlingame, CA 94010, USA).

For transmission electron microscopy, formalin-fixed or deparaffinized tissue was postfixed in buffered osmium tetroxide and thereafter routinely embedded in epoxy resins. Thin sections were contrasted with lead citrate and uranyl acetate.

Case 1

The boy (848/80) was born small for date. He was hospitalized with pneumonia following amniotic fluid aspiration and retardation for the first 6 weeks of life. During this time an enlarged heart (see Fig. 1a), supraventricular extrasystoles, a grade 2 to 3 crescendo-decrescendo holosystolic heart murmur and disturbances of repolarization were observed.

Ultrasound examination of the boy's heart revealed a low-grade aortic stenosis but no evidence of any myocardial malformation.

The boy was discharged clearly improved without signs of cardiac decompensation. Further screening examinations did not reveal any serious disease. At the age of 13 months the boy was found dead in his bed.

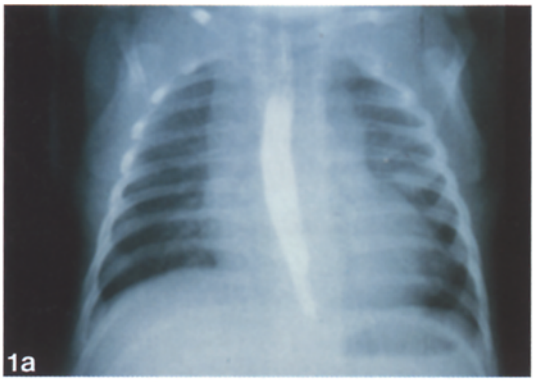
The autopsy showed a seromucous inflammation of the right middle ear without demonstrable bacteria. Screening tests for glucose and acetone in the pericardial fluid were positive. There was a bicuspid aortic valve, and the left ventricular wall was thickened up to 10 mm. In the epicardium, cardiac muscle and endocardium multiple, hard whitish nodules with a maximum diameter of 10 mm were observed, which were found on microscopical examination to be tumor nodules. The tumor was composed of spider cells. Routine histological staining disclosed several empty intracellular vacuoles and thin cytoplasmatic bundles with minute amounts of striated muscle. Electron-microscopical and immunohistochemical investigations showed that the tumor cells contained small amounts of intact myofibrils as well as desmin and myosin, confirming the diagnosis of rhabdomyomas (see Fig. 1b–d).

Further examination revealed moderate hemosiderosis of the lungs and a moderate cerebral edema. Under the ependyma of the right lateral ventricle three microscopically small nodules consisting of strands and whirls of enlarged astrocytes and single giant cells were detected. Nuclei showed moderate enlargement but no mitotic activity. As demonstrated immunohistochemically, the cy-

Fig. 1a–f. Tuberous sclerosis associated with multiple rhabdomyomas (case 1). **a** Chest X-ray film at the age of 6 weeks. **b** Spider cells *(right)* and normal myocardium *(left)*. H&E, 150 × **c** Single myofibrils with z-bands *(arrows)* scattered throughout the cytoplasm in a rhabdomyoma cell. Re-embedding, transmission electronmicroscopy (TEM), 12600 × **d** Single spider cells containing desmin, discrete striation *(arrows)*. Desmin, 300 × **e** Glioma nodule with single giant astrocytes from right central ganglia. H&E, 96 × **f** Glioma nodule with high content of GFAP in cytoplasma and cell processes of giant astrocytes, right central ganglia. GFAP, 150 ×

Fig. 2a–d. Fibrous histiocytoma (case 2). **a** Macroscopic appearance of the cut surface of the tumor in posterior parts of the septum and the left posterior free heart wall. **b** Central part of the tumor with rounded histiocyte-like to spindle-shaped cells in a vague storiform pattern. H&E, 96 × **c** Tumor margin. EvG, 96 × **d** Tumor cells with strongly positive signals for alpha-1-anti-chymotrypsin. Alpha-1-anti-chymotrypsin, 96 ×

Fig. 3a–f. Histiocytoid cardiomyopathy (case 3). **a** Subendocardially grouped myopathic cells in a papillary muscle surrounded by collagenous tissue. EvG, 66 × **b** Normal myocardium *(left)* and foamy myopathic cells *(right)*. H&E, 474 × **c** Weakly positive signals for desmin in myopathic cells. Desmin, 474 × **d** Myopathic cell with nucleus *(N)*, lipid droplets *(L)*, groups of glycogen granules *(G)* and a group of leptomer fibrils *(arrows)*. Primarily formalin fixed material, TEM, 4200 × **e** Detail from **d**: leptomere fibrils and small groups of glycogen granules. TEM, 12000 × **f** Single roughly normal myofibrils with central z-band *(arrows)* from a myopathic cell. TEM, 7200 ×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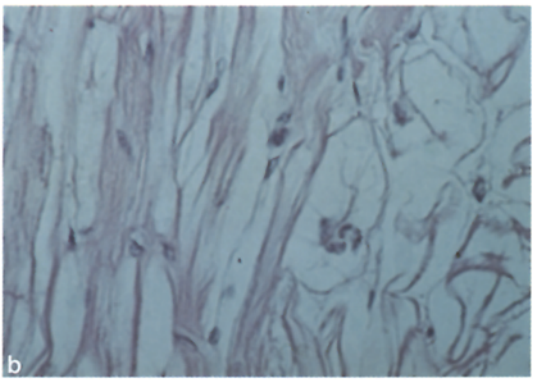
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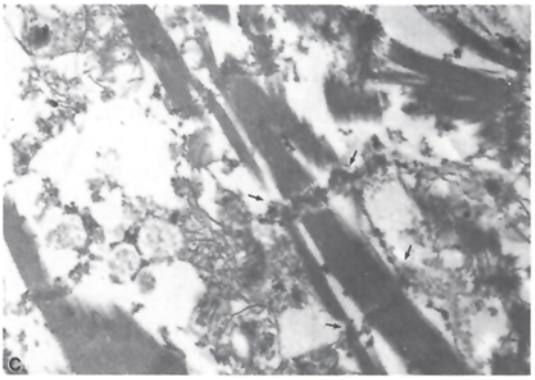
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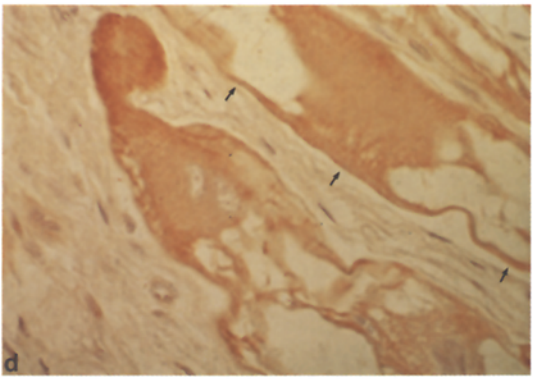
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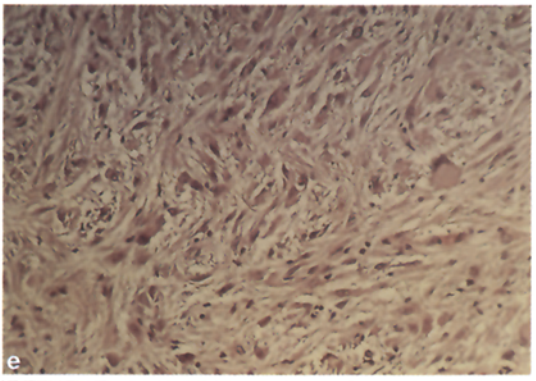
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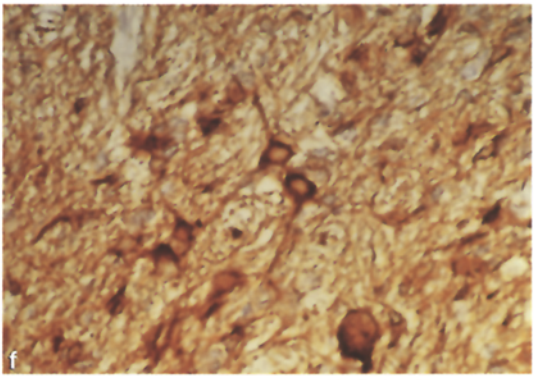
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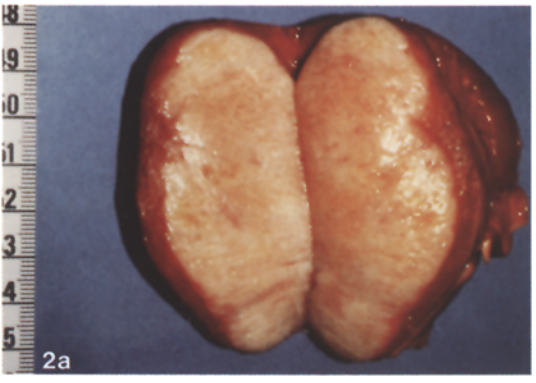
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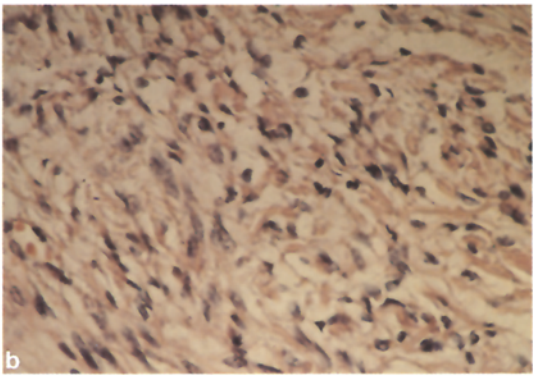
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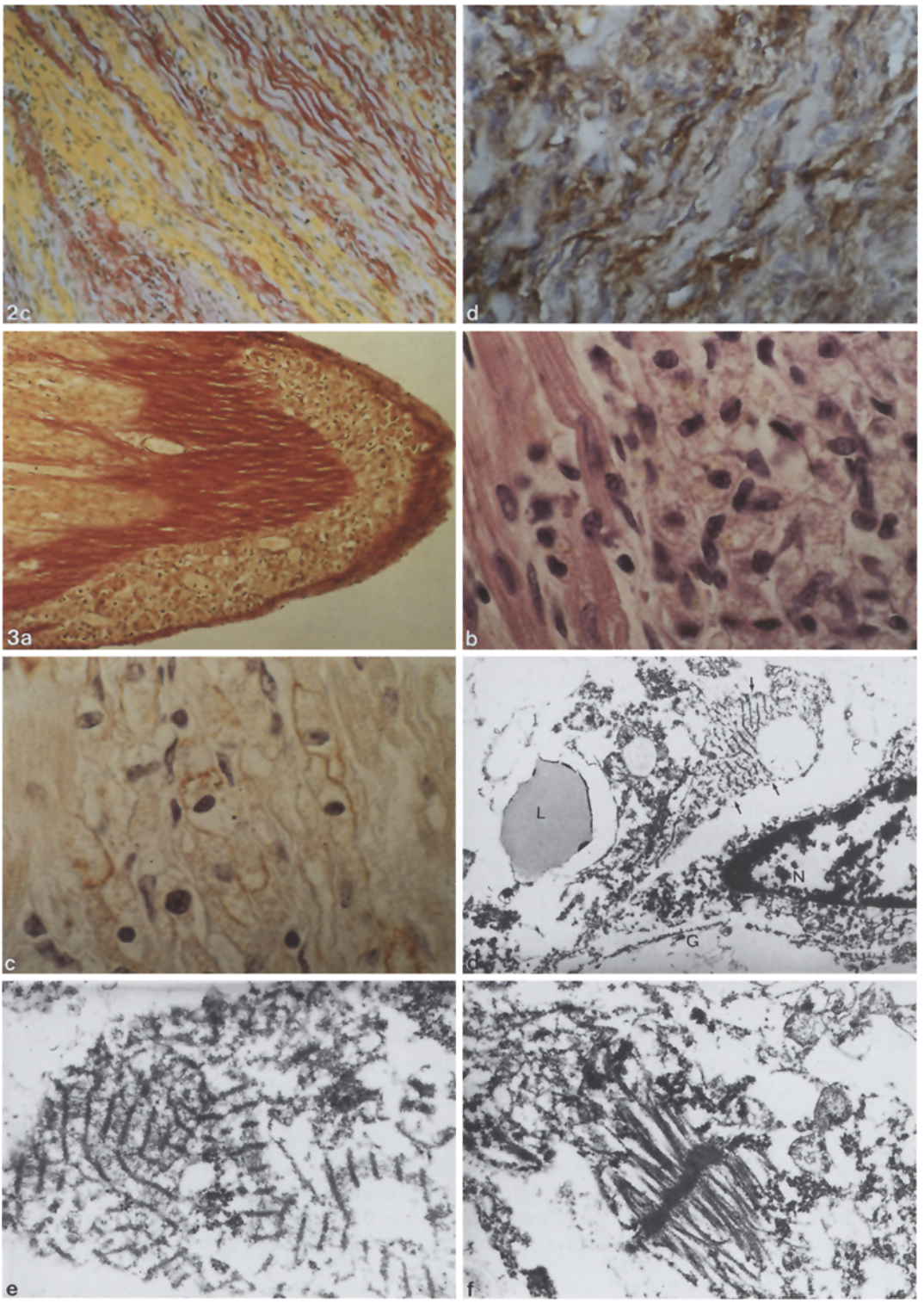
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toplasma and long cytoplasmic processes of these cells contained high amounts of GFAP (see Fig. 1e, f).

These findings are consistent with a benign astrocytoma grade 1 (gigantocellular subependymoma) and thus with the diagnosis of tuberous sclerosis of the brain (Bourneville's syndrome) combined with multiple rhabdomyomas of the heart [12]. Death was attributed to subacute cardiac failure following massive multifocal tumor invasion.

Case 2

The second boy (812/87) died unexpectedly at the age of 4 months. Resuscitation was unsuccessful. At autopsy a moderate cerebral edema, congestive bleeding in the thymus and a marked effusion in the pericardium were observed.

The heart weighed 105 g (more than three times the normal weight). The left posterior wall and parts of the posterior septum were replaced by a $6.5 \times 4 \times 4$ cm whitish tumor of considerable hardness.

Histologically the tumor was poorly demarcated and consited of whirls and strands of collagenous fibers and fibroblast-like cells with small nuclear abnormalities and little mitotic activity. The tumor cells were clearly positive for alpha-1-anti-chymotrypsin and, to a lesser degree, for lysozyme (see Fig. 2a–d), suggesting a benign fibrous histiocytoma [9, 10]. Further microscopical examination revealed markedly congested lungs with moderate signs of shock and moderate inflammatory infiltrations of alveoli and lung parenchyma of the early spreading stage. Death was attributed to cardiac failure following mechanical obstruction of ventricular outflow and disturbed contraction in combination with the onset of a bronchopneumonia.

Case 3

This female baby (910/87) had slight rhinitis at the age of 6 weeks. At the age of 2 months she was found dead in her crib.

At autopsy bilateral otitis media was observed. The secretion contained: *Pseudomonas aeroginosa, Aeromonas hydrophilia, E. coli* and *Streptococcus pneumoniae.* Moderate cerebral edema and moderate congestion of the lungs were also present. Both ventricles were slightly dilated, the left with a nearly spherical configuration. The trabeculae of the left ventricle had a coarse appearance and the endocardium of the atria and of the ventricles was diffusely thickened.

Microscopically, multiple strands and islands of small polygonal cells with vacuolized cytoplasm were observed mainly below the endocardium of ventricles and atria. These cell aggregations were partly surrounded by connective tissue.

Immunohistochemically these cells showed immune reactivity neither for intermediate filaments of connective tissue nor for any enzymes typical for macrophages or S-100. Isolated alpha-1-anti-chymotrypsin-positive macrophages were scattered among the altered cells, whereas the altered cells contained small amounts of desmin and myosin, thus confirming their myogenic origin (see Fig. 3a–c).

Electron microscopically, atypical myocytes containing fat droplets, fragments of myofibrils, leptomer fibrils, intracytoplasmatic desmosomes and glycogen granula were demonstrated in the re-embedded material (see Fig. 3d–f). These findings are consistent with a histiocytoid cardiomyopathy [1, 5, 6, 11, 13, 14, 15, 17–19, 21–23, 29, 30].

Further microscopical examination revealed moderate signs of shock in the lungs.

Death was attributed to arrhythmias as the most probable cardiac reason, caused by extensive cardiomyopathic alterations of the myocardium and especially of the subendocardial cell layers.

Discussion

Cardiomyopathies and tumors of the heart are usually accompanied by clinical symptoms such as pump failure and severe arrhythmias. Up to now, only a small number of cases of unexpected infant and child deaths attributable to cardiac tumors and cardiomyopathies have been reported, including tuberous sclerosis associated with multiple rhabdomyomas [28], solitary rhabdomyomas [4, 26], cardiac fibromas [2, 7, 24] and a fibrous histiocytoma [10].

While dilated and hypertrophic cardiomyopathies and cardiomyopathies in storage disease are well known in infants, histiocytoid cardiomyopathy is rare. Among reported cases of histiocytoid cardiomyopathy only 4 have caused sudden death without clinical symptoms [19, 21, 29].

In all three cases cited here the recent history was uneventful. Only in case 1 had the multiple rhabdomyomas caused moderate postnatal symptoms such as supraventricular extrasysoles, disturbances of repolarization, systolic heart murmur, aortic stenosis and heart enlargement. All these symptoms have been reported in cardiac rhabdomyomas [2–4, 25]. However, these signs are unspecific, and echocardiography had failed to reveal any severe cardiac abnormalities, probably because the tumor nodules were below the detection limits after birth. On the other hand, the large cardiac fibrous histiocytoma had not caused any symptoms during the child's lifetime.

Heart tumors may lead to sudden death by various mechanisms: they may cause arrhythmias due to invasion, replacement or compression of the conducting system. On the other hand they may lead to cardiac insufficiency [2, 4, 25, 26] by way of infiltration of myo-, endo- and epicardium, including coronary vessels or obstruction of intracavitary blood flow. In addition, in cases of tuberous sclerosis seizures have to be considered. However, morphological signs, such as lingual bite wounds, may be lacking or cannot be expected, for example in newborns [12, 28].

Moderate iron deposits in the lungs were indicative of chronic congestive heart failure in the case of multiple rhabdomyomas. Marked pericardial effusion and signs of shock in the case of fibrous histiocytoma were suggestive of subacute heart failure. In both cases heart failure was attributable to extensive spread of the tumor in the myocardium.

Our case of histiocytoid cardiomyopathy had not shown any clinical symptoms. In contrast, most of the cases reported in the literature had shown cardiac symptoms. One feature common to all these cases was the presence of moderate to severe arrhythmias. Nonetheless, histiocytoid cardiomyopathies may cause

sudden death [11, 22], especially by way of alterations to the conducting system. In our case the altered cells were widely spread throughout the myocardium, but especially in the subendocardial layers. Signs of shock were present in the lungs, suggesting subacute heart failure most probably caused by severe arrhythmias.

Since only mild clinical symptoms or none at all had been recorded in our observations, all cases were primarily considered to be cases of sudden infant death syndrome (SIDS); autopsy and mircroscopical examination were needed to reveal the presence of severe cardiac lesions. The tuberous sclerosis and the histiocytoid cardiomyopathy were not diagnosed until the results of histological investigations were available. This again emphasizes the importance of autopsy and exact microscopical examination of all infants and children who have died unexpectedly, to avoid overestimation of the frequency of SIDS. The presence of three microscopically small glioma nodules proves the need for an exact microscopical examination of the brains of infants with multiple rhabdomyomas of the heart to allow a proper genetic consultation [2, 12, 28].

In our case of tuberous sclerosis associated with multiple rhabdomyomas immunohistochemical and electron microscopical findings provided further confirmation. However, in the other two cases the diagnosis could only be established by means of immunohistochemical and electron microscopical methods. In cases of rhabdomyomas lacking typical spider cells, the presence of myogenic intermediate filaments can easily be ascertained by immunohistochemical examination and will facilitate the diagnosis.

It might well be speculated that as the use of immunohistochemistry becomes more widespread an increasing number of fibromas might be classified as fibrous histiocytomas.

Early descriptions of the histiocytoid cardiomyopathy focused on the high fat and glycogen contents [5, 13, 14, 15, 19, 27] of the altered cells, which were interpreted as a replacement of myocytes by histiocytes. Electron microscopical examinations revealed that the affected cells were clearly myocytes containing only minute amounts of roughly intact myofibrils and large numbers of swollen mitochondria and leptomer fibrils [5, 6, 11, 13]. Ferrans et al. [11] and Bruton et al. [6] finally coined the term "histiocytoid cardiomyopathy" for this disease. A further argument for the myogenic origin of these cells is given by the demonstration of intermediate filaments typical for myocytes in the altered cells.

The exact pathogenesis of this cardiomyopathy is as yet unknown. Tumors [20] and specific lesions of the conducting system [1, 14, 30] and of myocytes [19], as well as storage diseases and a deficiency in the cardiac cytochrome B system [5, 6, 14, 15, 18, 29] have been discussed. A viral etiology and abnormal development during gestation [11, 22, 23] have also been considered. However, the fact that the majority of these cases are female infants is still not understood.

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