Human Pathology: Case Reports 8 (2017) 51–54

Contents lists available at ScienceDirect

Human Pathology: Case Reports

journal homepage: http://www.humanpathologycasereports.com

Case Report

Histiocytoid cardiomyopathy in an eleven-month-old infant: A case report and literature review☆,☆☆

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ARTICLE INFO

Article history:
Received 23 October 2016
Received in revised form 10 January 2017
Accepted 19 January 2017

1. Introduction

We herein report a case of sudden death in an 11-month-old female infant diagnosed with histiocytoid cardiomyopathy (HC) in post-mortem examination, an extremely rare but distinctive disease responsible for severe ventricular arrhythmia and sudden death mainly in girls less than 2 years old. It is a very important diagnosis to make in order to perform genetic counseling and to rule out the differential diagnoses of child abuse and sudden infant death syndrome (SIDS).

1.1. Case report

An 11-month-old female infant, with an uneventful perinatal period and no clinical history except for a recent non-complicated rhinopharyngitis a week before death, was fed milk at 7 pm and was found pale and unresponsive by her parents in her bed at 10 pm with abnormal respiration. She presented a cardiorespiratory arrest and resuscitation attempts were unsuccessful.

Cerebrospinal fluid analysis, blood cultures and radiologic skeletal survey were normal. At autopsy, external and internal examinations were unremarkable; postmortem findings revealed no evidence of trauma or any argument evoking child abuse syndrome. Weight, length and head circumference measurements were within the average growth standards. All organs were macroscopically normal, including the heart that weighed 32 g.

Microscopically, sections of the heart showed multiple foci of clusters of large, plump, foamy and histiocyte-like cells in the subendocardium of the left ventricle and the septum (Fig. 1A, B). These cells were not seen in the thickness of the myocardium. Neither notable fibrosis nor significant inflammatory infiltrates were noted. Immunostaining showed cytoplasmic expression in numerous histiocytoid cells for the skeletal muscle transcription factor MyoD1 (Fig. 2A) but not for the histiocytic marker CD68 (Fig. 2B). The histiocyte-like cells were also diffusely stained with anti-mitochondria antibody. These findings resulted in the diagnosis of histiocytoid cardiomyopathy. Furthermore, lesions of bronchopneumonia were noted in the superior lobe of the right lung. The remaining organs were histologically within normal limits. Based on these results and in conjunction with the clinical history, the cause of death was ascribed to cardiac dysrhythmia due to histiocytoid cardiomyopathy in a context of bronchopneumonia.

Genetic testing was performed on maternal blood sample and on residual dried blood spot sample of the child. The most common mitochondrial DNA (mtDNA) point mutations (occurring in tRNA for Leucine, tRNA for Lysine, MT-ATPase 6 and MT-ND5 genes) and mtDNA deletion/duplication were ruled out respectively by Sanger sequencing and Southern-blot/long PCR. Furthermore, the m.15498G>A mutation in mtDNA-encoded cytochrome b and mutations in NDUFB9, NDUFB11 and NDUFAF2 genes were also excluded in the maternal blood. An attempt to assess the mutation profile of NDUFB9, NDUFB11 and NDUFAF2 genes was done using the paraffin-embedded heart sample of the child but the technique failed.

2. Discussion

Histiocytoid cardiomyopathy (OMIM number: #500000 [1,2]) was previously reported under many names such as arachnocytosis of the heart muscle, xanthomatous or lipid cardiomyopathy, oncocytic cardiomyopathy, foamy myocardial transformation of infancy, hamartoma or multifocal Purkinje-cell tumor [3–11]. It is a distinctive and rare arrhythmogenic cardiac disorder predominantly affecting infants below the age of 2 years, mostly diagnosed in the first year of life, with a male to female sex ratio of 1:3. It occurs most often in Caucasian infants (80%) [12]. Less than a hundred cases have been reported in the

☆ **Funding source**: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
☆☆ **Conflict of Interest**: The authors have indicated they have no potential conflicts of interest to disclose.
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http://dx.doi.org/10.1016/j.ehpc.2017.01.004

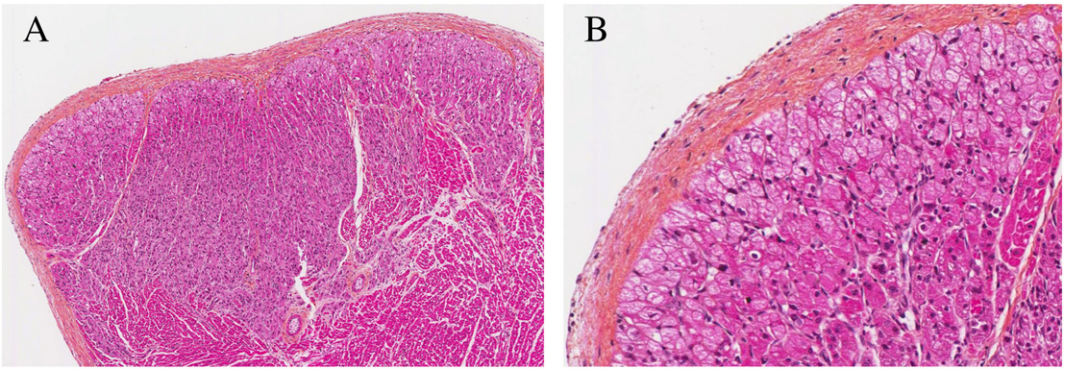

Fig. 1. A, Microscopic view of the subendocardial region showing large clusters of histiocytoid cells contrasting with normal myocytes (Hematoxylin and Eosin stain, original magnification 50×). B, Microscopic view of the same area at higher magnification (200×).

literature so far. The prevalence of this disease is probably underestimated since some cases are undoubtedly diagnosed as SIDS. In fact, some autopsies are refused by parents while others fail to diagnose HC owing to the multifocal distribution of the histiocytoid cells in the myocardium [13]. Therefore, it is very important to perform a systematic examination of the heart at autopsy and to adequately sample the conduction tissue [13–15].

HC manifests as severe cardiac arrhythmias, dilated cardiomyopathy or sudden death occurring respectively in 70%, 95% and 20% of the cases [16]. These manifestations may be preceded or accompanied by flu-like symptoms, such as in our case. Patients may also show cardiac and/or extracardiac malformations [9,17–19]. Clusters of histiocytoid cells may also be seen in exocrine and endocrine glands [5,20,21].

HC is macroscopically characterized by single or multiple subendocardial yellowish nodules occurring in the ventricles, the septum and the valves, ranging from 1 to 91 mm [22]. It may also occur in the myocardium and less frequently in the epicardium. In some cases, pathologic tissue is not macroscopically apparent. The histological findings are pathognomonic for the disease showing characteristic images of multifocal clusters of large histiocytoid cells with granular eosinophilic cytoplasm due to the accumulation of mitochondria. The nuclei are small, round to oval shaped with occasional nucleoli. Histiocytoid cells stain with cholinesterase and for lipids with Sudan black on frozen section [4,23–25]. The HC cells also react with antibodies to myoglobin, myosin and muscle specific actin but don't express histiocyte antigens. Cell proliferation markers are usually negative. The cytoplasm of histiocytoid cells contains a large amount of mitochondria and lipid droplets of variable size but lacks a T-tubule system [20,25–28]. The histiocytoid cells also show poorly developed intercellular junctions.

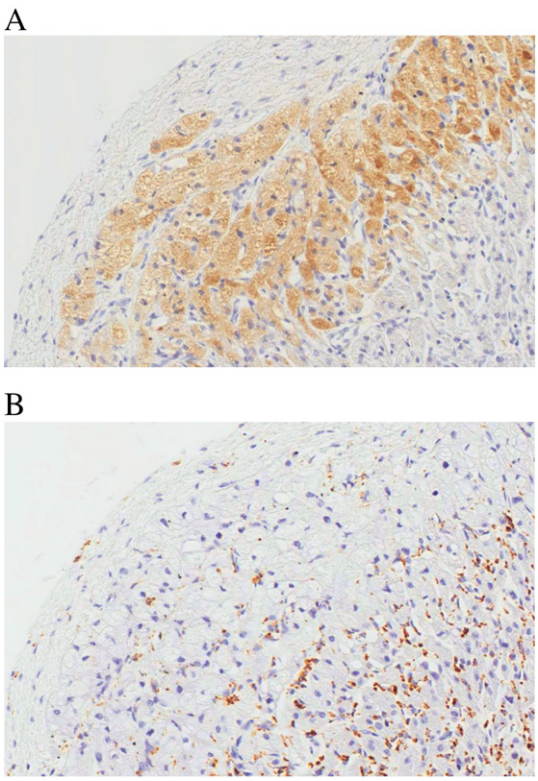

Fig. 2. A, Immunohistochemical expression of MyoD1 in numerous histiocytoid cells, predominantly localized in the superficial layer of the subendocardium (original magnification 200×). B, Absence of CD68 immunohistochemical expression in the histiocytoid cells (original magnification 200×).

The etiopathogenesis of HC is still not clearly defined. Several theories have been proposed including viral infection [20], myocardial ischemia [26], toxic exposure [16], metabolic disorders [11], cardiac lipidosis [29], developmental anomaly of the atrioventricular conduction system [20,25], developmental arrest of cardiac myocytes [5,20], mitochondrial disorder [30], multifocal tumor of Purkinje cells or hamartoma-like aggregations of cardiac myocytes [20]. The disorder was first confused with rhabdomyoma, a benign tumor of the myocardium, and was not recognized as a separate entity until 1962 [31]. It has been listed as a hamartoma among the benign tumor/tumor-like lesions in the 2015 WHO classification of heart tumors [16]. HC is nowadays largely suspected to be caused by a developmental anomaly of the conduction system [16,20,23–25] due to the clinical presentation and the distribution of histiocytoid cells in the myocardium, preferentially involving the conduction system [20,24,25]. Immunohistochemical and ultrastructural characteristics favor this hypothesis too: the primitive Purkinje cells of the developing heart show a remarkable resemblance to histiocytoid cells both showing a strong positivity for cholinesterase and Sudan black on frozen section which is present only in the conduction tissue of the heart and not in the contractile myocytes [20,23,25].

Some authors have also considered HC as a mitochondrial disease [30,32,33]. Early reports of missense mutation in mitochondrial cytochrome *b* gene [34] and biochemical changes in cytochrome *c* reductase activities [19] argued for this hypothesis and the role of complex III deficiency in HC. Another mitochondrial mutation was also found at m.8344A>G within the MT-TK gene in the mtDNA that has been previously described in myoclonic epilepsy associated with ragged-red fibers syndrome (MERRF) [35]. According to Edston and Perskvist [26], HC should be considered as a degenerative process of the cardiomyocytes of the conduction system due to the apoptotic and inflammatory changes frequently observed.

Furthermore, a familial tendency of approximately 5% following an autosomal recessive inheritance pattern has been noted [7,12]. However, X-linked transmission has also been suggested in cases of HC associated with Microphtalmia with linear skin defects syndrome [36,37] and