Short Communication

Histiocytoid Cardiomyopathy: A Mitochondrial Disorder

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ABSTRACT

Histiocytoid cardiomyopathy (HICMP) is a rare, genetic, cardiac disorder of infancy or childhood, predominantly affecting girls, and clinically manifesting as severe cardiac arrhythmias or dilated cardiomyopathy. Pathoanatomically, HICMP is characterized by subendocardial, epicardial, or valvular yellow-tan nodules, which are histologically built up of abnormal Purkinje fibers and multiple, scattered clusters of histiocytoid myocytes, which are filled with an increased number of normal or abnormal mitochondria. Within the myocardium, yellowish areas with irregular outlines are found and are histologically built up of enlarged, polygonal, histiocyte-like cells with foamy granular cytoplasm. Since HICMP is frequently found in patients with mitochondrial deoxyribonucleic acid (DNA) mutations, HICMP cardiomyocytes carry an increased number of normal or abnormal mitochondria, and may show markedly decreased succinate-cytochrome c reductase or NADH-cytochrome c reductase activity; HICMP should be regarded as mitochondrial cardiomyopathy.

Key words: cardiomyopathy, mitochondrial disorder, myocardium, rhythm abnormality, electrocardiogram, echocardiography

Histiocytoid cardiomyopathy (HICMP) is a rare, genetic, cardiac disorder of infancy or childhood, predominantly affecting girls below the age of 2 y, which manifests clinically as severe cardiac arrhythmias or dilated cardiomyopathy with heart failure.[1] Autosomal recessive,[2] X-linked,[3] and maternal inheritance has been described. Previously, HICMP was regarded as a developmental anomaly of the atrioventricular conduction system, multifocal tumor of Purkinje cells, or as a developmental arrest of cardiomyocytes with aggregations of hematoma-like cardiomyocytes, resembling oncocytes.[4,5] Meanwhile, several reports indicate that HICMP is a cardiac manifestation of a mitochondrial disorder,[6–9] justifying its classification as a primary genetic cardiomyopathy according to the classification proposed by the American Heart Association.[10]

Cardiac manifestations of HICMP may be rhythm abnormalities, such as Wolff-Parkinson-White syndrome,[11,12] ventricular tachycardia,[6] or ventricular fibrillation with cardiac arrest and sudden cardiac death.[5,7,13–21] Histiocytoid cardiomyopathy may also manifest as severe dilated cardiomyopathy and heart failure, requiring heart transplantation in specific cases.[22] In certain patients, HICMP may be also associated with left ventricular hypertrabeculation, also known as noncompaction.[23] Rarely, HICMP may present with endocardial fibroelastosis.[17] Extracardiac manifestations include abnormalities of the central nervous system (hydrocephalus), the eyes (corneal opacities, retinal hypoplasia, microphthalmia), the endocrine system (oncocytic cells in various glands), or steatosis of the liver.[4,7,12] Clinically, affected patients may present with palpitations, dyspnea, pulmonary rales, cardiac murmurs, neck vein distension, or edema.[4,19] The diagnosis is established on the basis of the clinical findings, electrocardiography (ECG), echocardiography, myocardial biopsy, or autopsy. There is no specific treatment for HICMP available. Arrhythmias or dilative cardiomoypathy usually respond to established treatment.[5] Supportive measures, as occasionally given for mitochondrial myopathy, have not been tried.

Pathohistologically, HICMP is characterized by the development of abnormal Purkinje fibers within the cardiac conduction system, which interfere with normal cardiac conduction,[2] myocardial thickening,[13,24] or subendocardial yellow-tan nodules,[3,6,25] also found epicardially or at the valves.[4] These nodules are built up of multiple, scattered clusters of histiocytoid myocytes, which are filled with abnormal mitochondria.[3,6,14] Within the myocardium, yellowish areas with irregular outlines have been described, built up of enlarged, polygonal, histiocyte-like cells with foamy granular cytoplasm.[1,6,13,14] These cells react positively with desmin and myoglobin and show disorganized myofibrils, resulting in abnormal striation.[13,14] Affected cardiomyocytes may also contain fat droplets, glycogen granules, leptomer myofibrils, and reduced amounts of myosin or desmin.[19] Cardiomyocytes may also contain poorly developed or absent intercellular junctions, few or no contractile elements, and markedly increased numbers of mitochondria, which tend to accumulate.[4,14,26] Mitochondria may show hyperplasia[1,6,7] or abnormal structure.[3] Granular histiocytoid cells may also be found within the cardiac conduction system with encasement and partial replacement of the bundle of His.[1,15] The abnormal

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cells appear to resemble transformed cardiomyocytes, which possess some features of cardiac conduction system fibers.[1] Aggregates of these cells may form atrioventricular and nodo-ventricular connections, possibly responsible for the arrhythmias frequently found in HICMP.[15] Contrary to previous speculations[3], mitochondrial cardiomyopathy should not be differentiated from HICMP, as histological features attributed only to the one also occur in the other.

Arguments for a mitochondrial disorder as the underlying cause of HICMP are that HICMP was frequently found in patients with mutations of the mitochondrial deoxyribonucleic acid (DNA). In an infant with steatosis of the liver, and bilateral retinal hypoplasia, HICMP was associated with the mitochondrial A8344G transition.[7] Ultrastructural investigations in this patient revealed striking mitochondrial hyperplasia with dispersion of sarcomers.[6,7] Biochemical investigations revealed reduced activity of complexes I and IV of the respiratory chain. In another patient, HICMP was associated with the G15498A mitochondrial cytochrome b mutation, resulting in the amino acid exchange of glycine with aspartic acid at position 251.[8] In a patient with microphthalmia with linear skin defects syndrome due to a mosaic, segmental monosomy of the Xp22.3 region (46, Y, inv [X] [p22.13 approx. 22.2p32 approx. 22.33]/46X) HICMP was found and associated with lactacidosis and agenesis of the corpus callosum.[9] In a female infant, HICMP was associated with skeletal muscle myopathy with generally decreased cytochrome c oxidase activity on muscle biopsy.[6] Further arguments for a mitochondrial defect as the underlying cause of HICMP are the markedly increased number of mitochondria within cardiomyocytes,[4,14,24,26] the extensive hyperplasia of these mitochondria,[3,6,12,24] and, occasionally, the abnormal structure of these mitochondria.[3,6,14] These mitochondria give the cytoplasm a granular or vacuolated appearance.[4] Biochemical investigations of cardiomyocytes may show markedly decreased succinate-cytochrome c reductase and NADH-cytochrome c reductase, why it was already previously interpreted as a defect of complex III of the respiratory chain.[26] Whether the predominance of females affected by HICMP indicates maternal transmission, remains speculative.

Overall, there is increasing evidence from clinical, histological, immunohistological, ultrastructural, biochemical, and genetic investigations that HICMP is a cardiac manifestation of multisystem mitochondrial disorders. Management of HICMP requires a multidisciplinary approach due to the frequent extracardiac comorbidity.

References

1. Ruszkiewicz AR, Vernon-Roberts E: Sudden death in an infant due to histiocytoid cardiomyopathy. A light-microscopic, ultrastructural, and immunohistochemical study. *Am J Forensic Med Pathol* 1995;16:74–80
2. Gilbert-Barness E: Review: metabolic cardiomyopathy and conduction system defects in children. *Ann Clin Lab Sci* 2004;34:15–34
3. Shehata BM, Patterson K, Thomas JE, Scala-Barnett D, Dasu S, et al.: Histiocytoid cardiomyopathy: three new cases and a review of the literature. *Pediatr Dev Pathol* 1998;1:56–69
4. Malhotra V, Ferrans VJ, Virmani R: Infantile histiocytoid cardiomyopathy: three cases and literature review. *Am Heart J* 1994;128:1009–1021
5. Gelb AB, Van Meter SH, Billingham ME, Berry GJ, Rouse RV: Infantile histiocytoid cardiomyopathy-myocardial or conduction system hamartoma: what is the cell type involved? *Hum Pathol* 1993;24:1226–1231
6. Otani M, Hoshida H, Saji T, Matsuo N, Kawamura S: Histiocytoid cardiomyopathy with hypotonia in an infant. *Pathol Int* 1995;45:774–780
7. Vallance HD, Jeven G, Wallace DC, Brown MD: A case of sporadic infantile histiocytoid cardiomyopathy caused by the A8344G (MERRF) mitochondrial DNA mutation. *Pediatr Cardiol* 2004;25:538–540
8. Andreu AL, Checcarelli N, Iwata S, Shanske S, DiMauro S: A missense mutation in the mitochondrial cytochrome b gene in a revisited case with histiocytoid cardiomyopathy. *Pediatr Res* 2000;48:311–314
9. Kutsche K, Werner W, Bartsch O, von der Wense A, Meinecke P, et al.: Microphthalmia with linear skin defects syndrome (MLS): a male with a mosaic paracentric inversion of Xp. *Cytogenet Genome Res* 2002;99:297–302
10. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, et al.: Contemporary definitions and classification of the cardiomyopathies: an American heart association scientific statement from the council on clinical cardiology, heart failure, and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention circulation. 2006;113:1807–1816
11. Cabana MD, Becher O, Smith A: Histiocytoid cardiomyopathy presenting with Wolff-Parkinson-White Syndrome. *Heart* 2000; 83:98–99
12. Bruton D, Herdson PB, Becroft DM: Histiocytoid cardiomyopathy of infancy: an unexplained myofibre degeneration. *Pathology* 1977;9:115–122
13. Boissy C, Chevallier A, Michiels JF, De Swarte M, Mariani R, et al.: Histiocytoid cardiomyopathy: a cause of sudden death in infancy. *Pathol Res Pract* 1997;193:589–596
14. Prahlow JA, Teot LA: Histiocytoid cardiomyopathy: case report and literature review. *J Forensic Sci* 1993;38:1427–1435
15. Koponen MA, Siegel RJ: Histiocytoid cardiomyopathy and sudden death. *Hum Pathol* 1996;27:420–423
16. Aksglaede L, Graem N, Jacobsen JR: Histiocytoid cardiomyopathy: a rare cause of ventricular tachycardia and sudden cardiac death in small children. *Ugeskr Laeger* 2006;168:61–62
17. Grech V, Ellul B, Montalto SA: Sudden cardiac death in infancy due to histiocytoid cardiomyopathy. *Cardiol Young* 2000;10: 49–51
18. Heifetz SA, Faught PR, Bauman M: Pathological case of the month: histiocytoid (oncocytic) cardiomyopathy. *Arch Pediatr Adolesc Med* 1995;149:464–465
19. Jacob B, Haarhoff K, Neuen-Jacob E, Burrig KF, Frenzel H, et al.: Unexpected infant death attributable to cardiac tumor or cardiomyopathy: immunohistochemical and electron microscopical findings in three cases. *Z Rechtsmed* 1990;103: 335–343
20. Saffitz JE, Ferrans VJ, Rodriguez ER, Lewis FR, Roberts WC: Histiocytoid cardiomyopathy: a cause of sudden death in apparently healthy infants. *Am J Cardiol* 1983;52:215–217

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21. Valdes-Dapena M, Gilbert-Barness E: Cardiovascular causes for sudden infant death. *Pediatr Pathol Mol Med* 2002;21: 195–211
22. Zangwill SD, Trost BA, Zlotocha J, Tweddell JS, Jaquiss RD, et al.: Orthotopic heart transplantation in a child with histiocytoid cardiomyopathy. *J Heart Lung Transplant* 2004;23: 902–904
23. Burke A, Mont E, Kutys R, Virmani R: Left ventricular non-compaction: a pathological study of 14 cases. *Hum Pathol* 2005;36:403–411
24. Ferrans VJ, McAllister HA Jr, Haese WH: Infantile cardiomyopathy with histiocytoid change in cardiac muscle cells: report of six patients. *Circulation* 1976;53:708–719
25. Baillie T, Chan YF, Koelmeyer TD, Cluroe AD: Test and teach: ill-defined subendocardial nodules in an infant; histiocytoid cardiomyopathy. *Pathology* 2001;33:230–234
26. Papadimitriou A, Neustein HB, Dimauro S, Stanton R, Bresolin N: Histiocytoid cardiomyopathy of infancy: deficiency of reducible cytochrome b in heart mitochondria. *Pediatr Res* 1984;18:1023–1028

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