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Clinical Case Report

Noncompaction cardiomyopathy in Hirschsprung's disease: a case report

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ABSTRACT

Noncompaction cardiomyopathy is a rare disorder, often associated with cardiac and noncardiac malformations. Hirschsprung's disease, a well-known aganglionosis, is associated with congenital heart diseases and has been reported to be due to impairment migration and differentiation of neural crest cells. Here, we present an 8-month-old male infant who died for cardiogenic shock after surgical resection of the involved bowel segment. The child was affected by both noncompaction cardiomyopathy and Hirschsprung's disease, two entities which can share a common neural crest-derived etiology.

1. Introduction

Noncompaction cardiomyopathy is a rare disorder, whose classification is still under debate. It is an unclassified cardiomyopathy, according to the ESC Working Group on Myocardial and Pericardial Diseases and the World Health Organization, or a primary genetically determined cardiomyopathy, according to the American Heart Association [1,2]. Some cardiologists regard the noncompacted ventricles as a complex dysregulation of the normal development of ventricular myocardial structure and function, induced by different etiologies and physiopathological mechanisms [3–5]. The pathogenesis behind noncompaction cardiomyopathy is not clearly defined. Multiple genetic defects were identified in these patients and an acquired pathology was also suggested [6]. We describe a case of this rare cardiomyopathy in association with Hirschsprung's disease, which, to the best of our knowledge, was never reported.

2. Case report

A term male baby was born by vaginal delivery, with an Apgar score of 8 at 1 min and 10 at 5 min and a birth weight of 3310 g. The familiar history was positive for Hirschsprung's disease (the baby's grandfather and his great-aunt).

Shortly after birth, he manifested symptoms of this disease, namely, delayed meconium passage and abdominal distension. A lower gastrointestinal tract XR examination (barium enema) showed the distension of the proximal sigma and multiple biopsies revealed the absence of ganglion cells in the rectum.

An echocardiography, performed at 4 days after the birth, was reported as normal.

The little patient was discharged at home after 2 weeks, with a conservative therapy.

At the age of 6 months, because of worsening disease, the baby underwent a surgical operation during which a tract involving the sigma and the distal part of the large bowel was excised. Preoperative electrocardiography and chest radiography were normal. After a week, a surgical revision was necessary.

After this second surgical operation, the patient's clinical conditions worsened, presenting with persistent vomiting accompanied by metabolic acidosis and hyponatremia. An exploratory laparotomy excluded that an obstructive bowel disease caused the symptoms. The baby underwent also electrocardiography and echocardiography, which pointed out a massive myocardial ischemia involving the septum and the anterior left ventricle wall and a remarkable cardiac hypokinesis. Extracorporeal membrane oxygenation was implanted, but the conditions deteriorated and, after a few days, the patient died.

Within the days before his death, a molecular genetic examination was also performed, identifying a mutation in homozygosis of methylenetetrahydrofolate reductase (MTHFR) gene, well known to determine a thrombophilic diathesis.

This case was brought to our attention as experts during a penal trial for medical responsibility. A forensic autopsy had previously been performed.

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We reexamined the records of the trial and the histopathologic slides, with the following results.

The presence of a severe Hirschsprung's disease, a well-known aganglionosis of the bowel, was observed, involving the whole large bowel; the lungs presented multiple areas of infarction, as well as the brain: these findings were attributed to the terminal phase.

The most remarkable results came from the morphological examination of the heart, which pointed out the following:

- The transverse section of the heart (at the level of the two-third apical), including both ventricles and the interventricular septum, showed an extensive, circumferential subacute myocardial infarction in the organizing phase of healing (Fig. 1A). Within myocardial infarction calcific deposits were observed (Fig. 1D).
- The inner two-thirds of both ventricles' wall showed a trabecular structure, partially not involved in the necrosis; a thickened endocardium layer plastered the trabecular myocardium. The intertrabecular recesses, covered with their own endocardium, penetrate between the trabeculae, until they nearly reach the epicardium. The absence of well-formed papillary muscles, a typical picture in keeping with noncompaction, has been detected. Histological examination was necessary to demonstrate the noncompacted portion. According to the Jenni's criteria [7], which establish a ratio noncompaction/compaction (NC/C) ≥2 in

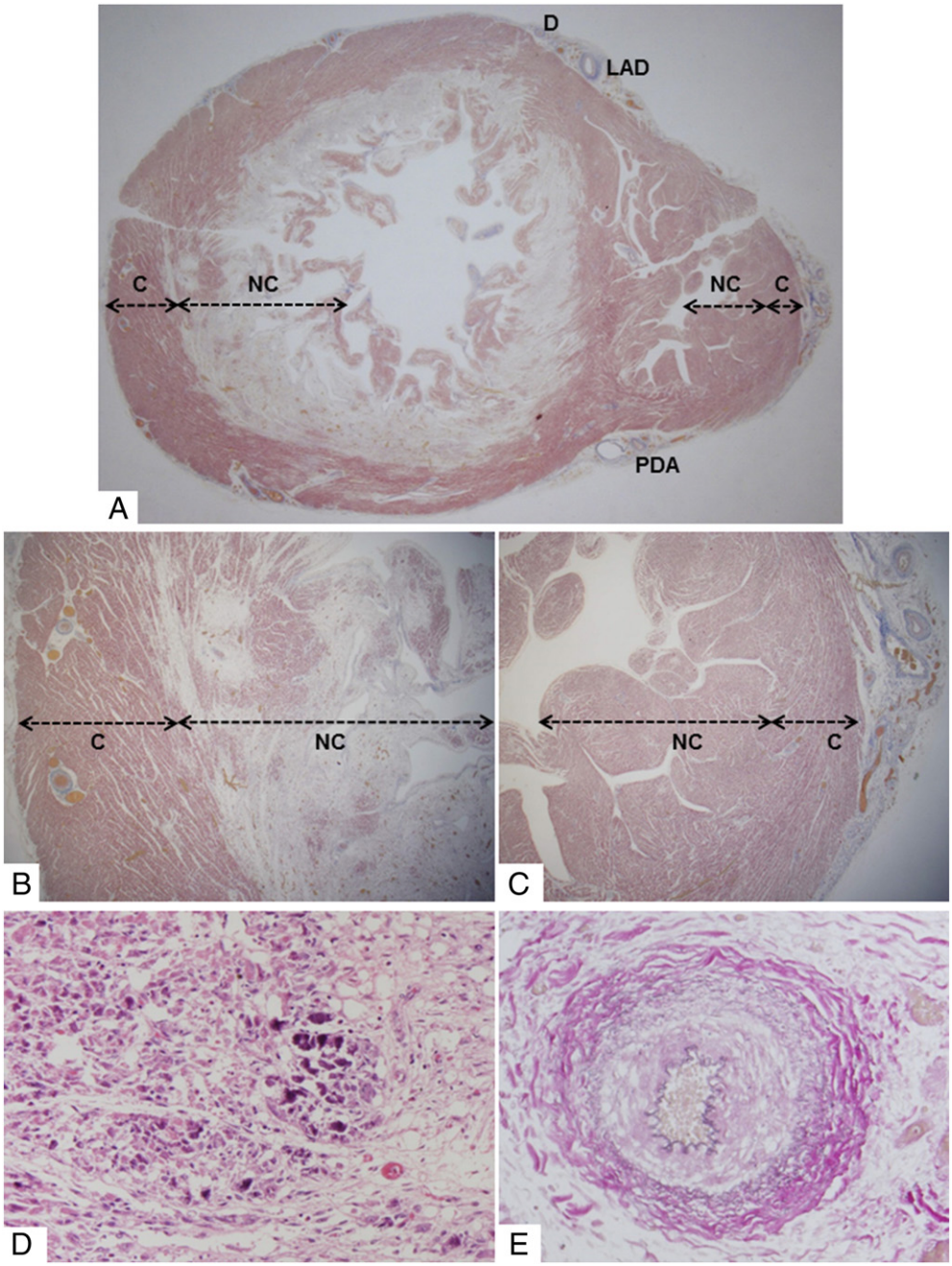

Fig. 1. (A) Histologic transverse section of the heart showing the hypertrabeculation and deep intertrabecular recesses of both left and right ventricular myocardium. The arrows depict the increased noncompaction (NC): compaction (C) ratio. Note also circumferential subacute subendocardial myocardial infarction. (B and C) Higher magnification of both left and right ventricles where morphometric analysis for NC/C ratio measurements was performed, according to the Jenni's criteria. (D) In the subendocardium, myocytes necrosis with focal calcification is visible. (E) Close-up of panel A, showing a branch of the diagonal artery with adventitial fibrosis and obstruction due to medial hypertrophy and intimal thickening. LAD, left anterior descending coronary artery; PDA, posterior descending artery; D, branch of a diagonal artery. A, Heidenhain trichrome, panoramic view; B and C, Heidenhain trichrome, ×10; D, hematoxylin–eosin, ×100; E, elastic Weigert Van–Gieson, ×160.

adults and at least 1.4 in children, morphometric analysis showed an NC/C of 3.45 (435.83/126.08 μm) in the right ventricle and of 1.8 (1254.92/695.16 μm) in the left ventricle (Fig. 1B, C).

- The main branches of coronary arteries were observed from the epicardium into the myocardium, without any lesion.
- The collateral branches of the diagonal arteries showed obstruction due to medial hypertrophy and intimal thickening, causing a critical stenosis of the lumen (Fig. 1E).

Therefore, the diagnosis of congenital noncompaction cardiomyopathy, involving both ventricles, was put forward, on the basis of the morphologic and morphometric findings, which were typical of the disease, in keeping with the established diagnostic criteria [7]. The ischemia which led the patient to his death was caused by the low cardiac output syndrome (due to the impairment of the left ventricle's function) associated with the obliteration of the collateral branches of the coronary arteries. The thrombophilia, due to the presence of the MTHFR mutation in homozygozis, remarkably might have contributed to the ischemia of the heart.

3. Discussion

The most updated literature reports that Hirschsprung's disease occurs as an isolated phenotype in 70% of affected infants and in combination with additional congenital anomalies or syndromes in approximately the 30% of patients [8]. Particularly, Hirschsprung's disease associated with congenital heart diseases has been reported in 5%–8% of cases. Several cardiac defects may be observed in patients with Hirschsprung's disease: septation defects, patent ductus arteriosus, vascular abnormalities, including stenosis and coarctation, valvular heart defects, tetralogy of Fallot, and hypoplastic left heart syndrome [9]. The noncompaction cardiomyopathy was never related to Hirschsprung's disease so far. In our opinion, this association warrants attention and might have an embryogenetic explanation. The pathogenesis of Hirschsprung's disease is currently attributed to cellular and molecular abnormalities during the development of the enteric nervous system, which derives from the neural crest cells; these cells first appear in the esophagus by 5 weeks of gestation and subsequently migrate in a craniocaudal direction to the anal canal. A deficiency of the migration process causes the aganglionosis.

Even though the pathogenesis of noncompaction cardiomyopathy is still undefined, the typical myocardium structure observed in the disease suggests an arrest in the development during the compaction process, occurring in the first trimester of intrauterine development. Between 5 and 8 weeks of gestation, the trabecular myocardium undergoes compaction in its deeper part [6].

Therefore, probably, the underlying basis of the two diseases may regard the same phase of the fetus development [9,10]. Neural crest cells could be the link between the two morbid entities [10], as already advanced for the association between Hirschsprung's disease and hypoplastic left heart syndrome [9]. Cardiac neural crest cells arise more cranially from the neural tube as compared to the gut neural crest, originating more distally at lumbar level. Cardiac neural crest cells contribute to the development of second heart field, thus impacting on the myocardium cell pool and also playing an indirect inductive function on cardiac development. However, in an animal model, they give origin to adventitia smooth muscle cells of the proximal coronary arteries [11]. Their role in noncompaction development could be through abnormalities of innervation of the coronary arteries which branch at the ventricular epicardial layer, disrupting the normal interaction between epicardium, myocardium, and endocardium for myocardial structural development. Moreover, in another animal model of cardiac neural crest ablation, it has been observed that the volume of myocardium was dramatically reduced and the compacted layer of the myocardium was thinner especially in the ventricles [10].

For this reason, the association of the two diseases is interesting and cannot be viewed as incidental, but may suggest a primary common abnormality of the neural crest as already suggested for the association between Hirschsprung and hypoplastic left heart syndrome.

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