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AGENESIS OF THE AORTIC VALVE ASSOCIATED WITH HYPOPLASTIC LEFT VENTRICLE – A PATHOLOGIST'S POINT OF VIEW

Pathology

Adrian Dumitru	Department of Pathology, University Emergency Hospital Bucharest, Romania, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
Alexandru Procop	Department of Pathology, Fundeni Clinical Institute, Bucharest, Romania
Tiberiu- Augustin Georgescu*	Department of Pathology, University Emergency Hospital Bucharest, Romania, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania *Corresponding Author
Mariana Costache	Department of Pathology, University Emergency Hospital Bucharest, Romania, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
Monica Mihaela Cirstoiu	Department of Obstetrics-Gynaecology III, University Emergency Hospital Bucharest, Romania
Adriana Elena Nica	Department of Anesthesiology and Intensive Care Unit II, University Emergency Hospital Bucharest, Romania
Maria Sajin	Department of Pathology, University Emergency Hospital Bucharest, Romania, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Congenital aortic valve agenesis is a rare heart anomaly usually associated with other developmental cardiac malformations, part of the so-called 'hypoplastic left-heart syndrome'. To the best of our knowledge, most reported cases of aortic valve atresia or agenesis have been associated with anomalies of the mitral valve, hypoplasia and/or coarctation of the ascending aorta, malformation of the left ventricle or the interventricular septum, patent foramen ovale and coronary abnormalities. These malformations are responsible for 25% to 40% of all neonatal cardiac deaths. We report a case of aortic valve agenesis associated with left ventricular fibroelastosis found in a 25-week miscarried fetus, product of the first pregnancy of two non-consanguineous healthy parents, with no history of drug abuse or exposure to toxic or teratogenic agents.

KEYWORDS

aortic valve agenesis, hypoplastic left ventricle, fibroelastosis, prenatal cardiac development, IHC

INTRODUCTION

Agenesis of the aortic valve is defined as total or subtotal absence of the valve leaflets usually associated with other developmental cardiac malformations such as coarctation of the ascending aorta, hypoplastic left ventricle, malformation of the interventricular septum or mitral valve anomalies. These phenotypic variations imply a very complex pathogenesis, particularly regarding cardiac developmental pathways and developmental errors of the neural crest cells during the early stages of embryogenesis (formation of atrioventricular cardiac valves from endocardial cushions – days 34-36 of gestation) [1]. Agenesis of the aortic valve can occur as an isolated anomaly in nonsyndromic patients or as part of a genetic disorder in syndromic patients. In contrast with the absence of the pulmonary valve, the absence of the aortic valve is much rarer and less frequently documented.

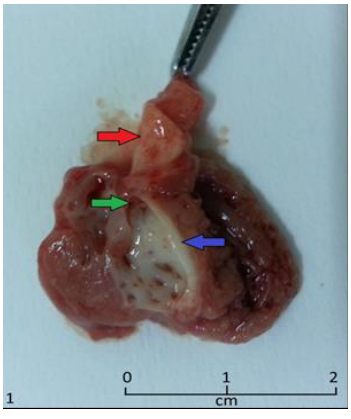
The incidence of aortic valve agenesis is unknown in fetuses resulted from spontaneous miscarriages or stillborn. The overall prevalence of hypoplastic left ventricle syndrome ranges between 2 to 3 cases per 10000 live births [17].

We report a case of absent aortic valve associated with hypoplastic left-sided heart syndrome in a 25-week fetus, diagnosed antepartum via echocardiography and confirmed on autopsy.

CASE REPORT

A 25-year-old pregnant woman with no history of genetic disorders was admitted to the Department of Obstetrics-Gynecology of the Emergency University Hospital Bucharest for expert advice after a routine second semester echography. Upon this presentation, a 25-week male fetus was found, weighing approximately 620g with a nuchal translucency of over 6mm, hyperechogenic left ventricle, inversed interatrial shunt and reduced mitral in-flow. Also, a hypoplastic aortic arch and a Pulmonary-Aortic high ratio of 1.96 was noted. Overall, the fetal echocardiography revealed a reduced cardiac volume and hypokinetic left ventricle, suggesting hypoplastic left heart syndrome. Other anthropometric parameters were consistent with fetal gestational age development. After further gynecological investigations, the above-mentioned diagnosis was confirmed. The fetus was the product of the first pregnancy of two non-consanguineous healthy parents, with no history of drug abuse or exposure to toxic or teratogenic agents.

Hours after admission, unfortunately, the patient had a spontaneous miscarriage. An autopsy was performed in the Pathology Department of the Emergency University Hospital of Bucharest. A thorough gross inspection of the heart revealed a small but well-formed left ventricle, an ascending aorta with a diameter of 1.2 mm and a rudimentary aortic valve evident at the aortic annulus. The valve leaflets were fused in a dome-shaped structure. The posterior and the interventricular walls were pale, having a fibrotic appearance, consistent with endocardial fibroelastosis (Figures 1 and 2). Ductus Arteriosus and Foramen Ovale were patent. The atrioventricular valves were normal. The pulmonary artery was well developed. There were no other organic abnormalities detected on gross examination. Tissue samples were collected and sent for histopathological examination. Each sample was processed using conventional histopathological methods, inclusion in paraffin and hematoxylin-eosin staining.



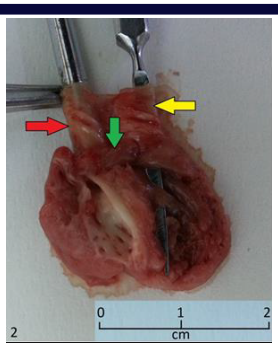


Figure.1 (above) Hypoplastic left ventricle, posterior view. Gross appearance of the aorta (red arrow), interventricular septum with marked endocardial fibroelastosis (blue arrow) and an atretic aortic valve (green arrow). **Figure.2 (bellow)** Same case, posterior view. The aorta (red arrow), pulmonary artery (yellow arrow) and a considerably engorged and misaligned ductus ateriosus (green arrows).

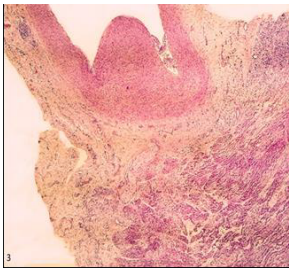


Figure 3. Microscopic image of the aortic orifice blocked by a dome-shaped structure replacing the aortic valve leaflets, HE and safranin, ob. 4x

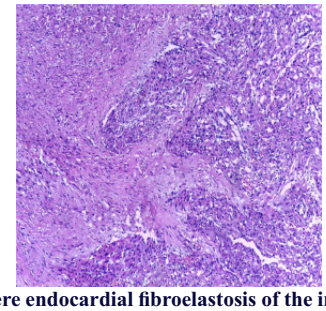


Figure 4. Severe endocardial fibroelastosis of the interventricular septum, HE, ob. 10x

We have performed special stains such as van Gieson (Figures 5, 6 and 11) and orcein (Figures 7 and 8) in order to document myocardial fibroelastosis. Moreover, we have also performed immunostains in order to highlight a peculiar lymphoid structure and some interstitial inflammatory cells that turned out to be mast cells (Figure 10). Histopathological examination supported and confirmed the initial diagnosis. Upon microscopic examination we identified the appearance of neonatal myocardium composed of cardiac-type muscle fibers with striated cytoplasm, centrally placed nuclei and intercalated discs. Sections revealed both longitudinal fibers and cross-sections of the cardiac myocytes, loosely arranged in bundles.

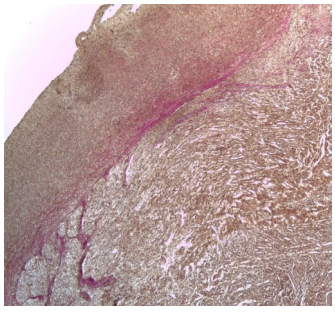


Figure 5. The endocardium was thickened with fibrous-like tissue underneath suggesting endocardial fibroelastosis. Van Gieson stain, ob.4x.

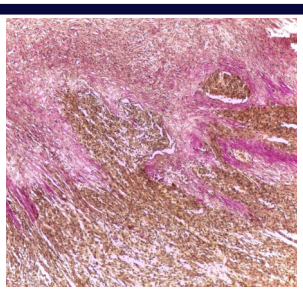


Figure 6. Severe endocardial fibroelastosis of the interventricular septum, van Gieson stain, ob.10x

These findings are consistent with early fetal myocytes featuring clear, vacuolated cytoplasm, secondary to high glycogen content (Figure 11). Myocardial cell nuclei were generally ovoid to slightly elongated with smooth nuclear borders. We have also identified some Anitschkow-like cells (Figure 12) commonly described in fetal and neonatal hearts. The significance of these cells is not clear, but it may represent a reactive change to stimuli such as hypoxia.

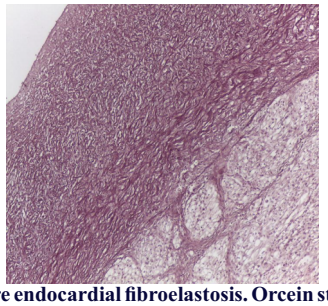


Figure 7. Severe endocardial fibroelastosis. Orcein stain, ob. 10x

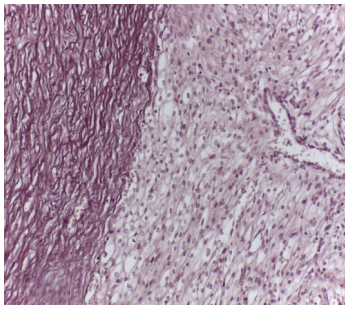


Figure 8. Severe endocardial fibroelastosis. Orcein stain, ob. 40x

The endocardium that normally appears as a simple layer of flattened endothelial cells supported by a very thin underlying connective tissue layer, was thickened in our case, with fibrous-like tissue underneath, confirming the endocardial fibroelastosis (Figures 5-8). At the root of the great vessels, we have discovered a lymphoid structure without germinative center, (Figure 9) composed mainly of small lymphocytes and histiocytes. Normal fetal valve leaflets are bland structures composed of a densely arranged central core of collagen fibers in a focally myxoid stroma. Nodular myxoid structures are considered a sign of valvular dysplasia. We found a similar dome-shaped structure replacing the aortic valve leaflets (Figure 3). The aortic diameter was significantly smaller than the pulmonary one.

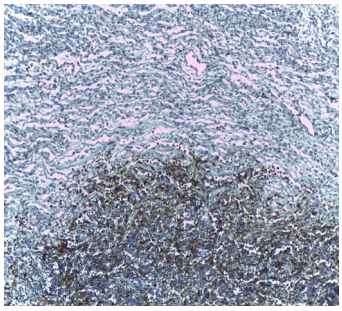


Figure 9. Intramyocardial lymphoid structure composed mainly of small lymphocytes and histiocytes. IHC staining: Anti-CD45/peroxidase conjugate and DAB chromogen, ob. 4X

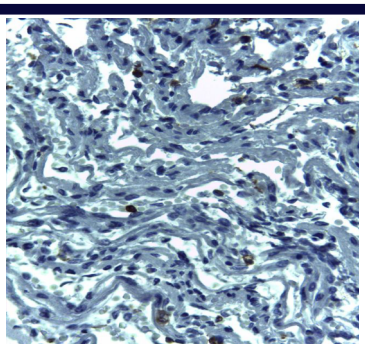


Figure 10. Interstitial mast cells showing a strong cytoplasmic immunostaining reaction for mast cell specific tryptase, Anti-Mast Cell Tryptase antibody/ DAB chromogen, ob. 20X

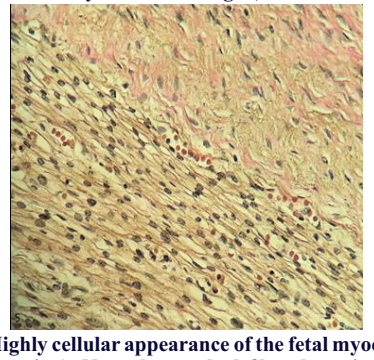


Figure 11. Highly cellular appearance of the fetal myocardium (25 weeks of gestation). Note the marked fibroelastosis in the right upper corner of the image. van Gieson stain, ob.20x

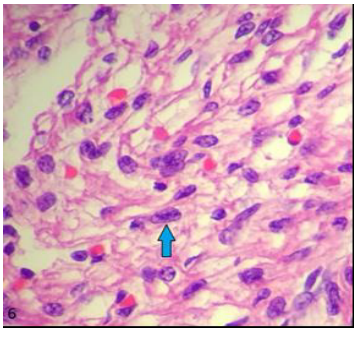


Figure 12. Anitschkow like cells (blue arrow) HE, ob. 40x

DISCUSSIONS

The causes of heart defects such as hypoplastic left heart syndrome are unknown. Some studies are suggesting genetic causes. Tbx1 gene, for instance, was found to be responsible for developmental arterial anomalies and outflow tract of the heart in mutant mice models. An analogue mutation in humans appears in syndromes like DiGeorge, Velocardiofacial syndrome, Sedlackova syndrome and Conotruncal Anomaly Face syndrome [12,13,15].

Although DiGeorge syndrome is mostly associated with Fallot tetralogy, other complex cardiac malformations such as agenesis of the aortic valve with or without interventricular septal defects may be found. Edwards syndrome (18th trisomy) constantly associates cardiac malformations such as hypoplastic left ventricle. Given the fact that these anomalies are found predominantly in males, they might be associated with an X-linked gene mutation. This hypothesis remains still unproven.

Recent studies revealed multiple expression and functional differences in hypoplastic left heart syndrome-derived cardiac myocytes, using an induced pluripotent stem cell model [14]. Hypoplastic left heart syndrome has a complex physiology due to dysfunctional anatomic architecture of the heart and special features of the fetal blood flow. Blood enters the left atrium, cannot exit due to hypoplasia/agenesis of the mitral valve and crosses the foramen ovale into the right atrium, through the tricuspid valve and enters the right ventricle. Blood enters through the pulmonary valve reaching the pulmonary artery and shunts from right to left through the patent ductus arteriosus into the systemic circulation. Normal pulmonary blood flow is codependent on the respective pulmonary and systemic resistance and the size of the ductus arteriosus, which provides retrograde filling of the coronaries [15]. Postnatal hemodynamic changes (the partial closure of foramen ovale and obliteration of ductus arteriosus) culminate with pulmonary edema, pulmonary hypertension, desaturation and low cardiac output.

We reviewed eleven cases reported in the medical literature, from neonates to young adults. [2-10]. In eight of these cases, associated hypoplastic left-sided heart syndrome was present [4-8,10]. Normal development of the great arteries with aortic ring stenosis was present in one [9] and in another two patients double outlet right ventricle was present [2,3]. Other cardiac defects have been described, for example total anomalous venous drainage, pulmonary venous stenosis [8], subaortic stenosis by abnormal chordae tendineae attachments and left ventricular endocardial fibroelastosis [4,5,8,10,11].

If the fetus survives throughout the pregnancy, afterbirth, medical and surgical procedures might be applied as treatment: prostaglandin to maintain ductal patency and systemic perfusion [16], balloon atrial septostomy [18] to open atrial defect to decompress the left atrium and the pulmonary veins. Also, the Norwood surgical intervention may be considered in some cases [19].

CONCLUSIONS

The prevalence of aortic agenesis associated with hypoplastic left heart syndrome is estimated at 2/3 cases per 10000 live births, although the reported overall incidence is likely underestimated because of the indeterminate rate of spontaneous abortions and elective termination of pregnancy of affected fetuses.

There is no known prevention for hypoplastic left heart syndrome. Like in many congenital diseases, the causes of hypoplastic left heart syndrome are uncertain and have not been linked to the mother's behavior or pathology or to a clear genetic trigger.

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