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8p23.1 Microdeletion syndrome and obstructing myxomatous heart valve nodules

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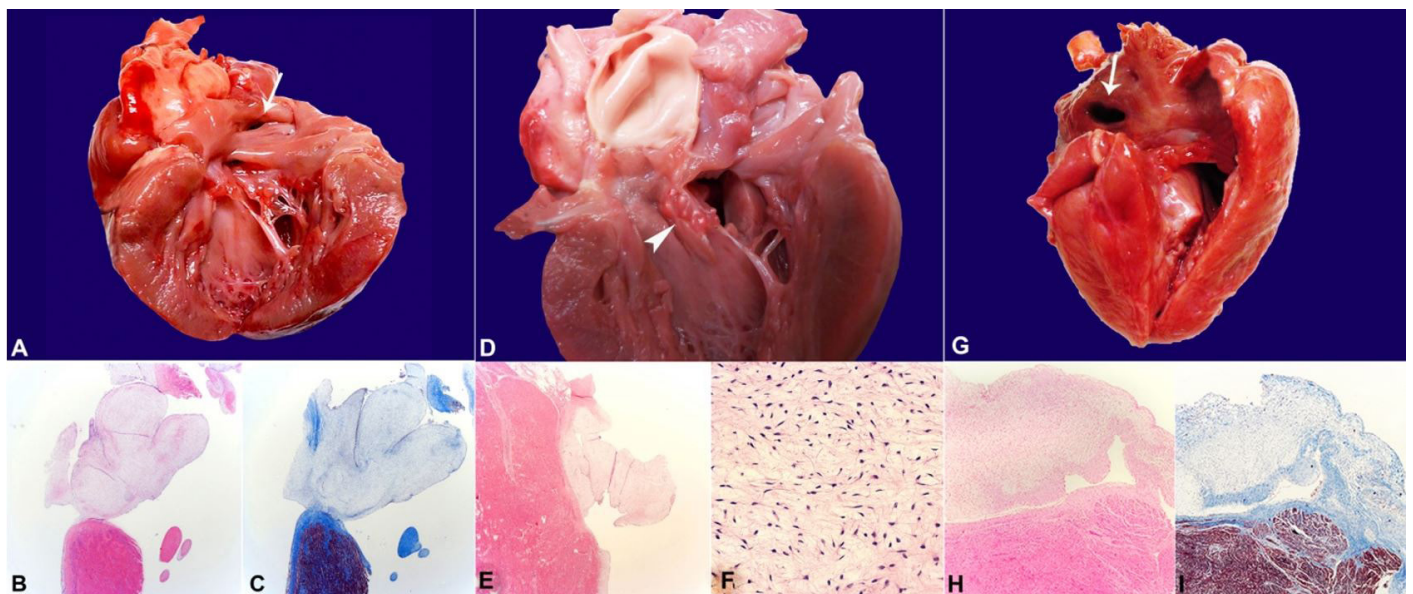


Figure 1. **A** – Left heart chambers with myxomatoid nodules on dysplastic leaflets and chordae tendineae. Arrow showing ostium secundum atrial septum defect; **B and C** – Papillary muscle with nodular thickening of chordae tendineae showing myxoid stroma devoid of collagen (**E** - H&E, **F** - Trichrome stain 50x); **D** – Pink, smooth and glistening sub-centimeter nodules on the aortic valve and subaortic area (arrowhead); **E** – An aortic valve leaflet showing diffuse thickening with expansion of the spongiosa layer by a myxoid stroma. Separate myxoid endocardial plaque. Hematoxylin and eosin (H&E, 25 x); **F** – Nodules composed of proliferating spindle cells in a loose stroma with myxoid changes (H&E, 400 x). **G** - Right heart chambers with myxomatoid nodules on dysplastic leaflets. Arrow showing ostium secundum atrial septum defect; **H and I** – Right valve leaflet showing expansion of the spongiosa layer by proliferating spindle cells in a myxoid background and relative preservation of fibrosa and atrialis layers (**H** - H&E, 50x, and **I** - Trichrome stain, 50x).

An 8-week female infant, with 8p23.1 deletion syndrome, was born via cesarean section at 37 weeks for severe intrauterine growth restriction. The mother was 22 years old and was Gravida2, Para1.

The echocardiography revealed an atrioventricular (AV) canal defect, small primum atrial septal defect, moderate ventricular septal defect and abnormal chordal attachment of the anterior papillary muscle

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to the left ventricular outflow tract with moderate to severe obstruction of the left ventricular outflow tract. Ultrasound confirmed the presence of congenital diaphragmatic hernia (CDH) of the left side with hypoplastic left lung. She then underwent surgery to repair CDH. During the postoperative period, she developed refractory septic shock in conjunction with cardiogenic shock as a result of severe left-sided obstructive lesion along with severe biventricular systolic dysfunction. Multiple attempts to resuscitate the patient were unsuccessful, and an autopsy was performed.

The heart dissection showed AV canal defect of the intermediate type, characterized by a common fibrous valve ring and two orifices. On the left heart chambers, the anterior and posterior leaflets appeared poorly formed and thickened, with multiple pink fleshy myxomatoid nodules, commonly described as valvar dysplasia. There was rotation of the left ventricular papillary muscles with the anterior leaflets/papillary muscle complex directed toward the ventricular septum. The left ventricular outflow tract appeared elongated with slight anterior displacement of the thickened aortic valve leaflets. Multiple subaortic myxomatoid nodules around the anomalous insertion of the anterior papillary muscle were noted. On the right heart chambers, the anterior component of the valve leaflets was absent while the posterior leaflets showed valvar dysplasia. The pulmonary valve was unremarkable.

This case is a typical example of valvar dysplasia in the AV canal malformation leading to left ventricular outflow tract obstruction and eventually heart failure.

The 8p23.1 microdeletion syndrome is a rare multisystem disorder characterized by a congenital diaphragmatic hernia, congenital heart disease, cognitive impairment, facial dysmorphisms, and microcephaly. Within 8p23.1 deletion, haploinsufficiency of *GATA4* and *SOX7* are the putative genes causing cardiac defects in humans.¹

Embryologically, the heart valves originate from endocardial cells that undergo an endothelial-to-mesenchymal transition (EMT) to form the primordial cardiac cushions, while post-EMT valve interstitial cells complete the morphogenesis of leaflets.² Initially, the mesenchymal cells grow in a random extracellular matrix (ECM).² These cushions elongate to form functionally mature valves. Structural

remodeling of the earliest leaflets is a process shaped by hemodynamical forces and involves the expression of matrix metalloproteinases and a decrease in cell proliferation.³ The spongiosa layer, which is highly hydrated and compressible, results from the deposition of chondroitin sulfate proteoglycans and hyaluronan. Proper distribution and organization of ECM are essential for normal valve function.³

The expression *GATA4* and *SOX7* are coordinated to ensure a normal AV valve development. *GATA4* and *SOX7* are found within a protein complex together and co-occupy genomic sites containing genes that are involved in heart development. Overall, *SOX7* inhibits *GATA4* transcriptional activity.⁴ *GATA4* is expressed in the endothelium and mesenchyme of the AV valves. *GATA4* plays a role in valvulogenesis by two mechanisms: firstly, by regulating the *ErbB3*-*Erk* pathway promoting EMT; secondly and subsequently, *GATA4* in cooperation with *FOG* (Friend of *GATA* cofactor), promotes the growth and fusion of the AV cushions.⁵ Inactivation of *GATA4* within the endothelial-derived cells can lead to failure of EMT, forming hypocellular cushions, and subsequently leading to AV septal defects.⁵ On the other hand, *SOX7* is required to downregulate pro-EMT signals, necessary to limit the cellular expansion during leaflet elongation.⁴

The cellular context and chromatin-specific interactions between *GATA4* and *SOX7* may explain the spectrum of congenital heart defects reported in patients with 8p23 microdeletion syndromes.

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