Title

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CASE REPORT

ADVANCED

CLINICAL CASE

Isolated Absent Aortic Valves

A Unique Fetal Case With Echocardiographic, Pathologic, and Genetic Correlation

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ABSTRACT

We present a 22-week fetus with isolated absent aortic valve and inverse circular shunt. The pregnancy was interrupted. Here, echocardiography and pathology images demonstrate this rare entity. Whole genome sequencing revealed a potentially disease-causing variant in the *APC* gene. Whole genome sequencing should be considered in severe and rare fetal diseases. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;11:101790) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 28-year-old G5P3 woman without past medical or family history was referred after abnormal fetal heart screening. Fetal anatomy was otherwise normal with male sex. Initial fetal echocardiogram images demonstrated cardiomegaly with free aortic insufficiency (AI). Severe fetal AI is rare.

LEARNING OBJECTIVES

- To understand inverse circular shunt physiology and protective role of LV and mitral hypoplasia.
- To promote WGS for rare fetal diseases.
- To highlight possible mechanism: loss of *APC* function perhaps prompted loss of cardiac NCCs necessary for AoV development.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included severe aortic valve (AoV) dysplasia, absent aortic valve (AAV), and aorticoventricular tunnel.

INVESTIGATIONS

Fetal echocardiography performed at 22 weeks showed normal segmental anatomy. The thin-walled left ventricle (LV) was massively dilated (z score +7.4, cardiothoracic ratio 0.68) with minimal contractility (**Figure 1A,** Video 1A). The left atrium was massively dilated. The aortic annulus, aortic root, and ascending aorta were normal in size (**Figure 1B**, Video 1B). There were no obvious aortic leaflets, but remnant tissue could not be excluded. Color revealed a wide, continuous jet of AI (**Figures 1C and 1D**, Video 1C). The mitral

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ABBREVIATIONS AND ACRONYMS

AAV = absent aortic valve

AI = aortic insufficiency

AoV = aortic valve

LV = left ventricle

NCC = neural crest cell

WGS = whole genome sequencing

valve was normal size with severe mitral insufficiency (mitral regurgitation) (**Figures 2A and 2B**). There was reversed flow across the patent foramen ovale (**Figure 2A**, Video 2A) and in the aortic arch (**Figure 2C**, Video 2B). The right ventricle had normal size with mildly diminished contractility. The pulmonary valve was normal. Biometry was consistent with dates. There was no hydrops.

MANAGEMENT AND FOLLOW-UP

The patient was counseled on AAV and the poor prognosis. They opted for termination of pregnancy and autopsy.

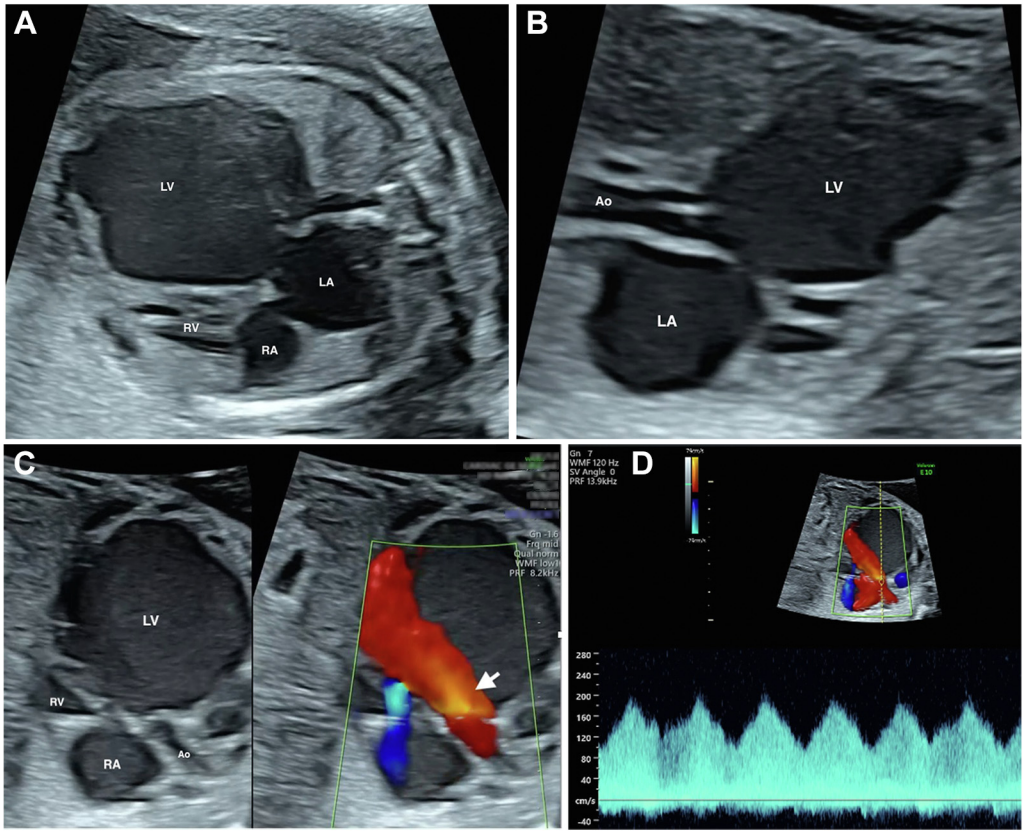
Autopsy showed massive cardiomegaly. The mitral valve was grossly normal. The LV wall thickness was 2 mm (**Figure 3A**). The aortic outflow included small pearly structures in the usual leaflet position (**Figure 3B**). Aortic sinuses and coronary ostia were normal. Histology showed fibrocollagenous replacement of the AoV (**Figures 3C and 3D**).

Chromosomal microarray was normal. Whole genome sequencing (WGS) (46X, 2x101 nucleotides) revealed a heterozygous pathogenic variant in the *APC* gene (c.3203C>G), resulting in premature termination and a truncated protein (p.Ser1068Ter). This variant has been described previously in patients with familial adenomatous polyposis-1 (Online Mendelian Inheritance in Man #175100, ClinVar #579696).

DISCUSSION

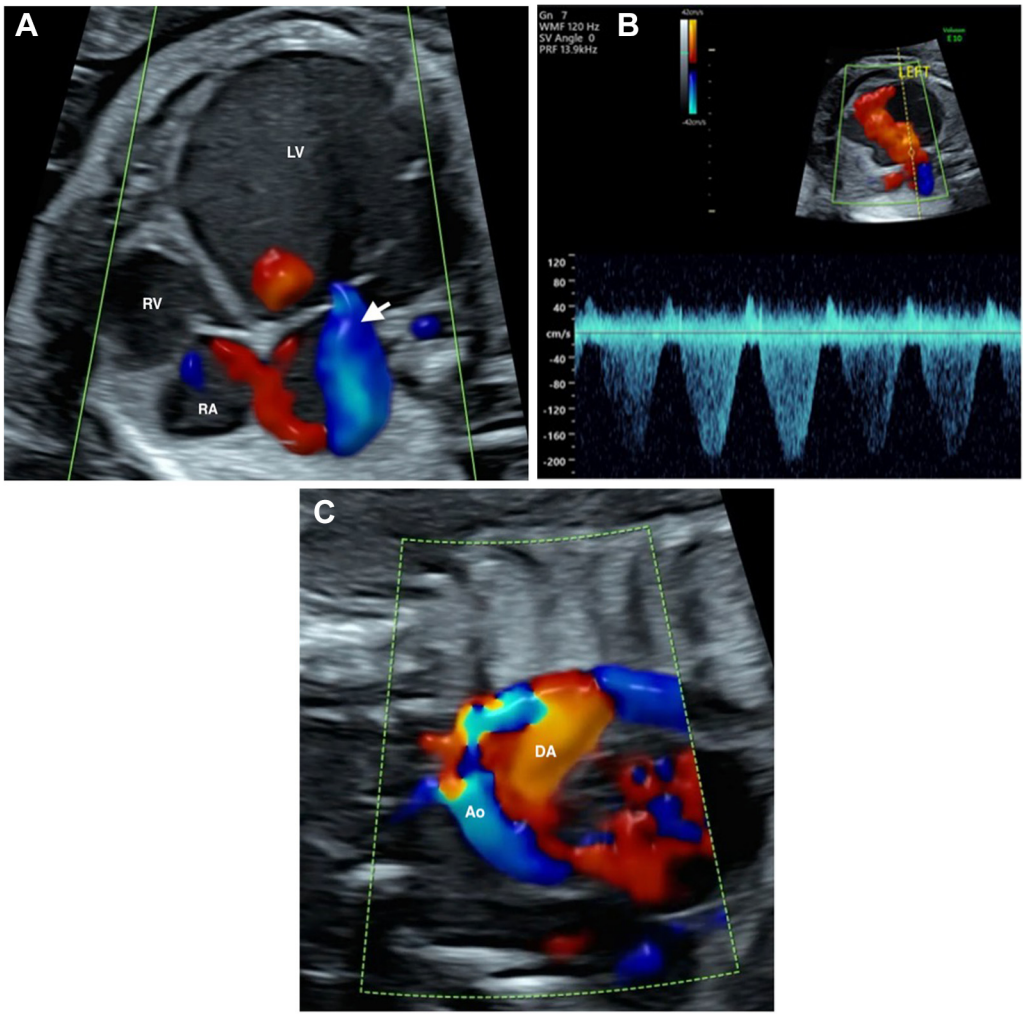
Congenital AoV defects are extremely common and range in severity from bicuspid to AAV. The genetic mechanisms are incompletely understood, but the

FIGURE 1 Fetal Echocardiogram



(A) A 4-chamber (4C) image at end-systole showed the massively dilated left heart (Video 1). **(B)** A 3-chamber image showed the normal-sized aortic root and ascending aorta (Ao). Annular tissue appeared abnormal. Note the lateral displacement of the mitral valve chords in the severely dilated left ventricle (LV) (Video 1). **(C)** Two-dimensional with color imaging showed the broad jet of aortic insufficiency **(arrow)** (Video 1). **(D)** Aortic insufficiency Doppler showed continuous retrograde aortic valve flow with a sawtooth pattern. LA = left atrium; RA = right atrium; RV = right ventricle.

FIGURE 2 **Inverse Circular Shunt by Fetal Echocardiogram**



(A) A 4C image with color showed left-to-right patent foramen ovale flow and mitral regurgitation (MR) **(arrow)** (Video 2). **(B)** Mitral valve continuous Doppler showed pansystolic MR, minimal antegrade flow. Systolic-to-diastolic ratio was extremely elevated at 4. MR velocity estimated LA-LV pressure gradient of 18 mm Hg. **(C)** Spine-up sagittal view with color showed right-to-left patent ductus arteriosus (DA) flow and retrograde aortic arch flow. These elements completed the inverse circular shunt. Abbreviations as in **Figure 1**.

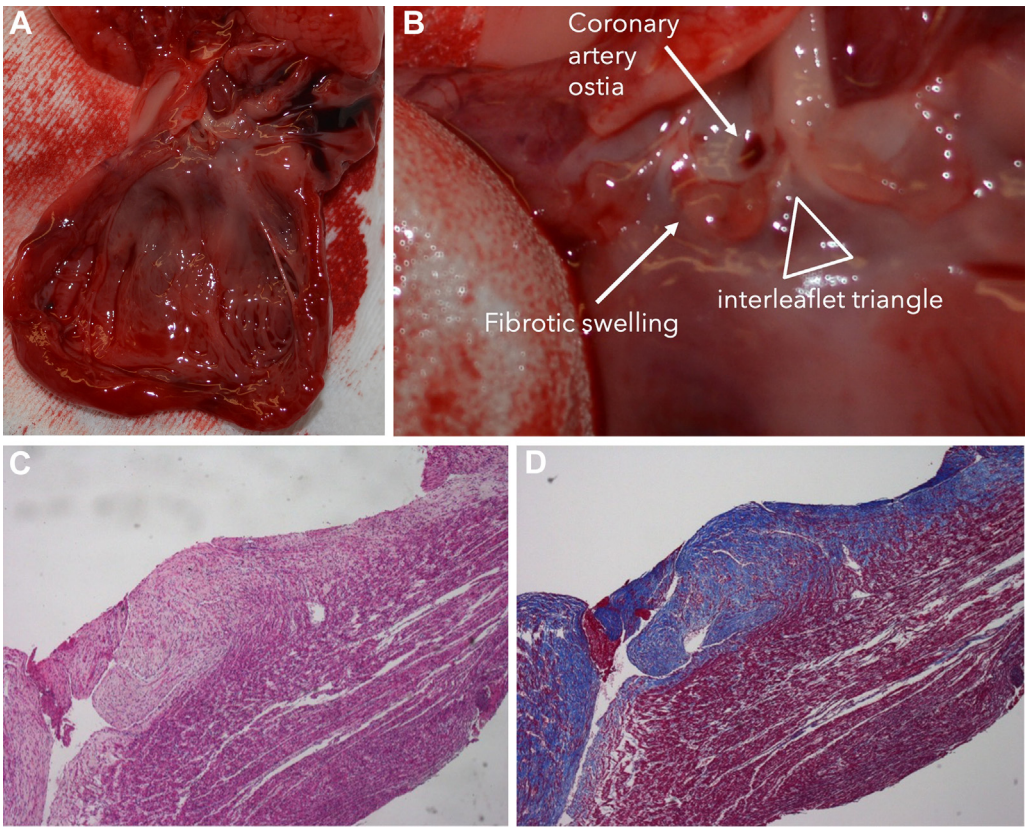
Notch pathway and genes regulating neural crest cell (NCC) development have been implicated.[1,2]

AAV without associated lesions—isolated AAV—is exceedingly rare, with 1 reported case.[3] Here, we present a second. Both had inverse circulatory shunt physiology, incompatible with survival. This is the first investigated by WGS.

INVERSE CIRCULAR SHUNT. We reviewed the 41 reported cases of AAV; the majority had additional cardiac lesions, many within the hypoplastic left heart syndrome spectrum (Supplemental Table 1). Five survived beyond the neonatal period. As Murakami et al[3] postulated, LV hypoplasia affords protection from the deleterious effects of severe AI. All survivors had some LV and mitral abnormality. Their management has primarily involved single ventricle palliation and/or transplantation.[4]

Like the Murakami et al[3] isolated AAV case, we observed an inverse circular shunt. In this physiology, severe AI likely begins in early gestation and the compliant LV is subjected to volume load and coronary steal. The resultant relative hypoperfusion results in severe dilation, which contributes to mitral

FIGURE 3 Pathology Findings



(A) Extremely thin-walled LV with normal trabeculation. Mitral valve morphology was normal, though distorted. The outflow tract was normal in size. Here, the aortic root is opened. **(B)** Aortic root close-up showed well-formed sinuses, a coronary ostia, and pearly fibrotic swellings in place of aortic valve leaflets. **(C)** Hematoxylin and eosin staining of the aortic root demonstrated a collagenous nodule in place of the valve leaflet. **(D)** Trichrome stain delineated fibrocollagenous deposition in the usual aortic valve location. Abbreviations as in **Figure 1**.

regurgitation, which ultimately reverses patent foramen ovale flow. Flow then proceeds through the right heart and patent ductus arteriosus, then retrograde in the transverse aorta. Systemic output is severely impaired, leading to hydrops and demise.

Murakami et al[3] outlined the importance of normal LV myocardium in inverse circular shunt development. Our case corroborates this, and we add emphasis on the role of mitral valve morphology. A normal mitral apparatus, when subjected to severe LV dilation, will develop regurgitation, permitting vicious progression. In contrast, in the Krasemann et al[4] case, the LV was dilated, but severe mitral hypoplasia prevented circular shunt. That fetus survived. No cases with an inverse circular shunt have survived.

IDENTIFICATION OF A GENETIC ETIOLOGY. Heterozygous truncation mutations in the *APC* gene cause juvenile polyposis and predispose to colon cancer. In zebrafish, *APC* loss results in proliferation of cells involved in atrioventricular valve development through increased beta-catenin signaling.[5] In mice NCCs, *APC* functions as a tumor suppressor gene, such that loss of function results in NCC apoptosis.[6] In humans, a de novo *APC* missense variant was identified in a bicuspid AoV patient.[7] Together, there is a plausible mechanism for AAV in our patient: loss of *APC* function resulted in loss of NCCs necessary for AoV development.[8]

Notably, our patient's pulmonary valve was normal, indicating failure of endocardial cushion development was isolated to the left side. A previous study demonstrated a critical role for NCCs in the development of the outflow cushions (or "the endocardial cushions at the ventricular arterial junction")[9] and for patterning the semilunar valves.[10] Our

patient's findings suggest that during this patterning process, there already existed gene regulatory differences between the AoV and pulmonary valve. In patients with both valves affected, the defect likely occurs earlier in development. We found that deletion of the ETS1 transcription factor in mice causes complete absence of one AoV leaflet and an unaffected pulmonary valve.[11] This is likely due to a migration defect in a cardiac NCC subset involved in AoV development. Similarly, studies in chicks provide evidence for cardiac NCC subsets with involvement in the development of specific, distinct components of the outflow tracts, including semilunar valves.[12] In our patient, loss of APC function may have occurred only in a subset of cardiac NCCs affecting the AoV.

CONCLUSIONS

Isolated AAV is extremely rare and carries a poor prognosis due to inverse circular shunt physiology. An inverse circular shunt involves continuous AI and retrograde flow through the left heart and arch. In our case, a pathogenic heterozygous *APC* variant was identified and perhaps was causative by impairing cardiac NCCs destined for AoV development. We encourage WGS in severe and rare fetal cardiac disease, as it may elucidate the complex mechanisms in aberrant cardiogenesis.

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REFERENCES

1. Garg V, Muth AM, Ransom JF, et al. Mutations in NOTCH1 cause aortic valve disease. *Nature*. 2005;437:270–274.

2. Anderson RH, Chaudhry B, Mohun TJ, et al. Normal and abnormal development of the intrapericardial arterial trunks in humans and mice. *Cardiovasc Res*. 2012;95:108–115.

3. Murakami T, Horigome H, Shiono J, et al. Prenatal diagnosis of congenital absence of aortic valve: a report of two cases with different outcomes and a literature review. *Fetal Diagn Ther*. 2015;38:307–314.

4. Krasemann T, Kehl HG, Hammel D, Asfour B. Congenital aortic regurgitation due to absent aortic cusps and high-degree mitral stenosis. *Pediatr Cardiol*. 2003;24:304–306.

5. Hurlstone AF, Haramis A-PG, Wienholds E, et al. The Wnt/beta-catenin pathway regulates cardiac valve formation. *Nature*. 2003;425:633–637.

6. Hasegawa S, Sato T, Akazawa H, et al. Apoptosis in neural crest cells by functional loss of APC tumor suppressor gene. *Proc Natl Acad Sci U S A*. 2002;99:297–302.

7. Bonachea EM, Zender G, White P, et al. Use of a targeted, combinatorial next-generation sequencing approach for the study of bicuspid aortic valve. *BMC Med Genomics*. 2014;7:56.

8. Henderson DJ, Eley L, Chaudhry B. New concepts in the development and malformation of the arterial valves. *J Cardiovasc Dev Dis*. 2020;7(4):38.

9. Hartwig NG, Vermeij-Keers C, De Vries HE, Gittenberger-De Groot AC. Aplasia of semilunar valve leaflets: two case reports and developmental aspects. *Pediatr Cardiol*. 1991;12:114–117.

10. Phillips HM, Mahendran P, Singh E, et al. Neural crest cells are required for correct positioning of the developing outflow cushions and pattern the arterial valve leaflets. *Cardiovasc Res*. 2013;99:452–460.

11. Lin L, Pinto A, Wang L, et al. ETS1 loss in mice impairs cardiac outflow tract septation via a cell migration defect autonomous to the neural crest. *Hum Mol Genet*. 2022;31(24):4217–4227.

12. Gandhi S, Ezin M, Bronner ME. Reprogramming axial level identity to rescue neural-crest-related congenital heart defects. *Dev Cell*. 2020;53:300–315.e4.

KEY WORDS aortic valve, fetal diagnosis, fetal echocardiography, whole genome sequencing

APPENDIX For a supplemental table and videos, please see the online version of this paper.