Fetal Diagnosis of Tetralogy of Fallot, Major Aortopulmonary Collateral Arteries, and an "Inverted" Pulmonary Valve Causing a Circular Shunt

Michael Satzer, MD, Emina Hodzic, MD, Michael Argilla, MD, and Nadine Choueiter, MD,
Bronx and New York, New York

INTRODUCTION

Tetralogy of Fallot is the most common type of cyanotic congenital heart disease and involves an anterior malalignment ventricular septal defect (VSD) with aortic override and varying degree of right ventricular outflow tract obstruction. Associated cardiovascular abnormalities may be observed, including right aortic arch. Two unusual subtypes include (1) tetralogy of Fallot with dysplastic/absent pulmonary valve syndrome and (2) tetralogy of Fallot and pulmonary atresia with major aortopulmonary collateral arteries (MAPCAs). We report the fetal and postnatal course of a patient with tetralogy of Fallot, MAPCAs, and a unique form of pulmonary valve dysplasia. Imaging demonstrates complete obstruction of antegrade flow across the pulmonary valve in systole and severe regurgitation in diastole, resulting in a circular shunt involving the VSD.

CASE PRESENTATION

A 35-year-old woman (gravida 5, para 1) presented for fetal echocardiography at 20 weeks' gestation due to an abnormal obstetric ultrasound. The pregnancy was complicated by pregestational diabetes with elevated hemoglobin A1C of 13% in the first trimester. Medications included labetalol (for chronic hypertension), low-dose aspirin (prophylaxis against preeclampsia), and insulin. There was no family history of congenital heart disease.

Fetal echocardiography revealed a large anterior malalignment VSD with overriding aorta and right aortic arch (Figure 1; Video 1). Vessels consistent with MAPCAs originated from the aorta. There was no antegrade blood flow across the pulmonary valve. However, retrograde flow returned to the right ventricle from the main and left pulmonary arteries throughout diastole (Figure 2; Videos 2 and 3). Thin and elongated pulmonary valve tissue appeared to prolapse into the right ventricular outflow tract during diastole, causing severe regurgitation. However, during systole the valve tissue seemed to coapt and obstruct antegrade flow (Figure 2C and 2D; Video 1).

Imaging through 31 weeks of gestation also documented confluent branch pulmonary arteries. The proximal branch pulmonary arteries were of normal diameter for gestational age, although the main pulmonary artery (MPA) and pulmonary annulus were moderately hypoplastic. Biventricular systolic function and the cardiothoracic ratio remained normal. No significant atrioventricular valve regurgitation was observed.

Labor was induced at 38 weeks' gestation. A transthoracic echocardiogram of the male infant confirmed the prenatal findings of abnormal pulmonary valve function (Figures 3 and 4; Videos 4 and 5). Attachments of valvular tissue to the right ventricular free wall were suspected, providing a potential explanation for the failure of valve leaflets to open into the pulmonary artery. The right ventricle was hypertrophied, and biventricular systolic function was normal. A small vessel inferior to the aortic arch was concluded to be a persistent fifth aortic arch (Figure 5).

The early postnatal course was marked by severe hypoxemia, systemic hypotension, and elevated serum lactate levels. The child was intubated, and intravenous prostaglandin was initiated to maintain patency of a ductus arteriosus. Additional therapy included inhaled nitric oxide, epinephrine, hydrocortisone, and triiodothyronine (T_3).

Cardiac catheterization was performed at day 1 of life. On FiO_2 of 1.0 and 40 ppm inhaled nitric oxide, systemic arterial oxygen saturation was low at 81% (PaO_2 44 mm Hg). Contrast filling defects consistent with pulmonary valve leaflets were noted in the expected location, whose hinge points coincided with an apparent annulus; the pulmonary root otherwise appeared anatomically normal.

Figure 1 Fetal echocardiogram (27 weeks' gestation) in transverse view showing right aortic arch (†) with aorta overriding the right ventricle (*). A hash mark (#) indicates the fetal spine.

VIDEO HIGHLIGHTS

Video 1: Fetal echocardiogram demonstrating overriding aorta, VSD, right aortic arch, and dysplastic pulmonary valve.

Video 2: Fetal echocardiogram with color comparison in transverse view showing diastolic pulmonary regurgitation via left pulmonary artery to MPA to right ventricle.

Video 3: Fetal echocardiogram with color comparison showing antegrade flow across the aortic valve during systole and retrograde pulmonary regurgitant flow during diastole.

Video 4: Transthoracic echocardiogram with parasternal short-axis color comparison.

Video 5: Transthoracic echocardiogram with parasternal long-axis sweep (sweeping initially posteriorly to the tricuspid valve, then anteriorly to the pulmonary valve).

Video 6: Lateral angiogram with injection into the MPA, demonstrating unrestricted pulmonary valve regurgitation and inverted (or reversed) pulmonary valve leaflet movement.

Video 7: Anterior-posterior angiogram with contrast injection in the right ventricle.

Video 8: Lateral angiogram with selective injection in a MAPCA from the descending aorta demonstrating contrast communicating with the central pulmonary arteries and then the right ventricle.

View the video content online at www.cvcasejournal.com.

However, in diastole there was hinged excursion of the valve leaflets backward into the right ventricular outflow tract, associated with unrestricted regurgitation. In systole, the leaflets hinged forward, arresting to form a plate at the annulus with the appearance of a closed valve (Figure 6; Video 6). Right ventricular angiography showed no antegrade flow across the pulmonary valve (Figure 7; Video 7). Pulmonary angiography demonstrated unrestricted pulmonary regurgitation. Several small MAPCAs supplied confluent branch pulmonary arteries (e.g., Figure 8; Video 8). Competitive flow from the MAPCAs resulted in retrograde flow from the pulmonary arteries to the right ventricle.

Prostaglandin was discontinued as there was no evidence of a true ductus arteriosus. Surgical intervention was performed at 5 days of age. As a palliative measure, the MPA was ligated without surgical division to abolish the circular shunt, while preserving the MPA for use in later repair. The procedure resulted in improvement in systemic oxygenation. Due to the small size of the MPA and pulmonary infundibulum, placement of a transannular patch (standard method of repair) could not reasonably be performed. Complete surgical repair was thus deferred, and a 3.5 mm modified Blalock-Taussig shunt was placed to augment pulmonary blood supply and allow the patient to grow. Signs of mild pulmonary overcirculation were subsequently evident, but well controlled by diuretic therapy. At 5 months of age, the infant was clinically well with slow but steady weight gain. Comprehensive repair of tetralogy of Fallot is anticipated within a period of months. A chromosomal microarray was normal.

DISCUSSION

This is the first report to the authors' knowledge of an unusual variant of tetralogy of Fallot with MAPCAs and absent antegrade pulmonary
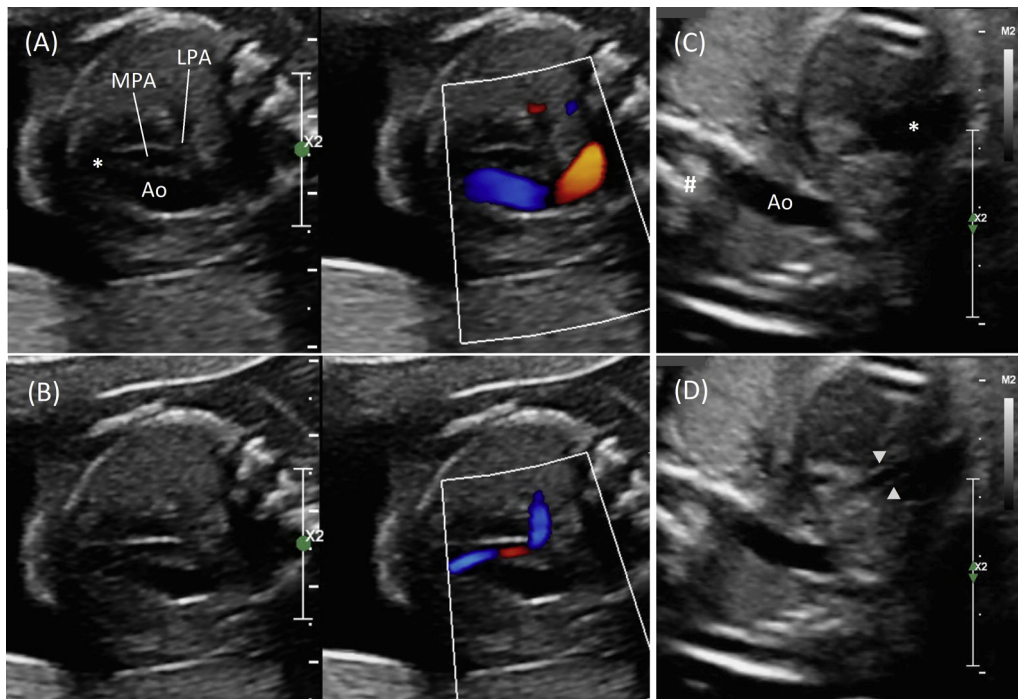

Figure 2 Fetal echocardiogram in systole **(A, C)** and diastole **(B, D)**. Diastolic pulmonary regurgitation is seen **(B)** via left pulmonary artery (LPA) to MPA to right ventricle (*). An off-axis view **(C, D)** shows pulmonary valve tissue (*triangles*) extending into the right ventricle in diastole. *Ao,* Aorta. A hash mark (#) indicates the fetal spine.
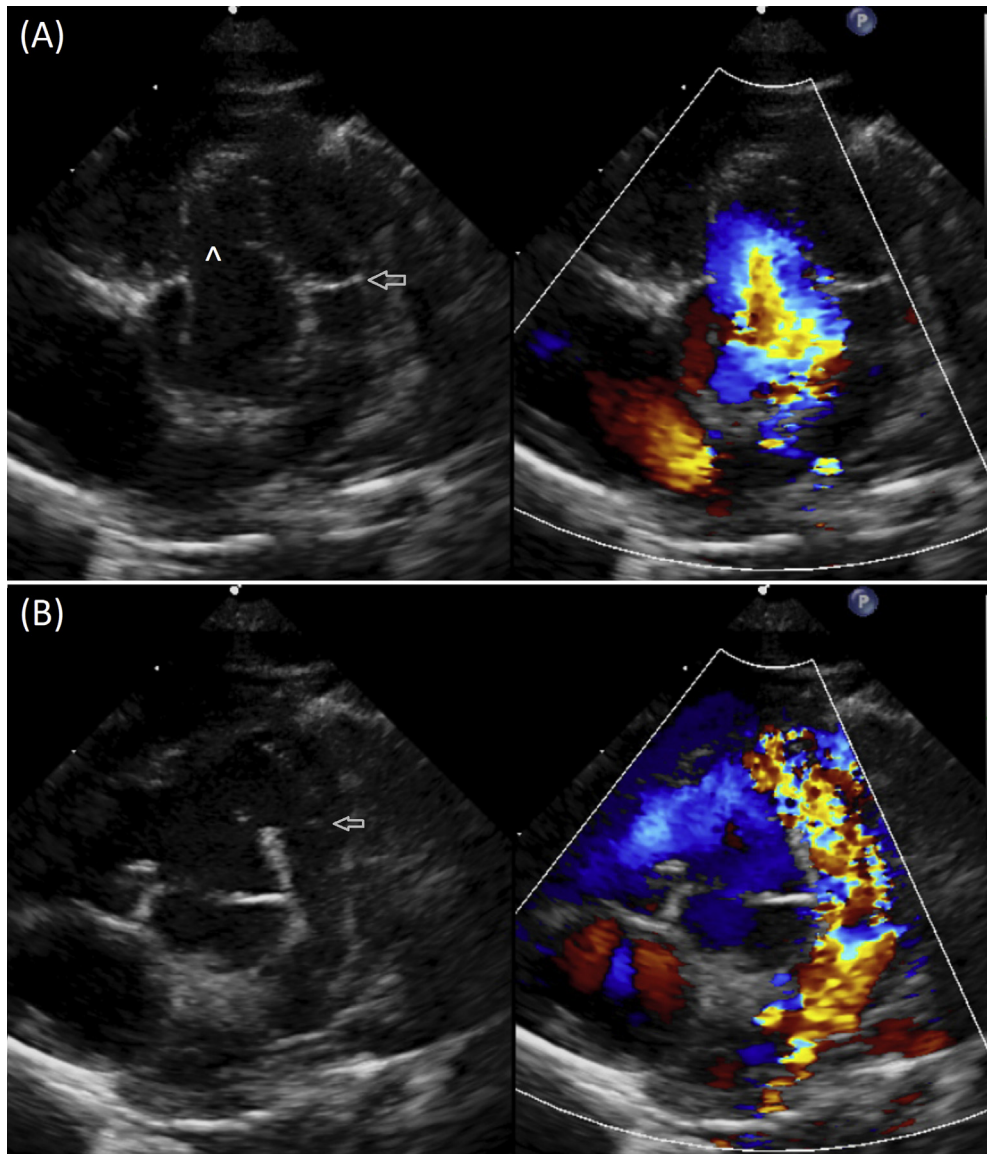
Figure 3 Transthoracic short-axis imaging analogous to Figure 3, in systole **(A)** and diastole **(B)**. Pulmonary valve tissue coapts in systole and opens into the infundibulum in diastole (*arrows*). A caret () indicates the VSD.
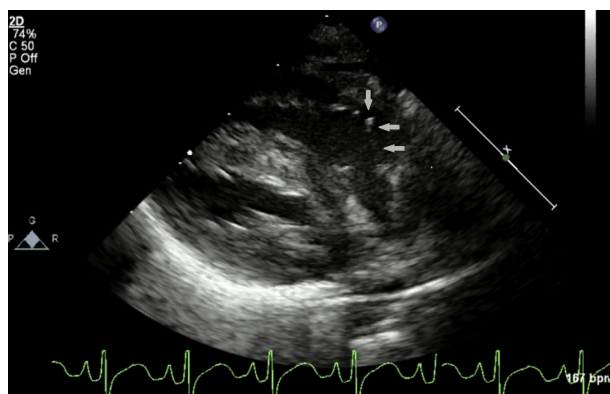

Figure 4 Parasternal long-axis view angled anteriorly to the right ventricular outflow tract, showing suspected attachment (*arrows*) of the pulmonary valvular material to the right ventricular free wall.
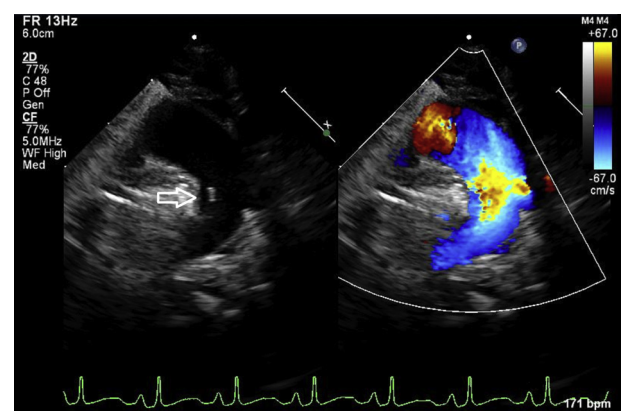

Figure 5 Transthoracic echocardiogram sagittal view of the aortic arch with inferior diminutive persistent fifth aortic arch (*arrow*).

Figure 7 Cardiac catheterization (anterior-posterior view) with contrast injection in the right ventricle (*). Contrast enters the aorta (†) through the VSD, although it does not cross the pulmonary annulus (*arrow*) in systole.
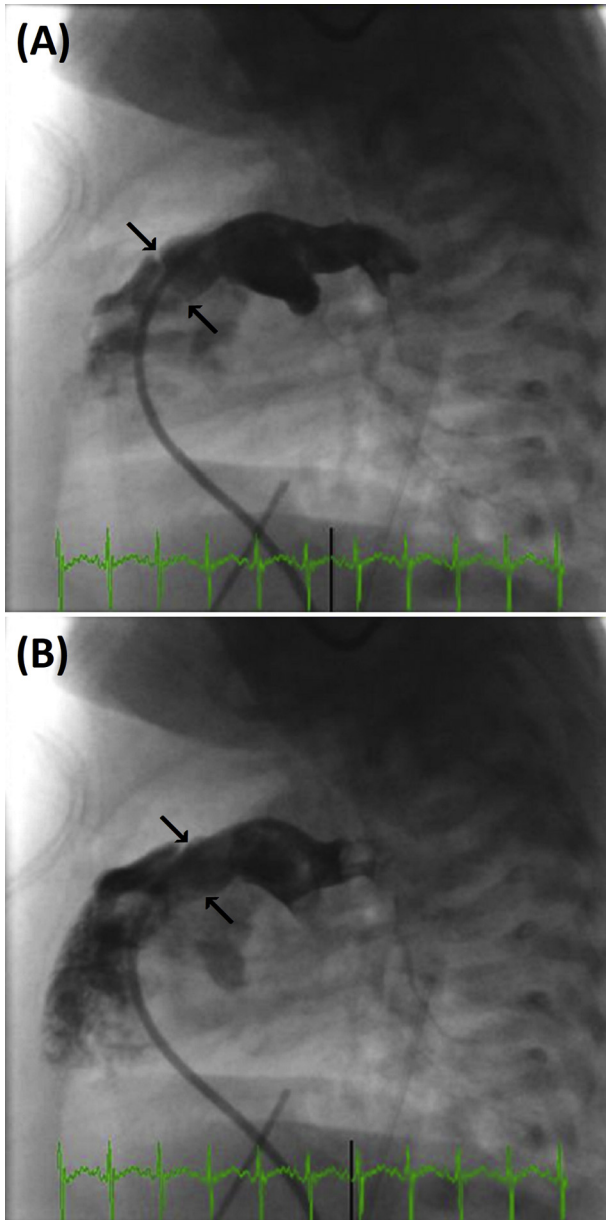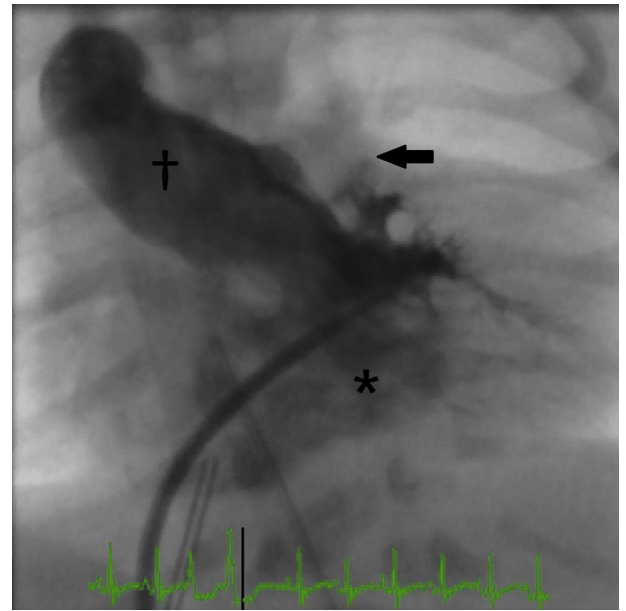
Figure 6 Lateral angiogram with injection into the MPA demonstrating the pulmonary valve leaflets closing at the level of the pulmonary valve annulus (*arrows*) in systole **(A)** and opening backward into the right ventricular outflow tract in diastole **(B)**.

blood flow, yet with severe pulmonary regurgitation due to a dysplastic pulmonary valve. Although findings are evocative of "functional pulmonary atresia," this label has traditionally been applied to cases with a structurally normal pulmonary valve. In such instances, absent antegrade flow results from tricuspid valve disease (e.g., Ebstein's anomaly), right ventricular dysfunction (e.g., Uhl's anomaly), or elevated pulmonary vascular resistance.[1,2] Instead, the present case of tetralogy of Fallot with "inverted" pulmonary valve demonstrates features of both dysplastic/absent pulmonary valve syndrome and anatomic pulmonary atresia.

Tetralogy of Fallot comprises pulmonary infundibular hypoplasia, anterior malalignment VSD, and varying degrees of pulmonary outflow obstruction.[3] In cases of pulmonary atresia, pulmonary blood flow may arise from a ductus arteriosus, MAPCAs, coronary arteries, and/or bronchial arteries.[4,5] Central pulmonary arteries are often hypoplastic or atretic in this situation. Absent/dysplastic pulmonary valve is another subtype of tetralogy of Fallot, wherein the valve is "rudimentary" with combined stenosis and severe regurgitation. The pulmonary arteries are typically massively dilated, causing tracheobronchial compression. A ductus arteriosus is almost universally absent. To our knowledge, the concurrent presence of MAPCAs has not been reported.[6-8]

Despite anatomic similarities between our case and these two subtypes of tetralogy of Fallot, the postnatal course of our patient differed significantly from both. The branch pulmonary arteries were not dilated, and there was no tracheobronchial obstruction. Pulmonary blood flow was supplied by several MAPCAs, though a large fraction was lost to circular shunting (with flow from aorta to MAPCAs to branch pulmonary arteries to main pulmonary artery to right ventricle to VSD to aorta). This shunt resulted in decreased effective pulmonary blood flow, especially in the setting of relatively elevated pulmonary vascular resistance of the newborn. Profound hypoxemia and tissue hypoxia ensued, although these improved with pulmonary vasodilator and systemic vasoconstrictor therapy and further improved following surgical ligation of the pulmonary artery by disrupting the circular shunt.

A comparison may be drawn with the circular shunt of Ebstein's anomaly accompanied by pulmonary regurgitation and patent ductus arteriosus. In our case the right ventricle participated in systemic output, which does not occur in Ebstein's anomaly. Notably, palliative surgical ligation of the pulmonary artery has also been described in cases of Ebstein's anomaly involving circular shunt.[9]

Any embryologic explanation of the findings in this case would be speculative. Cardiac valves develop from layers of extracellular matrix derived from endocardial cushions in the primitive heart tube. Layers are normally oriented with the direction of blood flow.[10] One may hypothesize that some factor—molecular or hemodynamic—disrupted
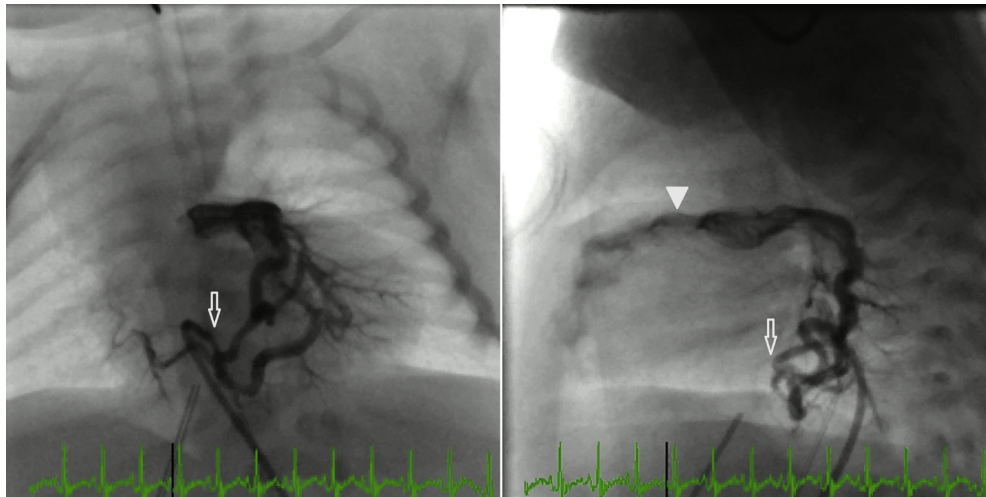
Figure 8 Cardiac catheterization with selective injection into a MAPCA supplying bilateral lower lung segments and ultimately communicating with the right ventricular outflow (*triangle*). *Left*: anterior-posterior view; *right*: lateral view; *arrow*: catheter tip.

the normal stratification or polarity of layering in the developing valve. Imaging also suggests the presence of anomalous tissue anchoring the valve to the right ventricular wall.

Surprisingly, the chromosomal microarray was normal. Tetralogy of Fallot with pulmonary atresia and MAPCAs is highly associated with 22q11.2 deletion syndrome, particularly in the presence of a right aortic arch.[11] Absent pulmonary valve is also strongly associated with this syndrome.[8] Increased incidence of tetralogy of Fallot is also observed in maternal diabetes, a potential factor in this case.[12]

Although rare, tetralogy of Fallot with persistent fifth aortic arch has been described elsewhere. This vessel functioned as a systemic-to-systemic shunt in our patient, rather than a systemic-to-pulmonary shunt that may be seen with severe right-sided obstructive lesions.[13] Thus, the finding did not significantly affect hemodynamics.

A final unexpected observation of this case is that fetal cardiac function was preserved despite severe pulmonary regurgitation and systemic-to-pulmonary artery shunting. Such physiology has been considered potentially lethal during fetal life in tetralogy of Fallot and absent pulmonary valve with patent ductus arteriosus.[14,15] While fetal imaging in our patient suggested that a ductus arteriosus might be present, postnatal angiography showed only MAPCAs. A key difference in this case, compared with absent pulmonary valve, is the lack of antegrade pulmonary flow. The right ventricle thus contributed more significantly to systemic blood flow. Additionally, the resistive properties of MAPCAs likely exceed those of a large ductus arteriosus, being of narrower diameter and more distal insertion into the pulmonary vasculature. Similarly, the hypoplastic MPA and normally sized (but relatively smaller) branch pulmonary arteries of the present case may have reduced the volume of pulmonary regurgitation.

CONCLUSION

This case demonstrates a previously undescribed variant of tetralogy of Fallot with MAPCAs, in which dysplastic pulmonary valve tissue functionally results in the reversal of normal pulmonary valve physiology, with absent antegrade blood flow and unrestricted regurgitation, with MAPCAs supplying pulmonary blood flow. Fetal echocardiographic diagnosis was possible by 20 weeks' gestation,

although complementary neonatal angiography was necessary to accurately define sources of pulmonary blood flow. Additionally, this case highlights therapeutic challenges posed by an unusual circular shunt.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2020.05.009.

REFERENCES

1. Freedom RM, Culham G, Moes F, Olley PM, Rowe RD. Differentiation of functional and structural pulmonary atresia: role of aortography. Am J Cardiol 1978;41:914-20.
2. Suzuki H, Nakasato M, Sato S, Komatsu H, Hayasaka K. Management of functional pulmonary atresia with isoproterenol in a neonate with Ebstein's anomaly. Tohoku J Exp Med 1997;181:459-65.
3. Van Praagh R, Van Praagh S, Nebesar RA, Muster AJ, Sinha SN, Paul MH. Tetralogy of Fallot: underdevelopment of the pulmonary infundibulum and its sequelae. Am J Cardiol 1970;26:25-33.
4. Liao PK, Edwards WD, Julsrud PR, Puga FJ, Danielson GK, Feldt RH. Pulmonary blood supply in patients with pulmonary atresia and ventricular septal defect. J Am Coll Cardiol 1985;6:1343-50.
5. Acherman RJ, Smallhorn JF, Freedom RM. Echocardiographic assessment of pulmonary blood supply in patients with pulmonary atresia and ventricular septal defect. J Am Coll Cardiol 1996;28:1308-13.
6. Lakier JB, Stanger P, Heymann MA, Hoffman JI, Rudolph AM. Tetralogy of Fallot with absent pulmonary valve. Natural history and hemodynamic considerations. Circulation 1974;50:167-75.
7. Donofrio MT, Jacobs ML, Rychik J. Tetralogy of Fallot with absent pulmonary valve: echocardiographic morphometric features of the right-sided

structures and their relationship to presentation and outcome. J Am Soc Echocardiogr 1997;10:556-61.

8. Wertaschnigg D, Jaeggi M, Chitayat D, Shannon P, Ryan G, Thompson M, et al. Prenatal diagnosis and outcome of absent pulmonary valve syndrome: contemporary single-center experience and review of the literature. Ultrasound Obstet Gynecol 2013;41:162-7.

9. Yanase Y, Watanabe M, Ishikawa N, Higami T. Surgical treatment for neonatal Ebstein's anomaly with circular shunting. Interact Cardiovasc Thorac Surg 2012;14:886-8.

10. Combs MD, Yutzey KE. Heart valve development: regulatory networks in development and disease. Circ Res 2009;105:408-21.

11. Peyvandi S, Lupo PJ, Garbarini J, Woyciechowski S, Edman S, Emanuel BS, et al. 22q11.2 deletions in patients with conotruncal defects: data from 1610 consecutive cases. Pediatr Cardiol 2013;34:1687-94.

12. Lisowski LA, Verheijen PM, Copel JA, Kleinman CS, Wassink S, Visser GH, et al. Congenital heart disease in pregnancies complicated by maternal diabetes mellitus. An international clinical collaboration, literature review, and meta-analysis. Herz 2010;35:19-26.

13. Lloyd DFA, Ho SY, Pushparajah K, Chakraborty S, Nasser M, Uemura H, et al. Persistent fifth aortic arch: the "great pretender" in clinical practice. Cardiol Young 2018;28:175-81.

14. Yeager SB, Van Der Velde ME, Waters BL, Sanders SP. Prenatal role of the ductus arteriosus in absent pulmonary valve syndrome. Echocardiography 2002;19:489-93.

15. Zach M, Beitzke A, Singer H, Hofler H, Schellmann B. The syndrome of absent pulmonary valve and ventricular septal defect—anatomical features and embryological implications. Basic Res Cardiol 1979;74: 54-68.