CASE REPORTS

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Successful surgical closure of an aortopulmonary window associated with Holt-Oram syndrome in adulthood

Uspešno hirurško zatvaranje aortopulmonalnog prozora udruženog sa Holt-Oramovim sindromom u odraslom dobu

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Abstract

Introduction. Aortopulmonary window (APW) is a rare congenital anomaly caused by incomplete division of the embryonic common arterial trunk which allows direct and usually unobstructed communication between the ascending aorta and pulmonary artery trunk. Holt-Oram syndrome (HOS) is an autosomal dominant disorder caused by the mutation in the TBX5 gene and it is characterized by bones abnormalities in at least one limb while the association with APW is extremely rare. **Case report.** We report a case of a female patient in her thirties with an extremely rare combination of the HOS and APW window that reached the adulthood without surgical correction. The adult patient came to our clinic with signs of severe heart failure and pulmonary hypertension. Although previously diagnosed as inoperable, after the decongestive medical treatment and detailed diagnostic procedures we proved reactive pulmonary vascular resistance and the patient was successfully surgically treated. **Conclusion.** This case confirms the absolute necessity of cautious and comprehensive examinations of each patient with congenital heart disease and pulmonary hypertension irrespective of age.

Key words:
aortopulmonary septal defect; holt-oram syndrome; adult; cardiovascular surgical procedures; treatment outcome.

Apstrakt

Uvod. Aortopulmonalni prozor (*aortopulmonary window* – APW) je retka kongenitalna anomalija uzrokovana nepotpunim razdvajanjem zajedničkog embrionalnog arterijskog stable koja se manifestuje direktnom i neuobičajenom komunikacijom između aorte i plućne arterije. Holt-Oramov sindrom je antozomno-dominantni poremećaj uzrokovan mutacijom TBX5 gena koga odlikuju anomalije kostiju bar na jednom od gornjih ekstremiteta. Njegova udruženost sa APW je veoma retka. **Prikaz bolesnika.** U radu je prikazana bolesnica u četvrtoj deceniji života sa vrlo retkom kombinacijom Holt-Oramovog sindroma i APW koji nije bio zatvoren do odraslog doba. Bolesnica je hospitalizovana sa znacima teške srčane insuficijencije i plućne hipertenzije. Iako prethodno dijagnostikovana kao inoperabilna, posle odgovarajućeg medicinskog tretmana i detaljnih dijagnostičkih procedura dokazana je još uvek značajno reaktivna plućna vaskularna rezistencija nakon čega je bolesnica uspešno operisana. **Zaključak.** Ovaj slučaj potvrđuje neophodnost pažljive i sveobuhvatne dijagnostike bolesnika sa hemodinamski značajnim urođenim srčanim manama i sekundarnom plućnom hipertenzijom bez obzira na njihovo životno doba.

Ključne reči:
aortopulmonalni septalni defect; holt-oram sindrom; odrasle osobe; hirurgija, kardiovaskularna, procedure; lečenje, ishod.

Introduction

Aortopulmonary window (APW) is a rare congenital anomaly caused by incomplete division of the embryonic common arterial trunk which allows direct and usually unobstructed communication between the ascending aorta and pulmonary artery trunk [1]. Usual morphological classification according to the nomenclature reported by Jacobs et al. [2] is based according to APW localization. Closure of APW, either surgical or percutaneous, is necessary and the optimal time to be performed is in early childhood, before irreversible pulmonary hypertension (PHT) and Eisenmenger syn-

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drome are developed [1]. If the pulmonary vascular disease is formed, there is often a "gray zone" between its reversibility or irreversibility [3, 4], which represents a diagnostic challenge and requires serious diagnostic procedures before pronouncing an adult with APW and PHT as inoperable.

Holt-Oram syndrome (HOS) is an autosomal dominant disorder caused by the mutation in the TBX5 gene [5–7] and it is characterized by bones abnormalities in at least one limb. Also, about 75% of individuals with Holt-Oram syndrome have heart abnormalities, most commonly atrial and ventricular septal defect and cardiac conduction disease while the association with APW is extremely rare [8].

Case report

We present a 31-year-old female patient admitted because of symptoms and signs of heart failure [New York Heart Assotiation Functional Classification (NYHA) class III]. According to her past medical history, aortopulmonary window was diagnosed in childhood as part of Holt-Oram syndrome (complete absence of the right hand). Lack of symptoms was the reason for her rejecting the recommended surgical closure. In August 2013, she experienced attacks of severe dyspnea and palpitations followed by leg edema and ascites. On admission, she was dyspneic, acyanotic (SpO_2 99%) and afebrile. The auscultation revealed bilateral basal inspiratory crackles, sinus tachycardia with a heart rate of 110 beats per minute (bpm), a 3/6 systolic and short diastolic murmur over the aorta and systolic regurgitated murmur at the apex. Her blood pressure was 120/50 mmHg on both arms. The abdomen was distended due to hepatomegaly and ascites. ECG showed atrial fibrillation and left ventricular strain. Chest X-ray confirmed cardiomegaly (cardiothoracic index – CTI) 0.75 with increased hilar vascularity and pulmonary congestion. Echocardiography revealed significant enlargemen and moderate reduced contractility of the left ventricle [end-systolic diameter (ESD) 7.9 cm, end-by diastolic diameter (EDD) 6.7 cm, ejection fraction (EF) 37%] with mitral regurgitation grade +3/4 (Table 1). The pulmonary artery was dilated (diameter 3.9 cm) with continuous left–to-right flow (maximal velocity 0.6 m/s by Doppler echocardiography) through a 10 mm wide aorto-pulmonary fenestration best seen on the parasternal short axis view. Moderate pulmonary regurgitation was registered in the normal sized right ventricle with +3/4 tricuspid regurgitation and estimated right ventricular systolic pressure about 74 mm Hg. There were no signs of pericardial effusion.

The patient was treated with diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, digoxin, amiodarone and anticoagulant therapy. After a few weeks under the therapy her condition was significantly better. After disappearance of ascites and regression of congestive heart failure, cardiac multislice computed tomography (MSCT) was performed for better visualization of the aorto-pulmonary window. Type I of APW diameter 10 mm was diagnosed, localized 39 mm above the sinotubular aortic junction. Cardiac catheterization was performed with testing the pulmonary vascular reactivity by breathing 100% oxygen and nitric oxide, and the results revealed that her mean pulmonary artery pressure decreased from 69 mmHg to 57 mmHg (>10%) and pulmonary vascular resistance decreased from 8.9 WU/m^2 to 0.72 WU/m^2, followed by significant increase of left-to-right shunting (Qp/Qs from 2.2 to 15). Aortography in caudal position revealed left-to-right aortopulmonary shunt through APW (Figure 1), but on pulmonary angiography there were no signs of right-to-left shunt. Since the attempt of percutaneous closure with an Amplatzer device had failed, surgery was indicated. In May 2014, she was successfully operated in Geneva, closing the APW by Gore Tex patch. Although, postoperative treatment with sildenafil was advised, yet she did not include it to her therapy consisting of digoxin, oral anticoagulant therapy and small doses of ACE inhibitors, beta blockers and amiodarone. One month after the operation, our patient was free of symptoms and with good exertion tolerance (NYHA class I). Atrial fibrillation persisted with well-controlled heart rate and blood pressure 130/80 mmHg. Echocardiographic examination revealed a decrease of left ventricle diameters (EDD 6.9 cm, ESD 5.4 cm) and significantly improved global systolic function (EF 55%) by reduction of mitral regurgitation grade to + 2/4. Systolic right ventricle pressure also decreased to about 43 mmHg estimated according to mild tricuspid regurgitation (Table 1).

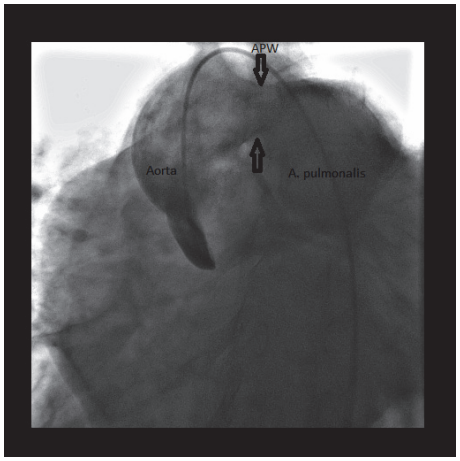

Fig. 1 – Aortography in caudal position revealed left-to-right aortopulmonary shunt through aortopulmonary window.

Table 1

Clinical and echocardiographic parameters before and after the operation of aorto-pulmonary window

Parameters	Preop.	Postop
LVD (mm)	79	69
LVS (mm)	67	54
EF (%)	37	55
MR (grade)	+ 3/4	+ 2/4
TR (mmHg)	74	43
NYHA class	III	I

LVD – left ventricular diastolic dimension; LVS – left ventricular systolic dimension; EF – ejection fraction; MR – mitral regurgitation; TR – pressure gradient of tricuspid regurgitation.

NYHA class – New York Heart Assotiation Functional Classification; Preop – preoperative; Postop – postoperative.

Table 2

Catheterization data before and after operation of aortopulmonary window

Parameters	Before testing	After testing with oxygen and nitric oxide	Postop.
Right atrium pressure (mmHg)	12	12	4
Pulmonary capillary wedge pressure (mmHg)	11	11	8
Mean PA pressure (mmHg)	69	58	18
Mean PA pressure / mean arterial pressure (mmHg)	0.97	0.77	0.22
Qp/Qs	2.2	15	0
Pulmonary vascular resistance (WU/m^2)	8.9	0.72	
Rp/Rs	0.44	0.05	

PA – pulmonary artery; Qp/Qs – ratio of pulmonary and systemic arterial flow; Rp/Rs – ratio between pulmonary and systemic arterial vascular resistance.

On the anterolateral wall of the aorta towards the pulmonary artery, a 12 mm large hiperechogenic zone was visualized, corresponding to the postoperative patch without signs of residual aortopulmonary shunt. Postoperative cardiac catheterization confirmed normalization of pressure in the pulmonary circulation (Table 2) and the absence of aortopulmonary shunt on aortography (Figure 2).

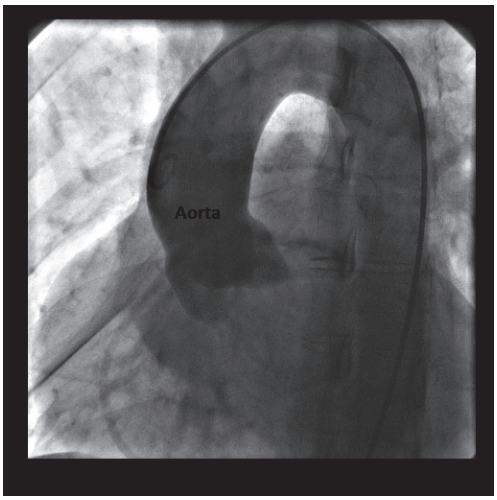

Fig. 2 – The absence of aortopulmonary shunt on aortography.

Discussion

Aortopulmonary window is a very rare cardiac anomaly with incidence from 0.1% to 0.2% of all congenital heart defects [1], described for the first time by Elliotson in 1830. It can be a simple, isolated defect presenting as the only cardiac malformation or associated with other cardiovascular malformations (in 47%–77% of the cases [1]). When diagnosed, APW should be promptly closed, whether surgically or with transcatheter intervention [9]. Diagnosis are usually made early at birth or in childhood and there are extremely rare reports of adults with this diagnosis and especially rare with successful treatment in adulthood. Su-Mei and Ju-Le [10] reported an adult female patient with Eisenmenger syndrome due to untreated APW that survived into adulthood, gave birth to three children in her early thirties, and died in her sixties.

Holt-Oram syndrome, also known as heart-hand syndrome, was first described by Holt M. and Oram S. in 1960 [7]. It is characterized by congenital heart abnormalities and skeletal malformations of the upper limb, ranging from subtle changes such as hypoplasia or absence of the thumb to complete absence of the hand with the left side usually being more often affected [8]. HOS must be differentiated from Okihiro syndrome [11], as those two syndromes have certain clinical features overlap, such as various forms of forearm malformations and ventricular and atrial septal defects that are sometimes presented in Okihiro syndrome. Unlike HOS, Okihiro syndrome is associated with Duane anomaly (limitation of eye abduction associated with retraction of the eye globe and narrowing of the palpebral fissure on adduction). Anal stenosis, renal abnormalities, pigmentary disturbance, hearing impairment, external ear malformations and facial asymmetry can also appear as part of Okihiro syndrome. Finally, Okihiro syndrome is caused by the mutation of SALL4 gene, and HOS by the TBX5 gene mutation.

Epidemiological and clinical aspects of HOS patients were presented using data from European Surveillance of Congenital Anomalies (EUROCAT) registries [12]. The mean prevalence of HOS diagnosed in European registries was 0.7 per 100,000 births or 1:135,615 births. EUROCAT studies collected data from 1990 to 2011 from 34 registries and identified a total of 73 cases of HOS. Congenital heart defects (CHD) were revealed in 78.7% (48/61) of patients. Isolated septal defects were present in 54.2% (26/48) while 25% (12/48) of the patients had complex/severe CHD. In EUROCAT registries there were not any patients with HOS in association with APW.

There are only two cases of APW associated with HOS in the literature (according to Medline database search); one was described by Ulrich et al. [8] in 2004, as the first such case. They presented a female patient with Mayer-von Rokitansky-Kuster-Hauser syndrome in association with a HOS and aortopulmonary window treated surgically when she was 6 months old. The other one is from 2014. Srinivas et al. [13]

presented a 4-month-old male infant who had absence of radius and the first metacarpal and phalangeal bones on the right side together with aortopulmonary window and small secundum atrial septal defect. APW was successfully treated by device closure. The main contraindication for the APW treatment in adulthood is already established pulmonary hypertension. In our case, the patient was hospitalized with signs of acute cardiac failure and atrial fibrillation for which she was initially treated with decongestive, antiarrhythmic, anticoagulant and pulmonary vasodilatation therapy. After the stabilization of the cardiac function and control of atrial fibrillation the next step was to define whether the pulmonary arterial hypertension was reversible or irreversible by testing pulmonary vasoreactivity during cardiac catheterization. Testing is usually conducted using short-acting vasodilators such as inhaled nitric oxide, intravenous epoprostenol, adenosine and inhaled 100% oxygen [14]. We performed the test with 100% oxygen and nitric oxide and got a reduction of pulmonary pressure for > 10%, significant increasing of left-to-right shunt and fall of pulmonary vascular resistance (Table 2). Those results, together with improved cardiac function and general health condition of the patient after intensive decongestive and antiarrhythmic therapy suggested that the closure of APW is possible with a relatively low operative risk.

After detailed examinations, APW was successfully surgically closed without complications in the postoperative period. Postoperatively, we registered significant clinical, echocardiographic and hemodynamic improvement in the patient with complete normalization of pressure in pulmonary circulation (Tables 1 and 2). Although the quality and length of life of the patient was significantly improved, it should be kept in mind that specific long-term consequences of left-right shunt in the form of moderate mitral regurgitation and left heart dilatation with atrial fibrillation still remain.

Conclusion

The outcome of hemodynamically significant congenital heart disease in adult patients can sometimes be surprisingly favorable, but making good decisions about further treatment requires detailed diagnosis and careful cross-analysis of numerous medical histories, clinical and hemodynamic parameters.

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