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Case Report

Management of pink tetralogy of Fallot in VACTERL association

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Tetralogy of Fallot (TOF) and vertebral abnormalities, anorectal malformation, cardiac defects, tracheoesophageal fistula with or without esophageal atresia, renal malformations, and limb abnormalities (VACTERL) are considered rare entities requiring medical attention with regards to diagnosis and management. When ToF is associated with VACTERL association, case management might differ from a simple case of ToF.

Tetralogy of Fallot (ToF) is defined as a complex congenital cardiac abnormality characterized by ventricular septal defect, right outflow tract obstruction, right ventricular hypertrophy, and overriding aorta.[1] The term was coined in 1888 by Fallot of Marseilles, even though the defect had been described in 1673 by Steno of Denmark. The entity was then studied extensively to deliver better care management through medical and surgical approaches.[2] **[Paediatr Indones. 2019;59:164-8; doi: http://dx.doi.org/10.14238/pi59.3.2019.164-8]**.

Keywords: *pink TOF; VACTERL association; ACE inhibitor; congenital solitary kidney*

Tetralogy of Fallot is considered the most prevalent cyanotic heart disease, comprising 10% of all congenital heart disease and occurring in three to six infants for every 10,000 births.[3] Among infants with ToF, acyanotic ToF or pink ToF is considered a small minority on the clinical spectrum of infants with ToF. Pink ToF is characterized by mild pulmonary stenosis and small left-to-right shunt in the ventricular septal defect.[4] However, to our knowledge, its prevalence has yet to be studied. Pink ToF itself is a rare entity, but being a part of VACTERL association is even rarer.[5] However, ToF is a common cardiac manifestation of VACTERL, with around 75% of VACTERL association cases having ToF.[6]

Standard management of ToF consists of early recognition, medical therapy, and surgery, divided into either staged palliation or a primary repair approach.[7] In the neonatal period, ToF may not manifest as a full-blown disease when presenting right after birth, as right ventricular failure may not be apparent. But as the condition progresses, right ventricular hypertrophy may develop and lead to right heart failure, if pressure reduction and anti-myocardial remodeling therapy is not given.[8] Standard ToF therapy, as mentioned above, may not be applicable in cases with other associated

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organ anomalies such as VACTERL association, further imposing a challenge to deliver optimal therapy to prevent long-term complications of ToF.

Therefore, the purpose of reporting this case was to emphasize the importance of early recognition for congenital heart disease that may be related to other organ anomalies, to report a method which can be applied in medical facilities with limited resources, and lastly, to define the best possible treatment based on scientific evidence in order to reduce or prevent long-term complications of ToF.

The Case

A three-day-old female neonate with cloacal-type anal atresia (**Figure 1**) was referred from a district hospital. She required a colostomy, but no other diagnosis was mentioned in the referral. The baby was delivered vaginally at 35 weeks gestation, with APGAR score 2/3/8 (at minute one, five, and ten), and birth weight of 2,100 gr. The mother denied consuming any alcohol, smoking, or experiencing any period of illness during the gestation period.

Upon examination in the referred hospital, a holosystolic grade 4/6 murmur best heard at the left lower sternal border was noticed, but with no central or peripheral cyanosis presentation. Echocardiography was done to confirm the diagnosis of acyanotic congenital heart defect. The heart was found to be situs solitus, with apparent subaortic ventricular septal defect (VSD), less than 30% overriding aorta, and infundibular region pulmonary valve stenosis, based on transthoracic echocardiography (TTE). The patient was then diagnosed with non-cyanotic ToF or pink ToF.

After finding anal atresia and pink ToF, the patient was further examined for other related anomalies. Head ultrasound showed no malformation, but abdominal ultrasound revealed right renal agenesis and left hydronephrosis. Chest x-ray revealed butterfly vertebrae at Th5 and Th9, as well as unilateral-unsegmented-bar sacral vertebrae (**Figure 2**). The child's feet were found to be internally rotated with straightened Achilles tendon, signifying the diagnosis of congenital talipes equinovarus (**Figure 3**). Based on the aforementioned anomalies, the patient was diagnosed with VACTERL association.

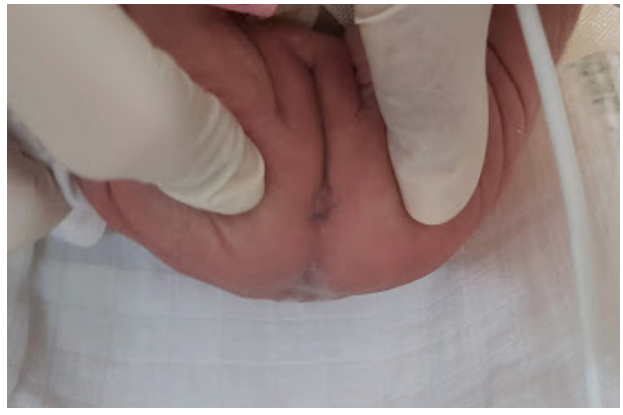

Figure 1.Anal atresia presented as cloaca

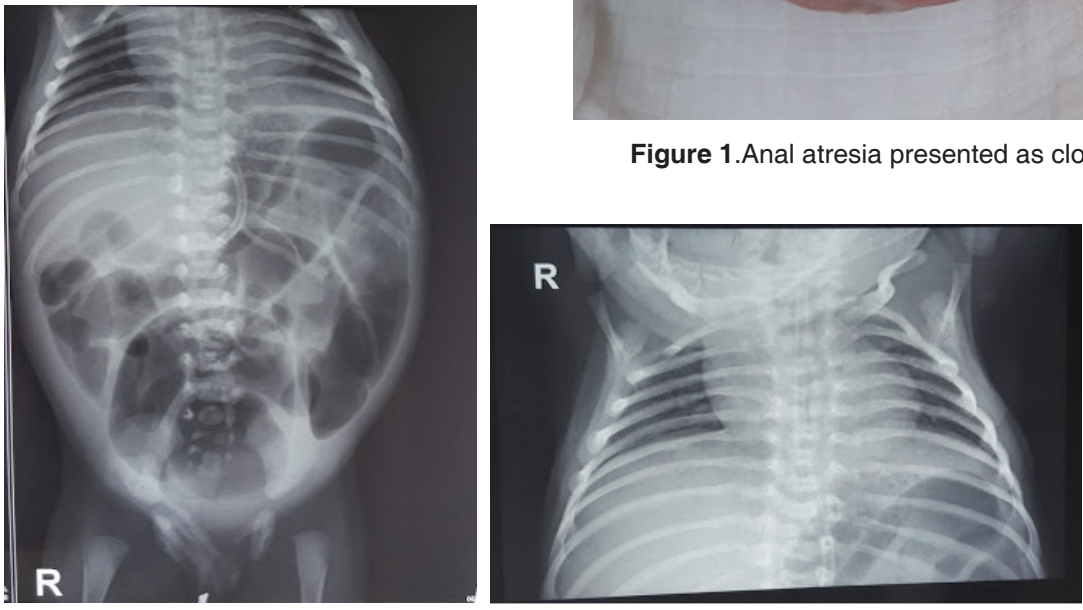

Figure 2. Butterfly vertebrae in Th5 and Th9 with unilateral-unsegmented-bar sacrum

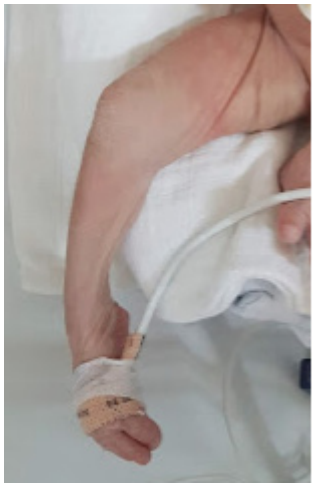

Figure 3. The patient's foot position was found to be internally rotated with straightened Achilles tendon (talipes equinovarus)

The patient underwent surgical colostomy as management for anal atresia. However, no surgical approach was planned for the other organ anomalies. With regards to pink ToF, a surgical approach was also withheld due to the clinical condition of the patient. The neonate would undergo watchful waiting and be re-evaluated in one month. Administration of angiotensin convertase (ACE) inhibitor was also withheld, due to the risk of renal failure since the infant had a congenital solitary kidney associated with VACTERL association.

MRI and right heart catheterization was prepared for further follow-up management plan. If the patient meets the criteria for ToF correction, the procedure of ToF correction would be done in the fourth month of life.

Discussion

The VACTERL association is considered to be a rare congenital disease with an incidence ranging from 1 in 10,000 to 1 in 40,000 live births,[9] which includes vertebral anomalies (V), anal atresia (A), cardiac malformation (C), tracheo-oesophageal fistula (TE) with or without esophageal atresia, renal dysplasia (R), and limb abnormalities (L). The entity was first mentioned as VATER association in 1973 and considered as multiple organ anomalies without evidence of a single unifying cause.[10] However, the likelihood of "developmental field defect" occurring in the blastogenesis phase has been speculated.[5]

A VACTERL association diagnosis requires the presence of at least three congenital malformations. In our case, the malformations were vertebral abnormalities (butterfly vertebrae and unilateral-unsegmented-bar sacrum), anorectal malformation (cloacal-type anal atresia), cardiac defects (pink ToF), renal abnormalities (right renal agenesis), and limb abnormality (congenital talipes equinovarus).[5]

Infants with congenital heart disease (CHD) may benefit from early screening as it may reduce morbidity and mortality from early intervention.[11] Early detection of CHD may be as early as in the prenatal period using fetal echocardiography screening.[12] However, the procedure cannot be implemented widely at the present time in Indonesia since there are a limited number of experts in fetal echocardiography. As such, screening neonates right after birth may also be done in medical centers with limited resources using oximetry screening. This tool measures oxygen saturation at the pre-ductal (right hand) and post-ductal (foot) levels, and may be useful for screening for possible CHD. This simple approach is more sensitive and specific (76.5% and 99.9%, respectively) to screen for CHD, rather than depending only on a cyanotic appearance of the infant.[13]

The short-, middle-, and long-term complications of ToF management should be considered in advance. Short-term management might be related to overcoming the hypoxic condition indicated by a cyanotic appearance. Middle- and long-term complications may be associated with heart failure and multi-organ diseases.[8] The pulmonary stenosis in ToF can be considered as RVOT if it results in cyanosis. This short-term complication of RVOT is influenced by the degree of RVOT obstruction and hypoplastic pulmonary valve annulus as the main culprit of the hypoxic condition.[14] In addition, middle- and long-term complications of TOF are endocarditis, cerebral infarction or abscess, right ventricular hypertrophy with right heart failure, or progressive hypoxia as the disease progresses. These entities will in turn be the major causes of morbidity and mortality of TOF patients. Implementing primary repair of the defect through a surgical approach is the best prevention.[15]

Standard medical management of ToF is especially needed if pulmonary atresia (ductal-dependent ToF) is present. Infusion of prostaglandins (initial: 0.05-0.1 mcg/kg/min IV; maintenance: 0.01-0.4 mcg/kg/min) is needed to ensure the patency of ductus arteriosus.[16] Alternatively, surgical management of ToF has developed significantly, shifting to an earlier age. Symptomatic ToF is categorized as ductal-dependent pulmonary circulation needing prostaglandins to open the ductus arteriosus and has been associated with less than 75% of oxygen saturation. Urgent primary surgical repair or Blalock-Taussig shunt is indicated for these patients.[14] However, for elective procedures, a two-stage surgery or primary repair approach has been proposed for as early as the neonatal period.[15] The size of the pulmonary artery branches should be considered when selecting between the palliative shunt approach and the primary repair approach.[17] A retrospective study in 1992 reported that primary repair of ToF in young infants less than three months of age was associated with high mortality.[18] However, with improved techniques, early primary repair has been associated with better outcomes, such as avoiding shunt-related complications, early relief of hypoxia, promotion of normal lung development, and avoidance of right ventricular hypertrophy.[19,20]

Our patient presented with a non-cyanotic appearance, consistent with a diagnosis of pink ToF. Therefore, she did not need prostaglandin therapy. Nonetheless, a medical approach which functions as anti-remodeling therapy is also noteworthy. Angiotensin convertase (ACE) inhibitor is considered as the cornerstone therapy to try to deter the progression of right ventricular hypertrophy related to pressure and volume overload.[21,22] However, ACE inhibitor administration was postponed in our patient, considering that she had a congenital solitary kidney as part of VACTERL association. Contrary to the belief that ACE inhibitors may lead to kidney damage, Simeoni M et al. showed that anti-renin angiotensin-aldosterone system drugs were renoprotective in patients with a solitary kidney.[23] As such, we considered the use of ACE inhibitors in our case, at an accordingly adjusted dose, but we ended up not doing so. Alongside the medical management of this child, the team concluded that watchful waiting for the need of surgical repair might be a safe path. Moreover, there was no urgent benefit to short-term management of complications of pink ToF. However, considering the possibility of worsening right ventricular function in the future, an earlier primary surgical repair approach should be considered as a rational step. Pozzi M *et al.* also mentioned that asymptomatic pink ToF might benefit the most from early repair.[15]

The ideal management of congenital heart disease starts with prenatal screening using fetal echocardiography, which is still not widely applicable in Indonesia. However, a simple approach such as pre-ductal and post-ductal oxygen saturation screening might significantly improve detection of congenital heart disease, especially in remote areas or hospitals with limited medical resources. Since early screening lead to early disease management, our patient with pink ToF and congenital solitary kidney, which are the part of VACTERL association, might have benefited from strictly adjusted ACE inhibitor administration and early primary surgical repair.

Conflict of Interest

None declared.

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