Educational Case: Tetralogy of Fallot and a Review of the Most Common Forms of Congenital Heart Disease

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> *The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]*

Primary Objective

Objective CH3.1: Congenital Heart Disease: Name the most common forms of congenital heart disease and outline their clinical presentation, natural history, and long- and short-term complications.

  Competency 2: Organ System Pathology; Topic Cardiovascular: Heart (CH); Learning Goal 3: Cardiovascular Malformation.

Secondary Objective

Objective CH3.4: Cardiac Shunts: Define the concepts of left-to-right shunt, right-to-left shunt, and shunt reversal and correlate with clinical presentation.

  Competency 2: Organ System Pathology; Topic Cardiovascular: Heart (CH); Learning Goal 3: Cardiovascular Malformation.

Patient Presentation

A 9-month-old boy presents to the emergency department with his mother, who reports episodes of tachypnea, cyanosis, and irritability during feeding. The mother explains that these episodes have become more frequent, with the patient becoming more cyanotic around the mouth and hands, but seem to resolve spontaneously. The patient currently appears comfortable, with no signs of respiratory distress, fever, or neurological impairment. The pregnancy and delivery of the patient were uncomplicated; the mother has had 2 prior pregnancies with no complications. Prenatal genetic tests were negative for trisomy 21. She denies smoking or alcohol use during pregnancy and has been vaccinated for rubella. The patient's vital signs include a pulse of 140 beats per minute, a respiration rate of 40 breaths per minute, and an oxygen saturation level of 80% (normal oxygen saturation levels: 95%-100%). Lung sounds are normal to auscultation. Heart auscultation is performed and a systolic crescendo–decrescendo ejection murmur is heard most strongly in the pulmonic area.

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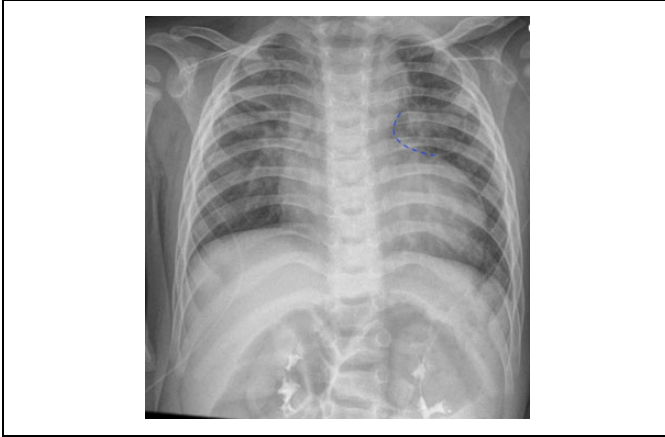Email: maddiehl@stanford.edu

Figure 1. An anteroposterior chest X-ray of a patient with tetralogy of Fallot shows an upturned cardiac apex, indicative of right ventricular hypertrophy, and a concave pulmonary segment (dashed blue line). These abnormalities lead to the boot-shaped appearance.

Diagnostic Findings, Part 1

An electrocardiogram (ECG) shows tall R waves in the right precordial leads and deep S waves in the left precordial leads. A chest radiograph (Figure 1) shows a "boot-shaped" heart, with an upturned cardiac apex.

Question/Discussion Points, Part 1

Discuss the Differential Diagnosis Based on the Clinical Presentation and Diagnostic Findings

The patient's spells of cyanosis and tachypnea, and his low oxygen saturation of 80%, suggest inadequate circulation of oxygenated blood. Normal lung sounds and an absence of fever indicate the cyanosis is likely due to a congenital heart abnormality and not lung infection or disease. A systolic crescendo–decrescendo ejection murmur in the pulmonic area suggests valvular or infundibular pulmonary stenosis (PS).[2] Further, the ECG findings and chest X-ray are indicative of right ventricular (RV) hypertrophy.[3] These results lead to a wide differential diagnosis of congenital heart malformations including, for the purposes of this discussion, pulmonic valvular stenosis, ventricular septal defect (VSD), and tetralogy of Fallot (TOF).

What Further Testing Is Indicated for This Patient?

While a congenital heart abnormality is suspected, echocardiography and Doppler examination will help reveal specific anatomical defects and their severity, as well as guide potential surgical intervention. Information gathered from the echocardiogram should include the location and number of atrial and VSDs, the degree of aortic override, anatomy of the aortic arch (presence of PDA), coronary and pulmonary artery anatomy, and degree of right ventricular outflow tract (RVOT)
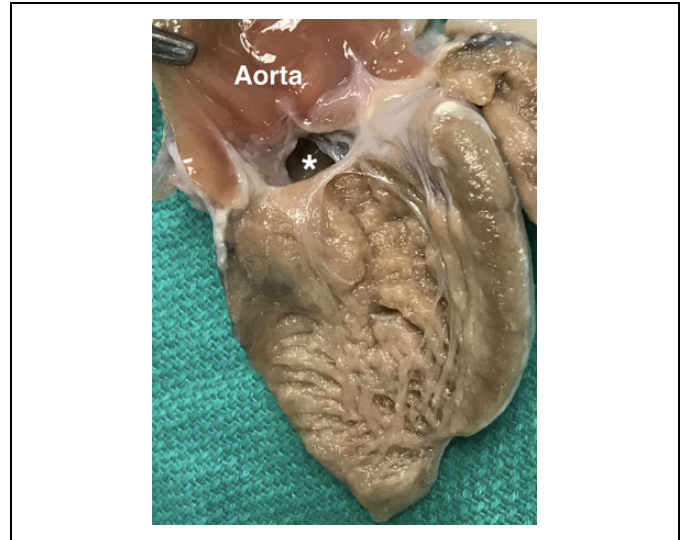

Figure 2. A perimembranous ventricular septal defect (*) viewed from the left ventricle can be identified just below the aortic valve.

obstruction. Pulsed Doppler and color-flow mapping may also provide information about the patient's RV outflow and shunt blood flows.

Discuss the Most Common Forms of Congenital Heart Disease. Include the Concepts of Left-to-Right Shunt, Right-to-Left Shunt, and Shunt Reversal in Your Discussion

The 5 most common subtypes of congenital heart disease are VSD, atrial septal defect (ASD), patent ductus arteriosus (PDA), PS, and TOF.[4] A discussion of each subtype's clinical presentation, natural history, and long- and short-term complications are discussed below.

Ventricular Septal Defect

The most common form of congenital heart disease is VSD. A VSD is a hole in the septum separating the heart's right and left ventricles (Figure 2). The uncomplicated VSD will cause a left-to-right shunt, where oxygenated blood passes from the high-pressure left ventricle to the low-pressure RV and returns to the lungs. Thus, the patient is acyanotic. In most cases, the VSD is present in utero but closes within the first few days of life. However, failure to close can lead to a range of prognoses, from a VSD that remains benign through adulthood to one that causes severe pulmonary hypertension and hypoxemia.[5]

Seventy-five percent of small VSDs (<4 mm) will close within the first 2 years of life,[6] and many adults with small VSDs live with no symptoms. The incidence of spontaneous closure varies depending on the defect location: muscular or perimembranous. Perimembranous defect sites, lying just beneath the aortic valve in the membranous region of the septum, are less likely to close spontaneously than muscular VSDs

in the center or apical region.[7] Small VSDs are typically not detected in utero and will often present as an asymptomatic cardiac murmur found incidentally during a physical examination. While the majority of patients with small VSDs have excellent long-term survival, possible complications of untreated small VSDs include risk of infective endocarditis (1.8% of patients), borderline left ventricular dilation (11%), and benign arrhythmias (13%).[8]

The prognosis of moderate VSDs (between 4 and 6 mm) is largely dependent on the magnitude of left-to-right shunting: blood "leaking" from the left ventricle to RV and thus from the systemic circulation back into the pulmonary circulation. The excess volume in the RV leads to increased pulmonary pressure and, if significant, damaged pulmonary vasculature. A significant left-to-right shunt may progress to and present symptoms of congestive heart failure, unlike right-to-left shunts, which allow deoxygenated blood to bypass the lungs into systemic circulation, leading to cyanosis and hemostatic abnormalities. Moderate VSDs can usually be detected in utero via ultrasound or fetal echocardiography. Spontaneous closures may occur but are less likely than in small VSDs. Symptoms of heart failure such as tachypnea, diaphoresis, and poor weight gain will typically present within the first month of life, with the severity dependent on the magnitude of the shunt. In restrictive VSDs, where RV and pulmonary arterial (PA) pressures are <50% systemic arterial pressures, moderate VSDs may be managed through medical therapy (eg, diuretics for congestive heart failure).[9] However, RV and PA pressure >50% typically warrant surgical intervention.

Large VSDs (>6 mm) will rarely close spontaneously, often have significant left-to-right shunts, and present with many of the same symptoms as moderate VSDs. Surgical intervention to close the defect should be performed within 6 to 12 months of life, as irreversible damage to the pulmonary vasculature can result from high RV pressures. If left untreated, increasing pulmonary hypertension leads to a compromised vascular bed and increasing PA resistance, until the RV hypertrophies and ultimately the shunt is reversed to become a right-to-left shunt.[7] This shunt reversal is also known as Eisenmenger syndrome and is accompanied by cyanosis, dyspnea, and right-sided heart failure.[7]

Atrial Septal Defect

An ASD is an opening between the right and left atria, allowing blood to pass between the two (Figure 3). An ASD also causes an acyanotic left-to-right shunt. There are several types of ASDs. When the septum secundum fails to grow over and cover the ostium secundum during development, a patient may be born with a *secundum ASD*, the most common type.[10] If the septum primum fails to close the ostium primum, a patient may be born with a *primum ASD*. For typical development of the atrial septum, refer to Figure 4. A third type, *sinus venosus ASD*, is an opening most commonly at the entry of the superior vena cava,[11] allowing oxygenated blood from the right upper pulmonary vein to enter the right atrium.
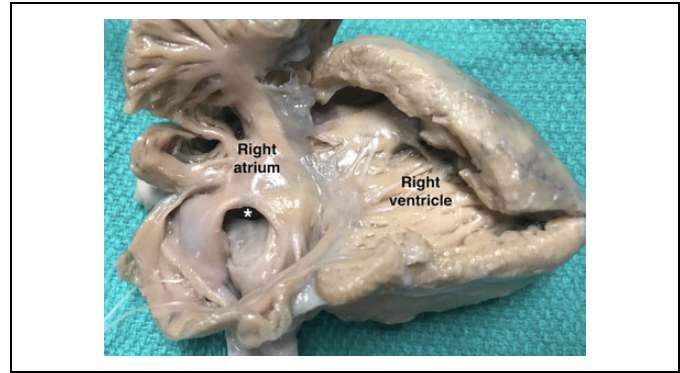

Figure 3. A secundum-type atrial septal defect (*) can be seen from the right atrium.

Like small VSDs, small ASDs often close spontaneously in infancy and have no symptoms throughout childhood.[12] Moderate and large ASDs may be tolerated for years; however, most patients will require surgical intervention by age 40.[13] These defects, due to left-to-right shunts that increase with age, can eventually cause volume overload, pulmonary hypertension, and heart failure. Typical symptoms of untreated large ASDs include dyspnea, exercise intolerance, and atrial fibrillations. Increasing pulmonary hypertension can lead to shunt reversal (Eisenmenger syndrome) and therefore cyanosis in patients who have developed right-to-left shunts. Another complication of ASDs, seen more often in older patients, is the risk of a paradoxical embolus: the passage of a thromboembolus from the venous side, through the ASD, and into systemic circulation.

Patent Ductus Arteriosus

A PDA arises through incomplete constriction of the ductus arteriosus (DA) at birth (Figure 5). During the prenatal period, the DA allows blood from the RV to bypass the pulmonary circuit into the descending aorta. If the DA remains patent, the postdelivery changes in pulmonary and systemic pressures may cause a left-to-right shunt, increasing blood flow to the pulmonary vessels and presenting as acyanotic congenital heart disease.[14] The ratio of pulmonary blood flow to systemic blood flow (Qp:Qs) is used to categorize the size of PDAs and corresponds to different clinical presentations.[14]

In cases where Qp:Qs < 1.5, the patient will often experience no symptoms; the PDA may go undetected or may be found incidentally from a cardiac murmur.[15] If 1.5 < Qp:Qs < 2.2, the elevated left ventricular volume can cause dilation and even dysfunction of the ventricle due to the increased preload returning from the pulmonary circuit. The patient may experience exercise intolerance, fatigue, and dyspnea that progress with age.[14] When Qp:Qs > 2.2, the same effects of left ventricular overload are present but are exacerbated by increased PA pressures. Pulmonary vascular resistance develops, leading to eventual shunt reversal (Eisenmenger syndrome) and its corresponding symptoms.[15]
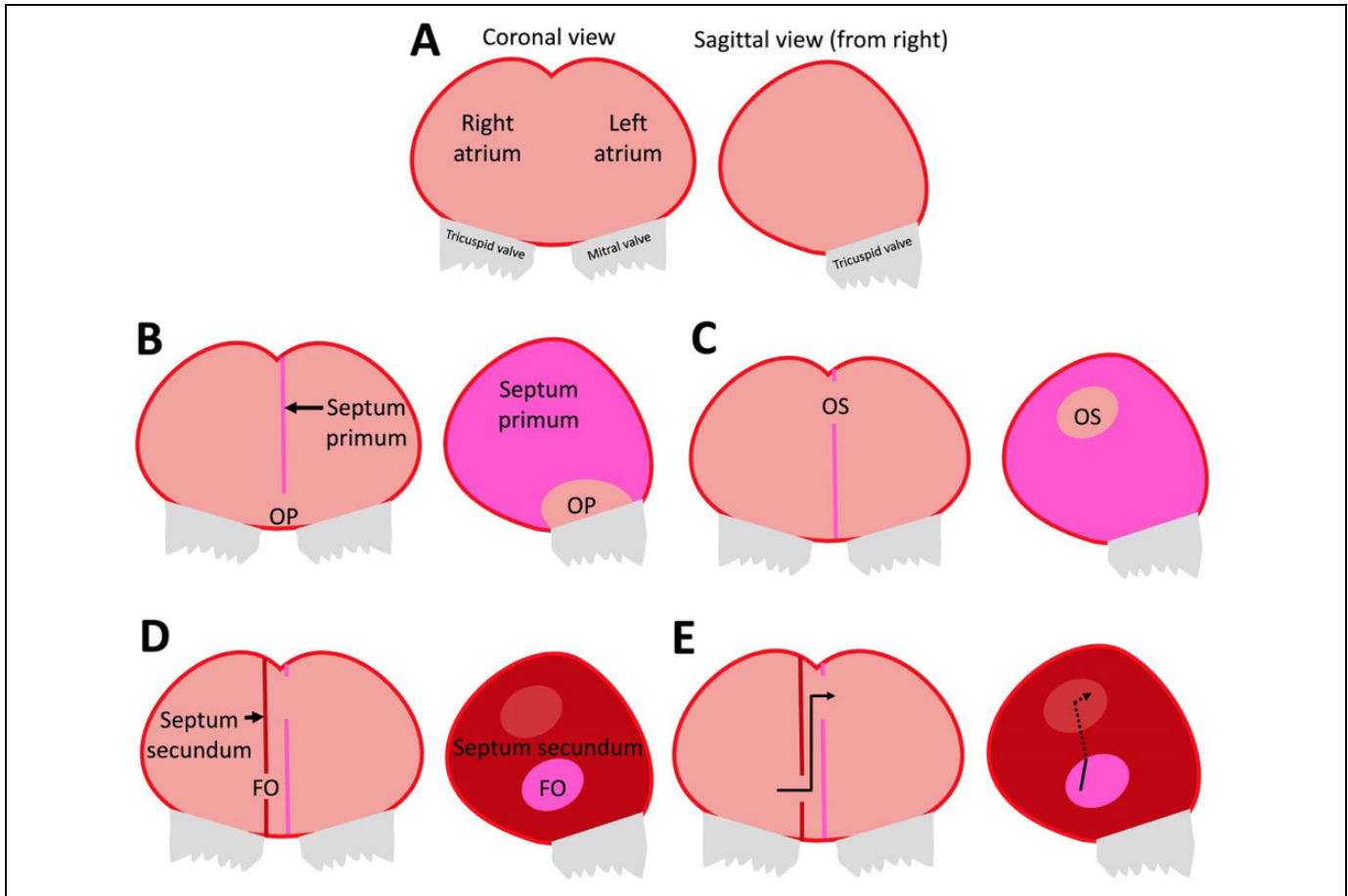
Figure 4. A, Schematic representations of the common atrium prior to septation. B, The first portion of the atrial septum, the septum primum, grows from the atrial wall toward the junction of the tricuspid and mitral valves. It leaves a small communication between the right and left atria called the ostium primum (OP). C, As the OP closes, apoptosis further back in the septum primum leads to another opening called the ostium secundum (OS). D, A second wall, the septum secundum, grows parallel and to the right of the septum primum. An opening remains in the septum secundum called the foramen ovale (FO). E, Together, the FO and the OS allow for blood to flow from the right atrium to the left atrium (arrows) during fetal life.

If left untreated, chronic overload of the left ventricle and atrium can lead to heart failure and irreversible pulmonary hypertension. Infective endocarditis is another, albeit rare, complication of PDA with an incidence of 0.24/1000 patient-years, one of the lowest of all congenital heart disease lesions.[16]

Pulmonary Stenosis

Pulmonary stenosis is a narrowing between the RV and pulmonary arteries, causing blood flow obstruction (Figure 6). The most common type is *valvar* PS, characterized by thickened leaflets, fused or absent commissures, and often a dome-shaped pulmonary valve. Other more rare types of PS are *subvalvar*, caused by fibromuscular narrowing below the valve; *supravalvar*, a narrowing just above the valve; and *peripheral* PS, discrete areas of narrowed pulmonary arteries, including in branch take-offs.[17]

Clinical presentation is dependent on the severity of the stenosis and on the likely presence of accompanying cardiac conditions. Severe PS causes a right-to-left shunt through a patent foramen ovale due to backflow of blood into the right atrium from obstructed RV outflow. The patent foramen ovale is maintained in cases of life-threatening RVOT obstruction by administering prostaglandin E1. This shunt will cause cyanosis and dyspnea from mixing of oxygenated and deoxygenated blood. Mild or moderate PS is usually asymptomatic until later in childhood, when symptoms of dyspnea, cyanosis, and fatigue with exertion can occur from increasing inefficiency of the RV. Flow obstruction from the PS leads to increased workload for the RV, which in turn can lead to RV hypertrophy and heart failure. Individuals with PS are also at an increased risk of developing cardiac arrhythmias, although they usually do not require medical management.[18]

Tetralogy of Fallot

Tetralogy of Fallot is the most common form of cyanotic congenital heart disease and has 4 main components. The first is a VSD, allowing a right-to-left shunt (Figure 7A and B). The
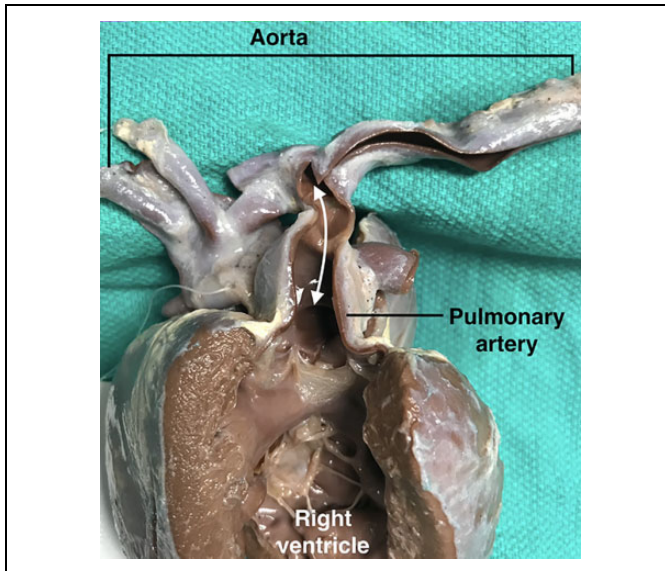
Figure 5. A patent ductus arteriosus, as viewed from the right ventricle, demonstrates communication between the aorta and pulmonary artery (arrow).
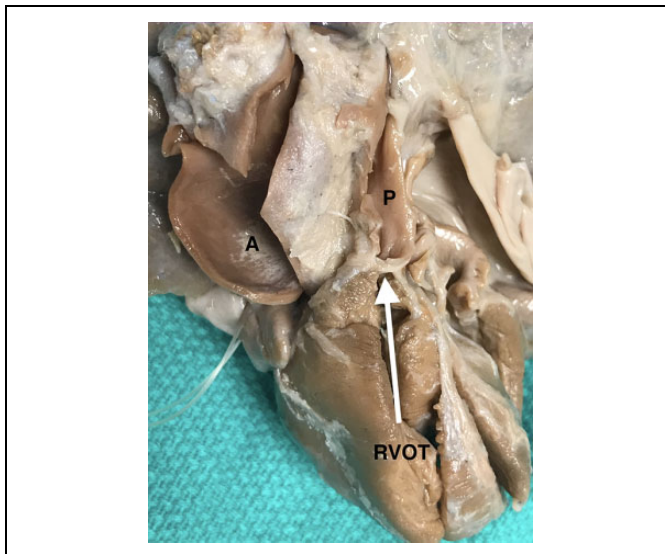

Figure 6. The right ventricular outflow tract (RVOT) leads to a stenotic pulmonary valve, which leads to a hypoplastic pulmonary artery (P). Compare the size of the pulmonary artery with the aorta (A). A hypertrophied RVOT also provides a component of subvalvular obstruction.

second is RVOT obstruction, constricting blood flow to the pulmonary circuit (Figure 7A). Note that in these patients, the pressure in the RV, due to RVOT obstruction, is higher than that in the left ventricle, causing a right-to-left shunt through the VSD. The systolic ejection murmur heard during heart auscultation performed on the patient is consistent with RVOT obstruction or pulmonic valvular stenosis.[2] The third, an overriding aorta, allows for more mixture of deoxygenated and oxygenated blood into the systemic circulation. Finally, RV

hypertrophy results from the increased workload to pump blood through the RV obstruction and overriding aorta.[19] The patient's ECG and chest radiograph in this case are consistent with the RV hypertrophy seen in TOF.[3]

The majority of infants with TOF are acyanotic at birth; however, by 6 months, most will begin experiencing cyanosis and hypoxic spells,[20] or "tet spells." Such spells are caused from increased RVOT obstruction with elevated RV pressures that force deoxygenated blood into the left ventricle and into the systemic circulation (right-to-left shunt). Patients' presentations will depend largely on the degree of outflow obstruction that may result in critically restricted pulmonary circulation. Patients with minimal obstruction can initially be asymptomatic or present with cyanosis and tachypnea only during periods of exertion such as during crying, breastfeeding, or after a bowel movement. Moderate to large obstruction, on the other hand, will present with earlier onset cyanosis and more frequent tet spells.[21]

Untreated TOF has a high mortality, with only 24% of patients with untreated TOF living more than 10 years.[22] Typical disease progression involves hypoplasia of the pulmonary vascular bed, fibrosis of the outflow tract, and heart failure. Because of the severe implications of untreated TOF, the majority of patients in developed countries will undergo surgical repair.[23]

Diagnostic Findings, Part 2

An echocardiogram is performed and reveals a large VSD and aortic override. Examination of RV outflow shows pulmonary annular stenosis and infundibular hypertrophy. Pulsed Doppler and color flow mapping show a right-to-left shunt at the VSD throughout the cardiac cycle. These findings are consistent with TOF.

Question/Discussion Points, Part 2

What Genetic Disorders Are Associated With TOF?

While this patient does not appear to have a genetic risk factor, approximately 30% of congenital heart disease is thought to be associated with genetic syndromes.[24] Down syndrome,[25] Alagille syndrome,[26] and a deletion on chromosome 22q11[26] are among those that increase the risk of TOF, all 3 of which have accompanying signs and symptoms. Patients with Down syndrome, along with an approximately 50% chance of congenital heart disease, can have a variety of dysmorphic features, intellectual disabilities, gastrointestinal tract abnormalities, and reduced growth rate, among other common features. Alagille syndrome is accompanied by abnormalities of the bile ducts, which cause liver damage, and characteristic facial features such as a broad forehead and pointed chin; some patients will also experience vascular and neurologic problems. Individuals with a 22q11 deletion often have palatal abnormalities, learning difficulties, and an immune deficiency.[27]
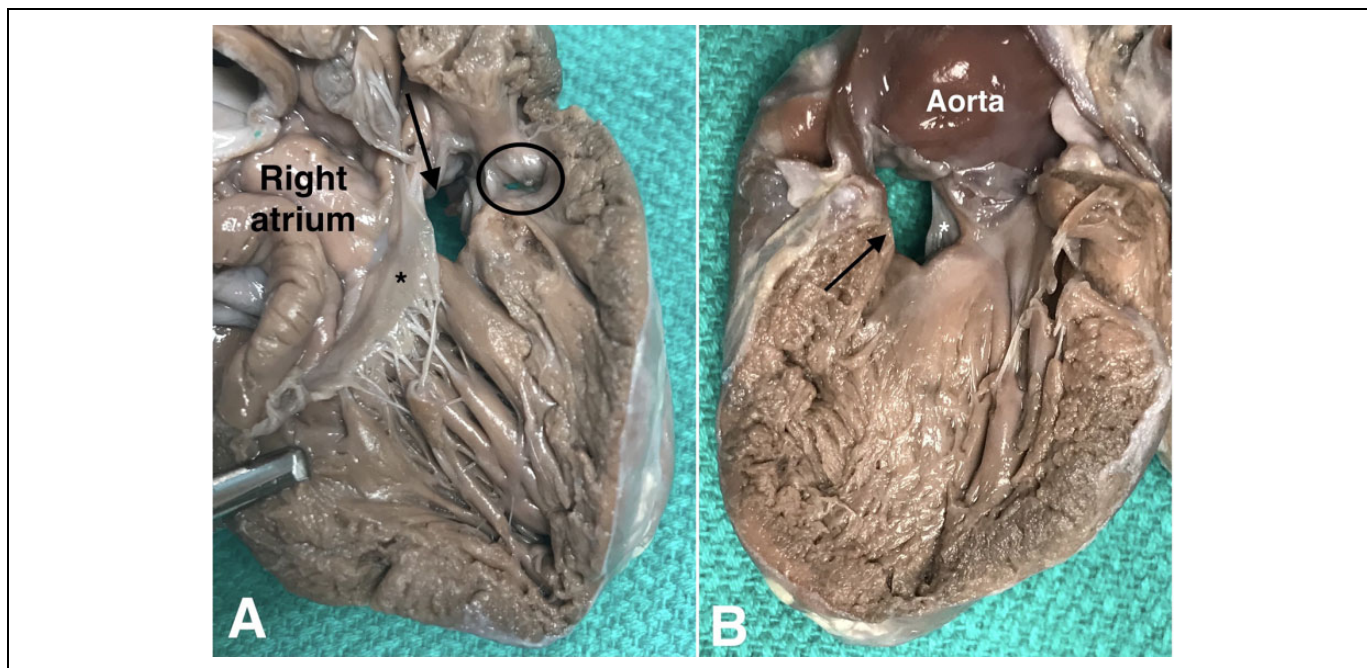
Figure 7. A, Tetralogy of Fallot (TOF) viewed from the right ventricle, the lateral wall of which is hypertrophied. The small opening indicated by the circle is the stenotic pulmonary valve, while the arrow indicates a ventricular septal defect (VSD). Below the right atrium, the tricuspid valve (*) can be seen. B, The TOF viewed from the left ventricle. The arrow indicates the VSD, through which a portion of the tricuspid valve (*) can be seen. The aortic valve and ascending aorta appear dilated and override the VSD and ventricular septum.

Discuss Treatment Options and Long-Term Outcomes for a Patient With TOF

Surgical repair is routine for nearly all TOF patients,[23] such that almost all can expect to survive into adulthood.[19] The 2 main goals of TOF repair are to separate the pulmonary and systemic circulations with a patch over the VSD and to relieve RVOT obstruction. Most commonly, RVOT obstruction is relieved with a transannular incision covered with a pericardial patch that extends from the RVOT through the annulus of the pulmonic valve into the main pulmonary artery trunk.

Patients who undergo TOF repair are at risk for chronic postoperative complications. When the surgical approach involves a transannular RVOT patch, patients often experience pulmonary regurgitation, leading to increased workload and enlargement of the RV.[28] While RV enlargement is not itself symptomatic, it can evolve into RV dysfunction, which is associated with decreased exercise tolerance and right heart failure.[29] Other common complications are aortic root dilation and atrial and ventricular tachycardias.[30]

It is suggested that postoperative TOF patients attend yearly health care visits concentrated on their cardiac status, looking especially for episodes of dizziness/syncope, irregular pulse, decreased exercise tolerance, and signs of heart failure. Patients should undergo annual echocardiograms and ECGs, and adults patients should receive a chest magnetic resonance imaging every 3 years to measure RV size.[29] In some cases, test results and risks of RV dysfunction will indicate the need for an additional surgery for pulmonary valve replacement.

Teaching Points

- A combination of patient history, heart auscultation, ECG, chest X-ray, and echocardiography can be used to diagnose congenital heart disease.
- The 5 most common subtypes of congenital heart disease are VSD, ASD, PDA, PS, and TOF. Their clinical presentations, natural histories, complications, and prognoses vary from benign and asymptomatic to requiring life-saving surgical intervention.
- Septal defects and PDA create cardiac shunts. Left-to-right shunts allow blood from left heart chambers to flow back toward right heart chambers, increasing blood volume in the pulmonary vasculature and often progressing toward congestive heart failure. When increasing pulmonary resistance leads to a shift in pulmonary and system pressures, a left-to-right shunt can reverse to a right-to-left shunt, known as Eisenmenger syndrome. Right-to-left shunts, which allow deoxygenated blood to bypass the lungs into systemic circulation, lead to cyanosis and hemostatic abnormalities.
- Approximately 30% of congenital heart disease is thought to be associated with genetic syndromes. Down syndrome, Alagille syndrome, and a deletion on chromosome 22q11 are among those that increase the risk of TOF.

Declaration of Conflicting Interests

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