CASE REPORT

Challenges in Managing Ivemark's Syndrome With Complete Congenital Heart Disease and Asplenia: A Rare Case Report From Developing Country

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ABSTRACT

Ivemark's syndrome or right-isomerism sequence is a rare condition in newborn, manifests with asplenia, complex congenital heart disease, and situs ambiguous. Diagnosis and managing this syndrome remain challenging, especially in developing countries. The mainstay of management involves surgical correction of cardiac abnormalities and infection prevention. We present a case of a newborn who exhibited cyanosis since birth and developed persistent respiratory distress despite intubation. The mother had not undergone fetal echocardiography or other prenatal screening. Upon physical examination, he looked respiratory distress with SpO_2 ranging from 29-70%. A systolic murmur was heard during cardiac examination, with no abnormalities observed in the face, abdomen, and extremities. Plain radiographs revealed situs inversus, right-located stomach and midline-located liver. This finding was supported by abdominal ultrasound and MSCT, which showed absence of the spleen and a right-sided pancreas. Echocardiography and cardiac catheterization identified situs ambiguous, along with complex cardiac anomalies. These findings confirmed the diagnosis of Ivemark's syndrome. Plans were made to transfer the infant to national cardiovascular center for cardiac surgery. Unfortunately, the infant succumbed to infection at three months of age. This case highlights the significant challenges in managing rare diseases, particularly Ivemark's syndrome in developing countries. Limited access to advanced diagnostic tools and specialized cardiac surgical expertise complicate timely diagnosis and intervention. The potential causes of mortality associated with complex cardiac malformation, the increased risk of severe infections due to asplenia, or a combination of both factors.
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INTRODUCTION

Ivemark's syndrome, also known as asplenia syndrome or right-isomerism sequence, is a rare disorder characterized by hypoplasia or absence of the spleen, congenital heart malformation and abnormal positioning of internal organ. This syndrome, initially described by pediatrician Ivemark in 1955, is exceedingly rare, with an estimated occurrence of one in 10.000 to 40.000 live births. Infants with Ivemark's syndrome frequently experience life-threatening complications during early life (1). Prenatal screening followed by physical and supportive diagnostic examination after birth are crucial for diagnosing this syndrome. The case is important to be reported to highlight the challenges in diagnosis and managing Ivemark's syndrome, particularly in developing countries where access to prenatal and postnatal tolls may be limited. Reporting such cases contributes to the medical literature, aiding healthcare providers in early identification and appropriate management of this rare and complex condition.

CASE REPORT

A male infant was born to a 24-year-old mother following vacuum extraction due to prolonged labor at 38 weeks of gestation. The amniotic fluid appeared greenish. At birth, the infant initially cried spontaneously but required resuscitation due to persistent cyanosis, necessitating supplemental oxygen. Apgar score at one, five and ten minutes were six, eight and nine, respectively. The baby weighed 2,515 grams, with a length of 49 cm and head circumference of 32 cm. There was no family history of

congenital abnormalities or parental consanguinity. The mother had an asymptomatic COVID-19 infection at 22 weeks of gestation and did not receive any treatment other than folic acid, iron, and calcium supplementation since early pregnancy. There were no known teratogenic exposures during pregnancy. Fetal echocardiography and TORCH screening were not performed.

At three hours of age, the infant exhibited severe respiratory distress characterized by chest indrawing dan persistent cyanosis persisted despite positive pressure ventilation. Intubation and mechanical ventilation were subsequently initiated. Blood gas analysis revealed pH 7.175, pCO2 53.7 mmHg, HCO3 19.8 mmol/l, BE -9 mmol/l, SO2 60%, Hb 14.2 g/dL. Physical examination showed central cyanosis with oxygen saturation ranging from 29-70%, accompanied by a pansystolic heart murmur. Abdomen examination was unremarkable, with no sign of distension, organomegaly, or acute abdomen. There were no dysmorphic facial or limb abnormalities noted. Chest and abdominal plain radiographs revealed pneumonia in the left lung and suggested of situs inversus of the stomach in the right lumbar paravertebral region (Figure 1). Subsequent abdominal sonographic examination showed a midline position of the liver, right-sided stomach and absence of a spleen. Multi-Slice Computed Tomography (MSCT) of the abdomen confirmed hepatomegaly with midline liver positioning, asplenia, and a right-sided pancreas. No abnormalities were detected in the gallbladder, right and left kidneys, urinary bladder or rectum. Echocardiography demonstrated situs ambiguous, complete atrioventricular septal defect, pulmonary atresia, double outlet right ventricle, vertical ductus arteriosus, and interrupted inferior vena cava. Cardiac catheterization performed by pediatric cardiologist confirmed situs ambiguous, double outlet right ventricle, pulmonary atresia, and a large patent ductus arteriosus, with Mc Goon ratio of 2.0 and aortic saturation of 68.2%.

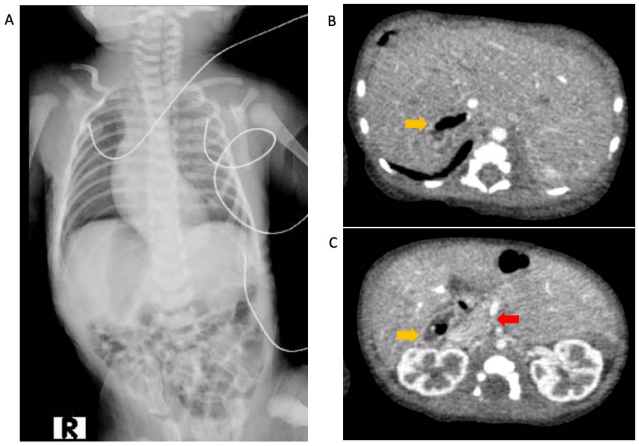

Figure 1: A: Thorax and abdominal X-ray showing pneumonia, a rotated heart, and situs inversus. The liver is midline, extending to the left, while the stomach shadow is located on the right. B and C: Axial views of an abdominal CT scan showing a right-sided stomach (yellow arrow), hepatomegaly with a midline liver, asplenia, right-located pancreas (red arrow). There are no abnormalities in the gallbladder, kidney, urinary bladder or rectum, which is compatible with heterotaxy syndrome

During hospitalization, the infant developed pneumonia and late-onset sepsis, evidenced by the growth of Streptococcus viridans in blood cultures. Ampisilin-sulbactam and amikacin were administered for 7 days according to bacterial sensitivity. Oxygenation was gradually weaned, and at 16 gays old, the patient was discharged from the hospital, although still using a feeding tube for breast milk nutrition.

Given the suspicion of Ivemark syndrome with complex cardiac anomalies, the infant was planned for palliative procedure, namely a Bi-directional Cavo-pulmonary shunt (BCPS), necessitating referral to a national cardiac center due to the complexity of the surgery (Figure 2). In addition to the potential need for cardiac surgery, the parents were educated about the risk of recurrent infections due to asplenia in the infant. At two months old, the infant experienced fever and respiratory distress, leading to rehospitalization. Three months after birth, infant died due to infection and cardiopulmonary decompensation.

DISCUSSION

Ivemark's syndrome is classified as a heterotaxic disorder or laterality disorder, characterized by a failure

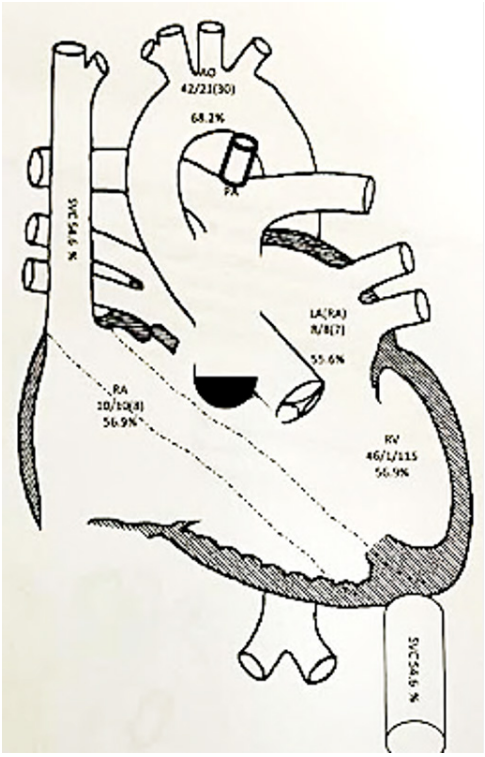

Figure 2: Systematic image of a heart catheterization performed by pediatric cardiologists, Noormanto, MD and Nadya Arafuri, MD, showing situs ambiguous, double outlet right ventricle, complete atrioventricular septal defect, pulmonary atresia, and large patent ductus arteriosus. We acknowledge Noormanto, MD and Nadya Arafuri, MD for performing the catheterization.

or misplacement of the internal organs within the chest and abdomen. Heterotaxic disorders are rare congenital anomalies involving multiple systems and encompass a broad spectrum of malformations, including cardiac and extracardiac manifestations (2). This syndrome may present with situs solitus (normal positioning of intrathoracic and abdominal organs), situs inversus (complete inversion of intrathoracic and abdominal organs); or situs ambiguous (random positioning of intrathoracic and abdominal organs, with some in correct and others in incorrect positions) (1).

Ivemark's syndrome arises from disruptions during early embryological development, where the determination of left and right axes is impaired (3). This results from defects in lateralization, leading to asymmetrical development of organs in the chest and abdomen. Insufficient production of the left determinant or abnormalities in nodal flow prevent activation of left-sided signaling, a condition known as right isomerism. Right isomerism constitutes a subset of heterotaxy disordes where paired structures on opposite sides of the body's left-right axis mirror each other morphologically, typically exhibiting normal right-sided structure. Ivemark's syndrome, a form of right-sided isomerism, typically manifests with congenital absence of the spleen alongside cardiac malformations, misplacement and malfunction of abdominal organs, and anomalous lung lobes. Variability in visceral, pulmonary and cardiac position may occur, and the isomerism may be incomplete. This syndrome predominantly affects males (1).

We presented the case of a male infant who exhibited cyanosis after birth that did not improve with oxygen therapy. Diagnostic investigation comprised plain chest and abdominal radiographs, abdominal ultrasound, echocardiography, multi-sliced computed tomography (MSCT), and cardiac catheterization, confirming Ivemark's Syndrome. The most common symptoms are cyanosis due to cyanotic heart disease and susceptibility to infection or immune disorders due to the absence of a spleen (3).

Heart abnormalities commonly found in patients with right isomerism include single atrium, single right ventricle, and atrioventricular valve regurgitation (3). A complete picture of cardiac abnormalities in right isomerism are typically characterized by abnormal heart positioning, such as dextrocardia or meso-cardia, although some cases may exhibit levocardia. Approximately 71% of cases exhibit bilateral superior vena cava (SVC), with both SCVs connecting to the upper corner of the atrium on the same side. The inferior vena cava drains into one atrium, while hepatic venous drainage empties into the contralateral atrium. The coronary sinus is absent in all cases of the syndrome. Extracardiac anomalies may include Total Anomalous Pulmonary Venous Connection (TAPVC), occurring in 50% of cases, while the remaining 50% exhibit no ducts, or are obstructed. Interatrial septal defects are present in some cases. A complete atrioventricular septal defect with a common atrioventricular valve is found in 93% of cases, and single ventricle occurs in 70% of cases. Ventricular outflow obstruction is common, with pulmonary stenosis or atresia is present in 96% cases, whereas obstruction to systemic arterial flow is rare. The majority (95%) of cases exhibit abnormalities in the ventriculoarterial connection, with right ventricular double outlets seen in 82% of these abnormalities. Disorders of the cardiac conduction system are frequent, often leading to symptoms of atrial tachyarrhythmias (1–3).

In addition to heart abnormalities, extra-cardiac abnormalities commonly observed include absent or non-functional spleen. Some cases exhibit trilobed lungs bilaterally, a midline liver position, and potential intestinal malrotation. Other reported finding is the entire colon positioned on the left side, with the small intestine and stomach on the right of the midline (4).

Gastrointestinal anomalies may involve annular pancreas and duodenal obstruction. Ultrasound examination of the abdomen can reveal the positioning of intra-abdominal organ, the presence and status of the spleen (whether absent, single, multiple or small), and assess the symmetry of the liver and the position of the gallbladder. Further evaluation with MSCT or MRI of the heart and abdomen can detect both cardiac and non-cardiac anatomical abnormalities, particularly complex ones. However, several considerations must be taken into account regarding these examinations. Not all centers or institutions have access to advanced imaging facilities, skilled personnel, or sufficient funding. Additionally, the radiation dose in neonates is critical concern that needs careful consideration (2).

The primary approach to managing patients with Ivemark's syndrome and complex cardiac abnormalities involves cardiac surgery and catheterization to address valve and chamber defects. Studies have demonstrated that advancements in cardiac surgical techniques such as enhancements in Fontan circulation and biventricular repair, can significantly improve the life expectancy of patients with Ivemark's syndrome. Following surgery, there has been a reduction the incidence of heart failure, with hospital mortality reported at only 13%. However, serious complications remain possible, including example cardiorespiratory failure and sepsis (1–3).

The prognosis for Ivemark's syndrome remains poor despite modern cardiac surgery. Sixty percent of patients died before reaching one year of age, with a mean age of death of 0.47 years. In a retrospective study, it was noted that survival could be up to a median of 65 months in 83% of cases with Ivemark's Syndrome. The severity of congenital heart disease is associated with a poor prognosis. Patients with complex cardiac anomalies have

a one-year mortality of >85% in patients with asplenia and >50% in patients with poly-splenia. The presence of intra-abdominal anomalies is becoming increasingly significant and visceral anomalies can contribute strongly to influencing long-term outcomes. Infections due to asplenia, sudden death due to arrhythmias and multiple and complex structural heart defects are the most common causes of death in Ivemark's syndrome. Other studies reported only 5-10% of patients with this syndrome who can reach adulthood with several disorders, for example pulmonary embolism, dysphagia and pancreatic cysts. Some cases that survive into adulthood may be due to less severe pulmonary stenosis, absence of arrhythmias and recurrent infections (3–5).

Prenatal diagnosis of right isomerism remains challenging. Common findings include complex cardiac abnormalities, parallel orientation of the inferior vena cava and aorta, and signs of viscero-cardiac heterotaxy. Early prenatal diagnosis provides a clearer understanding and enables appropriate counseling for parents regarding potential outcomes and postnatal care for the infant. However, despite advances in prenatal diagnostic capabilities, early detection does not improve prognosis significantly (1–5). Another challenge frequently encountered in developing countries is that not all pregnant women have the opportunity and access to receive antenatal and prenatal diagnostic examinations due to issues related to infrastructure, cost limitations, awareness, and education. This was evident in the case we reported, where despite regular prenatal check-ups, the patient's mother had never undergone fetal echocardiography or screening for congenital anomalies during pregnancy.

CONCLUSION

This case report illustrates the complex clinical presentation and management challenges associated with Ivemark syndrome, particularly in a male infant who exhibited severe congenital heart defects and respiratory distress shortly after birth. The diagnosis of Ivemark syndrome, characterized by heterotaxy and associated anomalies, underscores the critical need for early recognition and intervention. Despite the advancements in cardiac surgical techniques, the prognosis for infants with this syndrome remains poor, with a high mortality rate in the first year of life due to complications such as severe cardiac defects, infections related to asplenia, and arrhythmias.

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