Diagnostic dilemma in a case of neonatal cardiac tumor – The importance of histopathology and mutation analysis in clinical practice

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ABSTRACT

Fetal or neonatal cardiac tumors are rarely encountered in neonatal practice. Moreover, these can be the earliest manifestation of underlying systemic conditions, such as tuberous sclerosis. Cardiac tumors are primarily diagnosed by characteristic findings in transthoracic echocardiography. However, these findings are not absolute, and histopathology remains the gold standard in diagnosing cardiac tumors. Sometimes, doubtful imaging findings can delay the diagnosis and initiation of definitive management. We describe a case of fetal and neonatal cardiac tumor where histopathology served as a benchmark in making a diagnosis and helped in identifying the underlying systemic disease.

Keywords: Cardiac rhabdomyoma, cardiac tumor, histopathology, tuberous sclerosis complex, tuberous sclerosis complex 2 gene mutation

INTRODUCTION

Primary cardiac tumor in newborns is exceedingly rare. The reported incidence of cardiac tumors in the fetus in one series is 0.14%.[1] Due to the increased use of antenatal scans, majority of the cardiac tumors are identified before birth in the late second or third trimester. Some cases are diagnosed after birth because of heart failure, arrhythmia, or the presence of murmur. Almost 70% of fetal and neonatal cardiac tumors are contributed by rhabdomyoma and teratoma.[2] Although gold standard, histopathological diagnosis is rarely made and majority are diagnosed by either echocardiographic features, cardiac magnetic resonance imaging (MRI) findings, or associated clinical features. We report a case of antenatally diagnosed cardiac tumor with fatal outcome whose diagnosis changed after histopathological examination (HPE).

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CASE REPORT

A 21-year-old primigravida mother presented at 34 weeks with a third-trimester antenatal scan showing a pericardial mass and cardiomegaly. An anomaly scan at 18 weeks was normal. Pregnancy was otherwise uneventful. A girl baby was delivered at 38 weeks by elective cesarean section with a birth weight of 2670g. The baby did not require any resuscitation and was kept in the neonatal care unit for further evaluation of pericardial mass. The baby did not have any sign of respiratory distress, hemodynamic impairment, or murmur at birth. Arterial oxygen saturation (SaO_2) was >95% in both upper and lower limbs. Chest X-ray (CXR) on day 1 showed cardiomegaly (cardiothoracic ratio of 0.8) with no

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features of pulmonary edema [Figure 1]. A postnatal echocardiogram on day 2 showed a 30 mm × 20 mm echogenic pericardial mass surrounding the left ventricle with no intracardiac extension and mild pericardial effusion [Figure 2]. A provisional diagnosis of cardiac teratoma was made because of the pericardial location, the absence of myocardial involvement, and pericardial effusion. Serum alpha-fetoprotein, a marker of germ cell tumor, was also raised (5520 ng/ml), which further strengthen our diagnosis. As the baby was asymptomatic with no outflow obstruction, a cardiac computerized tomography (CT) was planned and was kept under observation. However, from day 7, the baby started having respiratory difficulties with features of cardiac failure. The baby was put on noninvasive respiratory support and was barely maintaining SaO_2 above 90%. Relevant blood works were sent to rule out sepsis. A repeat echocardiogram on day 7 showed poor cardiac contractility with an increase in pericardial mass (36 mm × 23 mm) and compression of the left ventricle [Figure 3]. CXR showed massive cardiomegaly and severe pulmonary edema [Figure 4]. Day 1 versus day 7 CXR [Figures 1 and 4] revealed progressive cardiomegaly and the appearance of pulmonary congestion. The baby was intubated and mechanically ventilated with a high ventilatory setting. Inotropic support was started, and supportive management was continued. Another echocardiogram performed after 72 h (day 10) in addition to earlier findings demonstrated progressive infiltration of the myocardium which was of the same intensity as that of cardiac mass [Figure 5]. Serial echocardiography assessment [Figures 2, 3, and 5] revealed a progressive enlargement of the pericardial mass, an increase in pericardial effusion, and also the involvement of myocardium, which was not obvious in the earlier images. This made us doubtful about the initial diagnosis of cardiac teratoma, which is usually of pericardial origin. Cardiac CT was planned to further characterize the cardiac mass. Cardiac CT showed a 4.7 cm × 3.4 cm × 4.7 cm heterogeneously

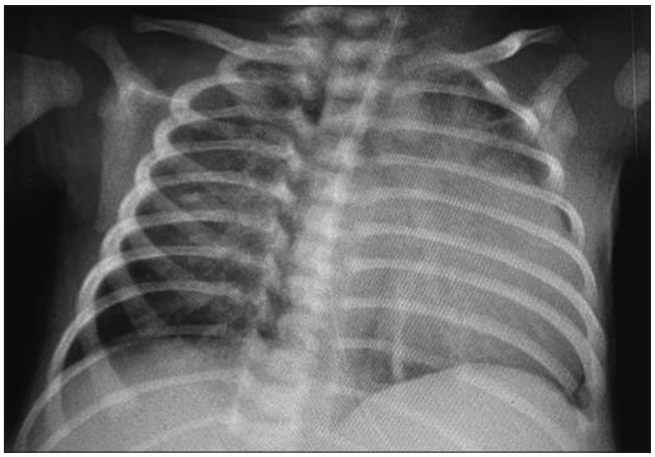

Figure 1: Chest X-ray on day 1 showing cardiomegaly (cardiothoracic ratio of 0.8)

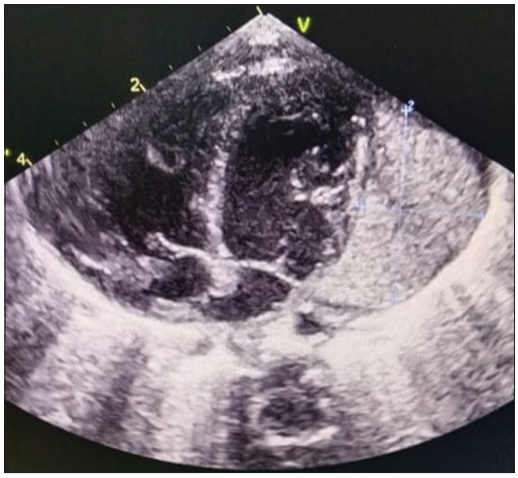

Figure 2: Transthoracic echocardiography on day 2 of life showing echogenic pericardial mass surrounding the left ventricle with no intracardiac extension and mild pericardial effusion

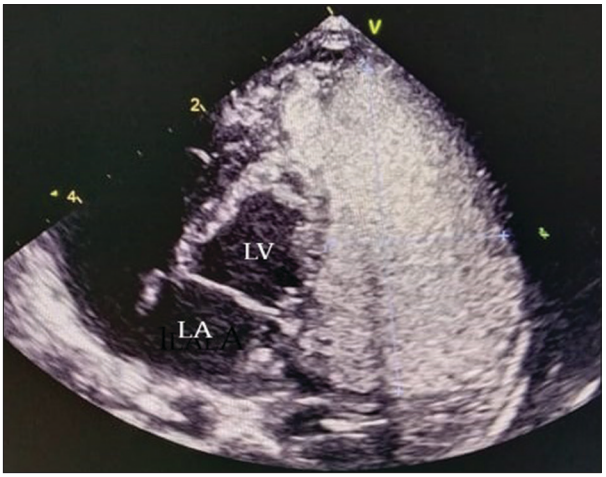

Figure 3: Echo on day 7 of life showing further increase in pericardial mass with compression of LV. LA: Left atrium, LV: Left ventricle

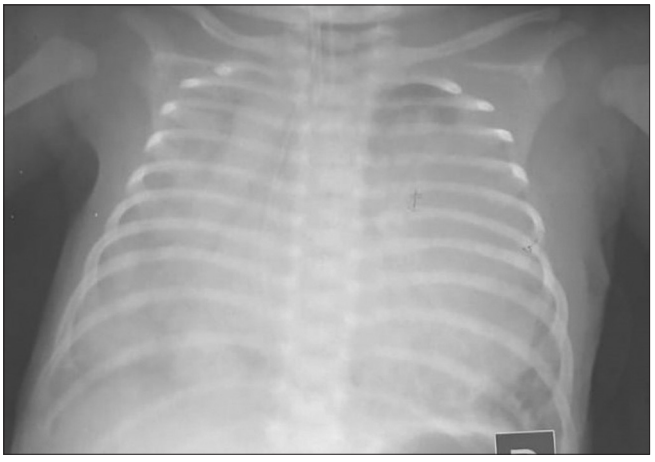

Figure 4: Chest X-ray on day 7 of life showing massive cardiomegaly and pulmonary edema

enhancing well-defined soft-tissue density mass lesion on the left side of pericardium abutting the left atrium and ventricle causing mild mediastinal shift with mild pericardial effusion. An indistinct margin between mass and myocardium indicated the possibility of infiltration with no obvious intra-atrial/ventricular component [Figure 6]. These CT findings further increased the possibility of germ cell tumors. However, CT angiogram was not performed which could demonstrate the vascularity of the cardiac mass. In view of extensive myocardial involvement, tumor excision was not an option. However, to confirm the histopathologic diagnosis of cardiac teratoma, a cardiac biopsy was planned in consultation with the cardiothoracic unit. HPE of the excised sample showed dilated and vacuolated myocytes with radiating pink thin cytoplasmic process resembling spider cells which are strongly PAS positive [Figure 7]. The above HPE was diagnostic of cardiac rhabdomyoma.[3]

Rhabdomyoma is most commonly associated with tuberous sclerosis complex (TSC). Although cardiac tumor is usually the earliest finding, often appearing between 20 and 30 weeks of gestation, it often resolves spontaneously after birth. In minority of cases, rhabdomyoma can lead to ventricular outflow obstruction, arrhythmia, intractable heart failure, and death. After histopathological confirmation of rhabdomyoma, we thoroughly looked for other pertinent clinical features suggestive of TSC in the infant. However, no other findings were present. MRI brain was normal. The infant was started on mTOR inhibitors (sirolimus at 1 mg/m^2/day) in an attempt to reduce the size of the tumor. In the absence of clinical diagnosis of TSC, a genetic panel for TSC1/TSC2 mutation analysis was sent. In the meantime, despite starting mTOR inhibitors and continued supportive management, the baby could not recover from refractory heart failure and passed away on day 32 of life. Mutation analysis revealed a heterozygous splice site variant (c. 848 + 2T>A) in the exon 9–intron 10 splice donor site in TSC2 gene on chromosome 16p13. This variant has been reported as likely pathogenic in the VarSome database and can cause altered splicing leading to absent or abnormal protein. Based on mutation analysis, tuberous sclerosis-2 (OMIM#613254) was confirmed in the infant.

DISCUSSION

The present case underlies the importance of HPE and genetic testing in neonatal practice. Although rhabdomyoma is the most common cardiac tumor in newborns, most of the imaging characteristics were in favor of teratoma. Only when it was examined histopathologically, it revealed a different diagnosis. Characteristic echocardiographic findings of

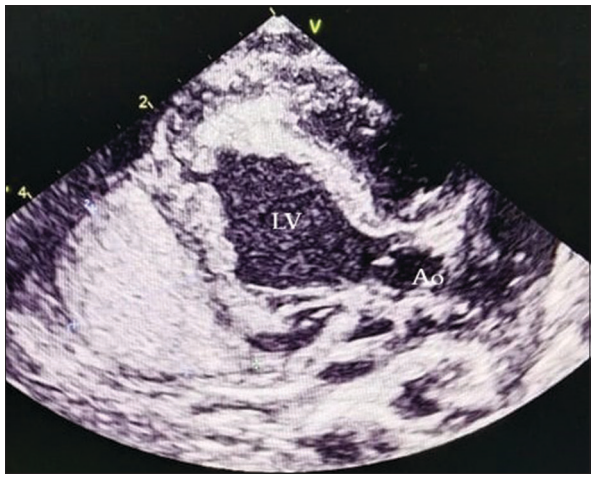

Figure 5: Echo on day 10 showing progressive increase in cardiac mass along with myocardial infiltration

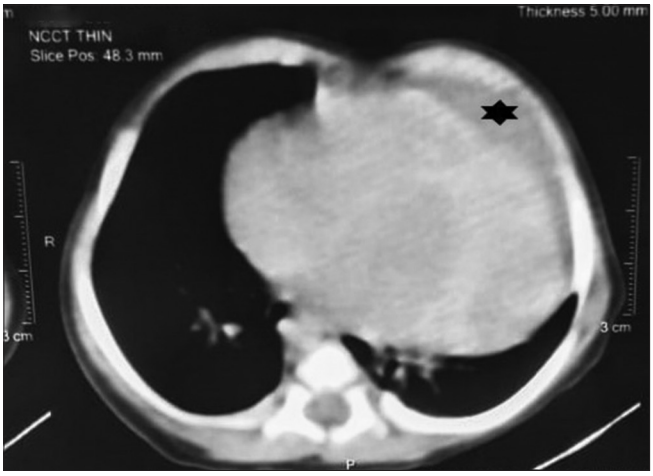

Figure 6: Cardiac CT revealing heterogeneous well-defined soft-tissue density mass lesion on the left side of the pericardium (marked by *). CT: Computerized tomography

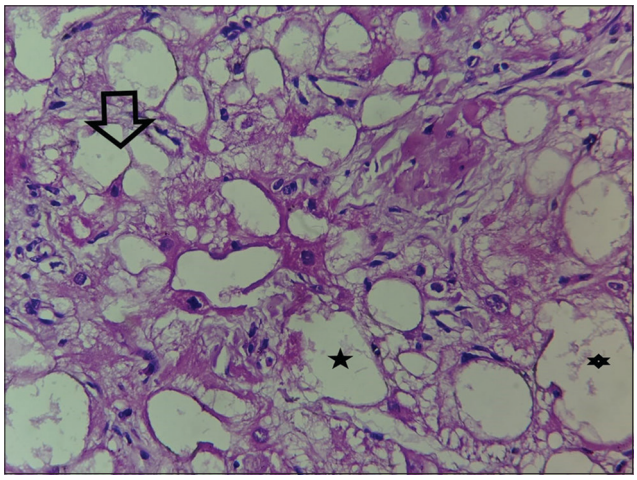

Figure 7: Histopathological examination (Hematoxylin-eosin stain, 200 magnification) of cardiac tumor specimen showing dilated and vacuolated myocytes (marked by *). Myocytes containing radiating thin pink cytoplasmic process resembling spider cells are also seen (broad arrow)

Table 1: Literature review of unusual location of cardiac rhabdomyoma in newborns

Author and year	Case	Findings
Erhunmwunsee *et al.*, 2016[6]	Late preterm infant delivered due to fetal bradycardia. Postnatally baby had atrial bigeminy and premature atrial contraction	CT chest revealed homogeneous right pericardial mass compressing RA. Surgical resection and HPE confirmed the mass as cardiac rhabdomyoma
Balan *et al.*, 2015[7]	Term infant with progressive respiratory failure after birth with antenatally detected mediastinal mass anterior to the heart and polyhydramnios	Postnatal CT chest showed a soft tissue density mass lesion in the anterior mediastinum, arising from the right ventricle, compressing the right side of the heart and encasing the origin of the great arteries with pericardial effusion. Surgical excision and frozen section biopsy confirmed it to be rhabdomyoma
Schlaegel *et al.*, 2013[8]	Antenatally diagnosed mediastinal mass in a late preterm infant	Fetal echo and MRI showed a large echogenic mass arising from LV, extending into mediastinum causing mediastinal shift and massive pericardial effusion. Postnatal echo confirmed the same. Tumor regressed spontaneously. Histologic diagnosis not done
Karnak *et al.*, 2007[9]	Term infant with respiratory failure. No antenatal scan. CXR-cardiomegaly	CT chest revealed a solid mass of soft tissue density in the anterior mediastinum causing the mediastinal shift. The mass cannot be separated from LV. Echo revealed intrapericardial mass adjacent to the left ventricle with pericardial effusion. HPE confirmed the diagnosis of rhabdomyoma
Sbragia *et al.*, 2001[10]	In a retrospective review, over a period of 6 years at the University of California, 16 fetuses were antenatally diagnosed with solid tumors	Out of 16 fetal solid tumors, 4 had mediastinal tumor. Two of them were diagnosed as rhabdomyoma

CXR: Chest X-ray, LV-Left ventricle, HPE: Histopathological examination, RA: Right atrium, CT: Computerized tomography, MRI: Magnetic resonance imaging

rhabdomyoma include multiple homogeneous echogenic intramural masses with intracavitary extension.[4] On the other hand, teratoma is identified as intrapericardial heterogeneous, encapsulated cystic masses with pericardial effusion.[5] Although cardiac rhabdomyoma usually presents as a single or multiple ventricular mass, it can also present as a mediastinal or pericardial mass in newborns. Table 1 compiles various reports showing unusual location and presentation of cardiac rhabdomyoma in fetuses and newborns.[6-10] The present case demonstrated mixed echocardiographic findings which prompted us to perform the HPE of cardiac mass. Sirolimus was delayed because of the diagnostic dilemma. However, in refractory cases, sirolimus might not be effective. The case also shows the importance of mutation analysis in the early diagnosis of TSC in clinically doubtful cases. As per 2012 recommendations of the International TSC Consensus, TSC1/TSC2 gene mutation analysis is required only when the diagnosis is not possible by clinical and or radiological criteria.[11] Newborns may present with only cardiac tumor making the diagnosis of TSC difficult. Hypomelanotic macules, cortical tuber, subependymal nodules, infantile spasm, or hypsarrhythmia in EEG is often late to appear creating a potential presymptomatic window, in which patients of genetically confirmed TSC can be treated with prophylactic vigabatrin to delay the onset of seizure and improve the neurodevelopmental outcome.[12]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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