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Ultrasound Detection of Holt Oram Syndrome in Early Pregnancy – A Case Report

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Abstract

Holt Oram Syndrome (HOS) is a rare genetic syndrome characterized by upper extremity deformities and congenital heart defects, and other cardiac conduction disturbances with or without septal defects. It is inherited in an autosomal dominant pattern, characterized by high penetrance and variable expression. We describe a case, where we prenatally diagnosed HOS associated with cardiomegaly. On autopsy, left kidney was absent. To the best of our knowledge, the prenatal diagnosis of HOS with cardiomegaly and single kidney has not been reported in the literature before.

Keywords: Congenital Heart Defects, Holt Oram Syndrome, Prenatal Diagnosis, Upper Extremity Deformities.

Introduction

Holt Oram Syndrome (HOS) is an autosomal dominant disorder, also called the heart-hand syndrome characterized by upper limb malformations and congenital heart disease (CHD)[1]. Clinical manifestations vary and range from subclinical radiographic findings to overt, life-threatening disease. While all individuals with HOS have upper limb malformations, 85 to 95% also have CHD[2,3]. Upper-limb anomalies are always present which may be unilateral or bilateral and involve structures derived from the embryonic radial ray, typically the radial, carpal and thenar bones.

We describe a prenatally diagnosed case of HOS associated with cardiomegaly and absent left kidney. This was a unique finding of HOS being associated with cardiomegaly and single kidney.

Case Report

A 26-year-old woman, G3P1L1A1 with one previous live male child delivered 7 years back and one spontaneous abortion at 12 weeks 1 year back, was scanned at the Department of OBG, IKDRC, Ahmedabad, for Nuchal Translucency at 11 weeks of gestation. The family history was unremarkable. On sonography, NT was 1.5mm; but upper limb defects ***[Figure – 1]*** and heart occupying the entire thorax was noted ***[Figure – 2]***. Cardiomegaly was quite evident. Fetal heart rate was 170 bpm with no notable conduction defects. There was absence of thumb in both the hands along with shortening of the right arm and forearm and medial deviation of both the hands. She was advised to undergo chorionic villus sampling but she came back for follow up after a week with absent fetal cardiac activity.

Medical termination of pregnancy was planned after obtaining written informed consent. Consent for autopsy was also obtained from the couple. Post-expulsion, fetal DNA was preserved and mutation study was done. Autopsy was performed and the sonographic findings were confirmed along with additional findings. The right upper arm and forearm was abnormally short ***[Figure – 3]***. There was radial (medial) deviation of both the hands with absent thumbs. The fetus had facial dysmorphism in the form of low-set ears and retrognathia ***[Figure – 4]***. Heart occupied the entire thorax, and appeared a bilobed cystic structure. Lungs appeared normal placed behind the heart. The left kidney was absent but both adrenal and the right kidney were present ***[Figure – 5]***. Molecular study revealed the presence of pathogenic mutation in the TBX5 gene.

Discussion

Holt Oram Syndrome is characterized by upper-limb defects, congenital heart malformation and cardiac conduction disease[4]. HOS is inherited in autosomal dominant manner and the disorder is as a result of a heterozygous *de novo* TBX5 pathogenic variant. Up to 85% of cases are caused by a *de novo* pathogenic variant[5], while approximately 15% of cases are familial[1]. The Holt Oram Syndrome is a rare genetic syndrome mostly reported in familial cases when a more detailed ultrasound examination is performed, rather than by prenatal screening[1,2,3.] The overall prenatal detection rate is low, at about 39%[1].

Virtually nothing is known about the cause or pathogenetic processes that account for these varied manifestations of HOS. The prevalence of this disorder has been estimated to be 0.95 per 100,000 total births; 85 percent of cases are attributed to new mutations due to a *de novo* pathogenic variant[5]. Craig et. al performed clinical and genetic studies in two families with HOS and concluded that mutations in a gene on chromosome 12q2 can produce a wide range of disease phenotypes. This gene has an important role in both skeletal and cardiac development. They proposed that the wide spectrum of clinical presentations of HOS is due to mutations in a single gene[6].

We present a sporadic case with typical features of Holt Oram Syndrome. The skeletal abnormalities were observed in both hands. In the Holt Oram Syndrome upper-limb malformations range from triphalangeal or absent thumb to phocomelia. In our case the fetus had abnormal shortening of the right upper arm and forearm with absent thumb and there was radial deviation of both the hands. Upper-limb deformities are always present. Aplasia, hypoplasia, fusion and anomalous development of these structures produce a wide spectrum of phenotypes including triphalangeal or absent thumbs, fore shortened arms and phocomelia[7]. Skeletal abnormalities are usually bilateral and asymmetric, with left side often more affected than the right side[8].

A congenital heart malformation is present in 75% of individuals with HOS and most commonly involve the septum. Cardiac abnormalities include single or multiple atrial and ventricular septal defects, or they may be absent. Disturbances of cardiac rhythm occur frequently in affected persons and include sinus bradycardia and variable degrees of atrioventricular block[4,9]. In 2014, Paladini et al. reported right atrial enlargement, a first time description[10]. In our case, the fetus had massive cardiomegaly with bilobed cystic heart with no definitely formed cardiac anatomy.

Conclusion

Detailed high-resolution prenatal ultrasound examination may detect upper-limb malformations and/or congenital heart malformations. Prenatal molecular genetic testing may be used to confirm a diagnosis, if

the TBX5 pathogenic variant has been identified in an affected case. The possibility of varied spectrum of HOS should be considered to reach at an appropriate diagnosis and also parent screening should be performed to rule out familial predisposition.

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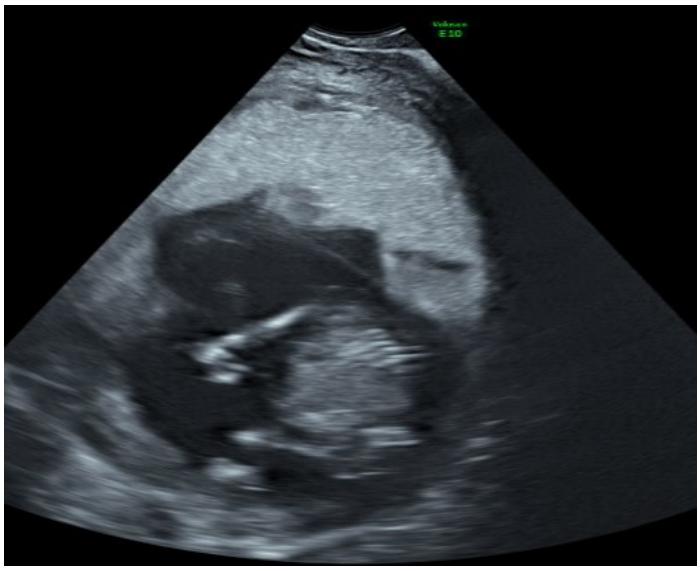

Figure 1: USG image of the fetus with upper limb deformity.

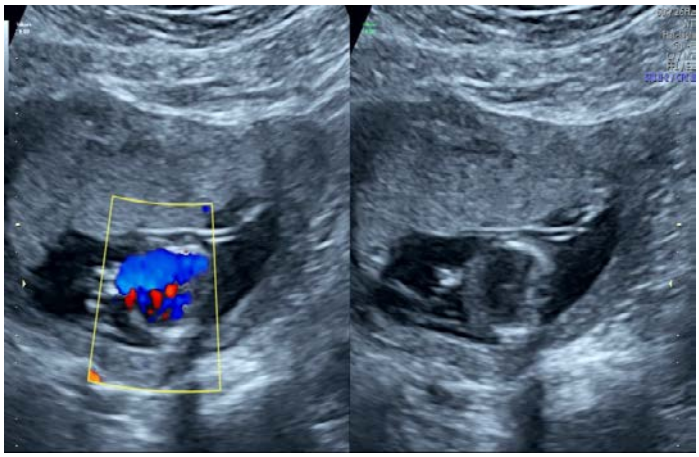

Figure 2: USG image of the fetus showing heart occupying entire thorax.

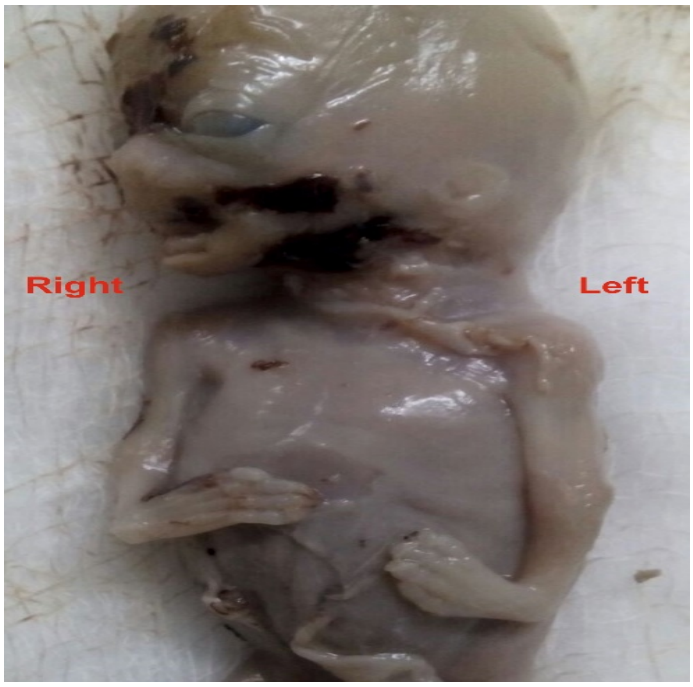

Figure 3: Autopsy revealing right upper arm and forearm being abnormally short; radial deviation of both the hands with absent thumbs

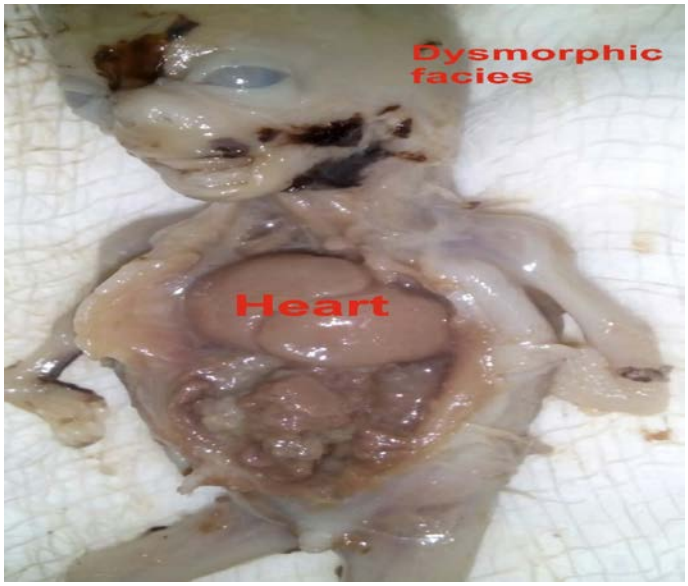

Figure 4 : Autopsy revealing dysmorphic facies and bilobed heart.

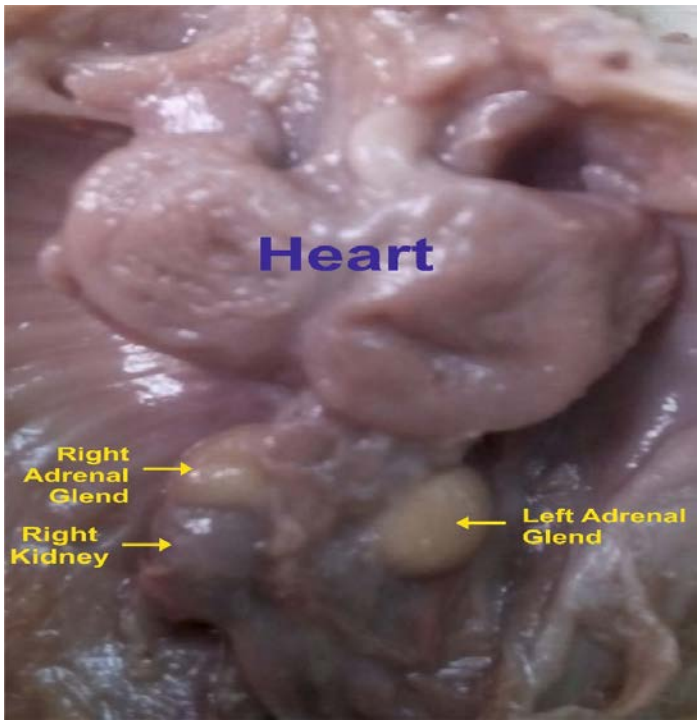

Figure 5: Autopsy revealing bilobed heart with absent left kidney