



Case Report

Holt-Oram Syndrome with Sacrococcygeal Teratoma – A Rare Association

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Abstract

Holt-Oram syndrome (HOS) is characterized by upper-limb defects and congenital heart malformation, and its prevalence is very rarely. Mature cystic teratoma is the most common tumor seen in neonates and its most common location is sacrococcygeal region. Diagnosis of a sacrococcygeal teratoma should be confirmed by pathology. Surgical resection is the mainstay therapeutic approach of this tumor. Some malformations such as genitourinary system, musculoskeletal anomalies, neural defects, cardiovascular anomalies, and pulmonary disorders associated with this tumor have been reported. Herein, we reported a male neonate diagnosed with HOS associated with sacrococcygeal teratoma. To our knowledge, it has been not reported a case with HOS associated with sacrococcygeal teratoma. Patients with sacrococcygeal teratomas (SCTs) may have multiple and extreme congenital abnormalities; therefore, patients with SCTs should be carefully evaluated clinically, laboratory, and radiologically and it should be also considered that HOS may accompany them.

Keywords: Holt-Oram syndrome, newborn, sacrococcygeal region, teratoma

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Holt-Oram syndrome (HOS) including skeletal and cardiovascular abnormalities was first described by Holt and Oram in 1960. The prevalence of this syndrome, characterized by upper-limb defects and congenital heart malformations, is approximately 1 in 100,000 live births.^[1,2] It has been reported that mutations of the TBX5 gene, linked to chromosome 12q24.1 and also detected in embryonic heart and limb tissues, are detected in approximately 25% of familial cases and up to 50% of sporadic cases.^[2] The diagnosis of HOS is established in a patient with a pre-axial radial ray anomaly and a personal or family history of cardi-

ac malformations and/or conduction defects.^[3,4] Sacrococcygeal teratomas (SCTs) are the most common germ cell tumor of childhood with reported incidence of 1/35,000 to 40,000 of live births affecting more frequently females.^[5-7] SCTs are classified histologically as either mature or immature, and mature types are more common in neonates. SCTs presented as a mass between the anus and coccyx can be easily diagnosed by ultrasonographic examination. Definitive diagnosis is confirmed by pathology. Surgical resection is the mainstay of therapy. Some malformations such as genitourinary system, musculoskeletal anomalies,

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neural defects, cardiovascular anomalies, and pulmonary disorders associated with SCTs have been reported.^[5-13] To our knowledge, this is the first reported male neonate with HOS associated with immature sacrococcygeal teratoma.

Case Report

A male neonate, born at 37 gestational age and 5 days by cesarean section from a 28-year-old mother, was admitted to the neonatal intensive care unit because of a large 3 mass covering on his sacral and genital regions. His Apgar scores are 8 and 9 at 1st and 5th min. In the patient's family history, a mass was detected in fetal ultrasonography at the 16th gestational week, fetal magnetic resonance imaging (MRI) was performed, and an appearance compatible with sacrococcygeal teratoma was detected.

On physical examination of the patient, his birth weight was 3100 g (50%), height was 48 cm (25–50%), and head circumference was 34 cm (50%). His umbilical cord had only a single artery and vein. He had minimal bilateral hydrocele, left upper limb defect, absence of left thumb, and a big mass (approximately 15 × 10 cm) on his sacrococcygeal region (Fig. 1). The other physical signs of the patient were normal. His hematological and biochemical parameters were at normal ranges. Serum alpha-fetoprotein (AFP) levels of the patient are 1210 ng/mL (normal range: 8000–130000 ng/mL). His chromosomal examination revealed as 46 XY; however, TBX5 gene mutation is not detected.

Lumbar, coccygeal, and sacral MRI of the patient showed a big mass formation (diameter 10 × 7 × 5 cm) in the sacrococcygeal region, consistent with type 2 sacrococcygeal teratoma, with cystic and solid components that fill the entire pelvis and extend into the lower abdomen, and have the same fat intensity in solid components (Fig. 2). Left radius and thumb were not seen in the X-ray of the patient (Fig. 3). When we evaluated the patient in terms of anomalies accompanying sacrococcygeal teratoma, while cranial ultrasonography was normal, echocardiography was revealed ostium secondary atrial septal defect



Figure 1. Approximately 15 × 10 cm protruding a mass covering the sacrococcygeal region of the patient and left upper limb defect with the absence of left thumb.

(ASD) (diameter 6 mm) and VSD (diameter 1.5 cm). On his urinary system ultrasonography, pelvicalyceal dilatation in the calyces, tortuous, and dilated bilateral ureters were detected. The patient with left upper limb abnormalities and congenital cardiac defects was diagnosed with HOS, clinically.

On the postnatal 5th day, the patient was operated on by the pediatric surgeon, and the 570 g sacrococcygeal mass and coccyx was totally excised without residual mass and sent to pathology. Pathology revealed Grade 2 immature sacrococcygeal teratoma. Contrast-enhanced abdominal and pelvic computed tomography was performed to investigate the residual tissue after surgery (post-operative, 24th day) and soft-tissue appearance, which could be compatible with granulation tissue measuring 3 × 2 cm in the widest part of the sacrococcygeal region, was detected. With these findings, the patient was referred to the pediatric oncology center. Serum AFP levels of the patient are 1115 ng/mL (300–70000 ng/mL) on post-operative 21st day.

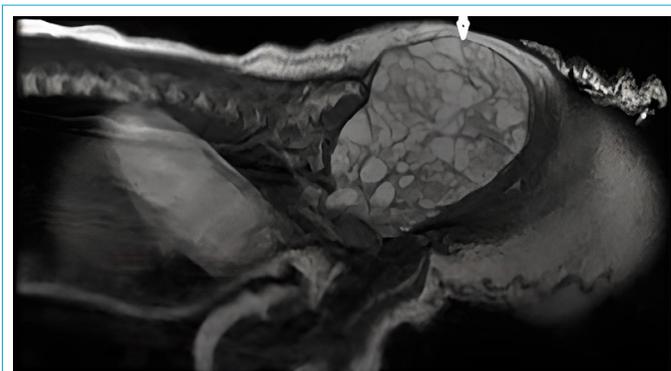


Figure 2. Magnetic resonance imaging of the patient reveals type II sacrococcygeal teratoma (white arrow).

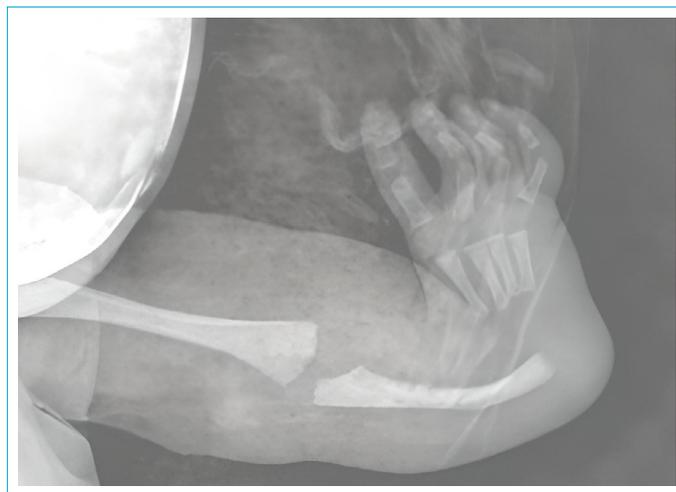


Figure 3. X-ray of the patient shows the aplasia of left radius and thumb.

Discussion

SCT is the most common germ cell tumor of neonates and is localized on sacrococcygeal region.^[8,9] It is reported that approximately half of the patients with SCTs may be diagnosed in utero during routine ultrasonographic examination.^[8,10] After birth, patients with SCTs can be easily diagnosed by the presence of a protruding mass on their sacrococcygeal region as seen in our patient.^[10] In patients with SCTs, abdominopelvic MRI is recommended to evaluate the extent of the tumor.^[10]

It has been reported that early complete surgical resection is the mainstay of the therapy for patients with SCTs because delayed treatment may lead to tumor rupture and hemorrhage.^[5,10] It has been reported that the surgical outcome and prognosis of the patients with SCTs are favorable; however, recurrences after surgery (after 6–36 months) may be seen in some patients, who had an uncompleted resection, resection without coccyx, and immature or malignant histology (10–15%), especially.^[10] After completed surgery resection, the presented patient was referred to a pediatric oncology center. Serum AFP levels are useful in monitoring for tumor recurrences in these patients.^[5,10]

Patients with SCTs may be also associated with many congenital other abnormalities such as genitourinary system, musculoskeletal system, neurological, cardiovascular system, and pulmonary system.^[8,10,11] The incidence of congenital abnormalities associated with this disease is reported to be 12–30% of the patients.^[8,12,13] Recently, Kremer et al.^[11] from Netherlands reported that 32.3% of the patients with SCTs had 5 at least one associated abnormality. According to this study, the genitourinary system abnormalities (18.7%), such as hydronephrosis (most of them, 16.2%), vesicoureteral reflux, hydroureter, sclerotic kidney, horseshoe kidney, renal agenesis, ureterovaginal fistula, vesicointestinal fistula, ectopic kidney at bifurcation of aorta, and hypospadias, were the most common. Musculoskeletal abnormalities (6.4%) such as hip dysplasia (4.3%), clubfeet, polydactyly, and Duchenne muscular dystrophy were second common abnormalities of the patient with SCTs. Neural defects (6%) such as paraplegia, encephalopathy, epilepsy, spina bifida, and loss of strength or sensation in the lower extremities were third abnormalities related to SCTs, followed by abnormalities of the cardiovascular system (VSD, ventricular anomaly, persistent ductus arteriosus, and stenosis of pulmonary artery), anorectal system (rectovaginal fistula, anorectal malformation, ventral positioned anus, and anal stenosis), pulmonary system (pulmonary hypertension, infantile respiratory distress syndrome, and bronchopulmonary dysplasia), facial dysmorphism (Freeman Sheldon syndrome,

not further specified), and other anomalies (not categorized) such as chromosomal aberration, esophageal atresia, congenital hyperthyreosis, omphalocele, intraperitoneal testes, hemangiomas, and Siamese twin.^[11]

HOS is an autosomal dominant disorder characterized by abnormalities of the upper limbs and girdle, associated with a congenital heart lesion. The typical combination is considered to be absent or a triphalangeal thumb with a secundum ASD, but there is a great range in the severity of both the heart and skeletal lesions.^[14]

The presented patient with HOS had only bilateral hydro-nephrosis, ostium secundum ASD and VSD, minimal hydrocele, single umbilical artery, and vein according to upper reported abnormalities. Interestingly, the presented patient had left radius and thumb aplasia.

The T-box transcriptional factor (Tbx) family has distinct roles in a wide range of embryonic differentiation or response pathways. Mutations in genes belonging to the Tbx 6 family impair the proliferation, migration, and differentiation of the embryonic mesoderm.^[15] Epiblast cells migrating from primitive node and proximal part of primitive streak lead to the intermediate plate mesoderm. It has been reported that failure of some of these epiblast cell migrations may lead to remnants at primitive streak which may persist in sacrococcygeal region as a teratoma.^[16] HOS is genetically heterogeneous, but mutations in the TBX5 gene are the most common cause.^[17] Therefore, we think that the association of HOS and SCT may be related to a mutation of T-box transcriptional factor more than coincidental association in our patient.

As a result, to our knowledge, it has been not reported a case with HOS associated with sacrococcygeal teratoma. Patients with SCTs may have multiple and extreme congenital abnormalities; therefore, patients with SCTs should be carefully evaluated clinically, laboratory, and radiologically and it should be also considered that HOS may accompany them.

Disclosures

Informed consent: Written informed consent was obtained from the patient's family for the publication of the case report and accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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