Goldenhar Syndrome with Neuroblastoma: A Case Report and Literature Review

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Hala Issa, MD[1], Hani Saleh, MD[2], Mahdi Aljamal, MD[1], and Ali Shakhshir, MD[1]

Abstract

Oculoauriculovertebral dysplasia, also called Goldenhar syndrome, involves several issues, such as small ears (microtia), underdeveloped jaw (mandibular hypoplasia), skin growths near the eyes (epibulbar dermoids or lipodermoids), and problems with bones, heart, spine, and kidneys, among others. It is rarely associated with neuroblastoma. This report highlights a case where neuroblastoma was diagnosed in a child with Goldenhar syndrome, which, to the best of our knowledge, is the second case of its kind in the literature.

Keywords

Goldenhar, neuroblastoma, oculoauriculovertebral dysplasia, Palestine

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Introduction

Goldenhar syndrome is a rare syndrome distinguished in 1952 when the first child with Goldenhar syndrome (GS) was born.[1] The syndrome is known to have a wide range of anomalies involving craniofacial structures, vertebrae, and internal organs. It usually occurs unilaterally. The incidence of Goldenhar syndrome has been reported to be 1:35,000-1:56,000, with a male-to-female ratio of 3:2.[2] This syndrome is known to have a sporadic hereditary pattern, except for some autosomal dominant cases.[3] The etiology of this syndrome is unclear since it varies genetically and is linked to a plethora of reasons. Michel-Adde et al[3] pointed to the possibility of the association between Goldenhar syndrome and neuroblastoma when they reported the first case of neuroblastoma in Goldenhar syndrome. Herein, this report highlights a case of neuroblastoma that was found in association with Goldenhar syndrome, which, to the best of our knowledge, is suspected to be the first case recorded in Palestine and the second worldwide.

Case Presentation

This report presents a 20-month-old male child who is a product of cesarean section (CS) due to breech presentation. He was a full-term neonate with a birth weight of 2.8 kg. The patient was admitted to the neonatal intensive care unit (NICU) for further investigations of dysmorphological features and suspected genetic syndrome. Echocardiography was done at that time and showed a large patent ductus arteriosus (PDA) along with left ventricular dilatation, which was treated by PDA ligation.

Moreover, the neonate was found to have multiple congenital abnormalities, such as ear and auditory abnormalities, including third-degree left microtia, a narrow patent external acoustic canal with approximately 70% stenosis and an intact but mildly retracted tympanic membrane (Figure 1), the right ear was normal with only bilateral preauricular skin tags (Figure 2). Formal hearing assessment using auditory brainstem response (ABR) demonstrated mild conductive hearing loss on the left side.

Ocular anomalies, including left eye microphthalmia (abnormally small eye) as seen in Figure 3. Craniofacial abnormalities include hemifacial microsomia, micrognathia, and macrostomia (a large, protruded tongue). Lateral skull radiographs demonstrated mandibular hypoplasia, whereas a computed tomography (CT) scan

[1]Arab American University, Jenin, Palestine
[2]Augusta-Victoria Hospital, East Jerusalem, Palestinian Territories

Corresponding Author:
Hala Issa, Faculty of Medicine-Department of Pediatrics, Arab American University, Jenin 240, Palestine.
Email: Hala.issa@aaup.edu

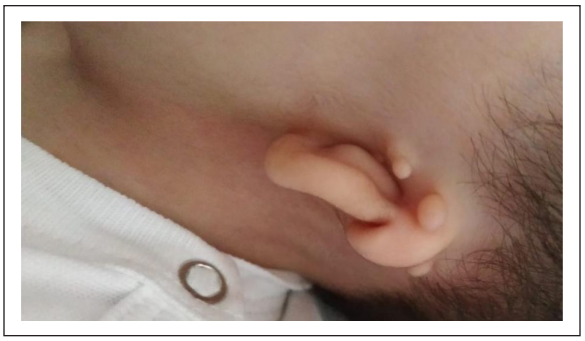

Figure 1. Showing left ear abnormalities with pre-auricular skin tags.

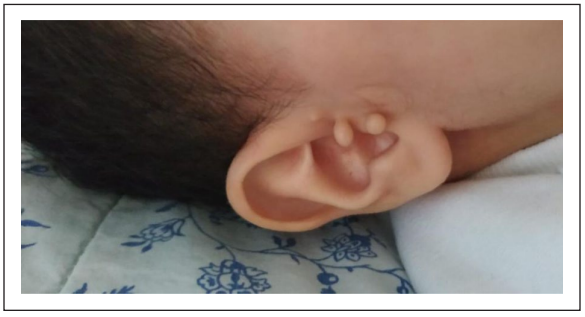

Figure 2. Showing normal right ear except pre-auricular skin tags.

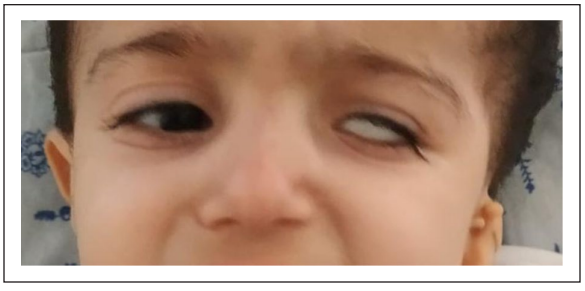

Figure 3. Shows left eye microphthalmia with normal right eye.

showed vertebral complete sacral agenesis, butterfly vertebra, and pedicles agenesis as shown in Figure 4.

Other clinical features found in the patient include a short neck, retractile testis bilaterally, hypospadias, a reducible right inguinal hernia, and right polydactyly with clubbed feet.

Karyotyping was done and showed a normal 46, XY male. Trio-whole exome sequencing (trio-WES) was not performed due to financial limitations and because parental consent for advanced genomic sequencing was not obtained at the time.

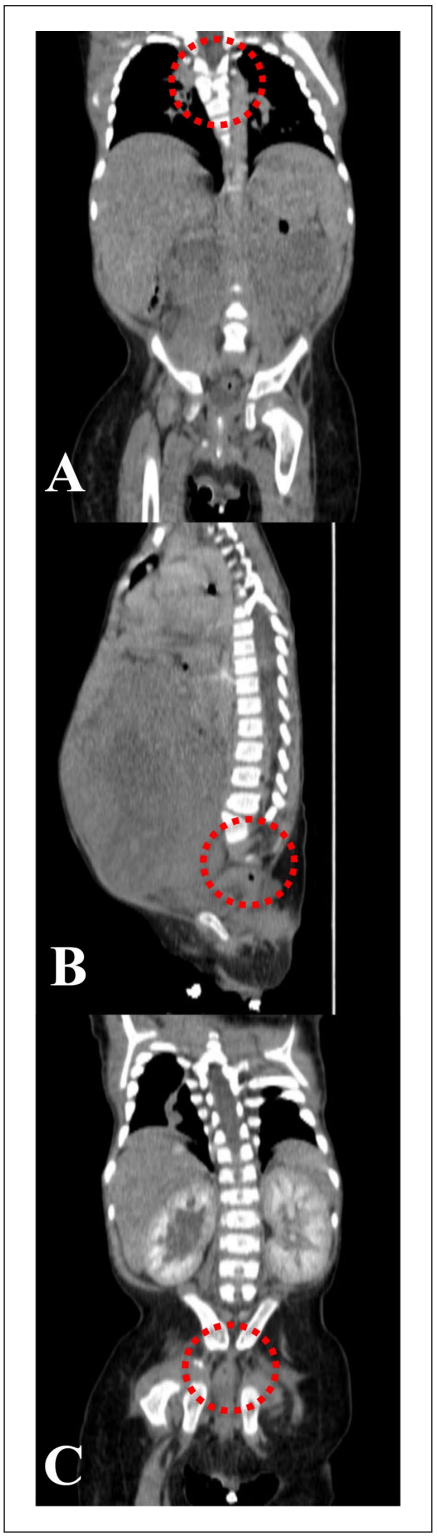

Figure 4. The figure demonstrates a contrast-enhanced CT of the abdomen and pelvis which showed butterfly vertebrae in the coronal view of in image A, complete sacral agenesis in the sagittal view of image B, and pedicles agenesis in the coronal view of image C.

The diagnosis of Goldenhar syndrome was made clinically based on the combination of major features (microtia, ocular anomalies, mandibular hypoplasia) and minor clinical features (preauricular tags, limb anomalies, and vertebral anomalies) affecting structures derived from the first and second branchial arches. There was no family history for similar conditions such as craniofacial, oculo-auricular or other skeletal abnormalities. Moreover, there was no family history of childhood malignancy including neuroblastoma, which favors the sporadic pattern of Goldenhar syndrome in this patient.

Later, at the age of 20 months, his mother noticed that he had abdominal distension with constipation. A trial of conservative management for constipation was done, and the constipation was resolved, but the distension progressed with a history of difficulty in breathing, decreased oral intake, and hypoactivity. Therefore, the patient was admitted to the pediatric ward for investigations. The patient was found to have a distended abdomen (62 cm in circumference) with dilated superficial veins and everted umbilicus, with a hard mass filling all the abdomen and dull on percussion (Figure 5). Abdominal and pelvic CT scans showed an abdominal mass, as shown in Figure 6. This mass was suspected to be neuroblastoma. Urine test was negative for Vanillylmandelic Acid (VMA) and homovanillic acid (HMV). Ultrasound-guided true-cut biopsy was sent for histopathology and showed undifferentiated neuroblastoma. Bilateral bone marrow biopsies were done and were free of disease, and the N-MYC gene was not amplified.

The child had high risk neuroblastoma according to COG risk stratification (COG ANBL00B1 neuroblastoma biology studies, age $>$ 547 days, stage III unresectable tumor, unfavorable histology, MYC non- amplified). The disease initially showed partial response to neoadjuvant chemotherapy but remained unresectable, then the child died due to disease progression while on intensive chemotherapy.

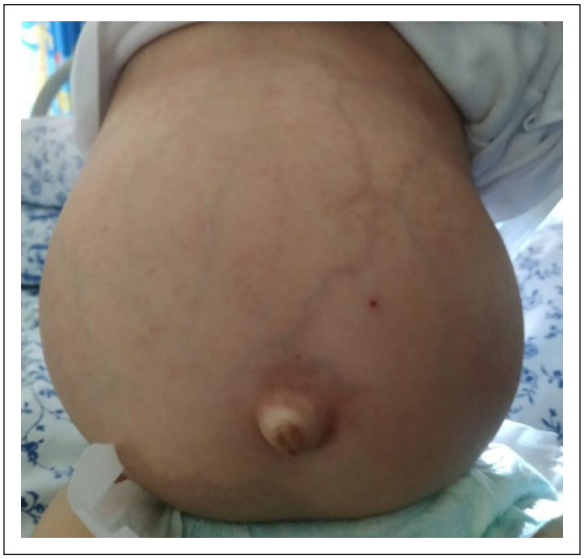

Figure 5. Distended abdomen due to a large abdominal mass (neuroblastoma) in a Goldenhar syndrome patient.

Discussion

Goldenhar syndrome, also known as oculo-auriculo-vertebral syndrome (OAVS), is a rare congenital condition. OAVS has been considered an anomaly of the first and second branchial arches.[1] Several conditions were associated with this syndrome, such as abnormalities in the chromosomes and neural crest cells. Moreover, predisposition to some environmental factors during pregnancy, like thalidomide, retinoic acid, and cocaine ingestion, in addition to the intake of alcohol by the mother, were also related to the development of the disease. Maternal diabetes has also been suggested as an etiologic factor.[4]

Clinically, the syndrome is characterized by impairments in several organs that develop from the first and second branchial arches, including the eyes, ears (with or without hearing loss), lips, tongue, palate, mandible, maxilla, and deformities of the tooth structures. Also, defects in the internal organs were reported, such as the heart, kidneys, or central nervous system, or in the skeleton, as well as different vertebral defects.[5] The syndrome is known to occur unilaterally in 85% of cases, more frequently on the right side than the left, with a ratio of 3:2.[6] Several prevalent features include dacryocystitis, auricular abnormalities, preauricular fistulas and appendages, epibulbar dermoids, and hypoplasia of the malar bones, mandible, maxilla, and zygomatic arch.[1] Additionally, there are concerns regarding delayed psychomotor development; retardation is more common in cases with cerebral developmental anomalies and microphthalmia. Other issues include articulation disorders, rhinolalia, various voice disorders with unusual timbre, psychosocial problems, autistic behavior, and general speech disorders.[7] Life-threatening problems could arise, such as airway obstruction and sleep apnea symptoms associated with the retruded maxilla and mandible constricting the oropharyngeal airway, as well as associated nasal airway obstruction.

Some studies suggest that abnormal vascularization develops in the fourth week of pregnancy, which affects the development of the first and second pharyngeal arches responsible for craniofacial structure growth. However, other studies suggested that this syndrome

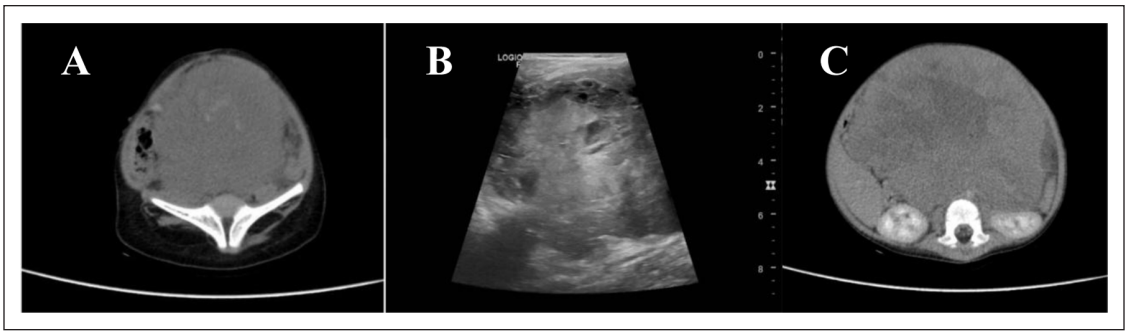

Figure 6. (A) Axial non-contrast CT shows a heterogeneous soft tissue mass with few linear calcifications. (B) Transabdominal ultrasound demonstrates a large, predominantly isoechoic abdominopelvic mass with multiple small anechoic foci suggestive of intratumoral necrosis. (C) Axial contrast-enhanced CT (portal venous phase) reveals a large heterogeneously enhancing mass centered in the mid-abdomen, with central areas of hypoenhancement consistent with necrosis. The lesion exerts a significant mass effect, displacing adjacent bowel loops, compressing the left kidney, and causing right-sided hydroureteronephrosis due to ureteral compression.

may be inherited, as the authors observed that 30% of the cases were familial and exhibited either autosomal dominant or recessive patterns, along with documented chromosomal abnormalities such as deletions on chromosomes 1, 5, 12, 14, 15, and 22; duplications on chromosomes 10, 14, and 22; trisomies on chromosomes 18 and 22; mosaicism of trisomy 7, 9, and 22; translocation between chromosomes 9 and 12; inversion in chromosome 14 between bands p11.2 and q22.3; inversion within chromosome 9 between bands p11 and q13; and aneuploidies in chromosome X.[8] Moreover, external factors like smoking, cocaine, exposure to thalidomide, hormonal therapy, and tamoxifen can contribute to interference with the normal growth of the first and second pharyngeal arches.[8]

Among cardiovascular anomalies, tetralogy of Fallot and ventricular septal defects are most commonly associated with OAVS.[9] The reported neonate was diagnosed with a large PDA. Cleft lip and palate, macrostomia, micrognathia, webbing of the neck, a short neck, tracheoesophageal fistulas, and abnormalities of the sternocleidomastoid muscle may be associated. Following the described features of the syndrome, the reported neonate was found to have third-degree left microtia, a narrow patent external acoustic canal, left eye microphthalmia, bilateral preauricular skin tags, a large protruded tongue, mandibular hypoplasia, a short neck, retractile testes bilaterally, hypospadias, a reducible right inguinal hernia, and right polydactyly with clubbed feet. Prenatal diagnosis can be performed with considerable accuracy using ultrasound, which may detect obvious defects.[10] The wide range of symptoms creates a broad differential diagnosis, necessitating distinguishing it from other syndromes like Treacher Collins syndrome (TCS), Nager syndrome, and Townes-Brocks syndrome. Unilateral facial involvement with consequent facial asymmetry is a hallmark of Goldenhar syndrome, while in TCS, involvement is frequently bilateral. Moreover, the mutation of the TCOF1 gene on human chromosome 5q31-34 is specifically linked to TCS and helps in the final diagnosis.[10]

Neuroblastoma is a well-known, malignant neoplasm of early life. It is composed of primitive neuroblasts derived from the neural crest. In its most primitive or simple form, the tumor consists of sheets and nests of cells similar to the early migratory neural crest cells in the embryo. Maturation or cytodifferentiation can occur as a ganglioneuroma in its most mature form. On the other side, Van Meter and Weaver[11] suggested that a deficiency in migration of neural crest cells, defective interaction between neural crest cells and mesoderm, or a deficiency of mesodermal formation may explain the pathogenesis of Goldenhar syndrome. The association between Goldenhar syndrome and neuroblastoma supports the hypothesis of a common origin for both pathologies and should therefore be considered in the neurocristopathy group.

When reviewing the literature, one case reported the concurrent diagnosis of neuroblastoma in a child with Goldenhar syndrome in 2003,[3] representing a full-term male patient with several features close to the current case. The newborn had fetal distress and was admitted to the NICU due to dysmorphic features such as bilateral microtia, bilateral preauricular fibrochondromas, bilateral epibulbar dermoids on the eyelids, nasal probosis, and retrognathia with a left maxillopalatal defect. All these abnormalities were asymmetrical and more marked on the left side. Investigation showed a normal karyotype similar to the current case. On the 29th day, the infant died. However, autopsy revealed a multinodular, necrotic-hemorrhagic retroperitoneal tumoral mass. The mass extended from the left adrenal gland without macroscopic invasion of the kidney and extension to

the thorax. At the same time as this case, tests showed a normal karyotype, and fluorescence in situ hybridization studies (FISH) did not show any N-myc amplification.

Conclusion

Goldenhar syndrome is a very rare and poorly understood condition, with several hypotheses that attempt to explain its underlying processes and the potential associated conditions. The diagnosis of neuroblastoma in a child who also has Goldenhar syndrome creates a unique case that raises additional questions about the potential associations between neuroblastoma and Goldenhar syndrome, given that they share a common pathophysiological origin.

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ORCID iDs

Hala Issa https://orcid.org/0009-0002-0150-8861
Ali Shakhshir https://orcid.org/0000-0003-4138-8497

Consent for publication

A written consent to publish this case was obtained from the patient's mother, who is her legal guardian.

Author contributions

Hala Issa participated in the clinical management of the patient, collected the clinical data, and drafted the case presentation.
Mahdi Aljamal contributed to writing the introduction and conducted the literature review.
Ali Shakhshir wrote the discussion section and contributed to the literature review.
Hani Saleh supervised the clinical management of the patient, followed up the case, and critically reviewed the manuscript, including responses to reviewers' comments
All authors read and approved the final manuscript.

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Declaration of conflicting interests

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