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Adams-Oliver Syndrome: Vestigial Tail and Genetics Update

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Abstract

Adams-Oliver syndrome is a well-recognized autosomal dominant disorder for which mutations in six genes are etiologic, but account for only one-third of the cases. We report a patient with two genetic disorders; Adams-Oliver and Xp22.33 deletion syndromes, as well as a vestigial pseudotail. The presence of a pseudotail has not previously been reported in either of these genetic conditions. Absence of a molecular etiology underlying Adams-Oliver syndrome confirms that there are additional genetic causes to be identified.

Keywords

- Adams-Oliver syndrome
- pseudotail
- vestigial tail
- genetics

Introduction

Adams-Oliver syndrome is a rare but well-characterized disorder that is recognized by the presence of aplasia cutis congenita and transverse limb reduction defects.[1] It has an incidence of 44 per 10 million births.[2] Mutations in six genes, *ARHGAP31*, *DLL4*, *DOCK6*, *EOGT*, *NOTCH1*, and *RBPJ*, are known to cause this condition.[1] A variety of other congenital malformations have been associated with the condition including growth deficiency, cardiac defects, cutis marmorata telangiectasia congenital, cleft lip/palate, accessory nipples, renal abnormalities, cryptorchidism, Poland sequence, and central nervous system (CNS) defects (►**Table 1**).[2] Vestigial tails, whether true tails or pseudotails, have not previously been reported in Adams-Oliver syndrome. Here, we report the first case of a pseudotail in a patient with Adams-Oliver syndrome in which no genetic mutation was identified. This case further confirms that additional etiologic genes are yet to be identified in this condition.

Case

The patient was an 8-year-old girl presenting for surgical excision of a vestigial tail. ►**Fig. 1** shows the abnormalities observed: residual cutis aplasia scar on the superior portion of her scalp that did not contain hair (►**Fig. 1A**) and terminal transverse limb defects (►**Fig. 1B, C**). There was absence of digits 2 to 4 on the left hand and digit 5 was short with only a single flexion crease. The right hand showed syndactyly of digits 2 and 3 with digits 4 and 5 being contracted secondary to surgical scars from web release (►**Fig. 1B**). Thumbs were normal. Toes 2 to 5 on the left foot were absent and there was a rudimentary great toe. The right foot had a rudimentary

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Table 1 Genetic and clinical features of Adams-Oliver syndrome and case report

Clinical features	
Adams-Oliver syndrome	Case report
Defining features	
Aplasia cutis congenita	Aplasia cutis congenita
Transverse limb reduction defects	Transverse limb reduction defects
Other associated conditions	
Growth deficiency	Growth deficiency (< 1 percentile height)
Cardiac defects	–
Cutis marmorata telangiectasia congenita	–
CNS defects	Plagiocephaly w/ facial asymmetry
Renal abnormalities	–
Cleft lip/palate	High arched palate
Accessory nipples	–
Cryptorchidism	–
Poland sequence	–
	Pseudotail
	Other facial features: epicanthal folds, mildly depressed nasal bridge, long philtrum, simple ears, short/wide neck, low posterior hairline
Associated gene anomalies	
Adams-Oliver syndrome	Case report
ARHGAP31	–
DLL4	–
DOCK6	–
EOGT	–
NOTCH1	–
RBPJ	–
	SMARCA4
	GDAP1
	MPDZ
	Xp22.33/SHOX

Abbreviation: CNS, central nervous system.

great toe, digits 2 and 3 appeared as tiny nubbins with no nails, and digit 5 was hypoplastic (►**Fig. 1C**). Additional findings included short height (< 1%), plagiocephaly with facial asymmetry, epicanthal folds, mildly depressed nasal bridge, long philtrum, high arched palate, simple ears, short and wide neck, and low posterior hairline. A lumbosacral, soft tissue appendage that appeared to be comprised primarily of skin and subcutaneous fat tissue was also present (►**Fig. 2**). Given the absence of muscle, bone, and movement capability of the appendage, it was diagnosed as a pseudotail. Magnetic resonance imaging (MRI) of the lumbosacral appendage and the spine suggested a tethered cord, fatty filum terminale, and low-lying conus medullaris (►**Fig. 3**). Surgical excision of soft tissue pseudotails, such as the one in this patient, usually involves simple elliptical excision and closure; however, due to the findings on MRI that suggested tethering of the spinal cord, neurosurgical involvement was requested to assist in releasing any attachments and ensure no damage to the spinal cord. The patient and mother signed an informed consent for the surgery. In the operating room, the pseudotail was excised via an elliptical excision and closure. The cord was entered via the dura at L5-S1 and was untethered by releasing the rostral end of the filum terminale. The diagnosis of Adams-Oliver syndrome was made based on the constellation of findings. Family history was negative suggesting that this was a de novo event. However, the patient's mother, maternal grandmother, and a maternal aunt all had short height (< 5%). At 4 months postoperatively, the patient returned for follow-up and the surgical site was photographed (►**Fig. 4**) and shown to heal without complications. The parents also reported improved ambulation and decreased lower extremity pain as a result of the cord untethering.

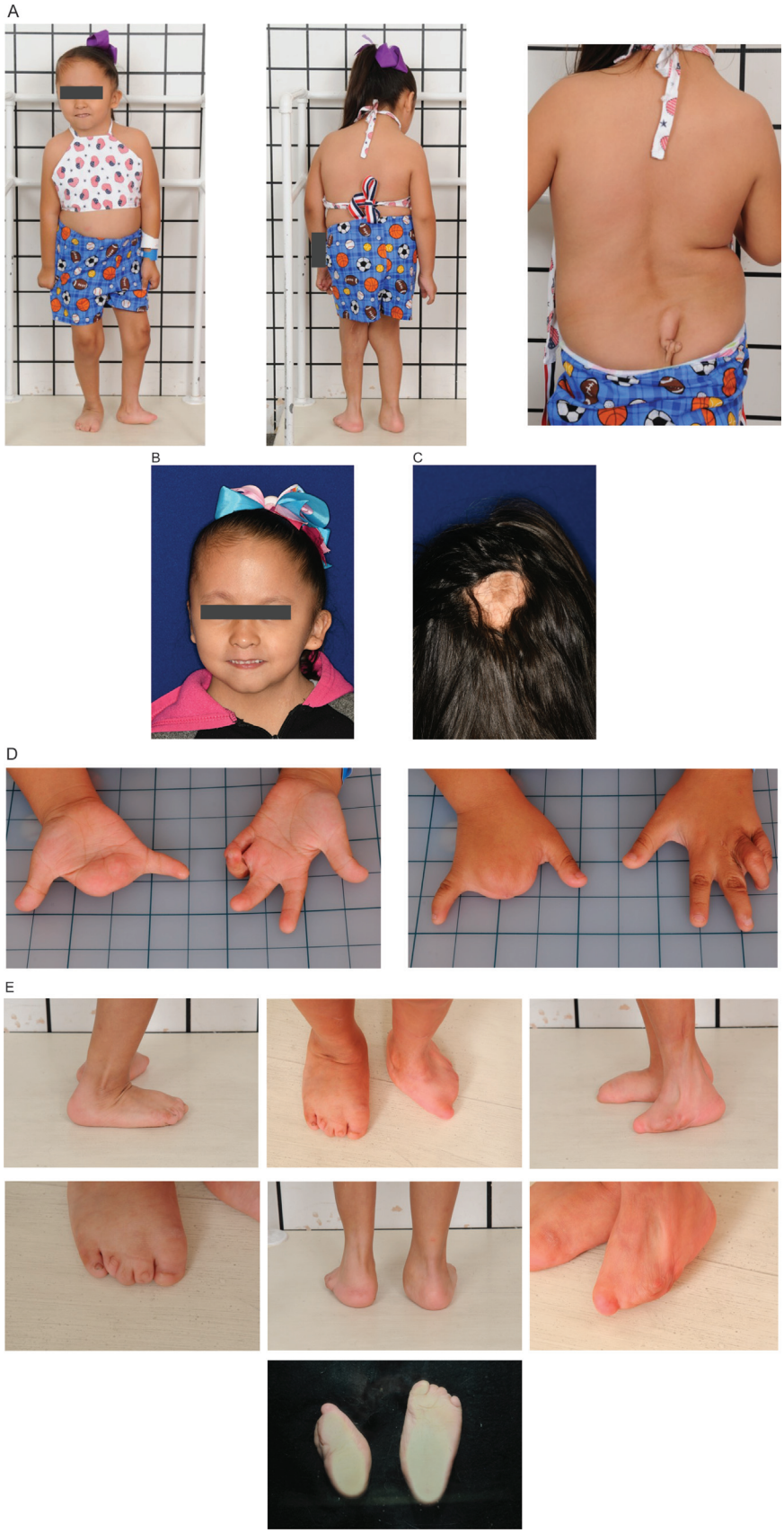

Fig. 1 Patient phenotypic findings. (**A**) Full body, (**B**) face, (**C**) cutis aplasia congenita, (**D**) transverse upper limb defects, and (**E**) transverse lower limb defects.

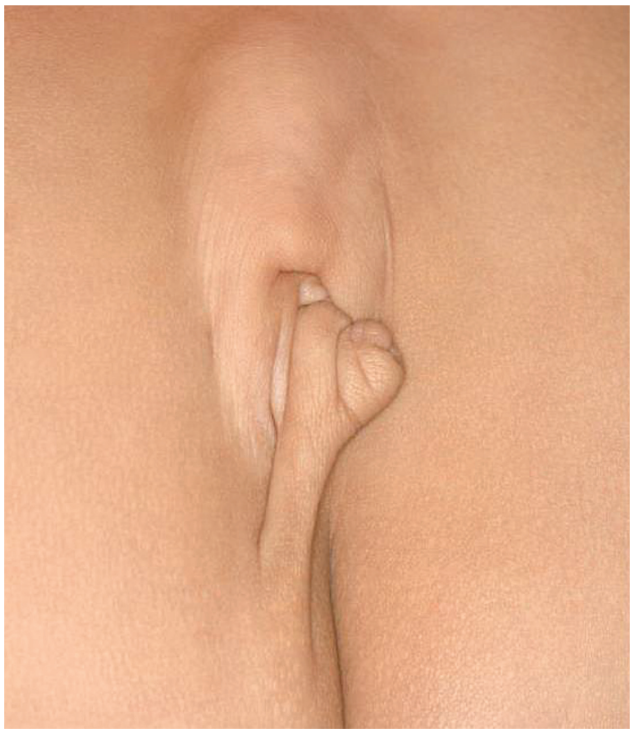

Fig. 2 Lumbosacral appendage, preoperatively.

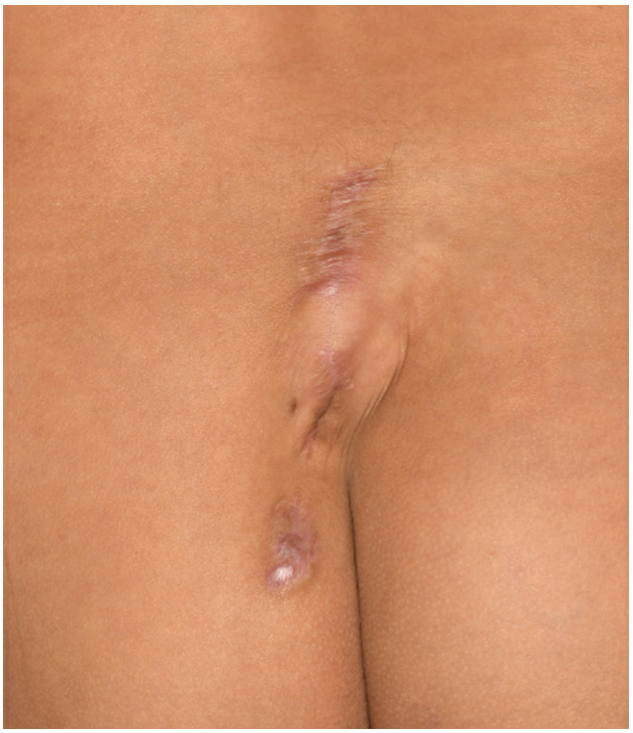

Fig. 4 Lumbosacral appendage, 4 months postoperatively.

Genetic Studies

Whole-exome sequencing was performed. No clinically significant sequence variants or copy number changes were found in any of the known causal genes for Adams-Oliver: *ARHGAP31*, *DLL4*, *DOCK6*, *EOGT*, *NOTCH1*, and *RBPJ*. A heterozygous variant of unknown significance was identified in *SMARCA4*, which is associated with autosomal dominant Coffin-Siris Type 4. The patient's phenotype was not consistent with that diagnosis. A pathogenic variant was identified in *GDAP1*, which causes autosomal recessive Charcot-Marie-Tooth and a variant of unknown significance was identified in *MPDZ* that causes autosomal recessive congenital hydrocephalus. None were considered etiologic. Chromosomal microarray identified a pathologic 38 kb deletion in Xp22.33 that contains enhancers of the *SHOX* gene. This deletion is associated with idiopathic short stature and Leri-Weill dyschondrosteosis. Parental fluorescence in situ hybridization analysis determined that the deletion was maternally inherited.

This project was undertaken as a case report project and, as such, was not formally supervised by an institutional review board (IRB). Similarly, no IRB is required at our organization for case reports.

Patient Consent

The patient and mother agreed to being a part of the case report and signed an authorization of disclosure of medical information for the purpose of this case report. As such, the patients provided written informed consent for the publication and the use of their images.

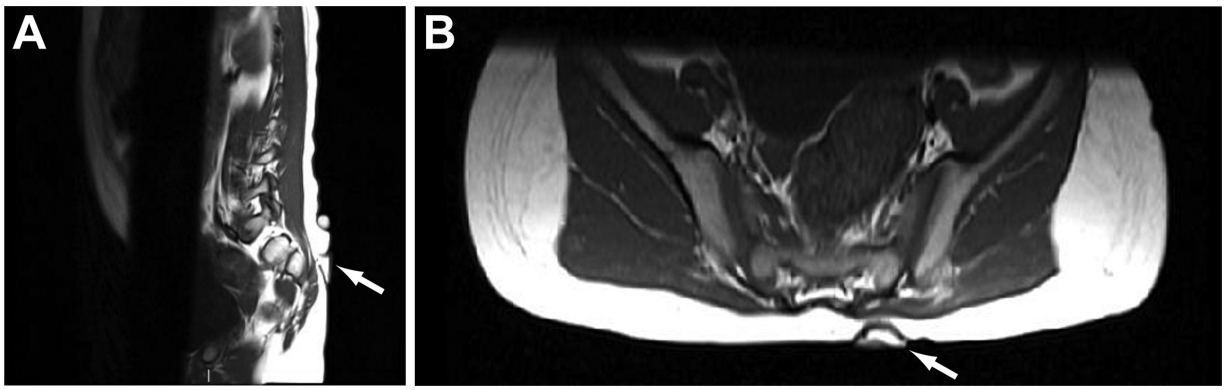

Fig. 3 T1 axial and sagittal magnetic resonance imaging (MRI) images of the lumbosacral appendage. (**A**) Axial and (**B**) sagittal.

Discussion

The diagnosis of Adams-Oliver syndrome was based on the presence of congenital cutis aplasia and transverse limb reduction defect. These limb defects can range from short to absent digits and limbs. Underappreciated is the finding that one-third of affected individuals have CNS anomalies, including microcephaly, encephalocele, pachygyria, polymicrogyria, cortical dysplasia, heterotopia, schizencephaly, colpocephaly, ocular anomalies, and intellectual disabilities.[1] Interestingly, all CNS anomalies have involved the brain or cranium with no reports of anomalies of the vertebrae or spinal cord. Other anomalies have also been reported including congenital heart defects, pulmonary hypertension, vascular anomalies, Poland anomaly, cleft lip/palate, and accessory nipple.[2] There have been no reports of vestigial tail.

Human tails are rare occurrences that can generally be divided into pseudo- and true tails. During human embryogenesis, the tail bud develops during the fourth gestational week and normally then involutes by apoptosis.[3] True human tails result from an abnormality in embryonic development and are defined as caudal, midline appendages that are capable of motion. They usually consist of skin, adipose tissue, connective tissue, muscle, and neurovascular components, but no bony elements.[4] In contrast, pseudotails are protrusions that do not contain the musculature and neurovascular components that allow for motion.[4,5] Pseudotails typically arise as a result of nonfusion of the neural tube during embryonic development. This nonfusion may induce formation of adipose tissue that can cause tethering of the cord.[6] Pseudotails can be associated with spinal dysraphism and tethered cord in 49 and 20% of patients, respectively.[3] As a result of this, it is often prudent to obtain further imaging and involve neurosurgery in operative excision of the pseudotail to prevent damage to the spinal cord and release any attachments to the cord. Besides damage to the cord, other typical surgical complications can include wound breakdown, infection, hematoma, and pain. Patients and families should be well apprised of these potential complications. Pseudotails may present as prolongation of the coccygeal vertebrae, lipomas, teratomas, or gliomas.[4] There have also been case reports of pseudotails being associated with syndactyly, clubfoot, and hypoplasia of digits.[3]

The vestigial appendage described in this report most closely resembles a pseudotail, comprised primarily of lipomatous tissue on MRI with tethering of the cord and incapable of motion. While not previously reported with Adams-Oliver syndrome, it may represent a secondary finding resulting from abnormal neural tube morphogenesis or may be a rare feature of this condition.

Adams-Oliver syndrome was first described in a three-generation family in 1945.[7] Recently, mutations in *ARHGAP31*, *DLL4*, *DOCK6*, *EOGT*, *NOTCH1*, and *RBPJ* have been shown to cause this condition. These genes function in the CDC42/RAC1 or NOTCH signaling pathways.[1] However, only one-third of Adams-Oliver cases have a mutation in one of these genes; two-thirds of cases, including this patient, do not have an identifiable genetic cause.[8] Moreover, half of Adams-Oliver cases occur as de novo events without a family history,[8] similar to our patient. This indicates that there are undiscovered genes yet to be identified as causal in Adams-Oliver syndrome.

The Xp22.33 deletion identified in the patient and her mother, deleted an enhancer of the *SHOX* gene that has been shown to cause idiopathic short stature and Leri-Weill dyschondrosteosis; a condition characterized by short height, mesomelia, and Madelung deformity.[9] Both the patient and her mother had proportionated short height consistent with this chromosomal deletion. Mesomelia or Madelung deformity was not present by radiographic exam and is also consistent with *SHOX*-associated regulatory region deletions. This likely explains the short height segregating in the maternal lineage. While the Xp22.33 deletion likely explains the short height in the patient, which is exacerbated by the lower limb deformities, it is unlikely to be related to the diagnosis of Adams-Oliver syndrome.

Here, we present the first case of a patient with Adams-Oliver syndrome and a pseudotail. Whether this is an unrelated and sporadic association will depend on findings reported in future cases. Importantly, our patient has two separate genetic conditions, Adams-Oliver syndrome without a molecular diagnosis and Xp22.33 deletion short stature disorder. Identification of additional Adams-Oliver genes in the future will be needed to provide a molecular diagnosis. This report shows that in plastic surgery practice, patients identified with Adams-Oliver syndrome or a pseudotail should be evaluated for both conditions in addition to other genetic and congenital anomalies. Additionally, it would be prudent to involve neurosurgery due to the high rate of pseudotail spinal tethering and dysraphism.

Author Contributions

Conception, analysis, and interpretation of data: V.Z.Z., E.H.-K., J.T.H., P.E.P.; drafting and review of paper: V.Z.Z., E.H.-K., J.T.H., P.E.P.; accuracy and integrity of work: V.Z.Z., E.H.-K., J.T.H., P.E.P.; final approval: V.Z.Z., E.H.-K., J.T.H., P.E.P.

Patient Consent

The patients provided written informed consent for the publication and the use of their images.

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None.

Conflict of Interest

None declared.

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