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HISTOPATHOLOGIC STUDY OF TEMPORAL BONE AND EUSTACHIAN TUBE IN OCULOAURICULOVERTEBRAL SPECTRUM

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Bilateral temporal bone specimens from a 21-month-old girl and a left temporal bone–eustachian tube (ET) specimen from a full-term female newborn, both with oculoauriculovertebral spectrum, were studied histopathologically. The external and middle ears demonstrated severe anomalies, similar to those of previous reports describing the histopathologic findings of this syndrome. In addition, despite having a normal auricle, the 21-month-old child had bilateral hypoplastic cochleas as seen in Mondini dysplasia. The newborn had several anomalies of the ET, including a widely opened cartilaginous portion of the ET lumen and absence of the lateral lamina of the ET cartilage. We discuss the implications of the observed anomalies with regard to developmental and clinical issues.

KEY WORDS — anomaly, eustachian tube, histopathology, oculoauriculovertebral spectrum, temporal bone.

INTRODUCTION

The term oculoauriculovertebral dysplasia was first proposed by Gorlin et al[1] to describe patients with epibulbar dermoids or lipodermoids, microtia, mandibular hypoplasia, and vertebral anomalies. The anomalies identified with oculoauriculovertebral dysplasia, including hemifacial microsomia and classic Goldenhar's syndrome, are considered to be congenital malformations secondary to developmental abnormalities of mostly first and second branchial arch derivatives.[2] Cohen et al[3] suggested the term oculoauriculovertebral spectrum (OAVS) to describe these conditions. The location and degree of anomalies of the ear recognized in OAVS vary in each case. There are numerous reports describing developmental anomalies affecting the ear, mandible, eye, vertebrae, skeleton, and central nervous and cardiovascular systems.[2-5] There is limited information describing histopathologic abnormalities of the temporal bone in OAVS,[4,6-8] and there has not been a histopathologic report describing the middle ear (ME) and inner ear (IE) abnormalities recognized in the contralateral temporal bone. Furthermore, the microscopic findings of the entire eustachian tube (ET) and its associated structures have not been recorded. The purpose of this report is to present and discuss the results of histopathologic examination of bilateral temporal bone specimens from one case of OAVS and a temporal bone–ET specimen from another case.

CASE REPORTS

Case 1. A 21-month-old girl died of increasing intracranial pressure and recurrent respiratory distress. She had hydrocephalus treated by a ventriculoperitoneal shunt, asymmetric micrognathia (severe on left side), aplasia of the left external ear, cleft palate, and a dermoid of the skull treated by surgical excision. No vestibuloauditory function testing was performed. The following abnormalities and anomalies were noted during the autopsy: 1) of the skull, macrocephaly; 2) of the brain, Dandy-Walker malformation with hydrocephalus, hypoplastic optic nerve and chiasm (bilateral), hypoplastic choroid plexuses, agenesis of the corpus callosum, and subacute leptomeningitis and choroiditis; 3) of the eye, cataracts (bilateral) and a hypoplastic optic nerve (left more severe than the right); 4) of the lung, acute pneumonia (bilateral) and fibrous adhesions of the right lung to the parietal pleura; and 5) of the abdomen, cyst formation connecting to the distal orifice of the ventriculoperitoneal shunt. In this patient, a chromosome analysis confirmed a normal female karyotype 46 XX.

Both temporal bones were obtained 8 hours after death. After fixation in 10% formalin, decalcification in 5% trichloroacetic acid, and dehydration in graded solutions of alcohol, the specimens were embedded in celloidin and sectioned horizontally at 20 μm. Every 10th section was stained with hematoxylin and eosin and examined under a light microscope.

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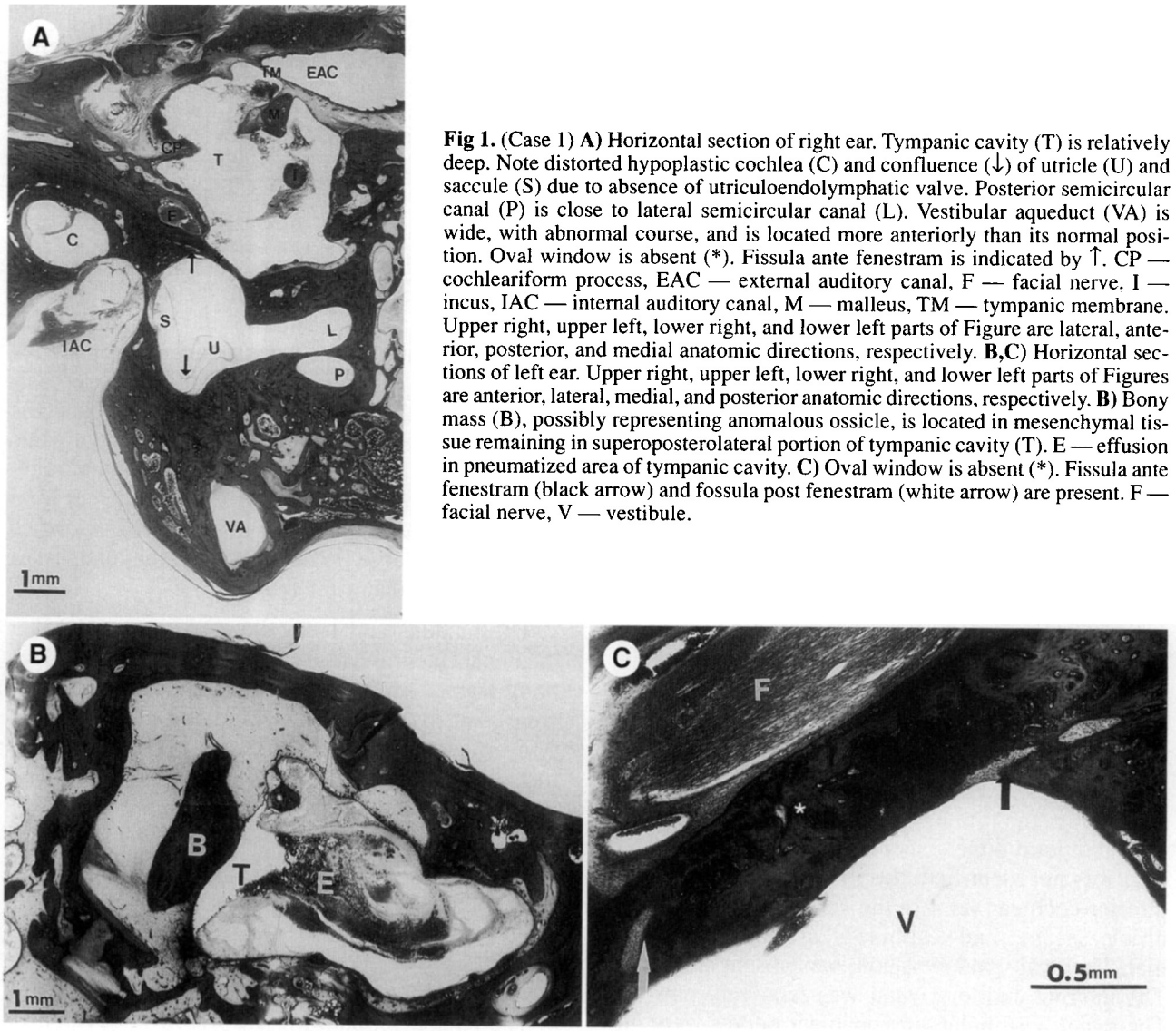

Fig 1. (Case 1) **A)** Horizontal section of right ear. Tympanic cavity (T) is relatively deep. Note distorted hypoplastic cochlea (C) and confluence (↓) of utricle (U) and saccule (S) due to absence of utriculoendolymphatic valve. Posterior semicircular canal (P) is close to lateral semicircular canal (L). Vestibular aqueduct (VA) is wide, with abnormal course, and is located more anteriorly than its normal position. Oval window is absent (*). Fissula ante fenestram is indicated by ↑. CP — cochleariform process, EAC — external auditory canal, F — facial nerve. I — incus, IAC — internal auditory canal, M — malleus, TM — tympanic membrane. Upper right, upper left, lower right, and lower left parts of Figure are lateral, anterior, posterior, and medial anatomic directions, respectively. **B,C)** Horizontal sections of left ear. Upper right, upper left, lower right, and lower left parts of Figures are anterior, lateral, medial, and posterior anatomic directions, respectively. **B)** Bony mass (B), possibly representing anomalous ossicle, is located in mesenchymal tissue remaining in superoposterolateral portion of tympanic cavity (T). E — effusion in pneumatized area of tympanic cavity. **C)** Oval window is absent (*). Fissula ante fenestram (black arrow) and fossula post fenestram (white arrow) are present. F — facial nerve, V — vestibule.

In the right ear, both the external auditory canal and the tympanic membrane appeared to be normal. The tympanic cavity was well pneumatized and relatively deep. An ME effusion with inflammatory cells was present. Submucosal inflammatory cell infiltration was observed in the ME mucosa. A moderate amount of mesenchymal tissue remained, mainly in the epitympanum and antrum. The poorly developed mastoid air cells were filled with effusion and cholesterol granuloma. The malleus had an anomalous manubrium widely attached to the tympanic membrane. The incus was bulky. The stapes was hypoplastic and represented only by its superstructure and was dislocated posteriorly. Both the tensor tympani muscle and the stapedius muscle were present; however, the latter was exposed into the ME cavity through the pyramidal eminence. The facial nerve had an aberrant route, running inferiorly between the round window niche and the sinus tympani. Both the chorda tympani nerve and Jacobson's nerve appeared to be normal. Similarly, the greater superficial petrosal nerve and the lesser superficial petrosal nerve could be identified.

The cochlea was distorted and hypoplastic, with approximately 1 turn (Fig 1A). The organ of Corti appeared to be well developed; however, it was difficult to evaluate further because of the presence of postmortem changes. The cochlear nerve, spiral ganglion cells, and cochlear aqueduct were noted to be within normal limits. In the vestibular system, because of the absence of the utriculoendolymphatic valve, confluence of the utricle and saccule was observed (Fig 1A). The posterior semicircular canal was very close to the nonampullated end of the lateral semicircular canal; otherwise, the semicircular canals were normal. The vestibular end organs, vestibular nerves, and Scarpa's ganglion cells appeared to be well developed and normal. However, the endolymphatic sac and vestibular aqueduct were wide,

with an abnormal route, running more anteromedially than the normal course (Fig 1A). The oval window was absent, and there was no connection between the anomalous stapes and the otic capsule. The round window appeared to be normal. The internal auditory canal was slightly wide. The facial, vestibular, and cochlear nerves all appeared to be within normal limits.

In the left ear, atresia of the external auditory canal was observed. The tympanic membrane was absent. The tympanic cavity was severely distorted and was filled with a large amount of mesenchymal tissue in its epitympanum. The mastoid antrum and air cells were also poorly developed. An effusion and inflammatory cell infiltration were present in the tympanic cavity and mastoid. The ossicles were not identified. Instead, a bony mass was present in the mesenchymal tissue in the superolateral portion of the tympanic cavity (Fig 1B). Neither the tensor tympani muscle nor the stapedius muscle could be identified. The facial nerve had an abnormal route, running more laterally than its normal course. The chorda tympani nerve could not be identified; however, Jacobson's nerve was observed. The greater superficial petrosal nerve and lesser superficial petrosal nerve were also identified and appeared to be within normal limits.

In the IE, the findings were similar to those in the right temporal bone, except that the cochlear aqueduct was not identified, despite the presence of the inferior cochlear vein. In the vestibular system, the utricle, saccule, and vestibule all appeared to be normal. The oval window, again, was absent (Fig 1C). The internal auditory canal was relatively narrow. The facial, vestibular, and cochlear nerves were all within normal limits.

Case 2. A full-term boy, weighing 2,700 g at birth, was delivered by cesarean section to a 33-year-old gravida IV para III mother. His Apgar score was 7, and he died of respiratory distress 2 days after birth. He had multiple anomalies. At the autopsy, the following abnormalities and anomalies were noted: 1) a small and asymmetric face with a cleft lip and microtia with bilateral preauricular ear tags (left side more abnormal than right); 2) of the brain, cerebellar hypoplasia, asymmetric hippocampal hypoplasia, dysgenesis of olfactory bulb and tract; 3) of the vertebrae, cervical and upper thoracic vertebral body hypoplasia; 4) of the limbs, radial aplasia (left) and absent thumb (left); and 5) of the heart, an atrial septal defect, a large ductus arteriosus, a ventricular septal defect, an interrupted aortic arch and aortic stenosis, and a double-outlet right ventricle. In this patient, a chromosome analysis confirmed a normal male karyotype 46 XY.

The left temporal bone with both the ET and its associated structures was obtained 18 hours after death. After being processed by the routine method mentioned above, the specimen was sectioned vertically in a plane perpendicular to the long axis of the ET at 20 μm.[9] Every 20th section was stained with hematoxylin and eosin and examined under a light microscope.

The external auditory canal was narrow and poorly developed. A normal tympanic membrane was not present. The early formation of the tympanic membrane was composed of a dense layer of connective tissue, lined by the medial extension of the epidermal layer of the external auditory meatus and the lateral extension of the mucosal layer of the tympanic cavity (Fig 2A). The poorly developed tympanic cavity was filled with mesenchymal tissue except for a very small space connecting to the tympanic orifice of the ET. A large amount of mesenchymal tissue remained in the antrum and mastoid.

The malleus and incus were so malformed that their exact identification could not be confirmed. Two bony masses presumed to be the malleus and incus were located in the mesenchymal tissue in the epitympanic cavity (Fig 2B). A strand of cartilaginous tissue, running inferomedially from the bony mass presumed to be the deformed body of the incus, was suggestive of the long process of the incus. The stapes was absent. The oval window niche was very narrow and deep; at its most medial extent, a small cartilaginous portion of the otic capsule, which probably was the primitive oval window, was observed (Fig 2C).

The tensor tympani muscle was well developed; however, its tendon was not inserted into the bone presumed to be the malleus. Similarly, the stapedius muscle, without its tendon, could be identified. The facial nerve was located in an inferoanteriorly dislocated position. Although the greater superficial petrosal nerve, the lesser superficial petrosal nerve, and Jacobson's nerve were present, the chorda tympani nerve could not be identified. There were no inflammatory findings within the ME.

Near the pharyngeal orifice of the ET, the lumen was moderately wide and patent. Both the torus tubarius and Rosenmuller's fossa were poorly developed (Fig 2D). In the cartilaginous portion of the ET, the lumen was also wide and open. There were a few ridges of mucosal folds along the floor of the ET lumen. The ET cartilage was anomalous. The lateral lamina (LL) of the ET cartilage was severely undeveloped and almost absent. The medial lamina (ML) of the ET cartilage was dislocated laterally with a counterclockwise rotation, lying between the ET

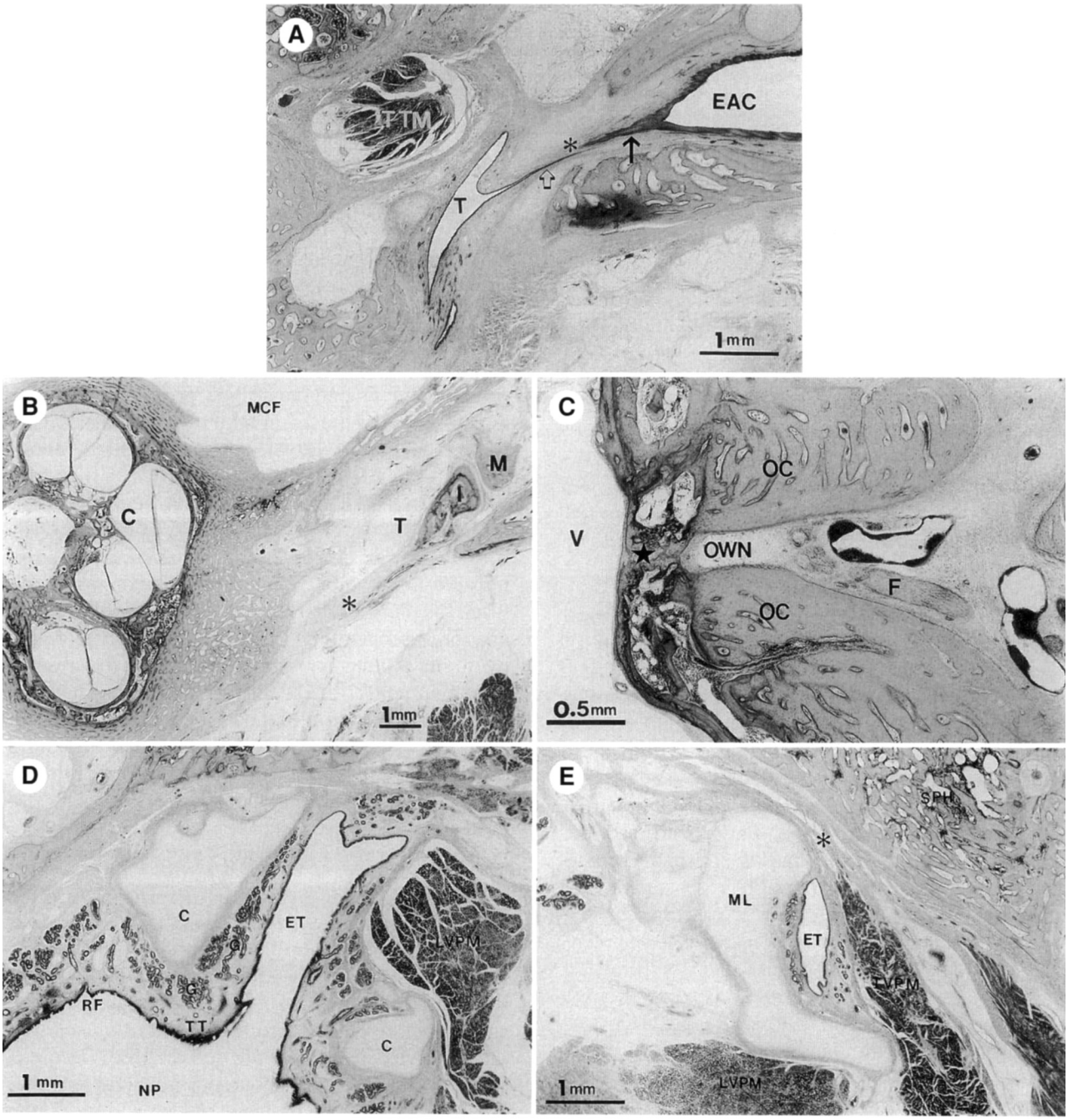

Fig 2. (Case 2) Vertical sections of left ear. Right, left, superior, and inferior parts of Figures are anterolateral, posteromedial, superior, and inferior anatomic directions, respectively. **A)** External auditory canal (EAC) is narrow. Note primordial tympanic membrane (*) and poorly developed tympanic cavity (T). Epidermal layer (black arrow) of EAC and mucosal layer (white arrow) of T start to form primitive tympanic membrane. Tensor tympani muscle (TTM) is well developed. **B)** Two bony masses, presumed to be malleus (M) and incus (I), are observed in mesenchymal tissue in superolateral portion of tympanic cavity (T). Strand of cartilaginous tissue (*), running inferomedially, is probably long process of incus attaching to rudimentary body of incus. Cochlea (C) is normally developed. MCF — middle cranial fossa. **C)** Very narrow, deep oval window niche (OWN) and small amount of cartilaginous tissue (star), which probably is primitive oval window, are observed. Otic capsule (OC) is very thick. F — facial nerve, V — vestibule. **D)** Pharyngeal orifice of eustachian tube (ET) is relatively wide and patent. Torus tubarius (TT) and Rosenmuller's fossa (RF) are poorly developed. C — ET cartilage, G — tubal glands, NP — nasopharynx, LVPM — levator veli palatini muscle. **E)** Midcartilaginous portion of ET demonstrates patent ET lumen, rather than normal slitlike luminal space. Lateral lamina of ET cartilage is absent (*). Medial lamina (ML) of ET cartilage shows its counterclockwise rotation, intervening between ET lumen above and LVPM below. Tensor veli palatini muscle (TVPM) is not attached to ET cartilage. Ostmann's fatty tissue is also undeveloped. SPH — sphenoid bone.

lumen above and the levator veli palatini muscle (LVPM) below (Fig 2E). Attachment of the tensor veli palatini muscle (TVPM) to the ET cartilage was not observed. The ET glands were well developed.

However, Ostmann's fatty tissue was undeveloped. In contrast, the ET lumen was rather narrow, with a slitlike shape in the junctional[10] and bony portions of the ET. As mentioned above, the narrowed ET then communicated with the very small tympanic cavity. There were no inflammatory findings within the ET.

The cochlea was normally developed, with 2 3/4 turns (Fig 2B). The organ of Corti appeared to be well developed; however, it could not be further analyzed because of the presence of postmortem changes. The cochlear aqueduct, cochlear nerve, and spiral ganglion cells all appeared to be normal. The round window was normal. In the vestibular system, the utricle, saccule, vestibule, 3 semicircular canals, endolymphatic sac, and vestibular aqueduct, as well as the vestibular nerves and Scarpa's ganglion cells, were also well developed and normal. The internal auditory canal was slightly shortened and widened. The facial, vestibular, and cochlear nerves were all present and appeared to be normal.

DISCUSSION

Although OAVS is a commonly accepted pathological condition, there remains little agreement in regard to nosology or even minimal diagnostic criteria.[2,3] Moreover, as many other terms, such as hemifacial microsomia, first and second branchial arch syndrome, facio-auriculo-vertebral malformation spectrum, and Goldenhar's syndrome, have been used to describe these congenital anomalies,[3] there is a great deal of confusion regarding this entity. Furthermore, OAVS has heterogeneous causes and pathogenicities.[3] Although the majority of OAVS cases are presumed to occur sporadically,[3,4,6,7] vascular insufficiencies and abnormalities are considered to be potential pathogenic factors that cause this syndrome.[1,11] Oculoauriculovertebral spectrum has a broad range of phenotypic expression.[2,3] Cases do not necessarily manifest all of the major and minor abnormalities. Despite the absence of some features in our cases (vertebral manifestations in case 1 and eye manifestations in case 2), the described findings seem to be compatible with the diagnosis of OAVS.

The abnormal temporal bone findings in these 2 cases can be categorized and summarized as follows. Case 1 showed atresia of the external auditory canal (left ear), distorted ME cavities (both ears), anomalous ossicles (both ears), absence of the stapes (left ear), an abnormal course of the facial nerve (both ears), absence of both the stapedius muscle and the tensor tympani muscle (left ear), absence of the oval window (both ears), hypoplastic cochleas (both ears), anomalously dislocated endolymphatic sacs and vestibular aqueducts (both ears), dislocated posterior semicircular canals (both ears), and otitis media with effusion associated with cholesterol granuloma (both ears).

Case 2 showed a hypoplastic external auditory canal, an undeveloped tympanic membrane, a hypoplastic ME cavity and mastoid, an anomalous malleus and incus, absence of the stapes, an abnormal course of the facial nerve, an anomalous ET, ET cartilage, and TVPM, and absence of the oval window.

This report, to our knowledge, is the first to describe the histopathologic findings of the entire ET and its associated structures in a patient with OAVS. The ET is derived from the expanding terminal end of the endoderm-lined first pharyngeal pouch and probably the second pharyngeal pouch.[12] During the development of the ET in fetal life, the cartilaginous portion of the ET lumen becomes slitlike[13] during the 16th week. The ET cartilage attains its final form with the LL and ML during the 20th week.[14] Accordingly, the maldevelopment of the ET lumen and cartilage observed in case 2 may be explained by an interruption that occurred before the 16th gestational week, because of the presence of an oval ET lumen and the absence of the LL of the ET cartilage. Moreover, since other anomalies, including the absence of attachment of the TVPM to the ET cartilage and an abnormal rotation of the L-shaped ML, were also observed in case 2, we hypothesize that the ET function in this case would be poor. Therefore, if this infant had survived through infancy with the ET structural anomalies described above, he would have likely suffered from otitis media with effusion, as did the patient in case 1.

The ME anomalies described in the present 2 cases were considerably similar to those of previous histopathologic reports.[4,7] Anomalies involving the ME of affected ears in cases of OAVS commonly involve such structures as the ossicles, stapedius muscle, and facial nerve canal. These are derived from the mesoderm of the first and/or second branchial arches.[12] An asymmetric appearance of the ear and face is one of the characteristic symptoms of OAVS. With regard to the ear, it is considered that approximately two thirds of OAVS patients have unilateral microtia.[2] However, in case 1, both the contralateral ear, with a nearly normal appearance of the auricle and external auditory canal, and the affected ear, with prominent, severe anomalies including auricular atresia, had several ME anomalies. Accordingly, our findings suggest that clinicians who care for patients with OAVS should carefully evaluate the contralateral ear, even if it has an almost normal appearance. In addition, since severe anomalies of the oval window and stapes were observed in the present study, it is assumed that patients with OAVS might have signifi-

cant conductive hearing loss. An otologist who is contemplating repair of the ossicular chain should be aware of the profound abnormalities potentially present in patients with OAVS. Thin-cut, bone-windowed CT imaging should be performed.

The IE is derived from the otic placode that invaginates from the surface ectoderm of the embryo in early fetal life.[12] It has been suggested that OAVS is closely related to abnormalities of the first and second branchial arches, since the IE is not necessarily involved. In previous histopathologic reports of OAVS, however, several IE anomalies were presented.[6-8] Furthermore, in our case 1, severe IE anomalies of the Mondini type[15] were observed in both ears. Although the precise pathogenesis of IE involvement in OAVS is not known, we speculate that the severity of the vascular insufficiency, presumed to be a causative factor of OAVS,[1,11] occurs early in fetal development. The IE involvement as manifested by a hypoplastic cochlea (case 1) likely occurs earlier than the 9th gestational week, because the cochlear duct has the full complement of $2^3/_4$ turns by the end of the 8th gestational week.[12]

Otologists should be aware that surgical correction of a conductive hearing loss attributable to anomalies of the ME and/or external auditory meatus in patients with OAVS may be hampered by other congenital anomalies. The potentially aberrant course of the facial nerve must be carefully investigated. Furthermore, Mondini-type IE anomalies may manifest themselves in sensorineural hearing loss and significant abnormalities of the stapes and oval window niche. Careful audiological and imaging studies should be performed to estimate the presence and degree of IE involvement. Severe abnormalities of the ME and otic capsule may warrant consideration of the use of a bone-anchored hearing aid,[16] if an external auditory canal cannot be constructed.

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