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Clinical Records

Temporal bone histopathological findings in campomelic dysplasia

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Abstract
Both temporal bones of a newborn (35 gestational weeks old) with campomelic syndrome were studied histopathologically. This is to our knowledge the second temporal bone report (third case) of this syndrome. The findings included: abnormal cartilagenous and osseous tissues and abnormality in the globuli interossei in the otic capsule; deformities of the vestibule and semicircular canals, probably due to compression by the abnormal cartilaginous tissue; hypoplastic cochlea and semicircular canals; aberrant course of the facial nerve; wide dehiscence of the facial canal in the tympanic portion; slight hypoplasia of the malleus and anomalies in the incus and stapes; and large epitympanic space. These findings closely resembled those of the first report, and suggest that: 1) campomelic dysplasia is a definite disease entity with consistent pathogenesis, and 2) similar otologic manifestations may be expected in the majority of patients with this syndrome.

Introduction

Campomelic dysplasia is a congenital systemic disorder represented by short-limb dwarfism affecting mainly the lower limbs, with anterior bending of the femur and tibia that is probably due to abnormal cartilage development; the disorder appears to be transmitted as an autosomal recessive trait with a recurrence rate of 25 per cent (Bergsma, 1979). This syndrome was first reported by Bound *et al.* (1952), but it did not become broadly recognized until the 1970s when the term 'campomelique', meaning a bent limb, was used to denote this disorder. Several other anomalies are usually present in those campomelic dysplasia including low-set ears, micrognathia, hypertelorism, posterior cleft palate, and sometimes absence of olfactory nerves (Bergsma, 1979). Although death frequently occurs in the neonatal period secondary to respiratory distress due to deformity of the ribs and tracheobronchomalacia (Bergsma, 1979), long-term survival has been reported in several cases (up to 17 years of age) probably as a result of the recent improvements in respiratory care of newborns and infants (Houston *et al.*, 1983). This fact has called for the necessity of further investigation of the pathological features in the otolaryngological field as well for the better patient care.

Regarding the otological manifestations of this syndrome, all four patients who have been reported to survive more than six months were found or suspected to have hearing loss (Houston *et al.*, 1983; Gillerot *et al.*, 1989). Tokita *et al.* (1979) reported finding in two individuals (four ears) with this syndrome the following temporal bone abnormalities: abnormal cartilage cells in the otic capsule (globuli interossei), short and flattened cochlea with scala communis, deformed vestibule and semicircular canals (SCCs), aberrant course of the facial nerve with wide dehiscence of its canal, and anomalous ossicles.

Recently, we had the opportunity to examine histologically both temporal bones of a newborn with this syndrome, and in this paper we report our findings. This report is, to our knowledge, only the second report (third case) of temporal bone histopathological findings in campomelic syndrome.

Case report

Clinical history

A 35-gestational-week-old black female infant weighed 3050 g at birth. Her Apgar scores were 1 and 3, and she died of respiratory distress two days after birth. At the autopsy, the following abnormalities and anomalies were noted:

1. Growth—short body, large head.
2. Skull—mild hydrocephalus, large fontanelles, platybasia.
3. Brain—megaloencephaly; dysmature gyral pattern; short olfactory bulbs; hypoplasia of cerebellum, hippocampus, and choroid plexus.
4. Face—flat, small face with high forehead; anterior frontal unsweep; low-set ears; low nasal bridge; micrognathia.
5. Trunk—hypoplastic scapulae, small thoracic cage.
6. Airway and lungs—tracheobronchomalacia, hypoplastic lungs.
7. Limbs—anterior bowing of tibiae with skin dimpling over convex areas, short fibulae, club feet.
8. Genitalia—hypertrophy of clitoris and labia.
9. Cytogenetics—karyotype 46 XX.

Family history

The patient was born as the third child of a 26-year-old woman, gravida VI who had a history of cocaine abuse. No congenital anomalies had been noted in the patient's mother or the mother's family, or the patient's siblings. Little information was available about the patient's father.

Histopathological methods

Both of the patient's temporal bones were obtained 10 hours after death. After being processed in the routine manner (Sando *et al.*, 1986), the specimens were sectioned horizontally at 30 microns. Every tenth section was stained with haematoxylin and eosin, and examined under a light microscope. To aid our under-

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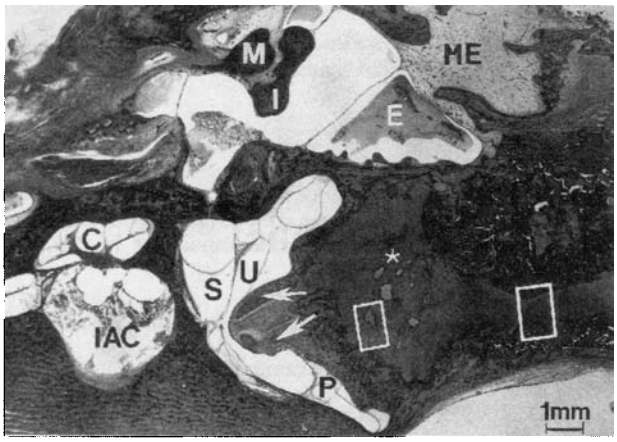

FIG. 1a

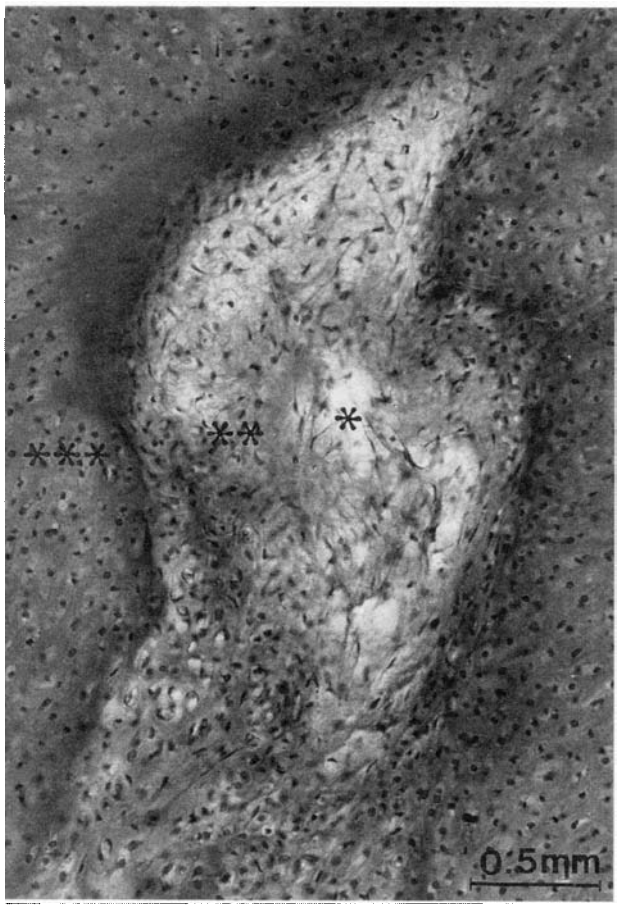

FIG. 1b

standing of spatial relationships of some anomalous structures in the middle and inner ears, these structures were three-dimensionally reconstructed by the computer-aided method we developed (Sando *et al.*, 1989; Takagi and Sando, 1989).

Temporal bone findings

Right temporal bone

In the middle ear, there were several anomalies in the ossicles: the malleus was slightly smaller than usual (6.1 mm in length) in spite of the normal shape; position and shape of the body of the incus were abnormal (Fig. 1a), both the long and short processes of the incus were absent, and the incudostapedial joint was represented only by a fibrous connective tissue band; the stapes was hypoplastic and had only one crus (Fig. 2). The epitympanum and aditus ad antrum were larger than usual. The facial nerve took an aberrant course, making almost a right angle (88.5 degrees) at the first genu as measured by our computer-aided method (Fig. 3). Wide dehiscence of the bony facial canal was observed at the inferior aspect of the tympanic portion. A moderate amount of mesenchymal tissue remained mainly in the epitympanum and antrum, and an effusion with inflammatory cells was observed in the tympanic cavity (Fig. 1a).

In the otic capsule, there were hardly any typical smooth oval cartilage cells; rather, irregularly shaped cells were seen in the intrachondral bone (globuli interossei) in the enchondral layer. In the posterior portion near the SCCs, there was a huge abnormal area of cartilagnous tissue showing various stages of development and ossification; the mesenchymal cells and precartilage cells were present at several foci near the centre while active ossification was notable at the several sites on the posterolateral margin, but on the medial margin, there was no active ossification. The area of cartilage tissue had osseous tissue at its anterior tip (Figs. 1a, b & c).

In the inner ear, the cochlea was flattened and hypoplastic with approximately two turns (a total of 24.2 mm for all cochlear turns) (Fig. 4) in spite of well developed organ of Corti and sufficient number of spiral ganglion cells and nerve fibres (Fig. 1a).

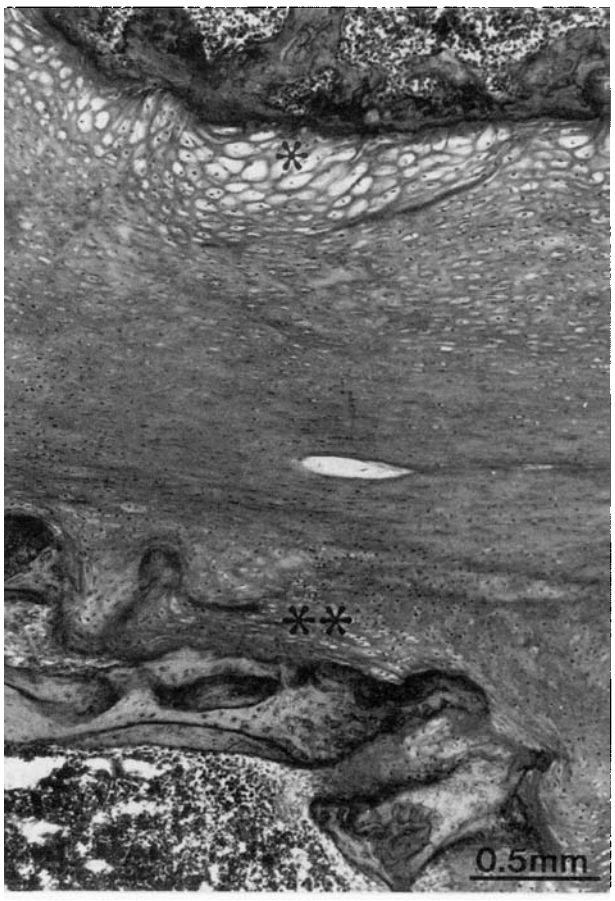

FIG. 1c

FIG. 1

a) Low-power view of right temporal bone of newborn with campomelic dysplasia. Note anomalous shape of incus (I), hypoplastic cochlea (C), and deformed vestibule and posterior semicircular canal (P). White star indicates huge area of cartilaginous tissue, and arrows indicate bony tissue protruding into vestibule. E indicates middle ear effusion; IAC, internal auditory canal; M, malleus; ME, mesenchymal tissue in antrum; S, saccule; and U, utricle. b) high power view of left rectangle outlined in 1a. Mesenchymal cells (*), precartilage cells (**), and mature cartilage cells (***) are evident. c) high-power view of right rectangle outlined in 1a. Active ossification was seen lateral (*) but not medial (**) to cartilaginous tissue.

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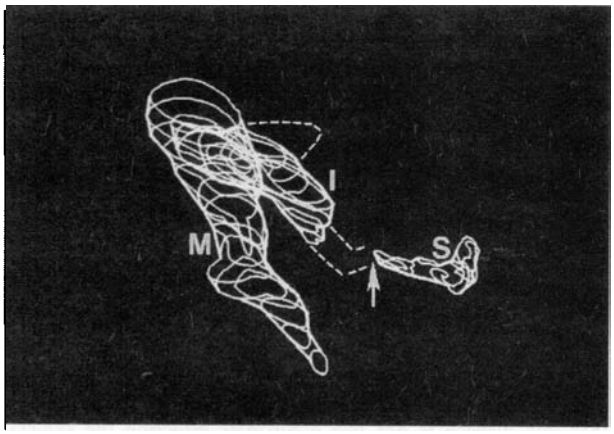

FIG. 2

Reconstructed image of right ossicles viewed from anterior to posterior. Note that both short and long processes of incus (I) are absent (dotted lines), incudostapedial joint (arrow) is also absent, and stapes (S) has only one crus. M indicates malleus.

Bony structures within the cochlea were also hypoplastic, the interscalar ossei was absent between the posterior part of the basal and second turn, the wall between Rosenthal's canal and the scala tympani was very thin at the second turn, and the cribriform plate at the basal turn was absent (Fig. 1a). Although the utricular and saccular maculae and their nerves were normal, the vestibule was severely deformed by bony tissue at the tip of the area of cartilaginous tissue that protruded from the posterior direction (Fig. 1a). The saccule was slightly collapsed. Although their cristae and nerve fibres were intact, all the SCCs were hypoplastic. The SCCs were also deformed, probably by the same osseous and/or cartilaginous tissue that deformed the vestibule. The deformity was particularly remarkable in the anterior and lateral SCCs, the anterior SCC was distorted and tilted posteriorly (Fig. 4), and its non-ampullated portion was extremely thin and was partially displaced to lie in the subdural space of the posterior fossa (Figs. 3 & 5); the non-ampullated end of the lateral SCC was also very thin and dislocated inferiorly (Fig. 4).

Left temporal bone

Findings were similar to those in the right temporal bone, except that: the endolymphatic space was collapsed in the cochlea as well as in the saccule, and the cochlear aqueduct was slightly smaller than usual on this side. The facial nerve also had an aberrant course, but the angle of the first genu was wider (103 degrees) than in the right side.

Discussion

Abnormal temporal bone findings in this case can be categorized and summarized as follows:

1. Abnormal cartilaginous and osseous tissue and abnormal globuli interossei in the otic capsule.
2. Hypoplastic and/or deformed cochlea, vestibule, and SCCs.
3. Hypoplastic and anomalous facial nerve, facial canal, and ossicles.
4. Large epitympanic space.
5. Otitis media with effusion.

What should be emphasized first is that these findings are strikingly similar to those in the only previous temporal bone histopathological report of this syndrome (Tokita *et al.*, 1979). The only differences are the paucity of spiral ganglion cells and an anomaly in the pyramidal eminence and stapedial tendon in the previously reported case but not in ours. The consistency in these histopathological findings leads us to two speculations: 1) campomelic dysplasia is a definite disease entity with quite consistent pathogenesis, and 2) we may expect to see quite similar otological manifestations in the majority of patients with this disease. For instance; we may expect mixed-type hearing loss in patients with this syndrome; the conductive component would be due to anomalies of the ossicles and to frequent otitis media, to which patients with this syndrome are quite susceptible because they have frequent upper respiratory infections (Houston *et al.*, 1983; Gillerot *et al.*, 1989) and often have a cleft palate, and the sensorineural component would be due to hypoplasia of the cochlea. Discrepancy in the spiral ganglion cell population between our case and those reported by Tokita *et al.* (1979) indicates that the severity of the sensorineural component may vary from individual to individual, but it should be kept in mind when examining for and managing the hearing loss in patients with this syndrome.

The most mysterious findings in the case we report are the huge area of cartilaginous and osseous tissue and the deformed vestibule and SCCs. Because peri- and endolymphatic structures in the vestibule and SCCs were completely developed, the deformation of the vestibule and SCCs may have occurred as a result of compression by the abnormal proliferation of cartilaginous and osseous tissue after formation of the endo- and perilymphatic spaces, which usually are completed by about the 17th

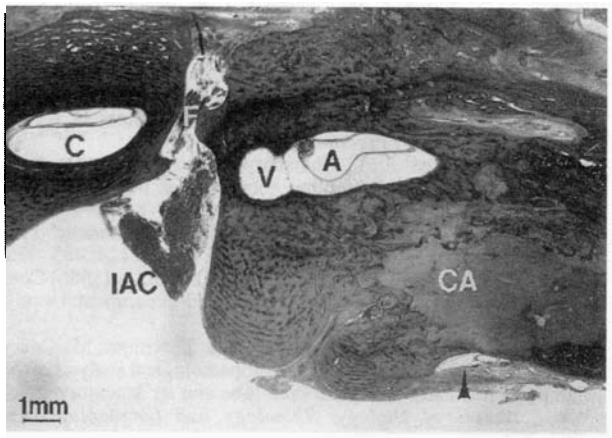

FIG. 3

Low-power view of upper part of right temporal bone. Note that ampullated end of anterior semicircular canal (A) is tilted posteriorly and non-ampullated portion of anterior semicircular canal (arrowhead) is deformed and displaced into subdural space of posterior fossa. C indicates cochlea; CA, huge area of cartilaginous tissue; F, facial nerve; IAC, internal auditory canal; and V, vestibule.

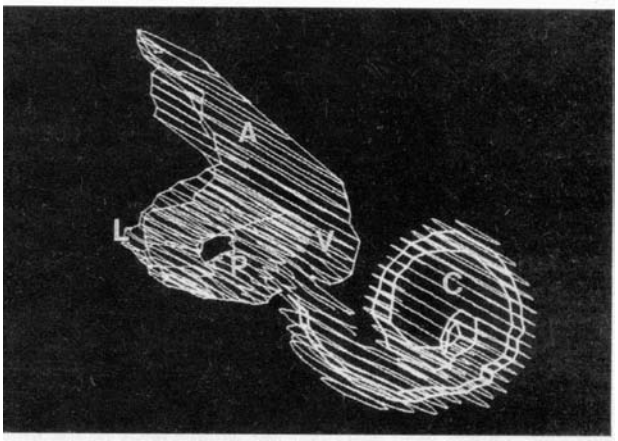

FIG. 4

Anterolateral view of reconstructed image of right bony labyrinth, with image of basilar membrane (thicker solid lines) superimposed. Note that cochlea (C) has only two turns, and posterior semicircular canal (P) is hypoplastic. Lateral semicircular canal (L) is not only hypoplastic but also distorted. A indicates anterior semicircular canal; and V, vestibule.

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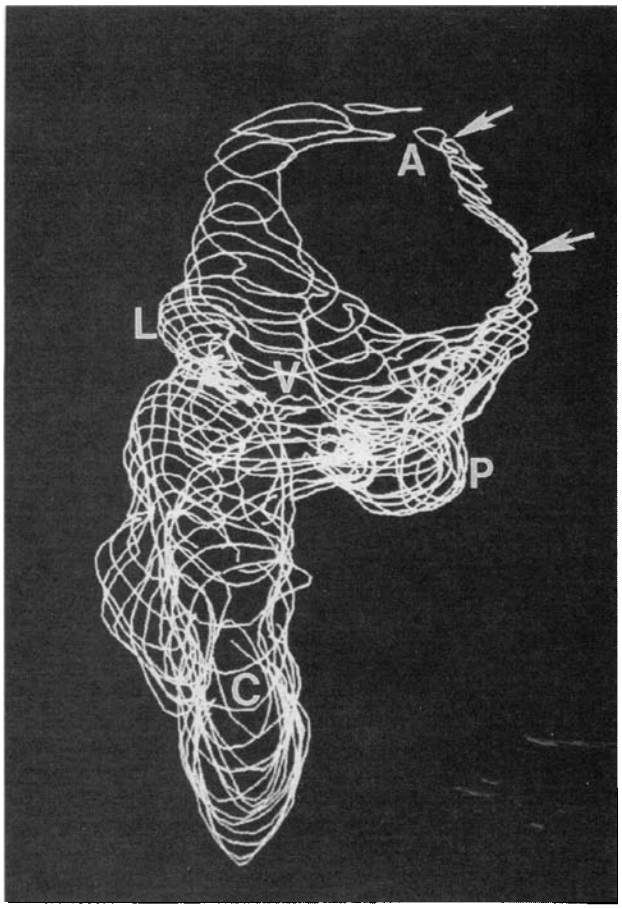

FIG. 5

Reconstructed image of right bony labyrinth viewed from anteromedial and slightly superior direction. Cochlea (C) is flattened. Non-ampullated portion of anterior semicircular canal (A) is thin, and part of canal between arrows lies outside temporal bone. L indicates lateral semicircular canal ampulla; P, posterior semicircular canal ampulla; and V, vestibule.

gestational week (GW) (Williams, 1990). We also speculate, because of its location near tissues usually ossified last in the fetal development (Anson and Donaldson, 1981), that the abnormal area of cartilaginous and osseous tissues might be a remnant of otic capsule cartilage that failed to ossify.

These abnormal cartilaginous and osseous tissues and abnormal globuli interossei in the otic capsule point to disorganization in the development of the otic capsule in this case. Evidence of such disorganization is that active ossification was occurring only at the lateral margin while mesenchymal cells and precartilage cells were still present at the centre of the area of cartilaginous tissue in the ears we studied. The non-uniformity of ossification in this cartilaginous tissue may indicate that active ossification had already occurred at the medial or anterior margin of the cartilaginous tissue and was related to the deformity of the vestibule and SCCs. Futhermore, the non-ampullated portion of the anterior SCC was dislocated to the subdural space of the posterior fossa; this cannot be the result solely of compression by the abnormal area of cartilaginous tissue, and may represent another aspect of abnormal development of the otic capsule in this case. Others have described the pathogenesis of the long bone deformity seen in the disease (Bain and Barrett, 1959; Lee *et al.*, 1972; Hwang, 1979; Tokita *et al.*, 1979; Nogami *et al.*, 1986; Lazjuk *et al.*, 1987) as being related to the cartilaginous phase of the development of the bone, and the abnormal cartilaginous tissue in the otic capsule in the case we report supports this hypothesis.

It is difficult to predict what kind of dysfunction they might show caused by hypoplasia of the SCCs or deformity of the vestibule and/or SCCs, because symptoms of vestibular dysfunction can usually be compensated for by brain stem or cerebellar system. If the abnormal cartilaginous and osseous tissues in this patient's ears continued to proliferate after birth, endorgans in the vestibule or SCCs might have been destroyed by progressive compression, and this destruction might have been accompanied by sudden transient vestibular symptoms.

Williams (1990) reported that in normal prenatal development the full 2½ turns of the cochlea have developed by about the VIIIth gestational week. The disturbance in development of the cochlea in this case shows that the effects of campomelic dysplasia occur early in gestation. Further, all the structures in the middle ear that showed anomalies except the small-sized malleus and large epitympanum were of second branchial arch origin. These malformations in the middle and inner ears indicate that this disease is not just a disorder affecting the skeletal system but a syndrome of multiple congenital anomalies.

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