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Clinical, pathological, and genetic evaluations of Chinese patient with otodental syndrome and multiple complex odontoma

Case report

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Abstract

Otodental syndrome is a rare autosomal-dominant disease characterized by globodontia, associated with sensorineural, high-frequency hearing loss. Here, we describe the clinical, pathological, and genetic evaluations of a 9-year-old girl with otodental syndrome and multiple complex odontoma.

The patient presented with a draining sinus tract in her left cheek, globodontia, and hearing loss. The odontomas which caused the cutaneous sinus tracts were extracted because of the odontogenic infection. The extracted odontoma and primary tooth was studied by micro-CT and further observed histopathologically. The micro-CT findings revealed that the primary tooth had three crowns with two separated pulp chambers, and their root canals were partially fused. The histological findings showed abnormal morphologies of odontoblasts and dentin, hyperplasia of enamel, and malformation of odontogenic epithelium. Furthermore, DNA sequencing and analyze of deafness associated gene GJB2, GJB3, and PDS had not revealed any SNP or mutation; but exon 3 of the causative gene FGF3 could not be amplified, which may be associated with the microdeletion at chromosome 11q13.3. Three month after surgery, the patient was found to be asymptomatic and even the evidence of the extra-oral sinus had disappeared.

The dental abnormality of otodental syndrome included congenital missing teeth, globodontia, and multiple complex odontoma. Globodontia exhibited characteristic features of fusion teeth. In addition, gene FGF3 haploinsufficiency was likely to be the cause of otodental syndrome. The report provides some new information in the field of otodental syndrome, which would make dentists more familiar with this disease.

Abbreviations: FGF3 = fibroblast growth factor 3, GJB2 = gap junction protein beta 2, GJB3 = gap junction protein beta 3, micro-CT = micro-computed tomography, PDS = Pendred syndrome gene, solute carrier family 26 member 4(SLC26A4), SNP = single nucleotide polymorphism.

Keywords: complex odontoma, cutaneous sinus tracts, globodontia, otodental syndrome

1. Introduction

Otodental syndrome is a rare autosomal dominant disease characterized by generalized posterior teeth enlargement and sensorineural, high-frequency hearing loss.[1–3] The condition has also been reported with various names, including otodental dysplasia[4] and oculo-oto-dental (OOD) syndrome.[5] Denes and Csiba[6] first described a case of otodental syndrome in 1969. In 1976, Witkop et al[7] named the typical abnormal tooth morphology as globodontia and proposed the concept of otodental syndrome. The dental phenotype of globodontia in

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AL and MWu contributed equally to this study.

Authorship—conceived and designed the experiments: KX and KW. Performed the experiments: AL, MW, XG, HG, LZ. Analyzed the data: AL, KX. Contributed reagents/materials/ analysis tools: KX and KW. Wrote the paper: AL, MW, ZZ, and KX.

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otodental syndrome affects both primary and permanent dentition and is the typical manifestation for the disease. Patients with globodontia generally presents enlarged canines and molars with globe-shaped crowns. However, no deterioration of incisors has been reported for this disease so far.[2]

Otologic symptom is the sensorineural hearing loss for frequencies above 1000 Hz. The hearing impairment always presents bilaterally, and the hearing loss would progress from early childhood even to the fourth decade correlating with retardation in speech development.[3] Beside dental and otologic changes, in 2002, Vieira et al[5] first described ocular abnormalities including transillumination defects in the inferior iris, chorioretinalcoloboma, microcornea, microphthalmos, lens opacity, and lens coloboma. However, patients that exhibited ocular coloboma was diagnosed as a different condition; because none of the reported case presented the same ocular trait.[8]

Human genomic loci associated with otodental syndrome have been localized to chromosomes 20q13.1[5] and 11q13.[9] Previous studies have shown that fibroblast growth factor 3 (FGF3) haploinsufficiency was likely to be the cause of dental and inner-ear diseases,[9] whereas Fas associated via death (FADD)[9] and EYA transcriptional coactivator and phosphatase 2 (EYA2)[5] may be the cause of ocular coloboma.

Odontoma is the most commonly seen odontogenic tumors in clinic which is composed of odontogenic epithelium and ectomesenchyme with dental hard tissue formation.[10] Although scholars considered odontoma as a tumor-like developmental malformation of dental hard tissues[11]; the World Health Organization classifies it as a benign odontogenic tumor. In most cases, odontoma is diagnosed in the first 2 decades of life, and there is a female predilection.[12,13] Histologically, odontoma is divided into 2 types: compound odontoma and complex odontoma. There were also mixed forms as reported previously. Compound odontoma is made up of tooth-like structures with typical normal arrangement patterns. However, complex odontoma lacks tooth-like structures, consisting of unorganized masses of dentin, enamel, odontogenic epithelium, and enamel matrix.[14]

This report describes the case of a Chinese patient with otodental syndrome and multiple complex odontoma. To our knowledge, this is the first study reporting the abnormal morphological and histological manifestations of affected teeth in otodental syndrome.

2. Case presentation

A 9-year-old Chinese girl was referred to our hospital. The patient's chief complaint was the pain of the posterior part of left mandibular and found a nodule with pus discharge 1 month before her visit. The patient was in a normal growth status without short height and developmental malformation. The parents of the patient were informed of the objectives of this research, and written informed consent was obtained prior to conducting the study. The study was approved by the Ethical Committee of the School of Stomatology, Fourth Military Medical University.

Physical examination revealed a nodule with pus discharge and swelling under the left of the chin. Gentle pressure on the surrounding tissue elicited thick purulent drainage from the central punctum (Fig. 1A). Intraoral examination (Fig. 1B–D) revealed the red and swollen alveolar mucosa in the primary left mandibular second molar (#75) region was obvious and the tooth was only partially erupted. What was more serious was that all teeth in the mixed dentition exhibited abnormal shape except the disorderly aligned bilateral permanent incisors both in maxillary and mandibular. The crowns of the primary canines and the

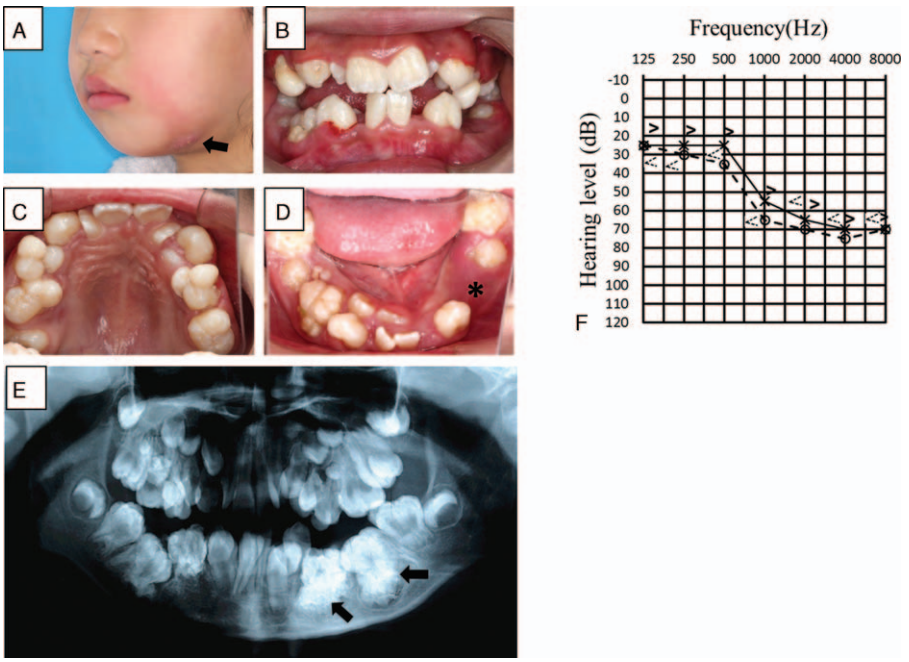

Figure 1. Otodental syndrome with complex odontomas. (A) Preoperative extraoral appearance of a nodule with pus discharge and swelling under the left of the chin. (B–D) Intraoral views showing abnormal primary canines and molars. The laterals incisors were lingually positioned with normal shape. The red and swollen alveolar mucosa in the tooth #75 region (indicated by asterisk). (E) Panoramic radiograph showing the absence of mandibular permanent premolars and complex odontomas (indicated by arrow). (F) Pure tone thresholds. Air conduction demonstrating high-frequency hearing loss (normal auditory thresholds: 25 dB; X, left ear; O, right ear). Bone conduction thresholds (>, left ear; <, right ear).

primary maxillary first molars (#54 and 64) were enlarged, bulbous, and malformed with 2 or 3 cusps, which looked like either fusion or germination. Furthermore, the tooth #64 had level III mobility with no positive signs under percussion or palpation. The primary maxillary second molar (#55 and 65) and the primary right mandibular first molar (#84) were similarly enlarged with developmental grooves existed dividing the crowns into different sizes of lobules. In addition, there were some small tooth-like structures around the #84. The first permanent molars lacked clearly recognized cusps, resembling the tied end of a sausage. The teeth #75 and 85 were only partially erupted. According to her guardians, the patient's incisors had started to erupt in her 4-year-old age and had never been replaced, which indicated that the patient's primary incisors were congenitally absent. Her parents also confirmed that the eruption of her primary dentition was delayed compared with normal children.

The panoramic radiograph (Fig. 1E) revealed tooth-like radiopaque masses surrounded by a large radiolucent zone with a well-defined margin in the molar area of left mandibular. Radiopaque masses in the bilateral primary mandibular molar region appeared to be 4 odontoma and the germs of bilateral permanent mandibular premolars were absent. Radiologic and clinical findings were mostly consistent with a diagnosis of pericoronitis causing cutaneous sinus tracts in the left mandibular premolar region. Besides, radiographic analysis of the abnormal molars showed taurodontism changes with larger pulp chambers, some of which were duplicated, and the root length was short compared with crown height; some were taurodont in configuration. The spiral CT images (Fig. 2A) of both jaws were reconstructed and the craniofacial skeletons were normal.

According to the otolaryngologic examination, the patient had distinct bilateral sensorineural hearing loss of acuity to frequencies above 1000 Hz. Her threshold was normal at low frequencies but obviously drop up to 75 dB at higher frequencies (Fig. 1F). The otolaryngologic examination confirmed her auditory structures, temporal bone, and ethmoid air cells were normal. Based on the typical dental phenotype and bilateral sensorineural, high-frequency hearing loss, the patient was clinically diagnosed as the otodental syndrome. The patient's parents were healthy and had no similar clinical signs, and neither radiographic examinations nor laboratory assays revealed any defects.

Tooth #64 and the tooth-like radiopaque mass in the #75 region were removed during surgery. Tooth #64 fused with abnormal morphology of 3 crowns and roots (Figs. 2B and C). During surgery, 2 teeth were found in the left mandibular region; one was globodontia with an enlarged crown, large pulp chamber, short roots, and pulp stones (Fig. 2D and E). The other was a tooth-like structure surrounded by a fibrous capsule like granulation tissues in the chronic inflammation condition (Fig. 2D and F).

We further used micro-computed tomography (micro-CT) to detect the inner structure of extracted #64; the findings showed the fusion of dentin and enamel defect in the grooves of cusps (Fig. 3A). The major root canal system was completely fused with 2 supernumerary components, and other components were incomplete, sharing part of the root canals with them (Fig. 3B). Cross-sectional images showed that the thickness of enamel was obviously increased (Fig. 3C), and there existed pulp stones in the root canals (Fig. 3D). In the fused regions, part of enamel invaginated into the dentin and irregular calcification could be observed (Fig. 3D).

The histologic staining of tooth #64 showed that the dentin was fused with 3 tooth-like structures and several pulp stones were existed. Moreover, we found that the necrotic tissue existed in a pulp cavity which was independent of the major root canal system. In addition, the morphology of odontoblast was in a high columnar shape with massive vacuolated changes (Fig. 4A–C). To our knowledge, this report was the first case of abnormal dentine–pulp complex of globodontia.

Microscopically, the tumor showed irregularly arranged dentin-like hard tissues with odontogenic epithelium, enamel matrix (Fig. 4D and E). At the periphery area, a dental follicle originated capsule could be found. The diagnosis of a complex odontoma was confirmed.

One month after surgery, there was a sign of healing of the extra oral lesion and in the follow-up appointment in the 3 month, the patient was found to be asymptomatic and even the

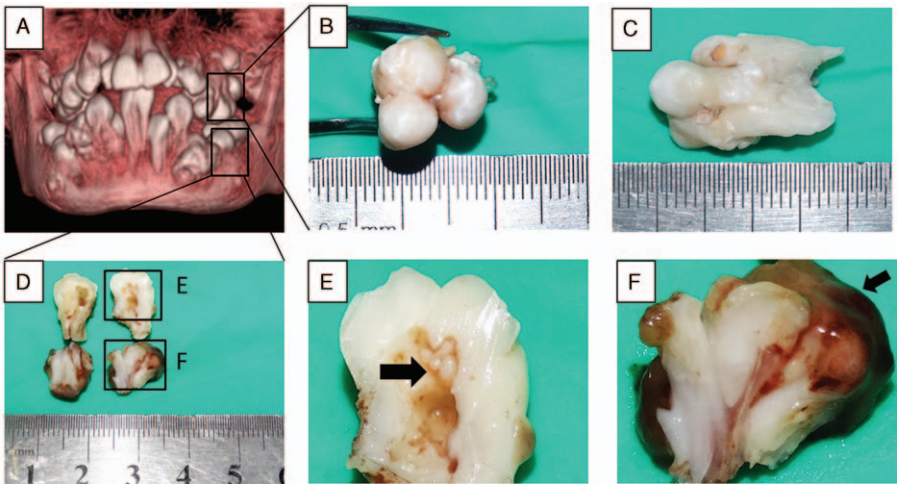

Figure 2. Extracted left primary maxillary first molar (#64) and complex odontomas in the left mandibular region. (A) The spiral CT images of both jaws were reconstructed. (B, C) Three crowns were fused with abnormal morphology and fused roots of #64. (D) Surgically extracted odontomas. (E) One of them had enlarged crown, large pulp chamber, short roots, and pulp stones (indicated by arrow). (E) Complex odontoma with fibrous capsule (indicated by arrow). CT = computed tomography.

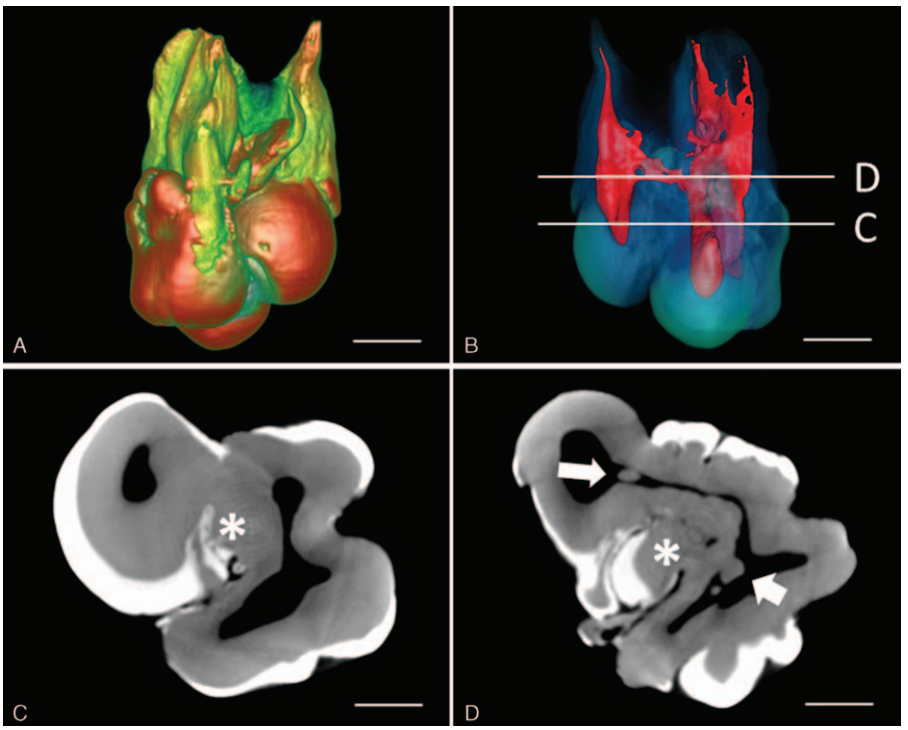

Figure 3. Micro-CT analysis of tooth #64. (A) 3D images of micro-CT for tooth #64 showing the enamel defect (red, enamel; green, dentin and cementum). (B) 3D images of micro-CT for the root canal system showing the fused canals. (C, D) The cross-sectional images showing the fused canals and irregular calcification tissues (indicated by asterisk), and pulp stones (indicated by arrow). (A–D) bar = 20 mm. micro-CT = micro-computed tomography.

evidence of the extra-oral sinus had disappeared (Fig. 5A). Intraoral examination (Fig. 5B–D) revealed the red and swollen fast wane in the #75 region and the tooth was partially erupted in the #74 region. The panoramic radiograph (Fig. 5E) showed that the tooth-like radiopaque masses were totally removed.

To further explore the causative gene, the genomic DNA was obtained from all members of the family and healthy individuals. However, DNA sequencing and analysis of deaf genes gap junction protein beta 2 (GJB2), gap junction protein beta 3 (GJB3), solute carrier family 26 member 4(PDS, or SLC26A4) had not revealed any mutation or single nucleotide polymorphism (SNP). Moreover, 3 exons of FGF3 were PCR amplified with the use of primer pairs, as previously reported.[9] The exon3 of causative gene FGF3 could be amplified in the unaffected family members and unrelated control individual but not in the affected patient. Furthermore, we amplified and screened the other exons of FGF3 gene of the patient and found no mutations in coding regions by DNA sequencing analyses. The results of our limited genetic examinations indicated that the microdeletion of FGF3 Gene at chromosome 11q13.3 could exist. Further genetic studies should be performed to assess the abnormal variant of FGF3 gene.

3. Discussion

Otodental syndrome is characterized by globodontia and sensorineural, high-frequency hearing loss.[1] It is a rare autosomal dominant condition. Up till now, only few cases from different families have been reported.[15] The typical phenotype of dental abnormality is the generously enlarged posterior teeth naming globodontia, which could be observed both in primary and permanent dentitions. Hearing loss of high-frequency is the other abnormality which would usually be found in the early age patients.[16]

According to the guardians of patient in this case, the patient's bilateral permanent mandibular central incisors had started to erupt until 4 years of age. Her primary teeth started to exfoliate from 9 years old. Clinical findings showed that although the bilateral central and lateral incisors both in the maxillary and mandibular were severely displaced, they were in normal size and morphology. The bilateral primary maxillary and mandibular central and lateral incisors were all congenitally missed in this case. It might be a new clinical feature of otodental syndrome.

Odontoma is the most common seen odontogenic tumor. They occur mainly in children and young adults, especially during their second decade of life.[17] Histologically, compound odontoma which usually forms in the anterior part of the jaws and may give rise to painless swellings consists of many separated small tooth-like structures. Complex odontoma tends to occur in the posterior part of the jaws and consists of disorganized masses of hard and soft dental tissues with no morphological resemblance to a normal tooth.[18] The World Health Organization classifies odontoma which is composed of odontogenic epithelium and odontogenic ectomesenchyme with dental hard-tissue formation as a benign odontogenic tumor.[10] The odontoma often be found when existing impaction of the permanent teeth with or without persistence of the primary teeth. Less frequently, symptomless swelling or accidental radiographic finding could also be the cause of discovering the odontoma.[19] Many studies have reported that odontomas are generally asymptomatic. However, there were approximately 9% of the chief complaints were pain.[18] In the present case, the odontomas

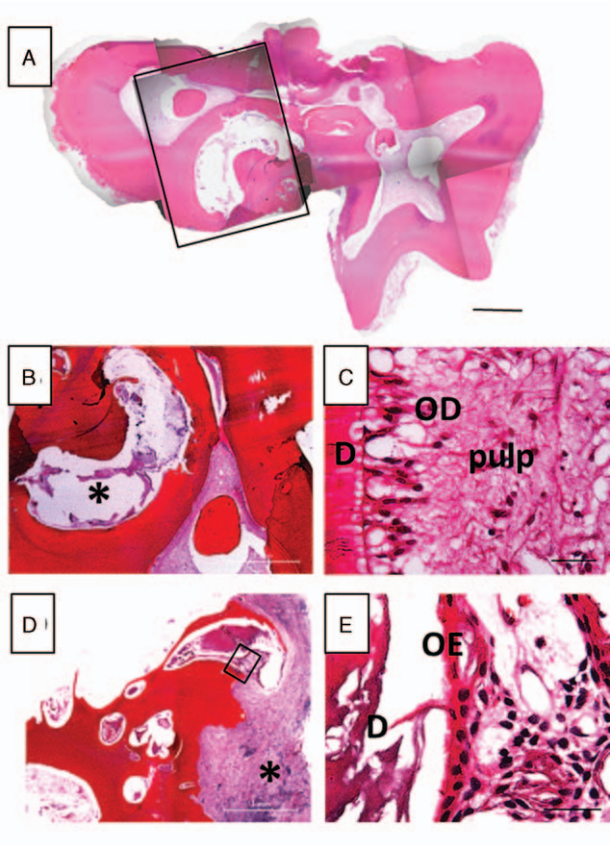

Figure 4. Histological staining images of tooth #64 and complex odontomas. (A) Whole view of tooth #64. (B) Magnification of the boxed area of (A). Necrotic tissue was indicated by an asterisk. (C) Tooth #64 showing vacuolus degenerative changes and increased dimension of odontoblasts (OD). (D) The complex odontomas exhibiting disorganized masses of hard and soft dental tissues; moreover, the tooth was surrounded by fibrous capsule (indicated by an asterisk). (E) Magnification of the boxed area of (D). The complex odontomas exhibiting dentin (D), odontogenic epithelium (OE), and empty spaces with dissolved enamel as a result of demineralization. (A) bar = 20 mm. (B, C) bar = 1 mm. (D, E) bar = 25 μm. OD = odontoblasts, OE = odontogenic epithelium.

were the cause of the pain and the cutaneous sinus tracts. After surgical removal of the odontomas in 75 region, the cutaneous sinus tracts had healed in 3 months.

The tooth-like structures in the left mandibular region of the patient in this case showed an irregular calcified masses with high radiodensity which were surrounded by a large radiolucent zone with a well-defined margin. After surgically removing of the lesion, the histopathologic study which confirmed the diagnosis of complex odontoma by observing the odontogenic epithelium and disorganized enamel and dentin was performed later on. The panoramic radiograph indicated that the mandibular premolars were absent, and complex odontomas were found in the mandible bilaterally. Although Beck-Mannagetta et al[20] reported odontoma found in an otodental syndrome patient in 1984, to our knowledge, this report was the first case of an Asian to have both odontoma and globodontia.

With the development of imaging examination technology, micro-CT as a noninvasive method has been widely used to investigate tooth morphology because of its ideal 3-dimensional view. In this current study, the 3D models were used to identify the root canal system of globodontia for the first time and we found that globodontia exhibited characteristic features of fusion teeth.

Fusion is commonly identified as the union of 2 separated tooth buds, which could occurs in any stage of the dental development. They are usually fused by the dentine and have separate pulp chambers. The incidence of fused teeth in the primary dentition is approximately 1% and predominantly occurs in the anterior region.[21] Tooth #64 in this case appeared to fuse with 2 supernumerary components showing 3 crowns and roots. It indicated that the cause of the abnormal morphology may occur during the early period of tooth development, because of the fusion of multiple tooth buds. Previous study[16] suggested that genes that were related with tooth development such as bone morphogenetic protein 4 (BMP4), muscle segment homeobox 1 (MSX1), distal-less homeobox 1 and 2 (DLX1 and DLX2), and FGF3) could play certain roles in the syndrome. However, after gene sequencing of the patients with otodental syndrome in this study, none of these genes revealed any mutation or SNP.

As for the abnormal taurodontism like molars, Levin et al[22] hypothesizes that the formation may come from the degenerative odontoblast fails to induce Hertwig's epithelial root sheath to form the normal roots. According to the images of odontomas like changes and the micro-CT results of tooth #64, several pulp stones were found in the pulp chambers and root canals. Pulp stones were often associated with dystrophic calcification and have been noted in patients with systemic or genetic diseases such as dentine dysplasia, dentinogenesis imperfecta, and certain syndromes such as Van der Woude syndrome.[23,24] Furthermore, taking the high columnar odontoblasts with vacuolar degeneration into consideration, the existed pulp stones might be associated with dysplasia of pulp. It is well known that odontoblasts which are derived from neural crest cells play an important role in the dentin and ectomesenchymal tissue formation[25]; hence, the abnormal odontoblasts may be the direct cause of the pathological dental phenotype.

The otodental syndrome is found to be mapped in 11q13, implying that haploinsufficiency of FGF3 could be the cause of the globodontia and hearing impairment.[9] FGF3 has been proved to be a key signaling pathway in inducing otic placode formation.[26,27] In the mean time, FGF3 is also a key signaling pathway in tooth formation by giving rise to new cusps and interconnecting cusps by new crests.[26,28,29] In our study, DNA sequencing and analysis of deafness-related genes GJB2, GJB3, and PDS did not reveal any mutation or SNP. But the otodental syndrome causative gene, FGF3, failed in gene amplification, which indicated that the cause of this disease may be associated with the microdeletion at chromosome 11q13.3.

The management of the otodental syndrome would be challenging. An interdisciplinary method combining scheduled tooth extraction, orthodontic treatment, and prosthetic treatment is recommended. The otolaryngologic examinations are also necessary, along with any needed treatment if necessary. According to the otolaryngologic examination, our patient had a distinct bilateral sensorineural hearing loss of acuity to frequencies above 1000 Hz. Sensorineural hearing loss is commonly seen in clinic. Without early detection and appropriate intervention, it may cause progressive hearing loss and speech development retardation together with relevant emotional, psychological, and social communication problems in children. Increased awareness among physicians of this systemic disease is important because early diagnosis and treatment can improve the clinical prognosis of patients.

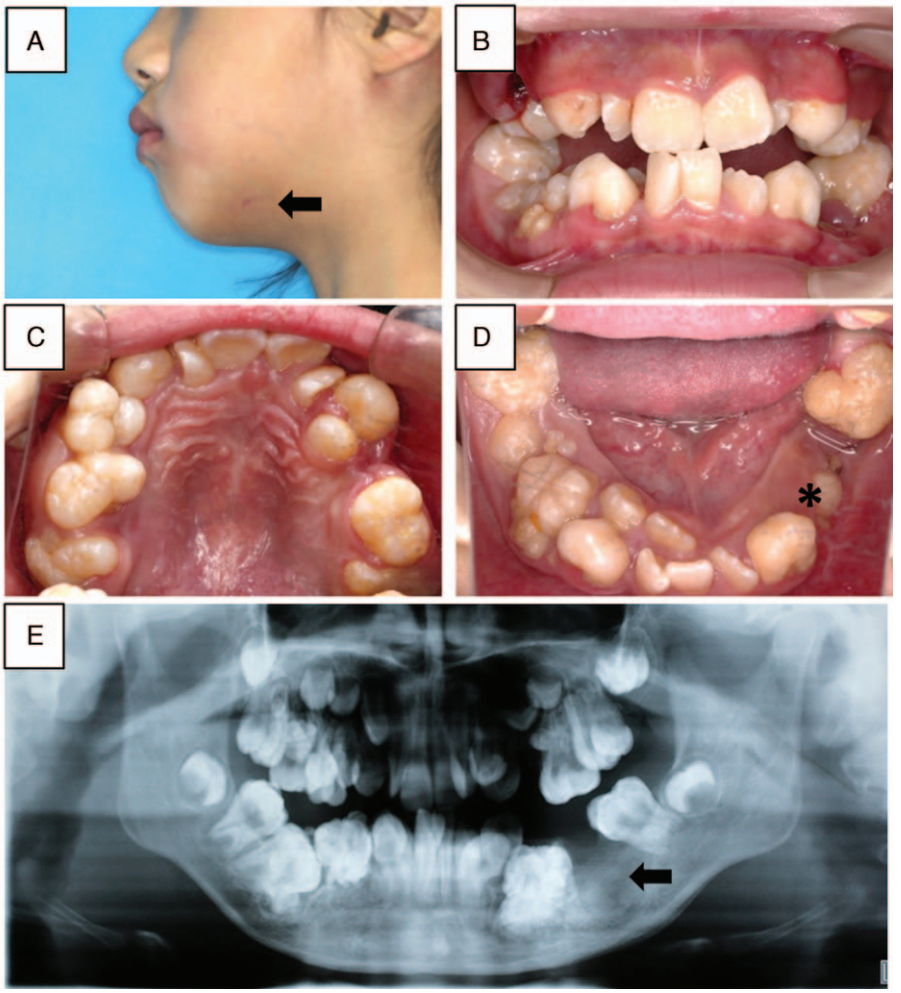

Figure 5. Postoperative appearance 3 months later after the removed the tooth-like radiopaque mass in the #75 region. (A) Postoperative appearance showing complete healing of the abscess with slightly hyperpigmented region (indicated by the arrow). (B–D) Intraoral views showing the red and swollen fast wane in the tooth #75 region (indicated by an asterisk). (D) The panoramic radiograph. (E) shows that the tooth-like radiopaque masses were totally removed (indicated by the arrow).

In the current study, the dental phenotype of the patient with otodental syndrome included missing teeth, globodontia, and multiple complex odontomas. For the first time, the abnormal arrangement of the dentine–pulp complex and the deformation of enamel were found. Furthermore, the 3D model was used first helping to identify the anatomy of the root canal system of globodontia. Authors also reported the absence of primary incisors as a new phenotype for this condition. Finally, Gene FGF3 haploinsufficiency was likely to be the cause of otodental syndrome, but the association requires further study.

4. Conclusions

In the current study, the dental phenotype of the patient with otodental syndrome included missing teeth, globodontia, and multiple complex odontomas. For the first time, the abnormal arrangement of the dentine–pulp complex and the deformation of enamel were found. Furthermore, the 3D model was used first helping to identify the anatomy of the root canal system of globodontia. Authors also reported the absence of primary incisors as a new phenotype for this condition. Finally, Gene FGF3 haploinsufficiency was likely to be the cause of otodental syndrome, but the association requires a further study.

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