A new type of dental anomaly: molar-incisor malformation (MIM)

Hyo-Seol Lee, DDS, MSD,[a,*] Soo-Hyun Kim, DDS,[a,*] Seong-Oh Kim, DDS, PhD,[a,b] Jae-Ho Lee, DDS, PhD,[a,b] Hyung-Jun Choi, DDS, PhD,[a,b] Han-Sung Jung, PhD,[c] and Je Seon Song, DDS, PhD[a,b]
Yonsei University, Seoul, South Korea

A molar-incisor malformation (MIM) is a newly discovered type of dental anomaly of the permanent first molars, deciduous second molars, and permanent maxillary central incisors. MIM anomalies of the permanent first molars and deciduous second molars may include normal crowns with a constricted cervical region and thin, narrow, and short roots, whereas the affected maxillary central incisors may exhibit a hypoplastic enamel notch near the cervical third of the clinical crown. Although the etiology of MIM remains to be determined, it is thought to be attributable to an epigenetic factor linked to brain- and central nervous system–related systemic diseases at around age 1 to 2 years. MIM teeth are associated with clinical problems such as impaction, early exfoliation, space loss, spontaneous pain, periapical abscess, and poor incisor esthetics. Children with MIM teeth should be observed closely with respect to their medical history, and dentists should formulate a wider-ranging treatment plan. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;118:101-109)

Dental development involves a sequential and reciprocal series of inductive signals that are transmitted between the epithelium and neural-crest-derived mesenchyme.[1] Dental anomalies are caused by complex interactions between genetic, epigenetic, and environmental factors during the long process of dental development.[2] Epigenetic factors are a relatively new concept and are defined as the causal interactions between genes and their products, which manifest the phenotype.[3] The phenotype of a tooth can be disturbed with respect to number, region, type, size, shape, and structure, depending on the prevailing epigenetic factors and the stage of dental development.[4] The causal factors underlying dental anomalies can be determined by investigating the normal dental development.

Anomalies of tooth structure, enamel, and dentin occur during the differentiation and biomineralization of tooth development. Developmental defects of enamel are complex and multifactorial. Amelogenesis imperfecta (AI) is a genetic enamel defect that presents in hypoplastic, hypocalcified, and hypomature forms.[2] Six genes have been associated with AI: *AMELX* (amelogenin, X-linked), *ENAM* (enamelin), *MMP20* (matrix metallopeptidase 20), *KLK4* (kallikrein-related peptidase 4), *FAM83H* (family with sequence similarity 83, member H), and *WDR72* (WD repeat domain 72).[5] Recently, SLC24A4 (solute carrier family 24 (sodium/potassium/calcium exchanger), member 4),[6] *ITGB6* (integrin, beta 6),[7] and *LAMB3* (laminin, beta 3)[8] also have been found to be correlated with AI. The local and systemic environmental factors affecting enamel malformation are trauma, periradicular infection, irradiation, chemicals (e.g., fluorides, tetracyclines, dioxins, and thalidomide), prematurity/low birth weight, thyroid and parathyroid disturbances, maternal diabetes, neonatal asphyxia, severe infections, severe malnutrition, neonatal hypocalcemia, vitamin D deficiency, bilirubinemia, and metabolic disorders.[9,10] Molar-incisor hypomineralization (MIH), which is the term given to enamel opacities of one or more permanent first molars and some of the permanent incisors, reportedly occurs with a frequency of between 4% and 17%.[11] It presents as a qualitative change in enamel that is initially of normal thickness, ranging from localized opacity through to opacity with discoloration and obvious poor quality, to posteruptive enamel breakdown; its etiology remains uncertain.[12]

Statement of Clinical Relevance

A molar-incisor malformation (MIM) is a newly discovered type of dental anomaly with molar root malformation and incisor crown defect. These abnormalities cause clinical problems such as impaction, space loss, early exfoliation, spontaneous pain, and poor incisor esthetics.

*These authors equally contributed to this work.

This research was supported by the Basic Science Research Program of the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (grant No. 2011-0022160), and by a grant of the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (No. A110112).

[a]Department of Pediatric Dentistry, College of Dentistry, Yonsei University.
[b]Oral Science Research Center, College of Dentistry, Yonsei University.
[c]Division of Anatomy & Developmental Biology, Department of Oral Biology, College of Dentistry, Yonsei University.

Received for publication Dec 2, 2013; returned for revision Mar 7, 2014; accepted for publication Mar 12, 2014.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2014.03.014

Structural anomalies of dentin mostly have a hereditary background. They are classified clinically into 3 types of dentinogenesis imperfecta (DGI) and 2 types of dentin dysplasia (DD).[13] DGI type 1 is the dental phenotype associated with osteogenesis imperfecta, which is caused by defects in the 2 genes encoding type I collagen (*COL1A1* and *COL1A2*).[14] In contrast, it has been found that DD type 2, DGI type 2, and DGI type 3, each of which has its own pattern of inherited defects limited to the dentition, are caused by various defects in the gene encoding the major noncollagenous proteins of dentin (dentin sialophosphoprotein [*DSPP*]).[15-17] DD type 1 is characterized by primary and permanent teeth that are clinically normal in size, shape, and consistency but have various root and pulp chamber malformations that are visible radiographically.[13,18] It is a rare anomaly of unclear etiology that affects approximately 1 in 100 000 patients.[17] Some developmental defects, such as odontodysplasia,[19,20] vitamin D–resistant rickets,[21,22] segmental odontomaxillary dysplasia,[23] hypoparathyroidism, and pseudohypoparathyroidism,[24] affect both the enamel and the dentin. In addition, an autosomal recessive multisystem disorder, Schimke immuno-osseous dysplasia (SIOD), presents with dental anomalies including microdontia, hypodontia, and molar root hypoplasia.[25] More recently, there have been reports of structural anomalies that lie outside the aforementioned categories. For example, cases of unique dentin dysplasia have been reported that exhibited the same patterns as conventional dentin dysplasia but were localized to only 1 or 2 teeth and were not heritable.[26,27] In the present report, we describe 12 patients with a new type of dental anomaly associated with molar-incisor malformation (MIM) that is entirely different from conventional types. The patients' characteristic tooth form, medical history, clinical and radiologic examination, treatment procedure, and supposed etiology are described herein.

CASE REPORTS

Patients

Twelve Korean patients of the Yonsei University Dental Hospital (YUDH) presented with a tooth with a thin and short root but with a normal crown. The protocol of this study was approved by the institutional review board of YUDH (approval No. 2-2013-0020). The gender and age of the patients, the affected tooth, history of systemic diseases, and clinical characteristics were investigated relative to their clinical and radiologic test findings (Table I).

The age of the patients ranged from 4 to 13 years, and the male-to-female ratio was 1:1. Examination of their systemic medical history found that 10 of the 12 patients had experienced a brain abnormality at age 1 to 2 years. The representative medical history included meningitis (patients 1, 4, and 8), spina bifida (patient 10), cerebral cyst (patient 8), cephalohematoma (patient 5), seizure (patients 3 and 11), hydrocephalus (patient 12), and brain injury by dystocia (patient 2), together with preterm birth in some cases. Even patients with no specific diagnosis had medical history of magnetic resonance imaging (MRI) scans owing to brainwave abnormality immediately after birth. There was no specific familial history except systemic medical conditions.

Radiography found that the root of the permanent first molar was characteristically thin, divergent, or short, exhibiting a form of hypoplasia or aplasia. The deciduous second molar was affected in some cases. In addition, the pulp cavity in the crown portion was constricted into a straight form. Of the 12 patients, 7 exhibited a wedge-shaped defect at the one-third to one-half cervical portion of the upper incisors, which was clearly observed on periapical radiographs (Figure 1, E).

Clinically, the crowns erupted in the oral cavity had a normal contour and surface strength. However, there were problems such as impaction of the permanent first molars, space loss due to early exfoliation of the deciduous second molar, impaction, hypo-occlusion, dental caries, poor oral hygiene, adjacent tooth eruption disorder, spontaneous pain, and periodontitis.

The intraoral and panoramic photographs and relevant records of 4 of the patients are described in detail in subsequent sections. These patients were chosen because they exhibited representative characteristics of the dental anomaly under discussion. Their data are used herein to provide the first description of the characteristics of a MIM tooth. Supplemental Figures 1 to 8, containing radiographic films and clinical photographs (patients 5 to 12 in Table I), are available at http://dx.doi.org/10.1016/j.oooo.2014.03.014.

Case 1 (patient 1 in Table I)

On the first visit, a 6-year-old girl attended the Department of Pediatric Dentistry at YUDH with the chief complaint of dental caries without a history of pain. The patient first visited a local dental clinic for an oral examination and then our dental hospital for further evaluation after the clinic reported the presence of dental caries on her upper bilateral first incisors. The patient had a medical history of 15 to 20 days of hospitalization in the intensive care unit of Severance Hospital (Yonsei University Health System) associated with her contracting bacterial meningitis 15 to 20 days after birth. A clinical examination found molar crowns with a normal contour that were erupted, whereas the upper central incisors on both sides exhibited a wedge-shaped defect at the labiocervical area (see Figure 1, A-C). Panoramic radiography found that the distal roots of the lower permanent first molars on both sides were vestigial and thought to be undeveloped, and the pulp cavities in the crown were constricted into a straight form (see Figure 1, D). In addition, a periapical radiograph of both upper central incisors found wedge-shape defects at the one-third to one-half cervical region of the crown (see Figure 1, E).

Case 2 (patient 2 in Table I)

On the first visit, a 5-year-old boy attended the Department of Pediatric Dentistry at YUDH with the chief complaint that it was difficult to undergo root canal treatment of the upper

Table I. Characteristics of patients with MIM teeth

Patient No.	*Sex*	*Age (y)*	*Affected tooth**	*Medical history*	*Clinical features*
1	F	6	1 1 6 6	Bacterial encephalomeningitis 15-20 days after birth	Upper bilateral first incisors: crown cervical notch
2	M	5	6E 1 1 E6 6E E6	Brain injury during birth (difficult delivery)	Upper bilateral first incisors: crown cervical notch Lower right permanent first molar: mesial tilting (disrupting eruption path of lower right second premolar) Lower left permanent first molar: distal tilting Upper left second premolar: space loss
3	F	7	E 1 1 E 6E E6	Electrocorticogram or MRI at 1 day after birth (owing to epilepsy)	Upper bilateral permanent first molars: mesially ectopic impaction (treatment by upper removable appliance distal screw) Lower bilateral permanent first molars: rotation
4	M	11	6 6 6 6	Bacterial encephalomeningitis 2 weeks after birth (hospitalization)	Lower left permanent first molar: fistula formation (extraction)
5	M	4	6E E6 6E E6	Cephalohematoma, birth injury (20 days ICU hospitalization), ventriculomegaly	Upper and lower bilateral permanent first molars: impacted (aged 7 years 1 month)
6	M	7	 6 6	Renal disease (diabetes insipidus)	Lower bilateral permanent first molars: hypo-occlusion Lower left permanent first molar: mesially ectopic impaction
7	F	7	6E E6 6E E6	Early birth (32 weeks), 1.98 kg (incubator)	Nothing specific
8	F	8	6E 1 1 E6 6E E6	MRI after birth (suspected cyst in brain), ingested meconium	Upper bilateral first incisors: crown cervical notch
9	F	8	6 1 1 6 6 6	Bacterial encephalomeningitis 2 months after birth	Upper bilateral first incisors: crown cervical notch Skeletal class 3 tendency: orthodontic treatment Extraction of upper and lower bilateral permanent first molars
10	F	9	6 6 6 6	Spina bifida, meningomyelocele, cerebral palsy	Upper and lower left permanent first molars: mesially ectopic impaction Upper right deciduous second molar: early loss Upper right permanent first molar: mesial shift (space loss on upper right second premolar) Skeletal class 3 tendency Upper bilateral first incisors: crown cervical notch
11	M	9	6 1 1 6 6 6	Hospitalized 1 day after birth (epilepsy) Eating low-phosphate powdered milk owing to low calcium levels, development retardation (1 year)	Upper bilateral first incisors: crown cervical notch Lower right permanent first molar: fistula formation (extraction)
12	M	13	6 1 1 6 6 6	Medical induction of labor (hydrocephalus)	Lower right permanent first molar: swelling on gingiva, visit dental hospital owing to pain Extraction of upper left and lower right permanent first molars (failure of endodontic treatment)

ICU, intensive care unit; *MRI*, magnetic resonance imaging; *F*, female; *M*, male.
*Tooth numbering according to the Fédération Dentaire Internationale system. *1*, central incisor; *6*, permanent first molar; *E*, deciduous second molar.

deciduous second molar, which had been already attempted at a local clinic, because bleeding was not controlled and the canals were calcified. The patient had no symptoms on visiting the local clinic, but dental caries was found on his upper deciduous second molar. The local dentist performed pulp treatment owing to pulp exposure during caries removal.

The boy had a medical history of computed tomography and MRI performed immediately after birth because his head was pressed down owing to dystocia. A clinical test found that the erupted tooth had a normal texture, but the lower bilateral permanent first molars, which were difficult to maintain in a good oral hygiene state, had moderate dental caries, and both the upper central incisors exhibited the cervical wedge-shape defect (Figure 2, C-E). Panoramic radiography revealed that the roots of the upper bilateral permanent first molars and upper and lower bilateral primary second molars were thin and divergent, and the pulp cavities in the crowns were constricted. The roots of the lower bilateral permanent first molars were not developed at all, and the distal root of the lower right primary second molar had undergone root resorption and impaction due to mesial tilting of the lower right permanent first molar (see Figure 2, A), which had progressed severely, thereby promoting early exfoliation of the lower right primary second molar and obstructing the eruption path of the lower right second premolar (see Figure 2, B). The distal tilting of the lower left permanent first molar obstructed the eruption of the lower left permanent

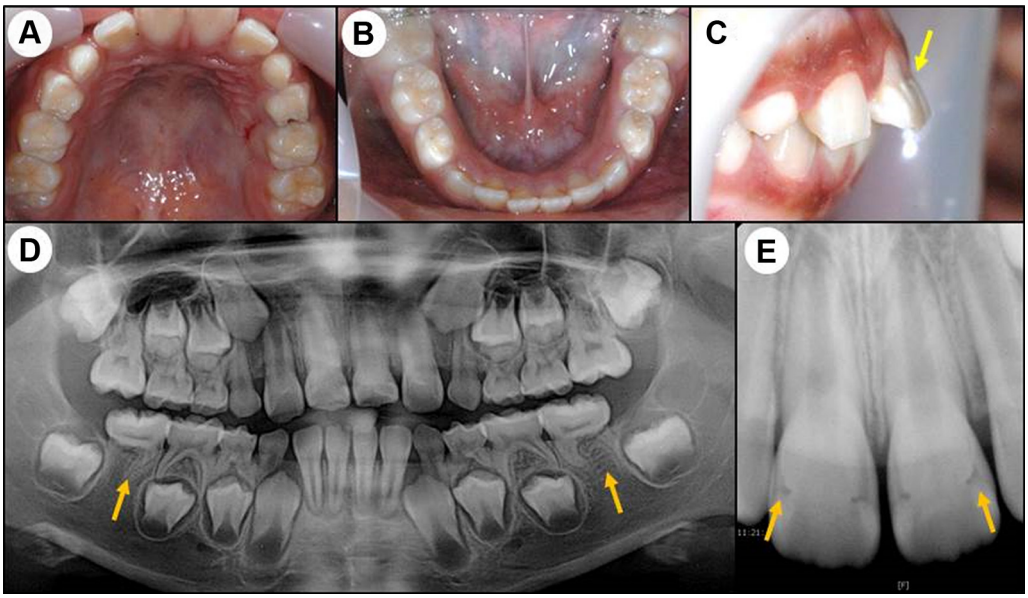


Fig. 1. Case 1 (patient 1). Clinical photographs and radiographic films. **A**, Clinical intraoral photograph (maxilla) of a girl aged 7 years and 8 months obtained 9 months after the first visit, showing a normal crown contour and alignment. **B**, Clinical intraoral photograph (mandible) obtained at the same time as **A**, showing normal crown form and alignment. **C**, Clinical intraoral photograph (lateral) obtained at the same time as **A**, showing wedge-shaped defects on the labial surface of the upper incisors (yellow arrow). **D**, In the panoramic film obtained on the first visit, both lower first permanent molars exhibit a normal crown contour, but the distal roots are vestigial or undeveloped (yellow arrows). In addition, the pulp cavities in the crowns seem to be constricted into a straight form. **E**, In the periapical film obtained at the same time as **D**, the cervical one-third to one-half of the crowns exhibits a wedge-shaped defect (yellow arrows).

second molar, and insufficient eruption space for the upper right second premolar was observed that was due to the early exfoliation of the upper right primary second molar due to impaction of the upper right permanent first molar (see Figure 2, B).

Case 3 (patient 3 in Table I)

On the first visit, a 7-year-old girl without a history of pain attended the Department of Pediatric Dentistry at YUDH with the chief complaint of unusual root development, which had been first noted at a local clinic. She had a medical history of an electroencephalogram and an MRI performed 1 day after birth because of seizure. However, she did not have any specific diagnosis and had a medical history of 2 to 3 months of incubation. A clinical examination found that the distal roots of the deciduous second teeth (i.e., both of the upper permanent first molars) had resorbed. Furthermore, there was a marked rotation of both of the lower permanent first molars (Figure 3, A). Panoramic radiography revealed that the roots of the lower bilateral permanent first molars were thin and divergent, and the pulp chamber within the tooth crown had been obliterated. The roots of the upper and lower bilateral primary second molars were barely developed, and the upper bilateral permanent first molars exhibited impaction toward the distal roots of the adjacent deciduous second teeth (see Figure 3, C). Normal eruption guidance was provided for the mesially ectopic impacted upper bilateral permanent first molars by attaching a button to the crown and using an appliance with a distal screw. Normal eruption was obtained after 9 months of treatment (see Figure 3, B).

Case 4 (patient 4 in Table I)

An 11-year-old boy attended the Department of Pediatric Dentistry at YUDH because of intermittent pain in the lower left permanent first molar at night. The patient had a medical history of hospitalization associated with bacterial meningitis, which he contracted 2 weeks after his birth. A clinical examination found that his lower left permanent first molar had a positive reaction to percussion. Ten months later he revisited our clinic with the same symptom. A clinical examination found that his lower left permanent first molar had a positive reaction to percussion, mobility (+), and fistula formation on the buccal gingiva (Figure 4, C). Panoramic radiography revealed alveolar bone loss of the lower left permanent first molar, in which an area of furcation was observed apically, and the roots of the upper and lower bilateral permanent first molars were thin and divergent. Furthermore, the pulp cavities in the crown were constricted into a straight form (see Figure 4, A). A periapical radiograph obtained 10 months after the first visit revealed that the alveolar bone loss had reached the apex (see Figure 4, B). A clinical intraoral photograph of the lower left permanent molar revealed a sinus tract on the buccal gingiva, and so it had to be extracted (see Figure 4, C). Histologic findings of the extracted tooth were obtained by staining it with hematoxylin-eosin (Figure 5, A). The extracted tooth had a normal crown but abnormal root morphology (see Figure 5, A). Normal dentin and pulp were observed in the upper portion of the crown (see Figure 5, B, C), but its middle portion exhibited a disconnected pulp chamber and amorphous dentin, like an osteoid (see Figure 5,

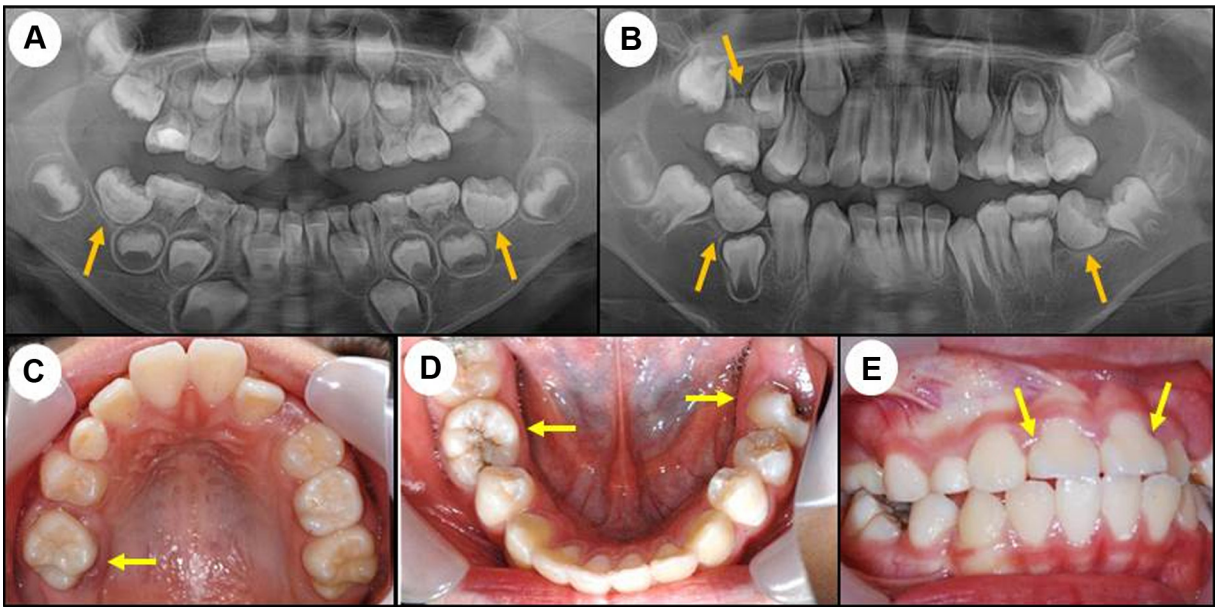


Fig. 2. Case 2 (patient 2). Clinical photographs and radiographic films. **A**, Panoramic film obtained at the first visit. The roots of the upper bilateral first permanent molars and upper and lower bilateral second primary molars appear to be thin and divergent, and constriction of the pulp cavities is evident. The roots of the lower bilateral first permanent molars are not formed (yellow arrows), and the distal root of the lower right second primary molar is resorbed owing to mesial tilting of the lower right first permanent molar. B, Panoramic film obtained at 3 years, 7 month after the first visit. The lower right second primary molar underwent early exfoliation owing to mesial tilting of the lower right first permanent molar, which also obstructed the eruption path of the lower right second premolar (lower left yellow arrow). The eruption space for the upper right second premolar is insufficient owing to early exfoliation of the upper right second primary molar (upper yellow arrow), and distal tilting of the lower left first permanent molar is obstructing the eruption path of the lower left second permanent molar (lower right arrow). **C**, At 4 years and 1 month after the first visit, the clinical intraoral photograph (maxilla) of this boy (at 9 years and 11 months old) reveals space loss due to early exfoliation of the upper right second primary molar and mesial rotation of the upper right first permanent molar (yellow arrow). **D**, Clinical intraoral photograph (mandible) obtained at the same time as **C**. The lower right first permanent molar exhibits moderate dental caries, and its mesial tilting is obstructing the eruption path of the lower right second premolar (yellow arrows). In addition, the lower left first permanent molar exhibits moderate dental caries, and its distal tilting is obstructing the eruption path of the lower left second permanent molar. **E**, Clinical intraoral photograph (right) obtained at the same time as **C**. A wedge-shaped defect is evident on the labiocervical surface of the upper incisors (yellow arrows).

D, E). There was no root fracture, but abnormal dentin and cementum (respectively labeled "ad" and "c" in the figure) were observed. Figure 5, F, shows a cell incorporated within abnormal dentin. Pulp tissue and inflammatory cells can be seen in the fissure of the abnormal root dentin (see Figure 5, G).

DISCUSSION

A MIM tooth has a unique shape in the molar and incisor areas. Above all, the affected permanent first molar has a normal crown and thin and short roots on a radiograph. The affected area is symmetrical and most frequently involves the lower permanent first molar, upper permanent first molar, and upper and lower deciduous second molars. In addition, in two-thirds of the patients in the present study, the incisor enamel exhibited an abnormal form, like a notch, at the cervical level.

The etiology of a MIM tooth is thought to differ from those of other previously described hereditary and environmental dental anomalies. Its form is most similar to that of DD type I, but with the difference that DD type I is hereditary and affects the entire dentition.[18,28] The dental anomaly associated with vitamin D–resistant rickets differs from a MIM tooth in that it often exhibits a large pulp cavity and spontaneous abscess.[21] Odontodysplasia differs from a MIM tooth because the affected tooth has thin enamel and a large pulp cavity.[26] Cases of hypoparathyroidism and pseudohypoparathyroidism have a similar short root form, but both are associated with a large pulp cavity and enamel hypoplasia.[24] In addition, 72% of patients with SIOD present with molar root hypoplasia that is very similar to that seen with MIM in both the deciduous and permanent dentition.[25] However, SIOD is accompanied by spondyloepiphyseal dysplasia, renal dysfunction, T-cell immunodeficiency, and facial dysmorphism, none of which were present in our patients.[29]

Local enamel hypoplasia of the permanent first molar and upper central incisor is termed MIH, which exhibits

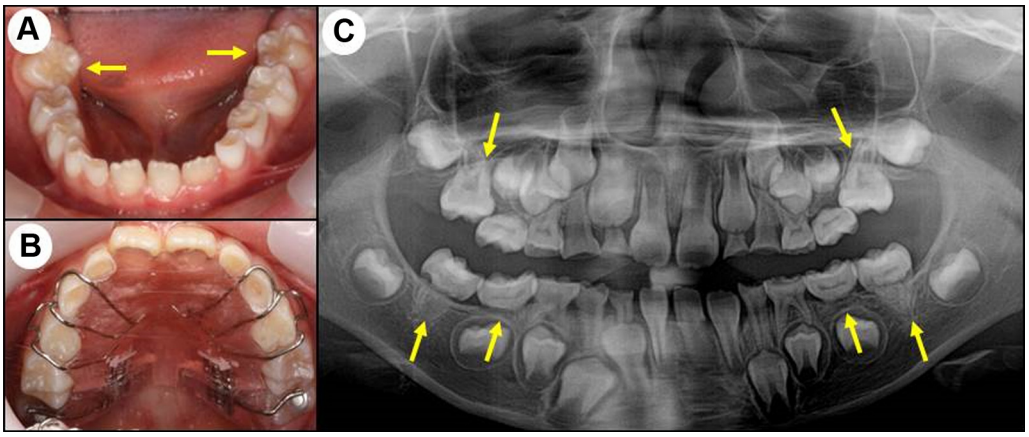


Fig. 3. Case 3 (patient 3). Clinical photographs and radiographic film. **A**, Clinical intraoral photograph (mandible) of a girl (at 7 years and 6 months old) obtained on the first visit. Rotation of the lower bilateral first permanent molars is evident (yellow arrows). **B**, Clinical intraoral photograph (maxilla) obtained 9 months after the first visit, showing a removable appliance with a distal screw for the relief of impaction of the upper bilateral first permanent molars. **C**, Panoramic film obtained at the same time as **A**. The roots of the lower bilateral first permanent molars are thin and divergent, and constriction of the pulp cavities is evident. The roots of the upper and lower bilateral second primary molars are not developed, and the upper bilateral first permanent molars show impaction (yellow arrow).

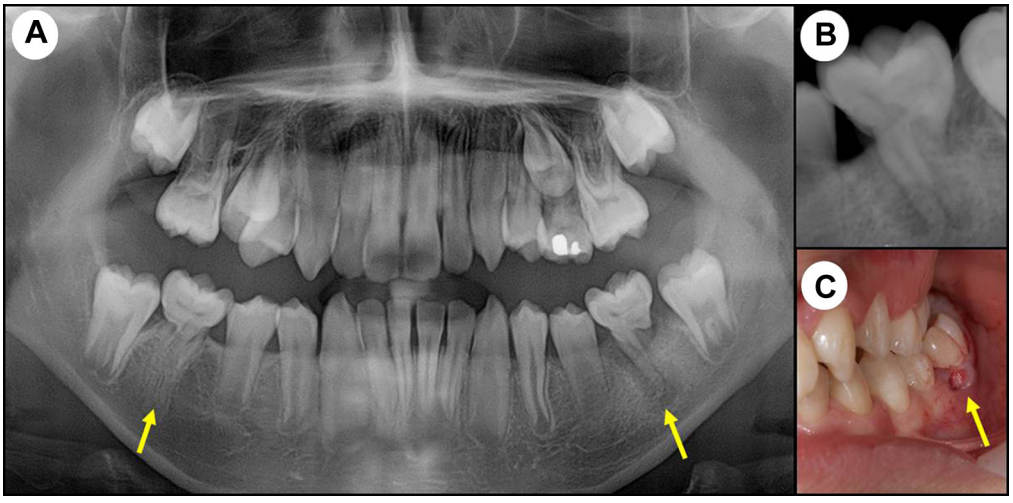


Fig. 4. Case 4 (patient 4). Clinical photographs and radiographic films. **A**, Panoramic film of a boy (at 12 years and 6 months old) obtained 10 months after his first visit. Alveolar bone loss is visible at the furcation and apical areas of the lower left permanent molar. The roots of the upper and lower bilateral first permanent molars are thin and divergent, and the pulp cavity in the crown is constricted into a straight form (yellow arrow). **B**, Periapical film of the lower left permanent molar obtained 10 months after the first visit. Alveolar bone loss has reached the apex. **C**, Clinical intraoral photograph obtained 10 months after the first visit showing fistula formation on the buccal gingiva of the lower left permanent molar. The tooth had to be extracted because of tooth mobility, a positive reaction to percussion (+), and apical involvement.

variable severity. The enamel hypoplasia in MIH occurs in an area similar to that seen in a MIM tooth. MIH is thought to be caused by systemic diseases and antibiotic medication, but the etiology has yet to be ascertained unequivocally.[11] MIH occurs in the enamel, so the affected tissue differs from a MIM tooth. However, the affected area is the same, so it can be inferred that the 2 types of dental anomaly originate in the same period from different cells, proteins, or tissues.

The etiology of MIM is thought to involve epigenetic factors that are related to brain-related systemic diseases and root development. Of the 12 patients in the present case series, 10 had a medical history of meningitis, spina bifida, seizure, hydrocephalus, and idiopathic brain diseases occurring 1 to 2 years after birth. Meningitis, which related to 3 of the patients, generally refers to various diseases with inflammation of the subarachnoid space. The most common cause of

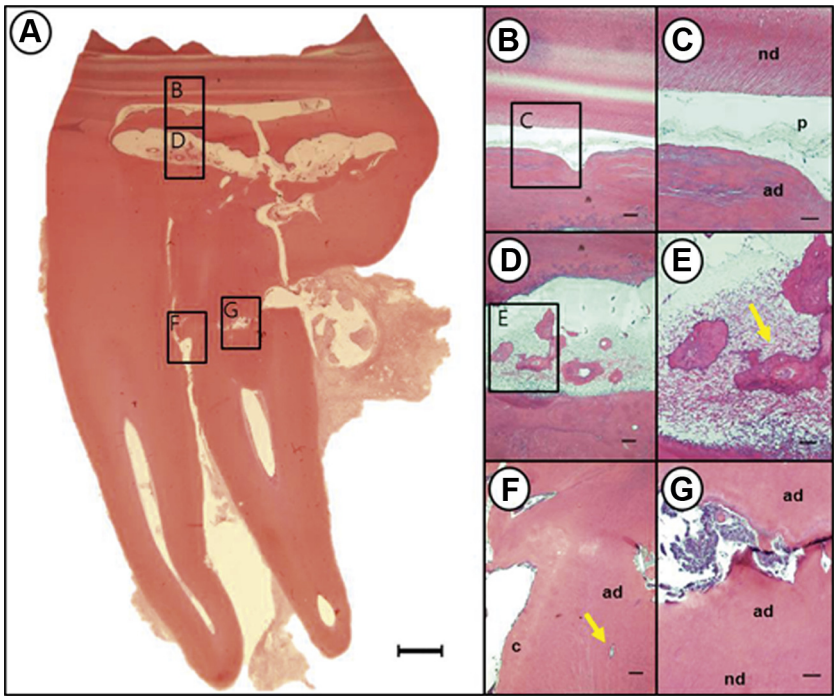


Fig. 5. Case 4 (patient 4). Histologic findings (hematoxylin-eosin staining). **A**, Histologic findings of the extracted lower left permanent molar, showing that the normal dentin discontinues at the middle portion of the pulp chamber, and amorphous hard tissues can be observed. In the furcation area, transmission of the pulp tissue to the outer space appears as a dens invaginatus (yellow arrow). The scale bar is 1.15 mm. **B**, Higher magnification view of **A**, focusing on the normal dentin and pulp and on amorphous dentin. The scale bar is 100 μm. **C**, Higher magnification view of **B**, focusing on the normal dentin (nd) and pulp (p) and on the abnormal dentin (ad). The scale bar is 50 μm. **D**, Higher magnification view of **A**, focusing on the amorphous hard tissue, like an osteoid, in the pulp chamber. The scale bar is 100 μm. **E**, Higher magnification view of **D**, focusing on the amorphous hard tissue (yellow arrow), like an osteoid, in the pulp chamber. The scale bar is 50 μm. **F**, Higher magnification of view **A**. There is no root fracture, but continuous abnormal dentin (ad) and cementum (c) can be observed. A cell incorporated into the abnormal dentin can be seen (yellow arrow). The scale bar is 100 μm. **G**, Higher magnification of view **A**. The pulp tissue and inflammation cells can be seen in the fissure of the abnormal root dentin (yellow arrow). The scale bar is 50 μm.

inflammation is meningitis caused by viral or bacterial infection in the subarachnoid space. Symptomatic treatment is sufficient for viral meningitis, which resolves naturally without special treatment. However, antibiotics should be immediately injected if bacterial meningitis is suspected.[30] Spina bifida is a developmental disorder caused by the inappropriate fusion of both ends of the neural plate during neural tube development. These neural tube defects including spina bifida are complex traits with multifactorial etiology encompassing both genetic and environmental components.[31] The symptoms manifest according to the location of the lesion, in a related dermatome.[32] The causal factor of MIM is also suspected to be medication or hormonal changes associated with a systemic disease; however, further evaluation is needed to establish the causal factor unequivocally.

A normal root develops as a result of the interaction between the Hertwig epithelial root sheath (HERS) and the dental papilla after the completion of crown formation.[33] The mechanism underlying the formation of a MIM is thought to involve the interaction between HERS and the dental papilla. The completion of crown formation occurs at age 2.5 to 3 years for the permanent first molar, and at 10 to 11 months for the deciduous second molar.[34] Given that the period in which the patients were ill and the periods of root development for the permanent first molar and deciduous second molar differ, the mechanism underlying this root malformation is unclear.

Several candidate genes for tooth root defects have been suggested in previous studies. In particular, nuclear factor Ic (*Nfic*) is thought to be a key regulator for root dentin formation.[35] Root dentin fails to form if *Nfic* is knocked out in the dental mesenchyme, with instead bone-like mineral material being detectable, with odontoblasts that are not polarized or embedded in the cellular dentin, in line with the histologic features of the present study. Furthermore, odontoblasts in the crown pulp differentiate and dentin develops in *Nfic* mutant mice.[33,36] Several genes are known to be related to root development in animal models, including *Msx2* (msh

homeobox 2), *Shh* (sonic hedgehog), *Sp6* (Sp6 transcription factor), *Nog* (noggin), *Smad4* (SMAD family member 4), *Ntl*, and *Rankl* (receptor activator of nuclear factor−κB ligand).[1,33] In addition, SIOD is caused by biallelic mutations of *SMARCAL1* (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1), which is expressed in all developing teeth and is associated with molar root hypoplasia.[25] However, the signaling pathways and genes involved in root development remain poorly understood compared with crown development.[33]

The relationship between brain disease and MIM can be explained by neuro-osteology, which is the study of the relevance of neural and hard-tissue development. According to this field, certain central nervous system (CNS) malformations and peripheral neural tissue disorders are linked with hard-tissue anomalies.[37,38] For example, myelomeningocele/spina bifida, a neural-tube development disorder, affects the sella turcica, where the pituitary gland is located. Thus, this disease may cause idiopathic endocrine disorders in children.[38] Moreover, owing to peripheral nerve defects, hypoplasia and tooth malformation can occur in the innervated dental arch field.[39] It can thus be inferred that the brain diseases of these patients in infancy affected either their CNS or peripheral neural tissue, thereby influencing root development. However, this hypothesis alone cannot clarify the mechanism by which only the root development is affected.

All of the 12 patients included in this report exhibited clinical problems such as impaction, early exfoliation, space loss, spontaneous pain, and periapical abscess of the permanent first molar and deciduous second molar and poor incisor esthetics. In case 2, impaction of the permanent first molar occurred when the deciduous second molar was classed as a MIM tooth. Thus, early extraction of the deciduous molar and space loss ensued. In addition, mesial tilting of the permanent first molar obstructed eruption of the second premolar. This kind of impaction could be relieved by the appliance used for case 3. However, extraction should be followed by prosthodontic or orthodontic treatment if spontaneous pain and mobility are severe, as for case 4. The permanent first molar is crucial for occlusion and mastication, and problems involving this tooth are thought to negatively influence the growth of a patient. The characteristic histologic features of MIM teeth were abnormal dentin and amorphous calcified tissue in the dental pulp and furcation area.

The spontaneous pain and mobility experienced by patient 4 (case 4) arose from the presence of an apical abscess, which may have developed in several possible ways. First, the dental pulp in the abnormal pulp chamber could be stimulated by the external tissue or affected directly by the transmission of bacteria, causing a pulpal inflammation. Second, the periodontal attachment could be incomplete owing to the abnormal hard tissue of the dentin, allowing the periodontal abscess to spread to the apex. However, the actual reason remains unknown, and further research is needed to avoid the spontaneous pain, abscess, and extraction associated with a MIM.

CONCLUSIONS

A MIM tooth is a newly discovered type of dental anomaly of the permanent first molars, deciduous second molars, and permanent maxillary central incisors. The MIM anomalies of the permanent first molars and deciduous second molars may include normal crowns with thin, narrow, and short roots, whereas affected maxillary central incisors may exhibit a hypoplastic enamel notch near the cervical third of the clinical crown. Although the etiology of MIM teeth remains to be determined, it is thought to involve an epigenetic factor related to a systemic disease occurring at around 1 to 2 years of age and influencing root development. MIM teeth are associated with clinical problems such as impaction, early exfoliation, space loss, spontaneous pain, and periapical abscess of the permanent first molar and deciduous second molar and poor incisor esthetics. Therefore, children with a MIM should be closely observed with respect to their medical history, and dentists should implement a wider-ranging treatment plan that takes into consideration management of the signs and symptoms, dental treatment requirements, progression, and projected prognosis.

REFERENCES

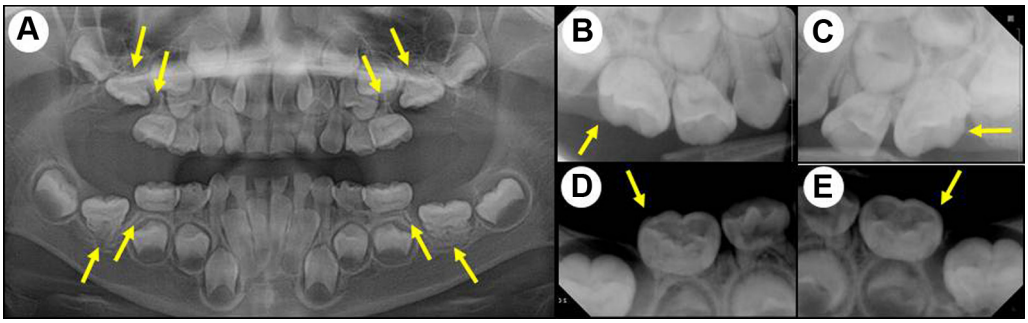
1. Bei M. Molecular genetics of tooth development. *Curr Opin Genet Dev*. 2009;19:504-510.
2. Brook AH. Multilevel complex interactions between genetic, epigenetic and environmental factors in the aetiology of anomalies of dental development. *Arch Oral Biol*. 2009;54(suppl 1): S3-S17.
3. Waddington CH. Towards a theoretical biology. *Nature*. 1968;218:525-527.
4. Townsend G, Bockmann M, Hughes T, Brook A. Genetic, environmental and epigenetic influences on variation in human tooth number, size and shape. *Odontology*. 2012;100:1-9.
5. Wright JT, Torain M, Long K, et al. Amelogenesis imperfecta: genotype-phenotype studies in 71 families. *Cells Tissues Organs*. 2011;194:279-283.
6. Seymen F, Lee KE, Tran Le CG, et al. Exonal deletion of SLC24A4 causes hypomaturation amelogenesis imperfecta [published online February 14, 2014]. *J Dent Res*. 2014;93:366-370. http://dx.doi.org/10.1177/0022034514523786.
7. Poulter JA, Brookes SJ, Shore RC, et al. A missense mutation in ITGB6 causes pitted hypomineralized amelogenesis imperfecta [published online December 6, 2013]. *Hum Mol Genet*. 2014;23: 2189-2197. http://dx.doi.org/10.1093/hmg/ddt616.
8. Kim JW, Seymen F, Lee KE, et al. LAMB3 mutations causing autosomal-dominant amelogenesis imperfecta. *J Dent Res*. 2013;92:899-904.
9. Brook AH, Fearne JM, Smith JM. Environmental causes of enamel defects. *Ciba Found Symp*. 1997;205:212-221:discussion 21-25.

10. Fearne JM, Bryan EM, Elliman AM, Brook AH, Williams DM. Enamel defects in the primary dentition of children born weighing less than 2000 g. *Br Dent J*. 1990;168:433-437.
11. Fagrell T. Molar incisor hypomineralization: morphological and chemical aspects, onset and possible etiological factors. *Swed Dent J Suppl*. 2011;5:11-83.
12. Whatling R, Fearne JM. Molar incisor hypomineralization: a study of aetiological factors in a group of UK children. *Int J Paediatr Dent*. 2008;18:155-162.
13. Shields ED, Bixler D, el-Kafrawy AM. A proposed classification for heritable human dentine defects with a description of a new entity. *Arch Oral Biol*. 1973;18:543-553.
14. Gajko-Galicka A. Mutations in type I collagen genes resulting in osteogenesis imperfecta in humans. *Acta Biochim Pol*. 2002;49:433-441.
15. Kim JW, Hu JC, Lee JI, et al. Mutational hot spot in the DSPP gene causing dentinogenesis imperfecta type II. *Hum Genet*. 2005;116:186-191.
16. Kim JW, Nam SH, Jang KT, et al. A novel splice acceptor mutation in the DSPP gene causing dentinogenesis imperfecta type II. *Hum Genet*. 2004;115:248-254.
17. Kim JW, Simmer JP. Hereditary dentin defects. *J Dent Res*. 2007;86:392-399.
18. O Carroll MK, Duncan WK, Perkins TM. Dentin dysplasia: review of the literature and a proposed subclassification based on radiographic findings. *Oral Surg Oral Med Oral Pathol*. 1991;72:119-125.
19. Fanibunda KB, Soames JV. Odontodysplasia, gingival manifestations, and accompanying abnormalities. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;81:84-88.
20. Crawford PJ, Aldred MJ. Regional odontodysplasia: a bibliography. *J Oral Pathol Med*. 1989;18:251-263.
21. Goodman JR, Gelbier MJ, Bennett JH, Winter GB. Dental problems associated with hypophosphataemic vitamin D resistant rickets. *Int J Paediatr Dent*. 1998;8:19-28.
22. Chaussain-Miller C, Sinding C, Wolikow M, Lasfargues JJ, Godeau G, Garabedian M. Dental abnormalities in patients with familial hypophosphatemic vitamin D-resistant rickets: prevention by early treatment with 1-hydroxyvitamin D. *J Pediatr*. 2003;142:324-331.
23. Azevedo RS, da Silveira LJ, Moliterno LF, Miranda AM, de Almeida OP, Pires FR. Segmental odontomaxillary dysplasia: report of a case emphasizing histopathological, immunohistochemical and scanning electron microscopic features. *J Oral Sci*. 2013;55:259-262.
24. Assif D. Dental changes in hypoparathyroidism. *Refuat Hapeh Vehashinayim*. 1977;26:13-19.
25. Morimoto M, Kerouredan O, Gendronneau M, et al. Dental abnormalities in Schimke immuno-osseous dysplasia. *J Dent Res*. 2012;91:29S-37S.
26. Spini TH, Sargenti-Neto S, Cardoso SV, et al. Progressive dental development in regional odontodysplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;104:e40-e45.
27. Rocha CT, Nelson-Filho P, Silva LA, Assed S, Queiroz AM. Variation of dentin dysplasia type I: report of atypical findings in the permanent dentition. *Braz Dent J*. 2011;22:74-78.
28. Toomarian L, Mashhadiabbas F, Mirkarimi M, Mehrdad L. Dentin dysplasia type I: a case report and review of the literature. *J Med Case Rep*. 2010;4:1.
29. Schimke RN, Horton WA, King CR. Chondroitin-6-sulphaturia, defective cellular immunity, and nephrotic syndrome. *Lancet*. 1971;2:1088-1089.
30. Bonthius DJ, Karacay B. Meningitis and encephalitis in children: an update. *Neurol Clin*. 2002;20:1013-1038:vi-vii.
31. Detrait ER, George TM, Etchevers HC, Gilbert JR, Vekemans M, Speer MC. Human neural tube defects: developmental biology, epidemiology, and genetics. *Neurotoxicol Teratol*. 2005;27:515-524.
32. Garg A, Revankar AV. Spina bifida and dental care: key clinical issues. *J Calif Dent Assoc*. 2012;40:861-865:8-9.
33. Huang XF, Chai Y. Molecular regulatory mechanism of tooth root development. *Int J Oral Sci*. 2012;4:177-181.
34. Logan WHG, Kronfeld R. Development of the human jaws and surrounding structures from birth to the age of fifteen years. *J Am Dent Assoc*. 1933;20:379-429.
35. Gronostajski RM. Roles of the NFI/CTF gene family in transcription and development. *Gene*. 2000;249:31-45.
36. Park JC, Herr Y, Kim HJ, Gronostajski RM, Cho MI. Nfic gene disruption inhibits differentiation of odontoblasts responsible for root formation and results in formation of short and abnormal roots in mice. *J Periodontol*. 2007;78:1795-1802.
37. Kjaer I. Correlated appearance of ossification and nerve tissue in human fetal jaws. *J Craniofac Genet Dev Biol*. 1990;10:329-336.
38. Kjaer I. Prenatal traces of aberrant neurofacial growth. *Acta Odontol Scand*. 1998;56:326-330.
39. Kjaer I, Kocsis G, Nodal M, Christensen LR. Aetiological aspects of mandibular tooth agenesis—focusing on the role of nerve, oral mucosa, and supporting tissues. *Eur J Orthod*. 1994;16:371-375.

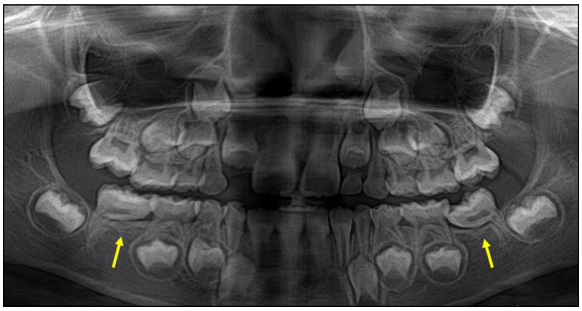
Reprint requests:

Je Seon Song
Department of Pediatric Dentistry
Yonsei University College of Dentistry
250 Seongsanno
Seodaemun-gu
Seoul 120-752
South Korea
songjs@yuhs.ac

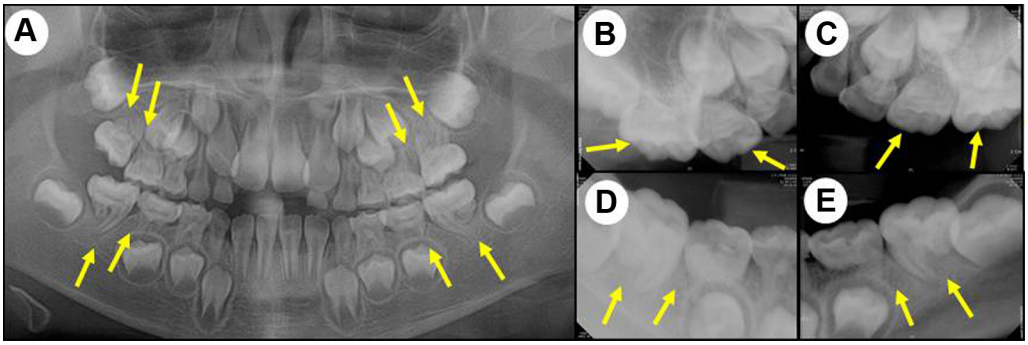
APPENDIX



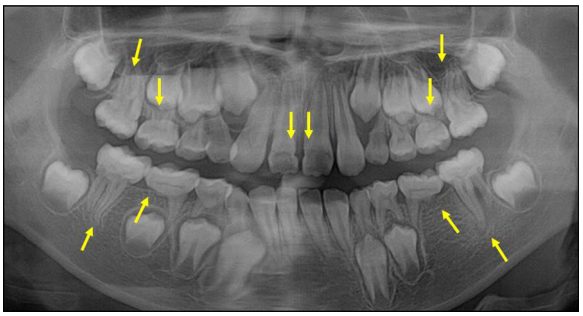
Supplemental Figure 1. Radiographic films of patient 5 (a 6-year-old boy; see Table I). **A**, Panoramic film obtained 2 years after the first visit. The upper and lower bilateral deciduous second molars exhibit a normal crown contour, but the roots are vestigial or undeveloped. In addition, the pulp cavities in the crowns appear to be constricted into a straight form. The upper and lower bilateral permanent first molars exhibit a normal contour and no root formation. **B-E**, Periapical films obtained at the first visit. The upper and lower bilateral deciduous second molars are affected (arrows).



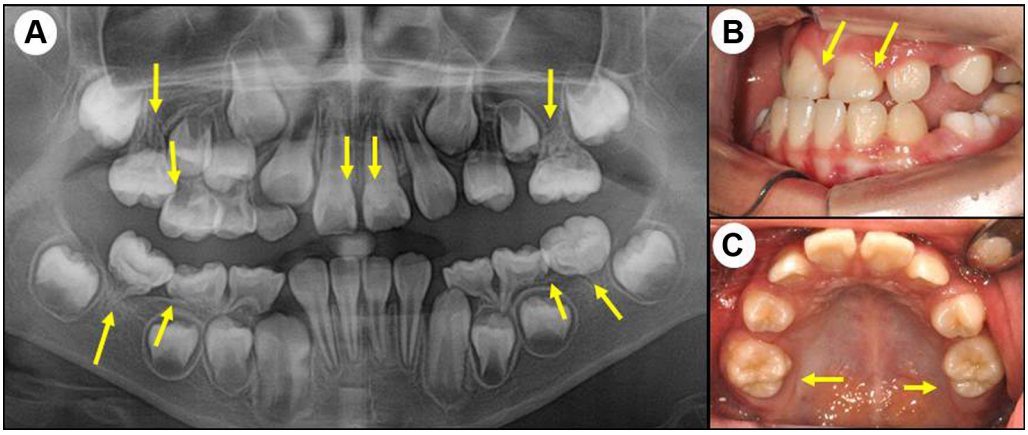
Supplemental Figure 2. Radiographic film of patient 6 (a 7-year-old boy; see Table I). Panoramic film obtained at the first visit. The lower bilateral permanent first molars exhibit a normal crown contour, but the mesial roots are vestigial or undeveloped (arrows).



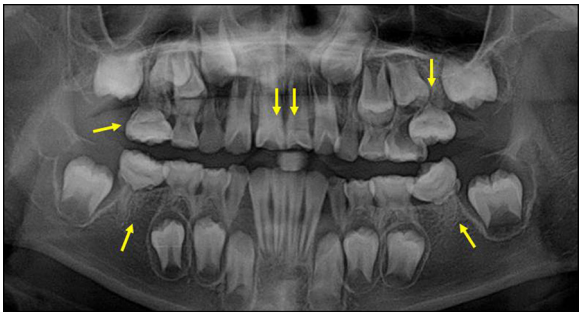
Supplemental Figure 3. Radiographic films of patient 7 (a 7-year-old girl; see Table I). **A**, Panoramic film obtained at the first visit. The upper and lower bilateral deciduous second molars exhibit a normal crown contour, but the roots are vestigial or undeveloped (arrows). In addition, the pulp cavities in the crowns appear to be constricted into a straight form. The upper and lower bilateral permanent first molars exhibit a normal contour, but dilaceration of the mesial roots and vestigial distal roots can be seen (arrows). **B-E**, Periapical films obtained at the same time as **A**. The upper and lower bilateral permanent first molars and upper and lower bilateral deciduous second molars are affected (arrows).



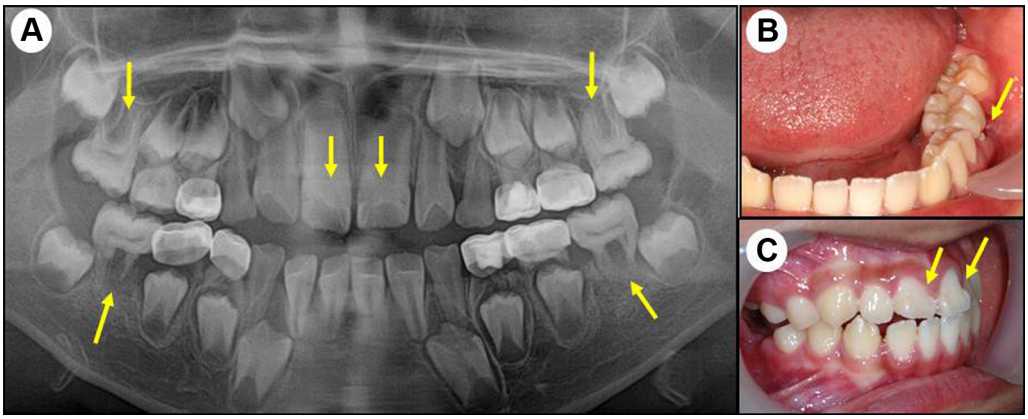
Supplemental Figure 4. Radiographic film of patient 8 (an 8-year-old girl; see Table I). Panoramic film obtained at the first visit. The upper and lower bilateral permanent first molars exhibit a normal crown contour, but the mesial roots are elongated and dilacerated. Although the patient had no symptoms, the furcation of the lower left permanent first molar exhibits a radiolucent lesion. In addition, the pulp cavities in the crowns of the upper and lower bilateral deciduous second molars appear to be constricted into a straight form, and the distal roots are undeveloped. The upper bilateral incisors have a cervical notch on the cervical one-third portion of the crown but have normal root formation.



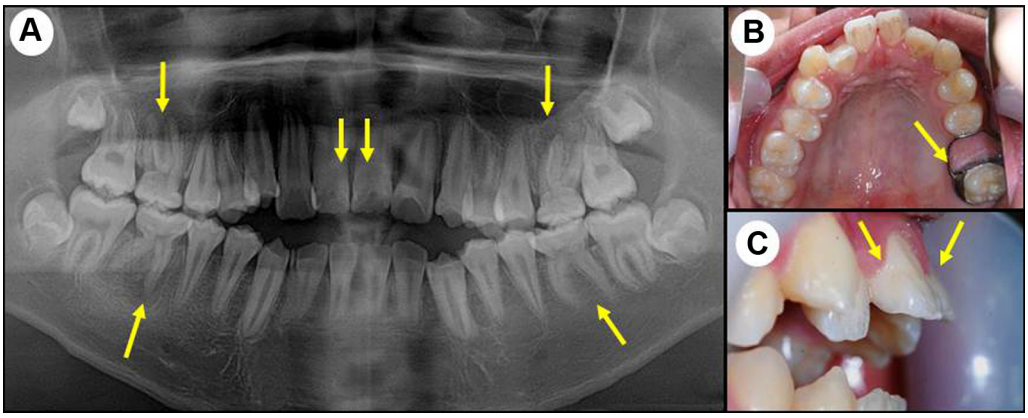
Supplemental Figure 5. Clinical photographs and radiographic film of patient 9 (an 8-year-old girl; see Table I). **A**, Panoramic film obtained at the first visit. The upper and lower bilateral permanent first molars exhibit a normal crown contour, but the roots are vestigial or undeveloped. The distal root of the upper right and lower bilateral deciduous second molars had been resorbed. In addition, the pulp cavities in the crowns appear to be constricted into a straight form. **B**, Clinical photograph (lateral view) obtained 1 year after the first visit. A wedge-shaped defect is evident on the labiocervical surface of the upper incisors (arrows). **C**, Clinical photograph (upper view) obtained at the same time as the photograph in B. The upper bilateral permanent first molars have a normal crown (arrows). Upper bilateral second premolar space loss has occurred owing to early loss of the upper bilateral deciduous second molars.



Supplemental Figure 6. Radiographic film of patient 10 (a 9-year-old girl; see Table I). Panoramic film obtained at the first visit. The upper and lower bilateral permanent first molars exhibit a normal crown contour, but the roots are elongated or dilacerated. The upper right permanent first molar has replaced the upper right deciduous second molar. It was supposed that the distal root of the upper right deciduous second molar had been absorbed by the upper right permanent first molar. The upper bilateral incisors have a cervical notch on the cervical one-third portion of the crown but have normal root formation.



Supplemental Figure 7. Clinical photographs and radiographic film of patient 11 (a 9-year-old boy; see Table I). **A**, Panoramic film obtained at the first visit. The upper and lower bilateral permanent first molars exhibit a normal crown contour, but the roots are vestigial or undeveloped. The patient experienced intermittent pain at nighttime. Although the lower bilateral permanent first molars had no clinical symptoms, a radiolucent lesion can be seen on the furcation area of those teeth. In addition, the pulp cavities in the crowns appear to be constricted into a straight form. The upper bilateral incisors have a cervical notch on the cervical one-third portion of the crown but have normal root formation. **B**, Clinical photograph (lower-left view) obtained at 3 years and 8 months after the first visit. Fistula formation can be observed on the buccal gingiva of the lower left permanent molar (arrow). The tooth had to be extracted because of tooth mobility (+), a positive reaction to percussion (+), and apical involvement. **C**, Clinical photograph (lateral view) obtained at the same time as the photograph in **B**. The upper bilateral incisors have a cervical notch on the cervical one-third portion of the crown (arrows) but have normal root formation.



Supplemental Figure 8. Clinical photographs and radiographic film of patient 12 (a 13-year-old boy; see Table I). **A**, Panoramic film obtained at his first visit. The upper and lower bilateral permanent first molars exhibit a normal crown contour, but the roots are vestigial or undeveloped. Although this patient had no symptoms, the lower right and upper left permanent first molars exhibit radiolucent lesions on the mesial root apex. In addition, the pulp cavities in the crowns appear to be constricted into a straight form. The upper bilateral incisors have a cervical notch on the cervical one-third portion of the crown but have normal root formation. B, Clinical photograph (upper view) obtained 2 years after the first visit. A band and loop can be seen at the upper left permanent molar space (arrow). This was placed after extraction of the tooth owing to failure of pulp treatment. **C**, Clinical photograph (lateral view) obtained at the same time as the photograph in **B**. The upper bilateral incisors have a cervical notch on the cervical one-third portion of the crown (arrows) but have normal root formation.