Inflammatory Paradental Cyst of the First Molar (Buccal Bifurcation Cyst) in a 6-Year-old Boy: Case Report with Respect to Immunohistochemical Findings

REINHARD E. FRIEDRICH¹, HANNA A. SCHEUER² and JOZEF ZUSTIN³

¹Oral and Cranio-Maxillofacial Surgery and ²Orthodontics, Eppendorf University Hospital, University of Hamburg, Germany; ³Pathology, University of Münster, Germany

Abstract. The inflammatory paradental cyst (IPC) is a relatively rarely reported lesion arising from the lateral periodontium of vital teeth. However, IPC appear to be under-represented in registers of odontogenic cysts due to the misinterpretation of IPC as infected dentigerous cysts, in particular IPC originating from third molars. IPCs exhibit some temporospatial associations with tooth eruptions and occur almost exclusively in the mandible. The IPC of the first molar is predominantly diagnosed in children younger than 10 years. Bony bulging in the area of cyst formation may alert parents to seek medical advice. This case report details the characteristic clinical and radiological features of a first molar IPC arising in a child. The features of the presented cyst correspond well to the attributes qualifying for a so-called buccal bifurcation cyst. A conservative treatment regimen proved to be successful. Certain immunohistochemical markers are reported to further characterize this entirely benign lesion.

The World Health Organization classification of odontogenic cysts includes two types of cysts with an inflammatory pathogenesis: the radicular cyst is caused by an infected and dead dental pulp with consequent cyst formation arising from the apex or lateral parts of the root. The paradental cyst is defined as a cyst ‘originating from the cervical margin of the lateral aspect of a root’ as a consequence of inflammation in the dental pocket in a vital tooth (1). The term inflammatory paradental cyst (IPC) has been proposed to describe this entity properly due to the inflammatory aspect of the cystic lining and to delineate this entity from the lateral periodontal cyst (2). However, there are plenty of synonyms used to ascribe this type of an odontogenic cyst (2). IPCs are preferentially diagnosed in mandibular molars (3, 4), in particular associated with incompletely erupted third molars (1). However, all molars can give rise to this type of cyst, presenting with a certain clinical and radiological phenotype (2), and even mandibular premolars appear to develop IPC (5). Maxillary IPCs are rarely reported (6). Usually IPCs are single findings of permanent teeth (2). Rarely have bilateral mandibular IPCs been treated (7). Localization of IPCs in relation to teeth is crucial for treatment planning (2). IPC of third molars is an indication for osteotomy of the tooth, whereas diagnosis of those arising in first and second molars should follow a conservative surgical approach (2, 7-10).

Due to their distinct clinical and radiological features, first and second molar IPCs are synonymously-termed ‘buccal bifurcation cysts’ (11-16). A large review on epidemiological data provided for IPC excluded any predilection for gender but revealed a preference for certain age periods and the development of IPC (2). This relation between the period of time of cyst diagnosis and preference for a certain molar to develop IPC was closely related to the known eruption times of mandibular molars (7, 17). Thus, first molar IPCs are preferentially diagnosed in the first and second decade of life, consequently the other two molars are diagnosed later. Despite efforts to make this entity known to the scientific community, IPCs are not well appreciated as a distinctive type of odontogenic cysts (2, 10). It is likely that many cases of IPC are registered as inflamed dentigerous cyst (2, 10).

We herein report the treatment, some diagnostic findings, and the follow-up of a young patient who developed a lesion of the jaw that proved to be an IPC with findings attributable to a so-called buccal bifurcation cyst.

Correspondence to: Professor R.E. Friedrich, MD, DMD, Ph.D., Oral and Cranio-Maxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Martinistr. 52, D-20246 Hamburg, Germany. Tel: +49 40741053259, e-mail: rfriedrich@uke.de

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Case Report

A 6-year-old boy was sent to the Oral and Maxillofacial Outpatient Clinic, Eppendorf University Hospital, for diagnosis and treatment of a swelling of the left mandible. Upon admission, the left cheek was slightly swollen, with no erythema, and the integument was intact. Oral investigation showed a caries-free mixed dentition. Testing for pulp sensitivity was performed with carbon dioxide snow that proved adequate sensitivity of all teeth. On oral palpation, below a healthy mucosal layer, the mandible markedly bulged into the vestibule of the left first molar region. The patient denied pain but refrained from further detailed oral examination. Firstly, a B-scan ultrasound investigation was performed. The ultrasound (7.5 MHz) was completely reflected from the bulged mandibular surface (Figure 1B). The patient had no lymphadenopathy visible by this method.

Radiography. A panoramic radiograph was performed that disclosed a mixed dentition according to age (Figure 1A). In the left molar region, a discrete transparency of the interradicular bone was detectable, but the lamina was not interrupted (Figure 1C). This radiological finding did not properly disclose the clinically-apparent underlying osseous pathology. Therefore, we decided to perform a cone beam computed tomogram (CBCT) of the left mandibular region. On CBCT, a roundish osteolytic lesion was seen lateral to the first molar that bulged into the extended vestibular cortex.
of the bone (Figure 2A-C). The transparent lesion was attached to the lateral surface of the first molar’s roots (Figure 2A–C). Interestingly, the alveolar ridge did not reach the enamel-cementum border (Figure 2A). An opening of the cyst-like lesion to the oral cavity was imaged best on sagittal tomograms (Figure 2A). The roots of the tooth were tilted to the lingual aspect of the mandible (Figure 2A–C). The osteolytic lesion appeared to be in close contact to the crown of the developing second molar (Figure 2D).

**Treatment.** Surgical exploration of the region via an oral approach disclosed an intact vestibular cortical layer (Figure 3A). A cortical lid was created (Figure 3B) and temporarily explanted; it had covered a unilocular cavity (Figure 3C). The sparse lining of the cystic cavity (Figure 3C and D) was peeled-off the osseous shell (Figure 3E) without damage to the exposed roots (Figure 3D). From the bottom of the vestibular side of the cyst, a small osseous biopsy was also obtained for histological analysis (Figure 4). The bony lid was re-inserted into the defect and the mucoperiosteal flap was fixed over the bone graft. The periodontal pocket on the distal side of the tooth was not removed. Healing was uneventful. Over a period of 15 months, the patient was repeatedly investigated. The first molar maintained sensitivity, although delayed compared to the other teeth of the quadrant. The final CBCT revealed complete osseous healing, with a
minor indentation of the vestibule into the bone in the osteotomy region (Figure 2G) and persistent bone loss at the origin of root bifurcation (Figure 2F). The periodontal fistula had disappeared spontaneously (Figure 2H). The height loss of the alveolar crest surrounding the first molar in the region of the former cyst was still present (Figure 2E).

**Histology.** The cyst wall was comprised of a fibrous connective tissue lined by a non-keratinized squamous stratified epithelium. There were neither mineralized structures nor other epithelia apparent within the lesion. The thickness of the epithelia varied considerably in close association with the amount of inflammation. The cyst was surrounded by a dense, chronic inflammatory cellular infiltrate consisting of lymphocytes and plasma cells, along with moderate active inflammation represented by diffuse infiltration by neutrophils. These histological findings allowed the diagnosis of IPC in due consideration of the radiological findings.

**Immunohistochemistry.** Representative sections from the formalin-fixed, paraffin-embedded tissue blocks were examined using automated immunohistochemical systems. The freshly-cut sections were loaded into a PT Link module (Dako, Glostrup, Denmark) and subjected to an antigen retrieval/de-waxing protocol with a Dako EnVision FLEX Target Retrieval Solution, at high pH, and then transferred to the Dako Autostainer Link 48 instrument. Immunostaining was performed using the primary antibodies to D2-40 (Dakor072), and to p40 (RBG054; Zytomed Systems, Berlin, Germany), and the Dako EnVision Flex detection system. Microscopic analyses were performed using a Zeiss...
microscope (Axiophot; Carl Zeiss, Jena, Germany) and representative microphotographs were taken using a digital camera (AxioCam MRC; Carl Zeiss), and AxioVision Rel.4.8 imaging software (Carl Zeiss).

The D2-40 antibody strongly marked basal epithelia (Figure 4C) and was not identified in the stroma. This antibody identifies podoplanin, a protein expressed in lymphatic vessels and in numerous epithelial tissues, both in benign and malignant lesions (18, 19). The antibody against p40 stained the thin epithelial layers of the cyst with preference for basal cells (Figure 4D). The antibody recognizes a small fragment of the p63 protein in humans (20), and appears to identify squamous epithelial cells more specifically than other antibodies recognizing members of the p63 family (20).

Discussion

This report details some findings indicative of an IPC that are relevant for diagnosis and treatment planning in oral surgery, particularly in children. IPC is an odontogenic cyst.

Figure 4. Histopathological findings of inflammatory paradental cyst. A: The inflammatory cyst wall (upper right) exhibited intraluminal purulent exudate and superficial cell-rich areas next to fibrous stroma. The latter was associated with abutment of the cortical bone (middle left), which was almost completely absent at the top of the lesion (lower right). The marrow spaces of the jaw bone were replaced with fibrous tissue with scattered inflammatory cell infiltrate. Neither fatty bone marrow nor hematopoiesis were apparent (undecalcified bone preparation, embedding in methylmethacrylate, stain: Goldner trichrome, original magnification: x25). B: Under higher power, the superficial cyst wall exhibited similar histopathological findings to radicular cyst, with stratified non-keratinized epithelium, moderate epitheliomatosis and dense lympho-plasmacellular infiltrate and neutrophil granulocytes (paraffin embedding, stain: hematoxylin-eosin, original magnification: x100). C: The nuclei of basal and parabasal epithelial cells showed positive reaction with p40 antibody (paraffin embedding, immunohistochemical reaction: p40, original magnification: x100). D: Similarly, we observed a positive reaction of the basal and parabasal epithelia for podoplanin (paraffin embedding, immunohistochemical reaction: D2-40, original magnification: x100).
developing in conjunction with vital teeth associated with pericoronal infection. The term IPC should only be used in cases with an inflammatory para-radicular cyst associated with a vital tooth and, irrespective of the cyst’s location, the associated tooth should be partly or fully erupted (2).

IPC is a relatively rarely reported entity in the scientific literature (2, 10). The entity is either widely unknown or neither radiologically nor clinically acknowledged (2). Furthermore, the histological distinction between dentigerous cysts and IPC may frequently not have been made, possibly due to inadequate clinical records (2). On the other hand, in rare cases, a follicular cyst in a molar which failed to erupt may be secondarily inflamed via a periodontal path and consequently exhibit an epithelial lining resembling an IPC (21). Indeed, some authors announced their uncertainty in clearly distinguishing between dentigerous cyst and IPC as entities of their own or simply as variants of cyst formation occurring in the process of tooth emergence (22). IPCs may occasionally simulate a periodontal pocket (23). Indeed, de Sousa et al. demonstrated the continuity of the cystic epithelial lining with the oral epithelium (24). Shear and Speight agree with these authors’ suggestions to describe the IPC as ‘equivalent to a dilated follicle lined by hyperplastic and proliferative follicular (reduced enamel) epithelium’ (10). The IPC possibly develops as a consequence of inflammation-driven swelling of the periodontal mucosa, leading to occlusion of the opening of the periodontal pocket (10). Food impaction could facilitate the occlusion of the drainage and support the inflammation (25).

Histologically, an IPC cannot be distinguished from a radicular cyst (2, 10). IPC of the third molars may be difficult to distinguish from dentigerous cysts, in particular in fragmented samples (10). The attachment of the cyst to the root surface covering the bifurcation is visible in the affected third molar after extraction (2, 4).

IPC of the first molar exhibits some clinical and radiological characteristics that caused some authors to distinguish the buccal bifurcation cyst from other inflammatory cysts of dental origin (12, 14, 16). However, it is widely accepted to assign these temporospatial variations of paradental cysts under the umbrella term “IPC” due to the likely common pathogenetic pathways of all these cysts (2). First molar IPCs are predominantly diagnosed in children (7). This type of IPC is closely associated with the time frame expected for first molar eruption (7, 8). IPCs appear to produce no or only mild symptoms. Clinical records of affected individuals occasionally may reveal modest pain and swelling, and painful occlusion of teeth of the affected molar region (2, 7). This was documented in our patient.

The cellular pathogenesis of IPC is still a matter of debate. Some authors suppose the epithelial origin of the cyst from junctional epithelium or cell nests of Malassez, others discuss reduced enamel epithelium as the site of origin (17). The cysts are usually associated with enamel projections or ridges extending into the buccal bifurcation of the dental roots (4). These developmental anomalies are purported to be instrumental in the pathogenesis of IPC (17). However, this theory has not yet been proven. The preference of IPC to arise in the buccal aspect of the bone was explained by Stoneman and Worth with reference to the sequence of the cusp emerging into the oral cavity: the mesio-buccal cusp is the first to penetrate through the covering soft tissues into the oral cavity (16).

Podoplanin is a protein of unknown function. Podoplanin is associated with the migration of cells (18). The continuous D2-40 immunostaining of the lining of the basal epithelia in the cyst wall possibly discloses the ability of the cystic epithelia to migrate and to displace cells, thereby promoting cyst extension.

p63 belongs to the p53 family and is probably the phylogenetically older protein from which p53 differentiated (20). Intact p63 has many functions and is required to denote damaged cells which should undergo apoptosis (10). The p40 protein is a small fragment of the p63 protein. The p40 protein is expressed in squamous epithelial cells. Antibodies against p40 are used to identify squamous epithelial cells, e.g. in undifferentiated cancer specimens. We are not aware of any other reports studying the expression of p63 or fragments of this protein in IPC. In this case, we revealed an intense accumulation of p40 in IPC, possibly occurring in the context of aberrant apoptosis.

Analysis of treatment options as derived from the literature still leads to controversial results, but recent reports detail a successful conservative approach to IPC originating from first or second molars (7, 15). In selected cases, even a wait-and-see policy may occasionally be adequate to manage affected individuals (26). However, the differential diagnosis of extensive cyst-like formations in the jaw requires for a clear clinical and histological diagnosis (7).

Conclusion

A distinct clinical phenotype of inflammatory odontogenic cysts, the IPC, is probably an underdiagnosed entity. The acute symptoms and findings sometimes associated with the first investigation of patients may suggest a harmful disease. IPC affecting first or second inferior molars are also called buccal bifurcation cyst. This subtype of IPC is closely associated with the emergence of first and second molars, and is thus predominantly diagnosed in children. Knowledge about the variations of odontogenic cysts, including the capacity to thoroughly distinguish radiological and physical findings, allows a conservative treatment of IPC of the first molar.
References

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