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Clinical Report

Primary Intraosseous Odontogenic Carcinoma Arising from a Dentigerous Cyst

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Abstract: Malignant tumors arising from dentigerous cysts are classified as primary squamous cell carcinoma derived from an odontogenic cyst or as odontogenic carcinoma according to the 2005 WHO classification and are extremely rare. We report a malignant tumor arising from a dentigerous cyst in the right maxillary anterior teeth , together with a literature review. The patient was a 75-year-old man who visited a hospital with complaining of discomfort in the lingual part of the right maxillary anterior teeth. On panoramic radiography and plain computed tomography (CT), dentigerous cyst, keratocystic odontogenic tumor or ameloblastoma was suspected. The extirpated material was histopathologically diagnosed as an odontogenic carcinoma (in situ) arising from the dentigerous cyst. Postoperative ultrasonography (US) and contrast enhanced CT revealed no metastasis to the cervical lymph nodes. The patient is currently being followed up without resection or anticancer drug administration. Neither local recurrence nor metastases were observed 18 month after surgery.

Key words: Dentigerous cyst, Maxilla, Primary intraosseous odontogenic carcinoma

Introduction

A dentigerous cyst arises from odontogenic epithelium at the end of crown formation. That is commonly developed in the mandibular impacted wisdom tooth or impacted supernumerary teeth between the incisor and canine region. Odontogenic cysts and odontogenic tumors rarely become malignant. In particular, a keratocystic odontogenic tumor has high proliferative activity and rarely causes malignant transformation of the lining epithelium in the cyst wall. Furthermore, it tends to recur with local infiltration[2]. However, the lining epithelium of the dentigerous cyst does not show remarkable proliferative activity in comparison with keratocystic odontogenic tumor, and seldom becomes malignant. There is little information about the cause of malignant tumors arising from dentigerous cyst. The cyst epithelium may be stimulated by chronic inflammation, resulting in malignant transformation[3,4]. Twenty-one case reports regarding malignant tumors arising from dentigerous cysts[3,4,5-23] were searched newly by PudMed, Science Links Japan of the Japan Science and Technology Agency (J-EAST: JST English Article of S&T database). These included a report by Yasuoka et a[l5]. Herein, we present our case with a malignant tumor arising from a dentigerous cyst in the maxillary anterior teeth and reviewed 21 other cases reported in the literature.

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Materials and Methods

The patient was a 75-year-old man. He had been aware of discomfort in the lingual part of the right maxillary anterior teeth since February 2010, but he ignored it. The patient subsequently visited our hospital at March 2010 because the discomfort still continued without remission. No abnormalities were observed in the oral mucosa overall, with neither swelling nor bone protrusion in the labial and palatal parts of the right maxillary anterior teeth, at first examination. In addition, no paresthesia was found around the upper lip. The cervical and submandibular lymph nodes were non-palpable. His past and family histories were unremarkable.

Panoramic radiography (Fig. 1a) and intraoral radiology (Fig. 1b) at first visit revealed a well-defined and irregularly-shaped radiolucent lesion including impacted supernumerary mediodens between the right maxillary central incisor and lateral incisor. CT imaging showed a well-defined round lesion including a uniform soft tissue density mass (Fig. 2a). Multi-planar reconstruction (MPR) of the CT images revealed thinning and partial absorption at the base of the nasal cavity (Fig. 2b). Incisive canals were

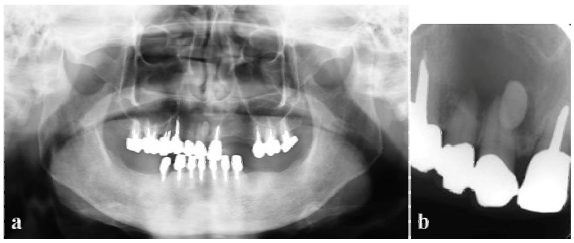

Figure 1a. Panoramic radiographs revealed a well-defined, round, radiolucent lesion including an impacted supernumerary tooth at the midline maxillary region.
Figure 1b. Intraoral image revealed a well-defined and irregularly-shaped radiolucent lesion including an impacted supernumerary mediodens between the right maxillary central incisor and the lateral incisor.

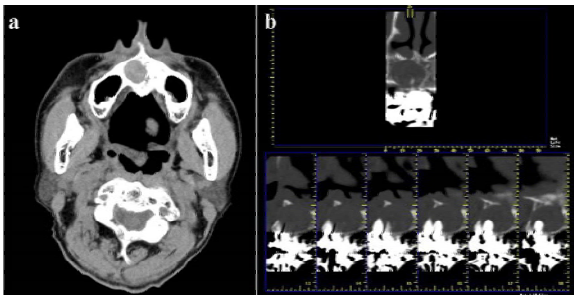

Figure 2a. CT images showed a well-defined round lesion including a uniform soft tissue density mass.
Figure 2b. Multi-planar reconstruction (MPR) of the CT revealed thinning and partial absorption at the base of the nasal cavity. Incisive canals were compressed to the left side by the lesion.

compressed to the left side by the lesion.

Results

Clinical symptoms and diagnostic imaging suggested a dentigerous cyst, keratocystic odontogenic tumor, or an ameloblastoma. Extraction of the right impacted supernumerary mediodens and extirpation of the cyst were performed under general anesthesia at June 2010. Intraoperatively, the mucoperiosteal flap was easily detached from the palatal bone without adhesion to surrounding structures. The fluid was white in a soft aqueous solution state. The extirpated material associated with the impacted tooth showed a unilocular cyst wall that was rough, corrugated and yellowish-white in color with brown spots (Fig. 3). Microscopically, the unilocular cyst wall was mainly lined by hypertrophic stratified squamous epithelium which was attached to the periodontal ligament of the impacted tooth (Fig. 4a). Most of the lining epithelium had a thickened keratinized layer, although non-keratinized epithelium was present in some parts. This epithelium showed markedly atypical cell proliferation. High power microscopic examination revealed atypical cells with hyperchromatism, anisocytosis, and atypical mitoses, whereas no atypical cells invaded the stroma (Fig. 4b). The cyst wall contained thin connective tissue with diffuse lymphocyte and plasma cell infiltrates. Immunohistochemically, the atypical epithelium showed a Ki-67 positive reaction in the nuclei of basal, parabasal and spinous cells (Fig. 5a). CK19 expression was observed in a full thickness layer of the non-keratinized epithelium without atypia, while no malignant keratinized epithelium was present (Fig. 5b). Conversely, CK17 was localized in the parabasal to superficial layers of the keratinized epithelium with strong atypia (Fig. 5c). Histopathologically, the diagnosis was odontogenic carcinoma (in situ) arising from a dentigerous cyst.

Postoperatively, US and contrast enhanced CT revealed no metastases to the cervical lymph nodes. We informed to the patient that adequate follow-up was essential. He is currently being followed up without resection of the right maxilla or chemotherapy. Neither local recurrence nor metastases were observed 18 month after surgery.

Discussion

According to the 2005 WHO odontogenic tumor histological classification,[1] odontogenic carcinoma is classified into metastasizing ameloblastoma, ameloblastic carcinoma-primary type, ameloblastic carcinoma-secondary type, intraosseous, ameloblastic carcinoma-secondary type, peripheral, primary intraosseous squamous cell carcinoma, primary intraosseous squamous cell carcinoma derived from keratocystic odontogenic tumour, primary intraosseous squamous cell carcinoma derived from odontogenic cysts, clear cell odontogenic carcinoma, and ghost cell odontogenic carcinoma. The causes of clinical symptoms or malignant transformation and histopathological morphology have not been adequately investigated because there are few reports on these lesions.

Odontogenic carcinoma is reported to be histologically derived from epithelial debris of the tooth germ, dental lamina, or Malassez, regressed enamel epithelium, epithelial debris of united projections, epithelium of the odontogenic cyst wall, epithelial components of odontogenic tumors, migrating salivary gland tissues in the jawbones, and mucous epithelium[24,25]. Malignant tumors rarely occur from the wall of the odontogenic cyst with the incidence rate of 0.3 to 2%[26,27]. Five cases (1.8%) of central carcinoma of the jaws were reported among 292 oral carcinomas by Van der Waal et al.[14] Otten et al.[26] reported 5 cases (1.6%) among 371 oral carcinomas. One case (0.14%) among 677 odontogenic cysts, reported by Stoelinga et al.[27] and one (0.13%) among 758 cystic diseases, reported by Kreidler et al. [28] were malignant tumors.

Malignant tumors arising from odontogenic cysts mainly included malignant transformation from radicular cyst, dentigerous cyst, residual cyst, and odontogenic keratocyst. Particularly, malignant transformation associated with basal nevus syndrome derived from odontogenic keratocyst has often been reported.

Only 22 cases (including our present case) with malignant

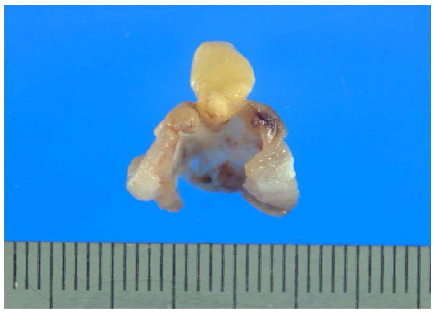

Figure 3. The extirpated material showed a unilocular cyst wall that was rough, corrugated, and yellowish-white in color with brown spots.

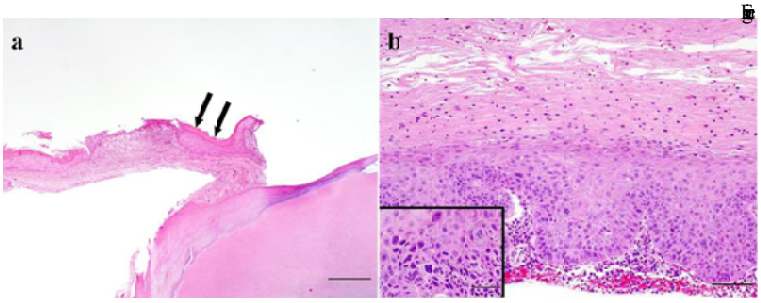

Figure 4a. The unilocular cyst wall was mainly lined by hypertrophic stratified squamous epithelium (arrows) which was attached to the periodontal ligament of the impacted tooth. (hematoxylin and eosin-stained).
Figure 4b. The lining of the cyst was thickened keratinized epithelium showing markedly atypical cell proliferation without invasion. Atypical cells with atypical mitoses are shown in the inset. (hematoxylin and eosin-stained). (a , scale bar = 500 μm ; b, scale bar = 100 μm ; inset, scale bar= 50 μm)

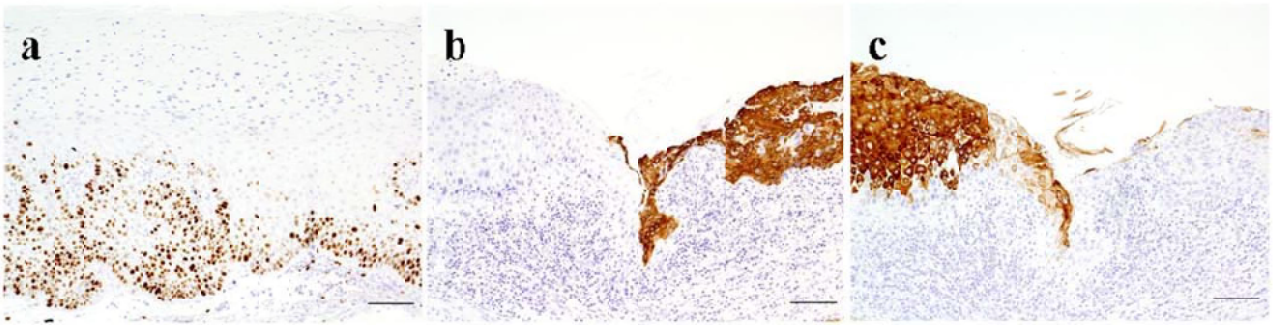

Figure 5a. The atypical epithelium showed a Ki-67-positive reaction in the nuclei of basal, parabasal, and spinous cells.
Figure 5b. CK19 expression was observed in a full thickness layer of the non-keratinized epithelium without atypia, but not in atypical epithelium.
Figure 5c. CK17 was localized in the parabasal to superficial layers of the atypical epithelium. (a - c, scale bar = 100μm)

tumors derived from dentigerous cysts have been reported in the literature. We investigated these reports based on the analysis of Yasuoka et al.[5] (Table 1). Age at onset varied, ranging from 18 months to 84 years with the mean of 57 years. Since a dentigerous cyst tends to develop more likely in subjects aged 20 to 30 years, malignant tumors from the cyst epithelium is expected to occur at the age of 50 to 60 years because 30 to 40 years may be required for slow development[29]. However, a report of 18-month old child suggests that malignant tumor developed from the cyst epithelium may not need a long time[3].

Malignant tumors from a dentigerous cyst develop more frequently in men than in women. Johnson et al.[17] and Manganaro et al.[19] reported that the ratio of a male to female was 2.5:1, that is consistent with other reports (other reference). Dentigerous cyst is sometimes associated with the mandibular third molar, maxillary canine, maxillary third molar and mandibular second premolar. Likewise, malignant tumors arising from a dentigerous cyst also commonly occur in the mandibular third molar. In our case, the malignant tumor rarely occured associated with a supernumerary tooth in the maxillary midline.

Histological type was a squamous carcinoma in nearly all cases with malignant tumors arising from a dentigerous cyst (Table 2) as follows: 3 cases with well-differentiated squamous carcinoma; 13 with an intermediate form between well-differentiated and

Table 1 Reported cases with squamous cell carcinomas arising from dentigerous cysts

Case No.	Authors	Age (year-old)	Gender	Chief Complaint	Site	Involved tooth
1	Bradfield et al, 1958	33	Female	Painless swelling	Lt mandible	Second premolar
2	Williams et al, 1963	59	Male	Asymptomatic	Rt maxilla	Central incisor
3	Howard et al, 1965	69	Male	Inadequately fitting lower partial denture	Lt mandible	Third molar
4	Angelopoulos et al, 1966	74	Male	Pain on opening mouth	Lt mandible	Third molar
5	Lee et al, 1967	57	Male	Fluctuant swelling	Rt maxilla	Central incisor
6	Chretien et al, 1970	55	Male	Asymptomatic	Lt mandible	Canine
7	Lapin et al, 1973	55	Male	Trismus	Lt mandible	Third molar
8	Norris et al, 1984	26	Male	Acute Pain	Rt mandible	Third molar
9	Van der Waal et al, 1985	48	Male	Asymptomatic	Lt mandible	Third molar
10	Bradley et al, 1988	63	Male	Dull pain	Lt mandible	Third molar
11	Berenholz et al, 1988	79	Female	III-fitting dentur	Lt maxilla	Canine
12	Maxymiw et al, 1991	72	Male	Asymptomatic	Rt mandible	Third molar
13	Johnson et al, 1994	63	Male	Facial swelling	Rt mandible	Third molar
14	Copete et al, 1996	41	Male	Discomfort	Lt mandible	Third molar
15	Manganaro et al, 1997	84	Male	Submandibular neck mass	Rt mandible	Third molar
16	Yasuoka et al, 1998	64	Female	Tingling pain	Lt mandible	Third molar
17	Roof et al, 1999	56	Male	Asymptomatic	Lt mandible	Lateral incisor
18	Morimoto et al, 2001	76	Male	Nasal obstruction	Lt maxilla	Unknown
19	Gulbranson, 2002	16 month-old	Female	Rapidly expanding mass	Rt mandible	Unknown
20	Oshima et al, 2002	43	Female	Diffuse-swelling	Lt maxilla	Second premolar
21	Saito et al, 2005	52	Male	Extraction of impacted tooth	Rt mandible	Third molar
22	Uchida et al (present), 2011	75	Male	Feeling of incorrect placement	Rt maxilla	Central incisor

moderately differentiated types; 2 with moderately differentiated type; 2 with squamous carcinoma; 2 with unknown histopathology. Our case was relatively early diagnosed as having a squamous carcinoma arising from a dentigerous cyst, which suggested a rare histological type.

Diagnostic imaging of malignant odontogenic cysts showed irregular borders, buccolingual destruction of cortical bones, and root resorption of the adjacent teeth. The lesion clinically may contribute to pathologic fractures[4]. Imaging findings of the previous 21 cases in addition to our case revealed no apparent characteristics suggesting malignant tumors. This may be due to that fact that plain radiograph was used in most cases. Contrast enhanced CT or contrast enhanced MRI is preferable to differentiate malignant tumors with cystic lesions. Morimoto et al[21] reported that enhanced CT as well as enhanced MRI clearly visualized the border between a dentigerous cyst and the tumor area. Plain CT, contrast enhanced CT, US and MRI are essential because lymph node metastasis or recurrences have been documented in some cases even in the case of malignant tumors arising from odontogenic cysts. It is essential to determine the sizes of regional lymph nodes as well as the internal properties of the lesions and signal intensity of bone marrow by contrast enhanced CT and MRI.

Verification that malignant tumors have arisen from the wall of odontogenic cysts, requires rigid criteria. The three diagnostic criteria of Gardner[30,31] are widely accepted: 1) a microscopic transition area from benign cystic epithelial lining to invasive malignant squamous cell carcinoma; 2) no carcinoma changes in the overlying epithelium; 3) no source of carcinoma in the adjacent structures. In our case, in accordance with criterion 1, CK17-positive and CK19-negative findings that corresponded to an in situ lesion were detected as illustrated by histopathological findings (Fig. 5b, 5c). A transition area from CK19-positive non-keratinized stratified squamous epithelium to an in situ lesion was also present. In this patient, distinct abnormal finding on p53 was not confirmed. However, there exists malignant epithelial tumor with p53 negative, thus expression of p53 is considered not always to be the ground of malignancy. In accordance with criterion 2, intraoral clinical examination showed neither ulcers nor neoplastic lesions. In accordance with criterion 3, imaging findings and

Table 2 Histological types of malignant tumors arising from a dentigerous cyst

Case No	Authors	Histopathology
1	Bradfield et al, 1958	Moderately-differentiated SCC
2	Williams et al, 1963	Well-differentiated SCC
3	Howard et al, 1965	Well-differentiated SCC
4	Angelopoulos et al, 1966	Well-differentiated SCC
5	Lee et al, 1967	Carcinoma in situ
6	Chretien et al, 1970	Well-differentiated SCC
7	Lapin et al, 1973	Well-differentiated SCC
8	Norris et al, 1984	Well-differentiated SCC
9	Van der Waal et al, 1985	Well-differentiated SCC
10	Bradley et al, 1988	Moderately-differentiated SCC
11	Berenholz et al, 1988	Well-differentiated SCC
12	Maxymiw et al, 1991	Well-differentiated SCC
13	Johnson et al, 1994	Well-differentiated SCC
14	Copete et al, 1996	Moderately to well-differentiated SCC
15	Manganaro et al, 1997	Moderately to well-differentiated SCC
16	Yasuoka et al, 1998	Moderately to well-differentiated SCC
17	Roof et al, 1999	SCC (unknown differentiation)
18	Morimoto et al, 2001	SCC (unknown differentiation)
19	Gulbranson, 2002	Well-differentiated SCC
20	Oshima et al, 2002	Well-differentiated SCC
21	Saito et al, 2005	Well-differentiated SCC
22	Uchida et al (present), 2012	Carcinoma in situ

histopathological examination showed no obvious infiltrations. Particularly, the disease may have progressed relatively asymptomatically, possibly making it difficult to determine the transition area from normal cyst wall epithelium to invasive squamous cell carcinoma in the early stages. However, immunological examination revealed an obvious transition area in this case. As noted above, our case could be diagnosed as having carcinoma in situ arising from a dentigerous cyst.

Although the clear mechanism of malignant transformation in the lining epithelium of the odontogenic cyst remains unknown, long-term chronic inflammation may stimulate the lining epithelium, resulting in this transformation[3, 31,32]. However, a dentigerous cyst is due to the development of a cyst in the odontogenic epithelium of tooth crown, and may rarely be associated with chronic inflammation unless complicated by secondary infection. Based on histopathological findings, current case may represent chronic inflammation because of inflammatory cellular infiltration in the epithelial connective tissue. Moreover, repeated inflammation caused by apical periodontitis in the maxillary lateral incisor or canine tooth attached to the lesion may also have caused malignant transformation.

In our case, clinical symptoms suggested no malignancy. Fanibunada et al[33]. reported that cancerous cells are limited to the cyst wall in the early stages of malignant transformation. Therefore, carcinomas can be detected as jaw lesions before invasion of nerve fascicles without symptoms of paresthesia in many cases. Thus, a small early lesion without destruction of the surrounding jaw bones may, on rare occasion, be diagnosed as a malignant tumor at the first examination due to the paucity of clinical symptoms and the asymptomatic development of malignant tumors arising from odontogenic cysts. Therefore, it might be diagnosed as a malignant tumor with an extirpated cyst sample from primary treatment or during follow-up after tooth extraction[33]. Some reports have shown that recurrences occurred in approximately half of cases after simple resection. Others recommend that aggressive treatments including radical neck dissection, radiotherapy and chemotherapy be performed based on wide excision[35]. Relatively few metastases to the lymph node have been found. There were no metastasis associated with squamous cell carcinomas derived from odontogenic cysts among 25 cases with central squamous carcinoma of the jaw, investigated by Gardener[30, 31]. On the other hand, Waldron et al.[36] reported one metastasis among 15 their cases. Histopathologically, our case had an in situ lesion without obvious infiltrative findings. Strict follow-up is thus being carried out without additional treatments at the maxillofacial and oral surgeon's discretion.

A dentigerous cyst is one of odontogenic cysts commonly encountered in routine practice. However, it is noteworthy that malignant progression is rarely possible. Preoperative clinical findings and diagnostic imaging revealed few findings suggesting malignant transformation of tumors arising from a dentigerous cyst. It is important to thoroughly investigate whether malignant transformation other than secondary inflammatory changes is suggested by preoperative biopsy or intraoperative histopathological examination, particularly observation of the cyst wall. Some case reports of malignant transformation of apical cysts or keratinized odontogenic tumors and central carcinoma of the jaw have described these tumors as possibly being caused by odontogenic cysts within the jaw. Therefore, possible malignant transformation should be added to the differential diagnosis, when cystic diseases are detected.

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