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ORAL SURGERY

CASE REPORT

Primary intraosseous carcinoma arising in a dentigerous cyst: A case report

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Abstract

Dentigerous cysts are among the most common cysts of the jaw. They are attached to the crown of an unerupted tooth, most frequently third molars and maxillary canines. They are often asymptomatic and may therefore be diagnosed late. We report a case of a primary intraosseous carcinoma arising from the wall of a dentigerous cyst and describe the expression of typical genes associated with tumour growth and prognosis. The tumour expressed cytokeratins (CK) 5/6, 8, 14 and 19, but not CK7. Ki-67 and P53 were upregulated in dysplastic epithelium and tumour tissue. Although rare, the possibility for tumour development in the wall of a common cyst should be considered. The case emphasizes the importance of histopathological examination of surgical specimens, even if the clinical diagnosis seems obvious.

KEYWORDS
carsinoma, cyst, dental

INTRODUCTION

The dentigerous cyst is the second most common odontogenic cyst of the jaws and the most common developmental cyst. They are attached to the tooth cervix at the cementoenamel junction of an unerupted tooth, most frequently third molars and maxillary canines. A dentigerous cyst may be discovered as an incidental radiographic finding or a clinical expansion. It frequently presents as a well-demarcated, unilocular radiolucency centred lesion enclosing the crown of an impacted tooth.[1,2]

Malignant transformation of a cyst wall is extremely rare. Primary intraosseous odontogenic carcinoma (PIOC) is a squamous cell carcinoma arising within the jaws. It is thought to arise from residual odontogenic epithelium, and was first described as a central epidermoid carcinoma of the jaw.[3,4] A recent systematic review found that a majority of PIOC arises from odontogenic cysts, more commonly residual and radicular cysts and less often dentigerous cysts and odontogenic keratocysts.[5] Synonyms used for PIOC in literature are primary intraosseous squamous cell carcinoma, primary intra-alveolar epidermoid carcinoma and primary odontogenic carcinoma.[5–8] Although a well-documented entity, more case reports of malignant transformations of cysts of odontogenic origin and also malignant odontogenic tumours are needed.[9] This report describes a case of a PIOC arising from a dentigerous cyst. Clinical and histopathological features are described, including typical markers associated with tumour growth and prognosis. The patient has given informed consent prior to the report.

CASE REPORT

A 61-year-old otherwise healthy male was referred to the Department of Maxillofacial Surgery of the Haukeland University Hospital (HUH) in Bergen, Norway to be assessed due to a cystic lesion in the mandibula related to the impacted right third molar. The patient had a history of local pain and mobility of the second molar, which had been removed at a general dental office in advance (Figure 1A,B).

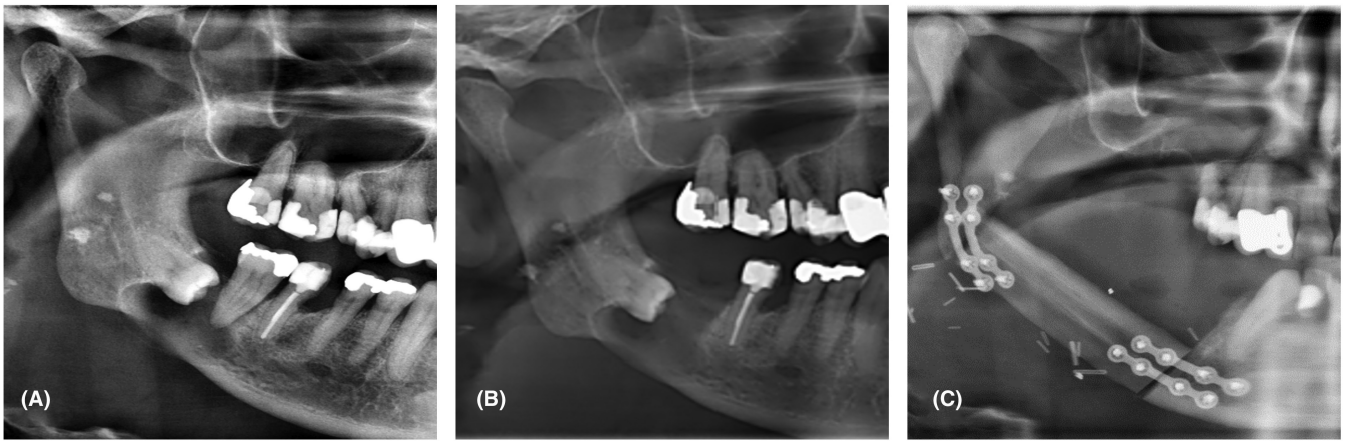

FIGURE 1 (A) Sectional panoramic radiograph reveals an impacted mandibular right third molar with a well-defined, round, unilocular radiolucent lesion surrounding the crown. The borders are well-defined with cortical demarcations. It was initially diagnosed as a dentigerous cyst; (B) Status after removing the right second molar at a general dentist's office; (C) Panoramic radiograph 1 month after surgical resection and reconstruction with a free vascularized fibula flap.

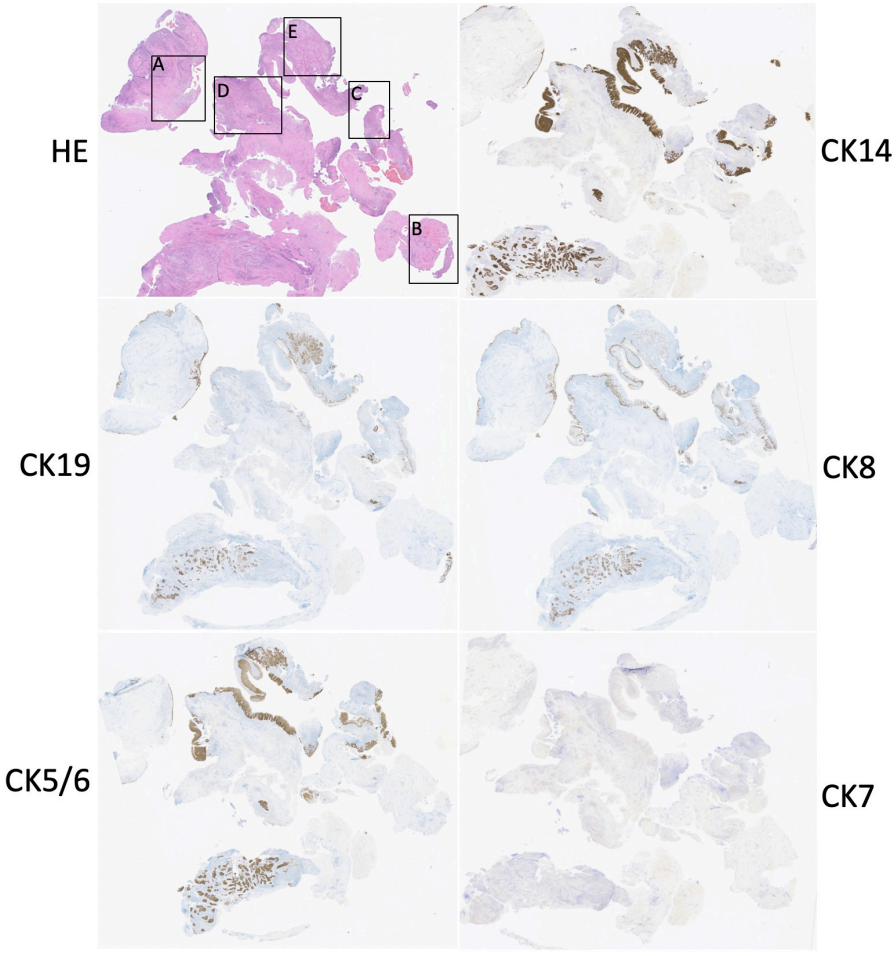

FIGURE 2 Overview of biopsy specimen stained with haematoxylin and eosin (HE) and a panel of cytokeratins (CK 19, CK8, CK5/6, CK14) showing irregular pieces of soft tissue which in some areas are covered with epithelium varying from normal nonkeratinized epithelium to dysplastic epithelium and areas of infiltrative growth of atypical squamous epithelium. Squares (A, B, C, D, E) are presented in Figure 3. CK7 is negative, while the other cytokeratins stain epithelium in different patterns (Figure 4). Original magnification: 0.6×.

Clinical examination revealed no oedema or enlarged lymph nodes, nor clinical signs of associated neuropathy. The oral mucosa was intact. A panoramic radiograph showed a relatively voluminous unilocular, well-defined and radiolucent cyst-like lesion, surrounding the crown of the impacted right third molar in the mandible (Figure 1A,B). Based on clinical and radiographic findings, the most likely diagnosis was a dentigerous cyst, or an odontogenic keratocyst. Surgical extraction of this molar and enucleation of the cyst was performed under general anaesthesia, due to risk for jaw fracture and subsequent need for other surgical measures. Treatment was done through an intraoral approach with ostectomy and removal of the tooth and cyst.

The histopathological examination showed cystic tissue with areas covered with non-keratinized epithelium, typical for a dentigerous cyst. However, other areas showed hyperplastic and dysplastic cyst epithelium and areas of atypical epithelium with infiltration into the underlying stroma consistent with a squamous cell carcinoma associated with chronic inflammatory cell infiltrate (Figures 2 and 3). There was chronic inflammation in the mature connective tissue stroma, especially related to the tumour tissue.

Immunohistochemistry showed that epithelial basal layers were positive for tumour suppressor gene p53 in dysplastic epithelium and tumour tissue, while there were only some scattered positive cells in normal cyst epithelium. The DNA polymerase Ki-67 indicated increased proliferation in the basal cells of the epithelium and in the periphery of the infiltrating tumour islands of dysplastic epithelium and tumour tissue, with only some few positive cells in the basal cell layer of normal cyst epithelium (Figures 2 and 4). Cytokeratins (CK) 8 and 19, high- and low-molecular weight CKs, respectively, of which both are associated with squamous cell epithelium dysplasia, were also positive in the basal layers.[10] Expression of these CKs may have prognostic impact.[10] CK5/6 and CK14 were strongly expressed throughout the epithelium. It has been suggested that these are associated with tumour size as well as lymph node status,[11] which was not the case in this later classified T1N0M0 tumour.[12] CK7 was not detected (Figure 2). The expression of CKs were largely similar in the non-dysplastic cyst epithelium.

A partial resection of the mandible including the mandibular canal was performed, followed by reconstruction with a free vascularized fibula flap (Figure 2C). The tumour was not invading adjacent bone and did not invade the mandibular canal. All tumour tissue was removed during the first operation. Chemo- or radiation therapy was deemed unnecessary as the tumour was classified, as mentioned, as a T1 primary intraosseous carcinoma according to the UICC guidelines for ICD-10 diagnosis C41.1, malignant tumour of the mandible.[12] Lymph node involvement or distant metastases were not suspected on CT- and MRI-scans. Regular follow-up for 12 months of a standard 5-year regime has not revealed any recurrence of the tumour.

DISCUSSION

Literature on PIOC is mostly limited to case series and case reports. It was probably first described in 1913 as a central epidermoid carcinoma.[4] Malignant transformations in odontogenic cysts have been described more recently.[13–15] The aetiology has not been clearly understood. There are reports that suggested that chronic inflammation of cyst epithelium for a long time could be a predisposing factor for malignant transformation.[3,16] The incidence is low and approximately 257 cases are reported in the literature. Bodner et al. described that PIOC was associated with a residual or radicular cyst in 60% of the cases, and a dentigerous cyst or an odontogenic keratocyst in the remaining 40%,[3,5] while Morita et al. described the odontogenic keratocyst as the more common precursor lesion.[7,17] A recent systematic review found that this type of malignancy is more frequent in males 69% in their fifth to seventh decade of life. PIOC

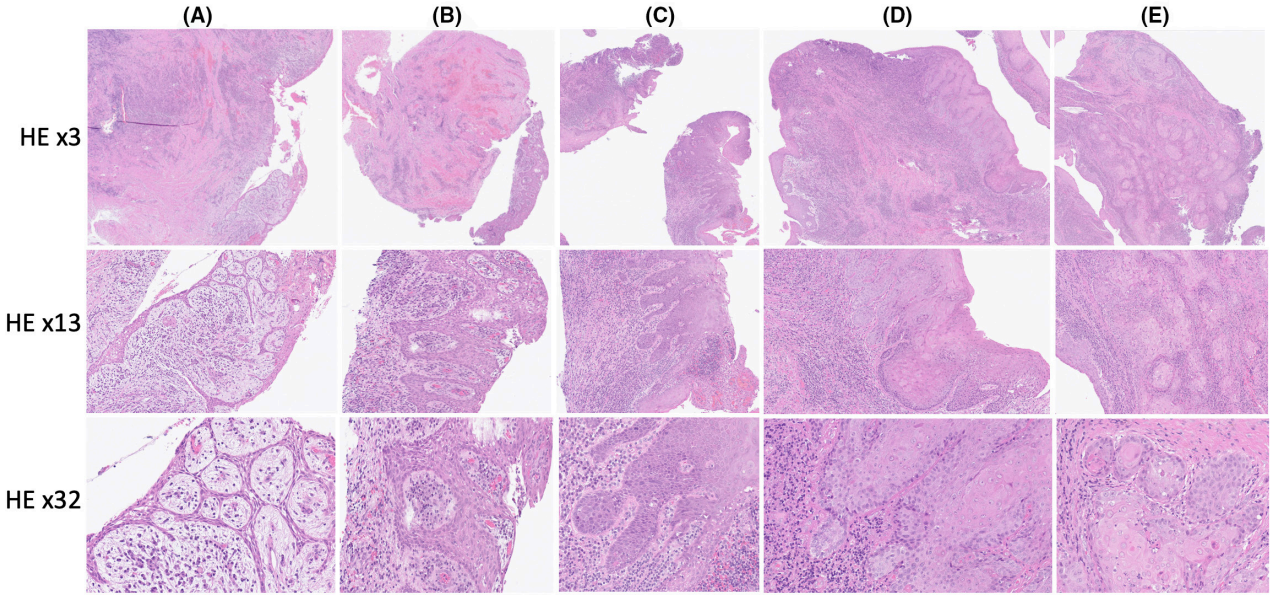

FIGURE 3 Microscopic details of H&E-stained section of the different regions of the cyst. (A) An area with non-keratinized cyst epithelium, proliferating into the connective tissue and lining chronically inflamed areas of the capsule; (B) Connective tissue covered by non-keratinized hyperplastic and non-dysplastic cyst epithelium lining chronically inflamed areas of the capsule; (C) Connective tissue covered by dysplastic epithelium, showing irregular rete pegs with cellular atypia; (D) Another area with dysplastic epithelium with drop shaped and irregular rete pegs, especially in the deepest parts; (E) Area with infiltrative growth of atypical squamous epithelium, surrounded by inflammatory cells in a mature connective tissue stroma.

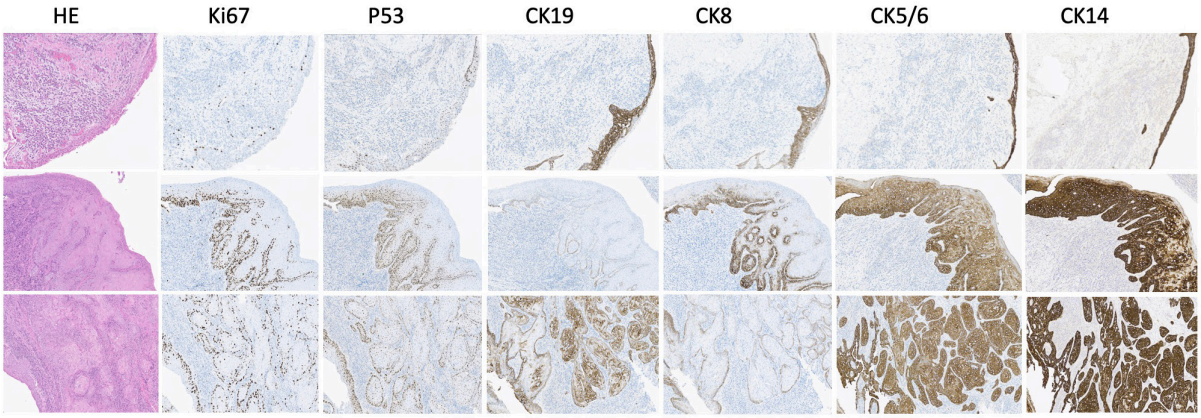

FIGURE 4 Immunohistochemistry of three different regions of the cyst capsule. Upper row: Area with normal non-keratinized cyst epithelium lining chronically inflamed connective tissue; Middle row: Area with dysplastic epithelium, partly also hyperplastic with elongated, irregular rete pegs; Lower row: Infiltrative growth of atypical squamous epithelium. In sections stained for CK19 and CK8, the direct infiltrative growth from the surface can be seen. In sections stained for CK5/6 and CK14, the surface epithelium is lost. Ki-67 shows hardly any positive cells in the normal cyst epithelium, while there is increased proliferation both in dysplastic epithelium and tumour tissue. P53 is also upregulated in dysplastic epithelium and tumour tissue, while normal cyst epithelium shows only some scattered positive cells. CK19 and CK8 are positive primarily in the basal cells in both normal cyst epithelium, dysplastic epithelium, and tumour tissue, while CK5/6 and CK14 are strongly expressed in all epithelial layers in all regions. Original magnification: 13×.

are more common in the mandible than maxilla with a proposed ratio of 7:1.[5] The most common tumour site is the posterior mandible (corpus and ramus). Cortical bone expansion, tooth mobility, pain and paraesthesia were relatively common clinical findings. Radiographically PIOC may appear as well defined as well as irregular lesions.[18] It has been reported that the incidence of PIOC is 0.3%–2% of all oral cancer cases. In one study, lymph node metastases were observed in 12.8% of the cases and local recurrence in 22.1%.[7] Most lesions are asymptomatic incidental radiographic findings. Kaffe et al. reported that 61% of PIOC cases presented as a unilocular radiolucent lesion.[19] Primary intraosseous carcinomas arising from odontogenic cysts may be misdiagnosed as a common dentigerous cyst, and proper diagnosis can usually be established only when histopathological analysis is performed. Cysts with irregular demarcation to adjacent bone, or paraesthesia of the affected area can be signs of a more aggressive lesion. In this present case, the lesion was a regular, well-defined radiolucency. Neural sensation was intact.

Surgical ablation or combined with neck dissection is performed in the majority of cases followed by surgical treatment combined with adjuvant radiotherapy, eventually combined with chemotherapy.[5,7] An insufficient number of cases have been reported to determine the outcome, but according to reported cases, the prognosis is generally poor and is best predicted by histological grade. The 2-year survival rate of reported cases is 62% and 5-year survival rate is 38%.[3]

Primary intraosseous odontogenic carcinoma of the jaws are quite rare, and a description of their genetic expressions may shed light on their aetiology and nature. In this case, the profile of CKs were quite similar in normal and dysplastic cyst epithelium, respectively, whereas Ki-67 and p53 were upregulated in the cancerous part of the lesion.

CONCLUSIONS

Malignant transformation in the epithelium of an odontogenic cyst is a rare occurrence that can be misdiagnosed as an odontogenic cyst due to lack of specific clinical and radiographic features. This case highlights the importance of a systematic submitting tissue for histological assessment of any lesion, even if it appears benign at first glance, and to be aware of the malignant potential of odontogenic cysts.

CONFLICT OF INTEREST STATEMENT

None of the authors declare any conflicts of interests regarding this paper.

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The authors have not recieved any particular funding for this project, which is considered part of the involved institution's requested activity.

DATA AVAILABILITY STATEMENT

I declare that all data underlying the results are available as part of the article, and no additional source data are required.

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