CASE REPORT

Primary intraosseous squamous cell carcinoma in odontogenic keratocyst: A rare entity

Chitrapriya Saxena, Pooja Aggarwal, Vijay Wadhwan, Vishal Bansal[1]
Departments of Oral Pathology and Microbiology and [1]Oral and Maxillofacial Surgery, Subharti Dental College, Meerut, Uttar Pradesh, India

Address for correspondence:
Dr. Chitrapriya Saxena,
Department of Oral Pathology and Microbiology,
Subharti Dental College,
Meerut, Uttar Pradesh, India.
E-mail: tripti.cp@gmail.com

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ABSTRACT

Squamous cell carcinoma (SCC) arising from the wall of an odontogenic cyst (also known as primary intraosseous carcinoma) is a rare tumor which occurs only in jaw bones. This tumor was first described by Loos in 1913 as a central epidermoid carcinoma of the jaw. Primary intraosseous carcinomas (PIOC) may theoretically arise from the lining of an odontogenic cyst or *de novo* from presumed odontogenic cell rests. According to the new histological classification of tumors of the World Health Organization, odontogenic keratocyst is nowadays considered a specific odontogenic tumor and the PIOC derived from it is considered as a specific entity which is different from other PIOCs derived from the odontogenic cysts. The following report describes a case of such extremely rare entity that is primary intraosseous SCC of the mandible derived from an OKC in a 60-year-old male patient with brief review of literature.

Key words: Mandible, odontogenic cyst, odontogenic keratocyst, primary intraosseous squamous cell carcinoma

INTRODUCTION

Carcinoma arising in the bone is an extremely rare condition. A primary intraosseous squamous cell carcinoma (PIOSCC) is defined as "a squamous cell carcinoma (SCC) arising within the jaw bones, which has no initial connection with the oral mucous membrane.[1]

Since the source of this lesion is epithelium involved in the odontogenesis, the World Health Organization (WHO) in 1972 suggested the term primary intraosseous carcinoma and classified the lesion as an odontogenic carcinoma.[2] The most recent WHO classification of odontogenic tumors categorizes primary intraosseous carcinomas (PIOC) as: Solid type carcinomas, carcinomas originating from keratocystic odontogenic tumor (KCOT) (odontogenic keratocyst [OKC]) and carcinomas arising from odontogenic cysts other than KCOTs. PIOC may theoretically arise from the lining of an odontogenic cyst or *de novo* from presumed odontogenic cell rests (e.g., reduced enamel epithelium).[3,4]

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The epithelial lining of odontogenic cysts can undergo simple cystic expansion, keratinization or dysplastic transformation. The most common neoplasms arising from the lining of odontogenic cysts are benign odontogenic tumor such as odontoma, calcifying epithelial odontogenic tumor, ameloblastic fibroma, calcifying epithelial odontogenic tumor and adenomatoid odontogenic tumor. However, it is well known that the lining of an odontogenic cyst may transform into a mucoepidermoid carcinoma or a SCC.[5-7]

Various odontogenic cysts have been associated with odontogenic SCC, including residual cyst, dentigerous cyst, calcifying odontogenic cyst and lateral periodontal cyst. The most common associated cyst is a residual cyst, followed by dentigerous cyst.[8] According to the new histological classification of tumors of the WHO, OKC is nowadays considered a specific odontogenic tumor and the PIOC derived from it is considered as a specific entity

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which is different from other PIOC's derived from the other odontogenic cysts.[2]

In this article, we report a rare case of SCC which originated from a KCOT in a 60-year-old patient.

Review of literature

PIOSCC was first described by Loos[9] in 1913 as a central epidermoid carcinoma of the jaw. Wills in 1948[10] renamed it an intraalveolar epidermoid carcinoma. It was then termed primary intraalveolar epidermoid carcinoma by Shear in 1969.[11] The WHO and Pindborg approved the term "primary intraosseous odontogenic carcinoma (PIOC)" in 1972 and classified the lesion as an odontogenic carcinoma.[12] Subsequently, Elzay[13] modified the WHO classification on PIOC of the jaw. Slootweg and Müller[14] slightly modified Elazy's classification in 1984 by considering various possible etiological factors. Waldron and Mustoe[3] completed the classification by addition of intraosseous mucoepidermoid carcinoma (IMEC) as a fourth type of PIOC. Finally, in the new WHO classification published in 2005, PIOSSC replaced the old terms and was sub-classified as (i) a solid tumor that invades marrow spaces and induces bone resorption, (ii) SCC arising from an OKC lining or carcinoma arising in other odontogenic cysts and (iii) SCC associated with benign epithelial odontogenic tumors.[1,15]

According to the new WHO classification of odontogenic cysts and tumors (2005), OKCs were designated as KCOTs.[1] PIOSSC arising from the wall of an OKC or KCOT is a rare tumor occurring within the jaw bones. Recently, Bodner *et al*. in 2011[16] conducted a retrospective study of 116 cases of PIOSCC between 1938 and 2010. The result of the study showed that there have been only 16 known cases of PIOSCC arising from an OKC comprising 14% of total odontogenic cyst.

CASE REPORT

A 60-year-old male patient reported with a chief complaint of swelling of the lower jaw since 6–7 months.

The patient was apparently asymptomatic 6–7 months back when he noticed swelling in the lower jaw which gradually increased to the present size and was associated with dull pain and paresthesia. Medical history was noncontributory. Dental history revealed multiple extractions 1 year back. Systemic evaluation of the patient was within permissible limits.

The patient had a history of bidi smoking, 2–3 packets/day since 40–45 years. On extraoral examination, facial asymmetry was present, swelling extending from right angle of mandible to left angle of mandible. Skin over the swelling was smooth, stretched and surrounding tissue appeared to be normal. There was no ulceration, sinus opening, or discoloration over the swelling [Figure 1].

On palpation, the swelling was nontender, bony hard in consistency, nonfluctuant, nonreducible and noncompressible with local rise in temperature. The regional lymphadenopathy was absent. Intraoral examination revealed partially edentulous maxillary and mandibular arch. Buccal vestibular region of mandible was obliterated. The overlying alveolar mucosa was intact without any evidence of any surface changes. The patient also complained of paresthesia [Figure 2].

Orthopantomogram revealed a multilocular radiolucent lesion extending from the right angle of mandible to the left angle of mandible, involvement of the inferior alveolar nerve canal and destruction of the lower border of the mandible [Figure 3].

Based on the clinical and radiographic examination, a provisional diagnosis of KCOT, ameloblastoma was given. Incisional biopsy was done and sent for histopathological examination. Hematoxylin and eosin stained section showed 8–10 layers thick parakeratinized stratified squamous epithelium with palisaded basal cell layer pattern suggestive of OKC [Figure 4]. At area, the proliferating odontogenic epithelium showed feature of dysplasia in the form of hyperchromatism, pleomorphism, basal cell hyperplasia, bizarre mitotic figure and altered nuclear cytoplasmic ratio [Figure 5]. Dysplastic islands were also evident in the underlying connective tissue stroma resembling moderately to poorly differentiated SCC [Figure 6]. To rule out IMEC, mucicarmine staining was performed which was negative. The histopathology was suggestive of PIOSCC arising from OKC lining.

The full body scan of the patient was done to rule out the distant metastasis. Hence, the final diagnosis of PIOSCC arising from OKC was confirmed.

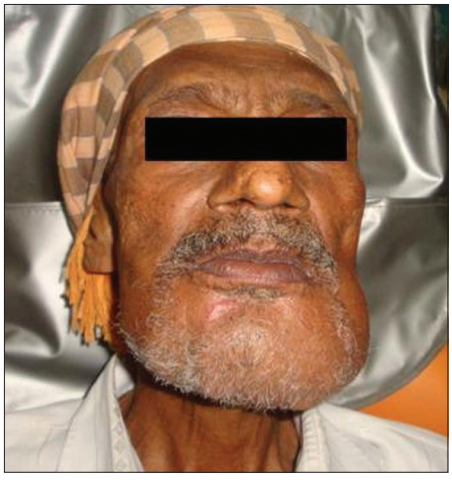

Figure 1: Extraoral swelling involving from the right angle to left angle of mandible

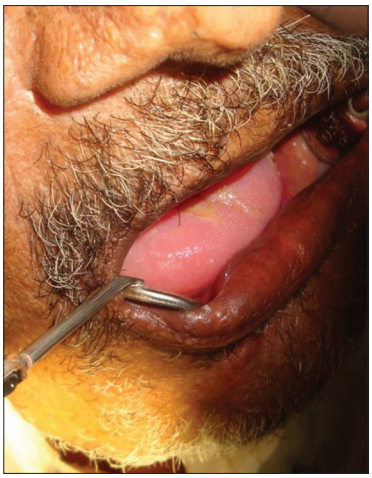

Figure 2: Intra-oral image showing intact overlying alveolar mucosa

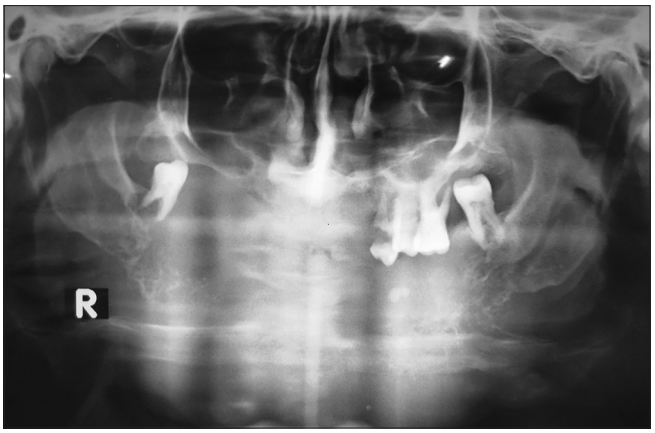

Figure 3: Orthopantomogram revealed a multilocular radiolucent lesion extending from the right angle of mandible to left angle of mandible

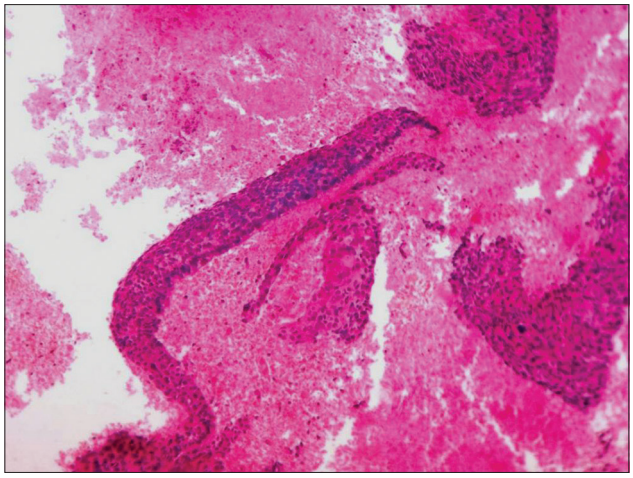

Figure 4: Photomicrograph of the section shows 8–10 layers thick parakeratinized stratified squamous epithelium with palisaded basal cell layer (H&E stain, x100)

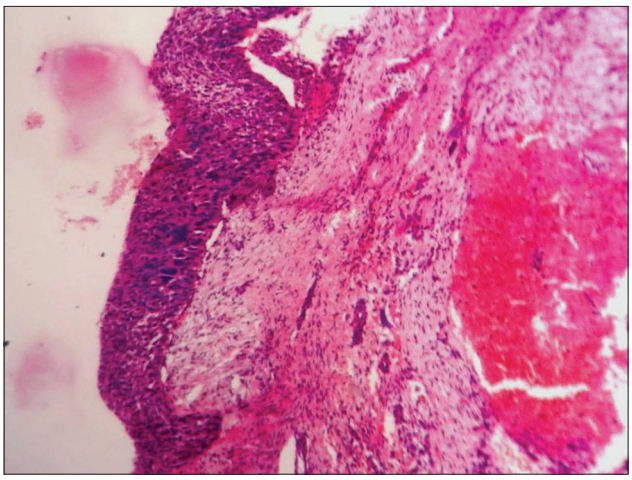

Figure 5: Photomicrograph of proliferating odontogenic epithelium with features of dysplasia (H&E stain, x200)

The patient did not turn up for evaluation or treatment. So, further management was not possible.

DISCUSSION

As it is accepted that KCOT is known by its unique and distinct histologic characteristic and by aggressive biologic behavior, the WHO considered it as a specific odontogenic tumor and the PIOC derived from it is considered as a specific entity which is different from other PIOC derived from the odontogenic cysts.[2,17]

The pathogenesis of this lesion is presently unknown. According to Browne and Gouch,[18] keratin metaplasia followed by epithelial hyperplasia and then epithelial dysplasia of cyst epithelia were the significant events in the development of SCC in OKCs. Therefore, van der wal *et al*.[19] mentioned that the presence of keratinization in the cyst lining results in a greater risk for malignant changes. According to Gardner[20] and Yu *et al*. 2003,[21] long-standing chronic inflammation has also been suggested as a possible predisposing factor. The main mechanism of the inflammation-induced carcinogenesis includes the formation of reactive oxygen metabolites, causing damage to DNA, protein and cell membranes and eventually showing compensatory proliferative response of neoplastic cells against the normal apoptotic mechanism.[1,16]

As in the present case, the patient had no genetic predisposition, but he had history of tobacco smoking and multiple tooth extraction in the last year which could be the main predisposing factor for the inflammation-induced malignant transformation.

Diagnosis of a carcinoma arising in an odontogenic cyst is given after eliminating secondary involvement of a cyst by an unrelated adjacent carcinoma or cystic degeneration in primary metastatic deposits. In 1975, Gardner proposed the following criteria for the diagnosis of SCC arising in an odontogenic cyst:

- A microscopic transition area from benign cystic epithelial lining to invasive SCC

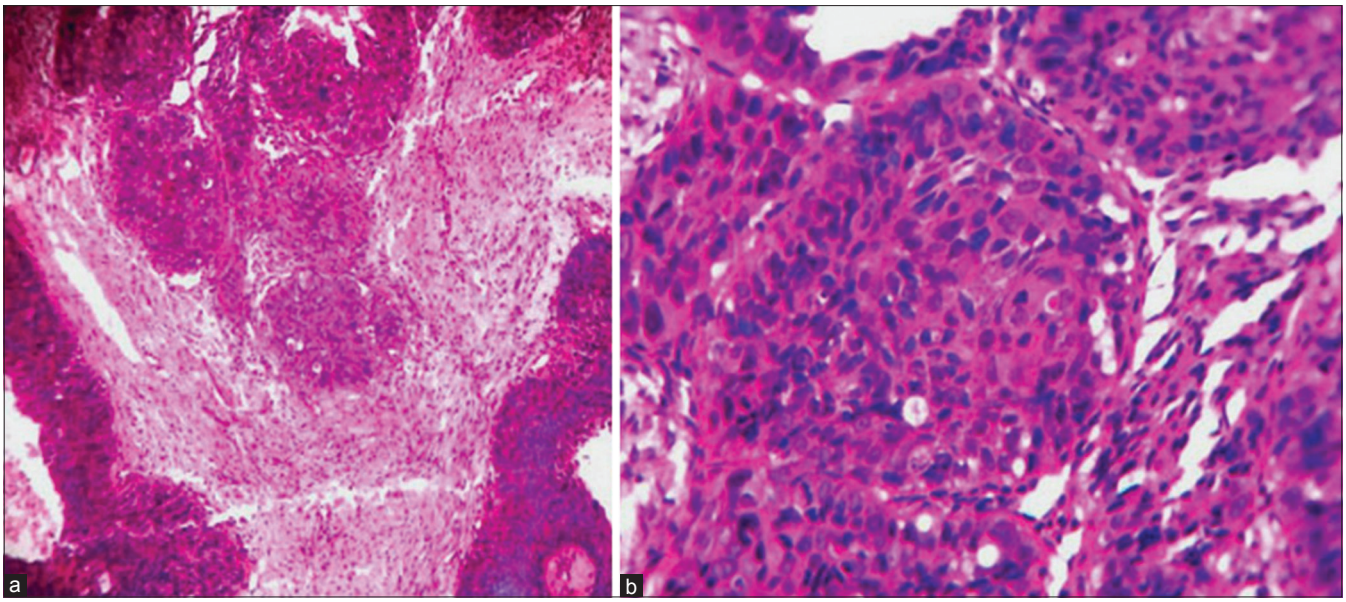

Figure 6: (a) Proliferated cystic lining with dysplastic islands in the cystic capsule (H&E stain, x40). (b) Dysplastic islands are made up of moderately to poorly differentiated squamous cell (H&E stain, x400)

- No carcinomatous changes in the overlying epithelium
- No source of carcinoma in the adjacent structure

A 4th criterion was added by Slootweg and Muller[14]

- To rule out the possibility of metastasis from a distinct tumor by physical and radiological examination. Our case fulfills all the criteria.

According to the literature, PIOSCC has predilection for mandible (79%) as the predominant site of occurrence as compared with the maxilla (21%).[1,16] PIOSCC arising from an OKC shows a wide age range, with a mean age of 57 years and the male: female ratio of 2:1. Similar findings were observed in our case and cases reported by Aboul-hosn Centenero *et al*. in 2006,[22] Mosqueda Taylor *et al*. in 2003[23] and Scheer *et al*. in 2004.[24]

Clinically, the patient presented with the typical symptoms of an odontogenic cyst, swelling and destruction of buccal and lingual cortical plates with an intact overlying oral mucosa, which were in accordance with the cases reported by others.[25]

Radiographically, PIOC shows great variations, presenting as either a unilocular or multilocular lesion with an ill-defined or well-defined but noncorticated borders. Our case presented with multilocular radiolucency involving almost complete lower jaw extending from the right angle of mandible to the left angle of mandible, resembling OKC, ameloblastoma and therefore other differential diagnosis such as well-circumscribed unilocular cystic lesions such as radicular cysts, dentigerous cysts and calcifying odontogenic cysts were excluded.[1]

The majority of cases of PIOSCC arising from an OKC represent well-differentiated SCCs. Evidence of a cystic component is a prerequisite for the diagnosis. The histopathologic criteria employed to document an odontogenic origin of lesion are (i) malignant transformation of the cyst lining, with a transition from the normal lining epithelium to dysplasia and to carcinoma, (ii) palisaded columnar cells and (iii) inductive influence of connective tissue.[1,12] The above-mentioned histopathologic criteria were also appreciated in the present case.

PIOC must be considered in the differential diagnosis of tumors of odontogenic epithelium, including ameloblastoma, lesser extent to CEOT, malignant tumor-like ameloblastic carcinoma, IMEC and clear cell odontogenic carcinoma. In addition, metastatic SCC must be ruled out.[8] Histopathologic characteristics reminiscent of ameloblastoma, such as alveolar or plexiform patterns and peripheral palisading of cells, may be exhibited in PIOSCC solid type; nonetheless, typical features of ameloblastic differentiation, which would justify a diagnosis of ameloblastic carcinoma, are lacking. CEOT histologically demonstrates sheets of polygonal cells with ample eosinophilic cytoplasm, distinct cell borders and very conspicuous intercellular bridges. In addition, other diagnostic features are amyloid deposition and Liesegang ring calcifications. Therefore, these findings allow discrimination between PIOSCC and CEOT.[1,26]

Ameloblastic carcinoma demonstrates malignant features of conventional ameloblastoma, that is, bland cytological features with nuclear palisading, reverse nuclear polarization of the nuclei and vacuolization of the cytoplasm of the cells within the tumor islands,[1,27] these were absent in our case of PIOSCC.

The absence of a mucous cell component in PIOSCC, verified by a negative mucicarmine staining, serves to distinguish

it from IMEC.[8] The nests and strands, intermingled with smaller islands of clear cells and eosinophilic polygonal cells, are always considered the histological hallmark of clear cell odontogenic carcinoma.[28] In contrast, PIOSCC exhibits sheets or islands of malignant epithelial cells, with an absence of a clear cell component.[1]

However, most of these cases were treated in 2 phases, with enucleation or incisional biopsy as phase 1. When carcinoma was found initially, usually unexpectedly, further treatment included radical resection in most cases, neck dissection in half of the cases and radiation or chemotherapy in one-third of cases. If the margins of the tumor were positive or there was carcinoma in the surrounding bone, additional therapy is indicated. Some combination of resection, radiation therapy and chemotherapy should be planned, with cervical lymph node dissection performed, if needed.[6] In general, the prognosis is poor and metastasis to cervical lymph nodes is observed in up to 50% of cases.[24] Two-year survival rate of patients has been reported in 53%.[29]

This case report analyzes the origin, clinical signs and symptoms, radiological features of malignant transformation of an OKC. A preoperative biopsy is mandatory; however, it can represent the entire lesion only in a few instances. In many cases, pathological tissue, including SCC, located in other parts of the cyst, may be overlooked. The true nature of an odontogenic cyst and the possible presence of SCC may only become evident when the entire specimen is available for histopathology.[30]

CONCLUSION

PIOSCC arising from the lining of an odontogenic cyst, including the former OKC, is a unique malignant lesion of the jaws. It has a predilection for adult men, occurs most frequently in the mandible and is associated mainly with an odontogenic cyst. The histopathology is usually a well-to-moderately differentiated SCC. Surgery alone or combined therapy of surgery and radiation was the most common approach. Following enucleation of a cystic jaw lesion, the entire surgical specimen should be examined histopathologically.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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