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Keratinized Primary De Novo Intraosseous Carcinoma of Mandible: Report of a Case and Literature Review

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Abstract: Primary intraosseous carcinoma of the jaws is a rare entity which is mostly discussed through case reports and literature reviews. Presentation of new cases would contribute to a better understanding of different aspects of the entity. The researchers have presented a case of the lesion arising in the mandible in the 4th decade of a female's life. The definite diagnosis of keratinized PIOC was confirmed based on the combination of pathological and clinical findings. The features of the case are further discussed comparatively through a literature review.

Key words: Primary intraosseous carcinoma of Mandible, literature review, jaws, PIOC, Tehran, Iran

INTRODUCTION

Squamous cell carcinoma, an often aggressive neoplasm is known as the most common malignancy of oral and maxillofacial origin. This lesion usually invades surrounding tissues directly and spreads through lymphatic pathways to distant targets (Eversole *et al*., 1975; McGregor and MacDonald, 1988; Waldron and Mustoe, 1989; Cavalcanti *et al*., 2005). Primary Intraosseous Odontogenic Carcinoma (PIOC) is defined as a squamous cell carcinoma arising within the jawbones which has no initial connection with the oral mucous membrane, adjoining skin or nasal or antral mucous membranes. It develops from remnants of the odontogenic epithelium deriving embryologically from the dental ledge or epithelial cell rests of Malassez. This is why these lesions are often named odontogenic carcinomas (Bruce and Jackson, 1991; Suei *et al*., 1994; Thomas *et al*., 2001; Murillo-Cortes *et al*., 2002; Chaisuparat *et al*., 2006). Malignant changes in the epithelial lining of odontogenic cysts, as well as de novo development of primary intraosseous carcinoma have been described in the literature (Bridgeman *et al*.,1996; Dayal and Rawal,1997; Ide *et al*., 1999; Scheer *et al*., 2004). Jaw bones are the only bones containing epithelial structures and are prone to the development of connective tissue tumors (Murillo-Cortes *et al*., 2002). According to the uncertainty of the diagnostic criteria of PIOC, reported cases of PIOC are quite few (Thomas *et al*., 2001). Differential diagnosis of PIOC includes malignant tumors of odontogenic epithelium, including ameloblastic carcinoma, intraosseous Mucoepidermoid Carcinoma (MEC), clear cell odontogenic carcinoma, odontogenic ghost cell carcinoma and malignant variant of Calcifying Epithelial Odontogenic Tumor (CEOT). In addition, squamous cell carcinoma of mucosal origin, acanthomatous ameloblastoma, squamous odontogenic tumor and CEOT also must be considered in differential diagnosis (Chaisuparat *et al*., 2006; Thomas *et al*., 2001; Cavalcanti *et al*., 2005; Suei *et al*., 1994; Bruce and Jackson, 1991; Scheer *et al*., 2004). Excluding the case presented in the present report, a total number of 85 Type I (Makowski *et al*., 2001; Saito *et al*., 2002; Mosqueda Taylor *et al*., 2003; Scheer *et al*., 2004; Chaisuparat *et al*., 2006) and 53 Type III (Bridgeman *et al*., 1996; Kaffe *et al*., 1998; Ide *et al*., 1999; Thomas *et al*., 2000, 2001; Zwetyenga *et al*., 2001; Saito *et al*., 2002; Mosqueda Taylor *et al*., 2003; Punnya *et al*., 2004). PIOCs have been reported through the literature. The following case study introduces a primary intraosseous carcinoma arising in mandible.

MATERIALS AND METHODS

Referral and primary clinical examination: On October 11, 2008 a suburban 31 years old female was referred to the Oral and Maxillofacial Surgery Department with the chief-complaint of persistent jaw abscess since four months in the right mandible (Fig. 1). Primary examinations revealed a 1.5×2 cm firm mass in the right mandibular

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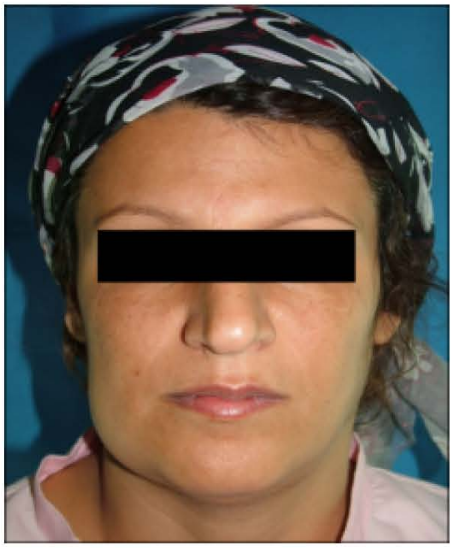

Fig. 1: 31 years old female with the chief-complaint of persistent jaw abscess since four months in the right mandible which had increasingly grown during a two months period. Note the asymmetry on the right side

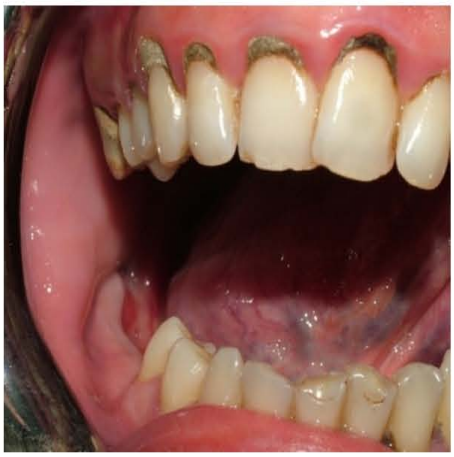

Fig. 2: A 1.5 × 2 cm firm erythematous tender mass in the right mandibular vestibule extended posteriorly from premolar area. No fistulae were found. Oral hygiene was poor. The mandibular right molars were extracted before patient's referral to the hospital

vestibule which was extended posteriorly from premolar area (Fig. 2). The patient showed erythematous and tenderness but no fistulae were found associated to the lesion. Though, no swelling was observed in the floor of the mouth, pterygomandibular swelling was evident. Aspiration was negative but bleeding on drainage was observed. Oral mucosa was found intact. Lymphadenopathy was not observed.

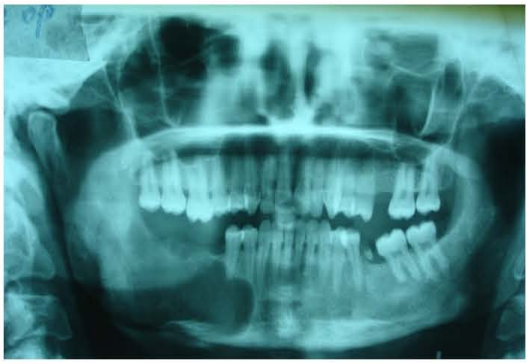

Fig. 3: Panoramic projection revealing radiolucency in the body of the mandible extended posteriorly from the apex of the first mandibular premolar

History: She initially (2 months prior to referral) had presented to her dentist with a chief-complaint of pain in the right mandibular molar area. She had also complained of an increasingly growing swelling in her mouth since 2 months. She had had her mandibular third molar extracted due to the pain and discomfort in the mandibular right vestibule. Her mandibular second molar was also extracted 1 week later for the same reason. Her symptoms, however did not disappear and she started to further develop swelling, pain and tenderness in the involved area. By the time, she was receiving therapeutic/prophylactic regimen consisted of paracetamol, amoxicillin and metronidazole.

Radiographic examinations: A panoramic projection was obtained which showed an extensive radiolucent lesion in the right mandibular body extended posteriorly from the apex of the first mandibular right premolar (Fig. 3). On October 14, axial spiral CT scan of cervical soft tissue with contrast media was performed by an oral and maxillofacial radiologist. Based on his report, a soft tissue massive lesion with bone destruction in the right side of the mandibular body was seen.

Thyroid gland, vocal cords, mandibular rami, nasopharynx and oropharynx were unremarkable. On October 14, CT scan of skull without contrast media showed soft tissue mass in the right side of the mandibular body associated with bone destruction (Fig. 4). As stated in the report of the radiologist primary mandibular mass lesion or soft tissue mass lesion with extension to mandibular bone should be considered and tissue biopsy is recommended.

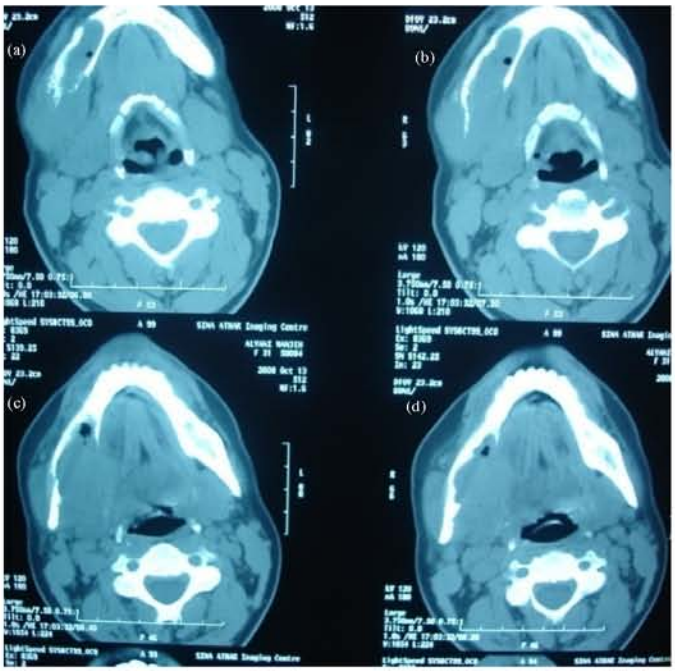

Fig. 4: a, b, c and d axial CT scan of skull without contrast media showed soft tissue mass in the right side of the mandibular body associated with bone destruction. The lingual bony table was disappeared on the CT

Surgery: On October 15, extraoral and intraoral preparations were carried out and glottal pack was placed under general anesthesia. An incision was made in the depth of the mandibular sulcus from the second premolar area. Residual ridge was removed till the lesion was reached. The lesion was reported soft and fragile by the surgeon.

The whole lesion was curetted radically in the anterior, posterior, buccal and lingual directions. A pathologic fracture was observed on the right mandibular angle. The soft tissue extensions of the lesion were also curetted in the lingual area and were submitted to the Department of Oral and Maxillofacial Pathology. A tetracycline-hydrocortisone mesh of about 20 cm in length was placed in the curetted area of the mandibular body and angle except for a 3 cm length of the mesh which was left out of the middle part of the ridge incision. 3-0 Vicryl suture was used. Multiple pieces of fragile tan-brown soft tissue totally measuring 5×3.8×0.5 cm were retrieved.

Histopathological examinations: Sections showed a malignant neoplasm composed of nests and islands of tumor cell predominantly epithelial cells with atypical nuclei, pleomorphism, nuclear hyperchromatism, abundant dyskeratotic cells and mitotic figures in some area without malignant mucous cells. Foci of degenerative bone, mucosal tissue with koilocyte cells, cholesterol clefts and foci of lympho-plasma cell infiltration were also evident (Fig. 5). All bony margins were invaded by the tumor. The mucicarmin staining ruled out MEC (no mucoid cells were present). The differential diagnosis of squamous cell carcinoma was confirmed by an oral pathologist.

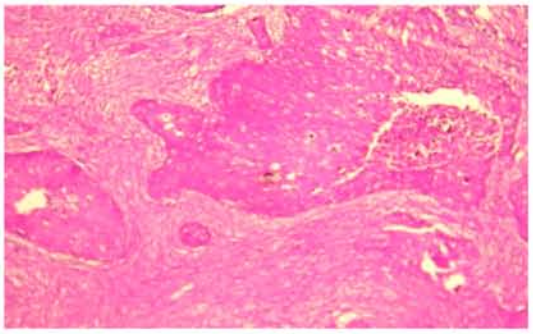

Fig. 5: Nests of epithelial cells with atypical nuclei with foci of mucoid stroma. Foci of degenerative bone, mucosal tissue with koilocyte cells, cholesterol clefts and foci of lympho-plasma cell infiltration are also evident

Surgical removal: A few days later with the same procedure of the first surgery, radical neck dissection and hemimandibulectomy were performed by an oral and

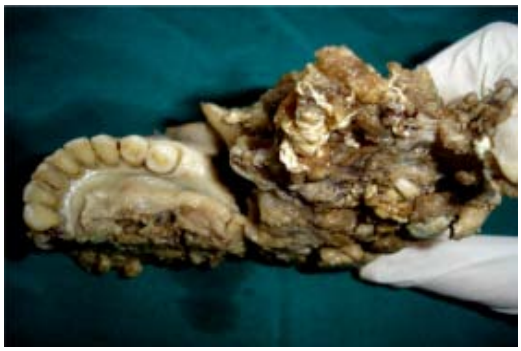

Fig. 6: Radical neck dissection and hemimandibulectomy: submental, sublingual and submandibular spaces were resected

maxillofacial surgeon. Submental, sublingual and submandibular spaces were resected. Superficial parotidectomy and parajugular lymph nodes were resected (Fig. 6).

Further examinations: Chest X-ray was normal. Also, in gray scale ultrasonographic assessment performed on November 2, liver, pancreas, spleen and kidneys were of normal size, regular contour and homogenous parenchymal echotexture, lacking any space-occupying lesion. The definite diagnosis of keratinized PIOC was confirmed based on the combination of pathological and clinical findings.

RESULTS AND DISCUSSION

History (PIOC): Intraosseous squamous cell carcinoma was first described as a central epidermoid carcinoma of the jaw in 1913. In 1948, it was renamed as intra-alveolar epidermoid carcinoma (Kaffe *et al*., 1998; Suei *et al*., 2004; Cavalcanti *et al*., 2005; Dimitrakopoulos *et al*., 2005). Shear (1969) suggested the term primary intra-alveolar epidermoid carcinoma in 1969. Finally in 1971, Pindborg *et al*. (1972) modified the term to Primary Intraosseous Carcinoma (PIOC) which is still in use. The World Health Organization (WHO) approved the term primary intraosseous carcinoma in 1972 and classified the lesion as an odontogenic carcinoma (Pindborg *et al*., 1972). Subsequently, Elzay (1982) modified the WHO classification on PIOC of the jaw based on a literature review. Slutweg and Muller (1984) modified Elzay's classification based on the various possible origins of PIOC. Waldron and Mustoe (1989) completed he classification by the inclusion of Intraosseous MEC (IMEC) as a fourth type of PIOC. This inclusion was based on the fact that evidence supports an origin of epithelial lining of odontogenic cysts for a significant number of these intraosseous tumors though they are usually classified as salivary gland tumors and are histologically identical to salivary MEC (Cavalcanti *et al*., 2005). Although most recent types of odontogenic epithelial malignancies, such as clear cell odontogenic carcinoma (Braunshtein *et al*., 2003; Siriwardena *et al*., 2004), odontogenic ghost cell carcinoma (Kim *et al*., 2000; Goldenberg *et al*., 2004) and the malignant variant of CEOT (Veness *et al*., 2001; Cheng *et al*., 2002) are yet to be included, this classification remains the basis of taxonomy of odontogenic carcinomas (Chaisuparat *et al*., 2006).

Odontogenic carcinomas include malignant ameloblastoma, malignant variants of other odontogenic epithelial tumors, primary intraosseous carcinoma and malignant changes in odontogenic cysts based on the revised WHO-Classification of 1992 (Kramer *et al*., 1992).

Differential diagnosis and classification (PIOC): PIOC is often difficult to distinguish from bony invasion of overlying alveolar carcinoma or from the jaw metastasis of a distant tumor and from the tumors of sinonasal origin (Eversole, 1999). Differential diagnosis of this pathologic entity would then be challenging (Suei *et al*., 1994; Thomas *et al*., 2001). The diagnostic criteria of PIOC proposed by Gardner (1975), revised by Suei *et al*. (1994) and completed by Eversole (1999) observe the following rules:

Since metastatic carcinoma (especially from primary squamous cell carcinoma of the bronchus) is the most common malignancy of the jaws, a metastasis should be ruled out. The exclusion of metastasis is both based on the absence of initial connection with an ulcer in the overlying mucosa or skin (except when of other etiology) and a distant primary tumor by physical and radiographic examination (especially chest radiographs) during at least a 6 months follow-up period (Suei *et al*., 1994; Veness *et al*., 2001; Scheer *et al*., 2004; Chaisuparat *et al*., 2006). Sometimes it may not be possible to demonstrate histopathologically a transition area from cystic to neoplastic epithelial lining. The maintenance of cyst-like structures within the CT projection of the lesion mass and the morphology of the lesion may help in the identification (Cavalcanti *et al*., 2005).

The direct transition from the benign epithelial lining of a pre-existing odontogenic cyst to a squamous cell carcinoma is the basis of the differential diagnosis of PIOC type 1 and the absence of a cystic component would classify the lesion as PIOC type 3 (Scheer *et al*., 2004; Chaisuparat *et al*., 2006). Differential diagnosis for the presented case included osteosarcoma, ameloblastic

carcinoma, carcinoma ex odontogenic cyst, IMEC, metastatic carcinoma to the jaws, eosinophilic granuloma fibrosarcoma, leiomyosarcoma, pleomorphic sarcoma, malignant minor salivary gland carcinoma, intraosseous SCC. To rule out Ameloblastic carcinoma, it must be noted that malignant features along with prominent peripheral palisading and reverse nuclear polarization are absent in PIOC (Avon *et al*., 2003; Datta *et al*., 2003) to differentiate PIOC from IMEC, the absence of a mucous component in PIOC, verified by a negative mucicarmine staining is useful (Maremonti *et al*., 2001). In contrast with PIOC which exhibits sheets or islands of malignant epithelial cells with negligible or absent clear cell component, a biphasic pattern characterized by clear cells and eosinophilic polygonal cells is the histopathologic hallmark of clear cell odontogenic carcinoma (Braunshtein *et al*., 2003; Siriwardena *et al*., 2004). Odontogenic ghost cell carcinoma shows a malignant epithelial component and the classic features of calcifying odontogenic cyst or tumor such as the presence of ghost cells and calcified material which are ignorable or absent in PIOC (Bruce and Jackson,1991; Scheer *et al*., 2004) to rule out benign odontogenic tumors it must be noted that they generally do not show of invasive growth, the only exception is ameloblastoma and to a lesser degree, CEOT which is locally invasive. Additionally, cellular and nuclear atypia are not present in a benign tumor except for the atypia seen in benign CEOT. To distinguish both benign and malignant CEOT from PIOC, additional diagnostic features such as amyloid deposition and Liesegang ring calcifications are helpful (Loos, 1913; Cheng *et al*., 2002).

To distinguish PIOC from other primary and metastatic squamous cell carcinomas of the jawbone, the WHO has published criteria (Kramer *et al*., 1992). Suei *et al*. (1994) suggested additional criteria for classifying a lesion as PIOC, including: intact oral mucosa; squamous cell carcinoma without a cystic component or other odontogenic tumour cells in microscopic view and absence of primary tumor in chest radiographs at the time of diagnosis and during a 6 month follow-up period. For the ultimate diagnosis of PIOC, exclusion of a metastatic lesion from a distant primary tumor is inevitable. Main tumors in thyroid, kidney, prostate and lung can cause metastasic lesions in the jawbone (Avon *et al*., 2003). Therefore a comprehensive systemic evaluation should be performed (Kramer *et al*., 1992; Punnya *et al*., 2004).

Origin (PIOC type 3): PIOC type 3 is an uncommon neoplasm arising de novo from ameloblastomas or odontogenic cysts. It is defined as a squamous cell carcinoma coming up within the jawbone without connection to the oral mucosa (Kramer *et al*., 1992). PIOC originates from the epithelial remnants of odontogenesis, encompassing the tooth germ, reduced enamel epithelium, Hertwig's epithelial root sheath and dental lamina. These epithelial remnants proliferate and transform into odontogenic carcinoma due to some unknown stimuli (Thomas *et al*., 2001).

The fact that PIOCs essentially occur only in the tooth-bearing areas of the jawbone, but not in the maxillary incisive canal (Spouge, 1967) makes this hypothesis seems acceptable. The activation of the epithelial rests, alone or in combination with mesodermal tissues, results in their proliferation and their consequent growth into odontogenic cysts or carcinomas (Waldron and Mustoe, 1989). Alcohol, tobacco and betel quid abuse are usually not a remarkable history in PIOC patients. The most common risk factors include inflammatory stimulus in the presence or absence of a predisposing genetic cofactor (Muller and Waldron,1991). Since, the presented example was found in the edentulous mandible of the patient, this excluded involvement of the periodontal space and indicated association with both the bone marrow and subepithelial soft-tissue analogues.

Histopathology (PIOC type 3): The histopathologic features of different PIOC types are consistent with a diagnosis of squamous cell carcinoma. PIOC type 3 shows low differentiation with keratinizing and nonkeratinizing subtypes. The two subtypes are equally reported through the literature (Elzay, 1982; Thomas *et al*., 2001). It is also possible to observe some histopathologic characteristics suggestive of ameloblastoma, such as alveolar or plexiform patterns and peripheral palisading of cells, in PIOC type 3 (Elzay, 1982) while typical features of ameloblastic differentiation which would give reason for a diagnosis of ameloblastic carcinoma do not exist. In this case, keratinization area was observed.

Epidemiology (PIOC type 3): PIOC type 3 occurs in a wide age range from 4-81 years with a higher frequency in the 6th and 7th decades of life, affecting more males than females (M:F ¼ 3:2) (Muller and Waldron, 1991; Ide *et al*., 1999; Thomas *et al*., 2000, 2001; Zwetyenga *et al*., 2001; Cavalcante *et al*., 2002). It is more commonly located in the mandible, with an outstanding preference for posterior regions; Maxillary lesions are mainly found in the anterior jaw (Muller and Waldron, 1991; Kaffe *et al*., 1998; Thomas *et al*., 2001; Zwetyenga *et al*., 2001). The rarity of posterior maxillary cases of PIOC might be related to the difficulty in differentiating this lesion from carcinoma with maxillary sinus origin (Punnya *et al*., 2004). The case was a 31 years old female with the lesion located in the mandible, the location was consistent with the previous findings.

Clinical manifestations (PIOC): Pain and swelling are the most common symptoms of PIOC patients (Muller and Waldron, 1991). It has been reported that sensory disturbances such as paresthesia and numbness are principal manifestations for some samples of de novo PIOC cases (Thomas *et al*., 2001). A sensory disturbance of the jaw, mimicking facial neurological problems, especially without a history of trauma and the absence of any obvious mucosal abnormalities within the oral cavity, in the case of the early lesion should be alarming for a possible diagnosis of malignancy, including PIOC (Thomas *et al*., 2001). In the case pain, swelling and tenderness was observed but no paresthesia or numbness was detected.

Radiography (PIOC): Radiographic examination can be used as an effective method for the diagnosis of PIOCs (Kaffe *et al*., 1998). A lesion which is entirely surrounded by bone can be assumed to have intraosseous origin. Great variations in radiographic features of PIOC are detectable. Either a unilocular or a multilocular presentation with an ill-defined or well defined but noncorticated border might be seen in the projections. Kaffe *et al*. (1998) suggested the presence of indistinct margins without sclerotic outline as an important feature of PIOC. CT scan can also be helpful for a correct diagnosis. However in some cases, the radiographic artifact caused by the secondary irradiation from intraoral metal prosthesis reduces the reliability of this method (To *et al*., 1991; Van der Waal *et al*., 2003). In this case, the researchers used panoramic radiography and CT scan for the detection.

Treatment (PIOC type 3): Treatment of choice for PIOC de novo is surgery with or without radiation therapy (Thomas *et al*., 2001; Zwetyenga *et al*., 2001) treatment methods such as radiotherapy or chemotherapy are used in lesions that cannot be surgically controlled (Thomas *et al*., 2001). Treatment plan in the presented case was segmental mandibular resection. The survival time for the patient has been 9 months since the initial diagnosis.

Prognosis (PIOC type 3): Metastatic spread in PIOC types 3 usually involves the cervical lymph nodes (Elzay, 1982; Muller and Waldron,1991). Previous studies have shown a poor prognosis for PIOC (Makowski *et al*., 2001). To *et al*. (1991) reported a 6 months to 5 years survival rate of 46% for the PIOC patients. The 2 years survival rates of patients with PIOC type 3 have been reported to be 40% in another report (Eversole *et al*., 1975). Delayed diagnosis, ranging from a few weeks to as long as 18 months have been associated with poorer prognosis (Lin *et al*., 2005). Early identification and appropriate treatment are the keys to the prognosis of PIOCs (To *et al*., 1991; Thomas *et al*., 2001).

CONCLUSION

The classical classification of odontogenic carcinomas by Waldron and Mustoe (1989) includes the 2 types of PIOC, the malignant variants of ameloblastoma and the IMEC, omitting some recently described malignant odontogenic epithelial tumors. Consequently, it is possible that the reexamination of some previously reported cases of PIOC be more accurately classified as one of the most recently known types of odontogenic carcinomas. In the most recent review of PIOC by Suei *et al*. (2004), they proposed a modified classification for odontogenic carcinomas. It was proposed that the tumor may involve the bone marrow space and the periodontal and the subepithelial soft-tissue analogues either as epithelial rests may exist in all of them.

RECOMMENDATION

Therefore, researchers suggest the term odontogenic squamous cell carcinoma to replace PIOC whereas the term intraosseous would be used only to indicate origin of bone-marrow space (Suei *et al*., 2004).

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