

CASE REPORT

Primary intraosseous carcinoma of the mandible

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Primary intraosseous carcinoma (PIOC) is a rare lesion in the jawbone. We report a case of *de novo* PIOC of the mandible, first seen by the family dentist. Our case highlights that radiographic examination is one of the most effective methods for detecting PIOC.

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Case report

A 75-year-old Chinese female complained of numbness over the right lower lip for approximately 1 month. At first, she did not pay much attention to this symptom; however, she visited her family dentist after it became more serious, and medication (the details could not be known) was prescribed for 1 week, but the symptom persisted. The patient was then referred to the Oral Pathology Department at the Kaohsiung Medical University for further assessment. Upon clinical examination, a mild right facial swelling was noted and the patient was then referred to the Oral Radiology Department for a panoramic radiograph to evaluate whether the swelling was related to the lip numbness. Subsequently, the patient was referred to the Department of Oral and Maxillofacial Surgery for further evaluation of a bony destructive lesion within the right mandible first observed on the panoramic radiograph.

The patient did not have a history of cigarette smoking, alcoholism, or betel-quid use. No significant previous medical history was noted other than hypertension. The patient complained of spontaneous dull pain originating from the right cheek and numbness of the right lower lip. On extraoral examination, a mild enlargement was observed in the facial aspect of the right mandible. The overlying skin was hyperaemic, but there was no detectable lymphadenopathy of the head and neck. Intraoral examination revealed that the right side of the mandible was edentulous and covered by an intact alveolar mucosa of normal appearance (Figure 1a). There was no evidence or history of a mucosal mass or ulceration in this region, which had been edentulous for about 10 years.

Panoramic radiography revealed an ill-defined osteolytic lesion measuring 6.0 × 3.0 cm in diameter, and extending anteroposteriorly through the right mandibular body and from the superior alveolar border to the lower border of the right mandible superoinferiorly; cortical involvement of the inferior border was also noted (Figure 1b). Computed tomography (CT) also revealed intrabony destruction within the right mandibular body; however, image detail was unsatisfactory owing to an extensive artefact caused by secondary irradiation derived from the metal prosthesis of the oral cavity. The provisional diagnosis was chronic osteomyelitis or intrabony malignancy. During the subsequent incisional biopsy, an intact mucosal surface of the right edentulous ridge was grossly noted. The specimen was sent for histopathological examination.

Microscopic examination of the tissue fragments revealed an epithelial malignant neoplasm with extensive infiltration of different sized tumour islands within the fibrous connective-tissue stroma (Figure 2a). The tumour cells consisted of intercellular bridges and cytoplasmic accumulation of keratin, characteristics indicative of squamous origin (Figure 2a). Malignant features, including cellular and nuclear pleomorphism and hyperchromatism were prominent (Figure 2a). The morphological features of the tumour were consistent with the histological diagnosis of squamous cell carcinoma, with metastasis suspected.

One week subsequent to tumour histopathology, the diagnosis of mandibular malignancy was explained to the patient. Further examinations, including chest X-ray and whole-abdomen ultrasound, were performed. A whole-body CT scan and bone scintigraphy to exclude distant metastasis (lung and bone) were also conducted. With the exception of the destroyed area of the right mandible, all the above-mentioned systemic evaluations excluded abnormality. Furthermore, other laboratory results were

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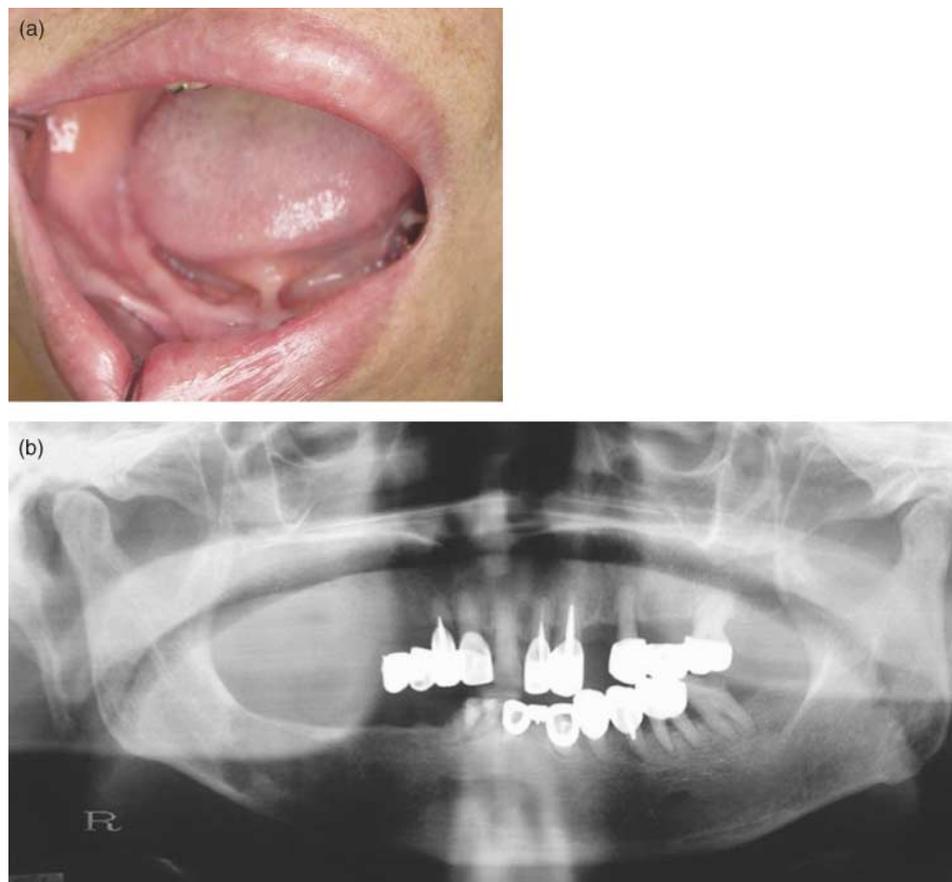


Figure 1 (a) Intraoral examination revealed that the right side of the mandible was edentulous with intact and normal-appearing alveolar mucosa. (b) Panoramic radiography revealed a poorly defined osteolytic lesion, extending anteroposteriorly through the right mandibular body and from the superior alveolar border to the lower border of the right mandible superoinferiorly. Cortical involvement of the inferior border was also noted

within normal limits. The serological titres of tumour markers, including squamous cell carcinoma (SCC), carcinoembryonic antigen (CEA), and alpha feto protein (AFP), were also within normal limits. Thus, the possibility of a metastatic lesion could not be confirmed. A segmental resection of the right mandible and dissection of the regional submandibular lymph nodes (level 1) were subsequently performed under general anaesthesia. All frozen sections of the submitted tissues from the surgical margins were free of tumour. The mandible was subsequently reconstructed using a reconstruction plate.

The surgical specimen, measuring approximately 7.0 cm × 3.5 cm × 2.5 cm in size, was greyish in colour. The cut surface revealed a whitish intrabony lesion covered with intact alveolar mucosa. Involvement of the lower cortical border by the lesion was evident, however (Figure 2b). Microscopy of the decalcified specimen revealed multiple tumour islands invading the bony tissue (Figure 2c). Using a higher power view, pleomorphic squamous cells with atypical nuclei and hyperchromatism were visible in the tumour islands (Figure 2d). Except for the periosteum of the lower cortex, other section margins were free of tumour cells. The final histopathological diagnosis was primary intraosseous carcinoma (PIOC) arising *de novo* within the right mandibular body.

Post-operative radiotherapy was undertaken at the Department of Radiation Oncology, with a total delivery dosage of 54 Gy. Local recurrence, which has since been treated by a second surgery, was noted in the right submandibular region 12 months after the radiation therapy. Eighteen months after the initial diagnosis, the patient was still alive and the disease remained under control.

Discussion

Primary intraosseous carcinoma is an uncommon neoplasm. According to the most recent edition of the World Health Organization (WHO) classification for histological typing of odontogenic tumours, it is defined as a squamous cell carcinoma arising within the jawbone without connection to the oral mucosa, probably from odontogenic epithelial residues.¹ PIOC includes carcinomas arising *de novo* and from ameloblastomas or odontogenic cysts.¹

This tumour was firstly described by Loos in 1913.² Pindborg coined the term PIOC in the first edition of the WHO classification for histological typing of odontogenic tumours.³ Elazy⁴ subsequently recommended a modification of this WHO classification after reviewing a sample of subjects with PIOC. Slotweg and Muller⁵ further

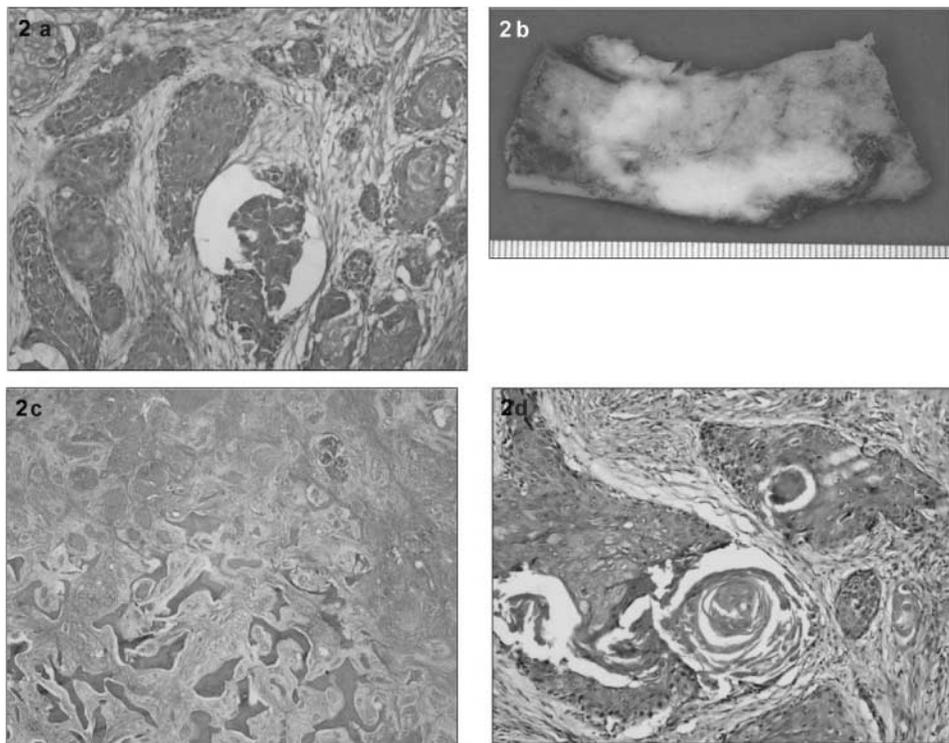


Figure 2 (a) Microscopic examination of the incisional biopsy-tissue fragment revealed an epithelial malignant neoplasm with extensive infiltration of tumour islands within the fibrous connective-tissue stroma (haematoxylin and eosin $\times 100$). (b) The cut surface of the surgical specimen revealed a whitish intrabony lesion covered with intact alveolar mucosa; involvement of the lower cortical border by the lesion could also be seen. (c) The low-power view of the surgical specimen revealed multiple tumour islands invading the bony tissue (haematoxylin and eosin $\times 40$). (d) The tumour islands showed pleomorphic squamous cells with atypical nuclei and hyperchromatism on higher magnification (haematoxylin and eosin $\times 100$)

modified Elazy's⁴ classification taking into account the various possible origins of PIOC. Waldron and Mustoe⁶ later suggested adding intraosseous mucoepidermoid carcinoma to this classification (Table 1). This was based on the rationale that despite the fact that these growths are usually considered salivary gland tumours, microscopically identical with salivary mucoepidermoid carcinoma, there is evidence to suggest that a number of these intraosseous tumours originate in the epithelial lining of odontogenic cysts.⁶

Reviewing the English-language literature and excluding cases with ulceration of the oral mucosa and those where a search for another primary site had not been conducted, 40 cases of *de novo* PIOC were identified between 1970 and 2004.⁷⁻¹¹ Affecting more males than females (M:F = 3:2), PIOC is more frequent in the sixth and seventh decades of life.⁷⁻¹¹ It occurs more frequently in the mandible (especially the posterior section) than in

the maxilla.⁷⁻¹¹ In the classification proposed by Waldron and Mustoe (Table 1),⁶ our case was a type-3a PIOC, based on the representative histological findings of the individual cell keratoses. Discrimination between type-3a and 3b PIOC is based on the former lesion possessing keratin pearls and/or individual keratoses, whereas these features are absent in the latter.

The WHO has published criteria to differentiate PIOC from other primary and metastatic squamous cell carcinomas of the jawbone.¹ Additional criteria for categorizing a lesion as PIOC, such as: (a) intact oral mucosa before diagnosis; (b) microscopic evidence of squamous cell carcinoma without a cystic component or other odontogenic tumour cells; and (c) absence of another primary tumour on chest radiographs obtained at the time of diagnosis and during a follow-up period of more than 6 months, have been suggested by Sueti *et al.*¹² Therefore, exclusion of the possibility of metastatic lesion from a distant primary tumour is always necessary for the final diagnosis of PIOC. Metastatic carcinoma of the jawbone is mainly derived from the thyroid, kidney, prostate, and lung.¹³ The possibility of metastasis can be eliminated by a careful review of the history and comprehensive systemic evaluation. Furthermore, the finding of an intact mucosa in the present case made the possibility of direct extension of squamous cell lesions from the oral mucosa appear unlikely. Hence, the tumour described in this paper completely fulfilled the aforementioned strict criteria.^{1,11}

Table 1 Classification of primary intraosseous carcinoma (PIOC) according to Waldron and Mustoe⁶

Type 1	PIOC <i>ex</i> odontogenic cyst
Type 2a	Malignant ameloblastoma
Type 2b	Ameloblastic carcinoma arising <i>de novo</i> , <i>ex</i> ameloblastoma or <i>ex</i> odontogenic cyst
Type 3	PIOC arising <i>de novo</i> (a) Keratinizing type (b) Non-keratinizing type
Type 4	Intraosseous mucoepidermoid carcinoma

Although the clinical features of PIOC are non-specific, Zewetyenga *et al*⁷ have reported that principal manifestations for half of a number of samples of *de novo* PIOC cases (12/28) were sensory disturbances like paraesthesia and numbness, mimicking facial neurological problems. Given the solely neurological disturbances, and the absence of any obvious mucosal abnormalities within the oral cavity, especially in the case of the early lesion, the first professional consultation may be with the family dentist, increasing the probability of delayed diagnosis. Delays in correct diagnosis, ranging from a few weeks to as long as 18 months, have been reported by To *et al*.¹⁴ Clearly, this will worsen prognosis; hence, it is important to consider intraosseous carcinoma in the jawbone in the differential diagnosis for all cases of facial paraesthesia and numbness to facilitate the early identification of PIOC and enabling prompt institution of suitable treatment.

Radiographic examination is one of the most effective methods for detecting PIOC.¹⁵ A lesion that is completely surrounded by bone can be regarded as of intraosseous origin. CT scan can also facilitate correct diagnosis. However, for some particular circumstances, as in the presented case, the radiographic artefact caused by the serious secondary irradiation owing to the intraoral metal prosthesis greatly limits the usefulness of this scanning modality in terms of adequate diagnosis. Panoramic radiography, a simple, effective and low-cost examination, a standard facility that is generally available to the dental department of a teaching hospital, can be used in its stead.

In the review by To *et al*¹⁴ 46% of the PIOC patients survived for periods ranging from 6 months to 5 years. There is insufficient information, however, to distinguish the survival times for the different PIOC types listed in Table 1. However, there appears to be a difference in survival rates comparing type-1 and type-3 PIOC. Eversole *et al*¹⁶ reported a 53% 2-year survival rate for the type-1 entity, whereas Elazy⁴ demonstrated a 40% 2-year survival rate for the *de novo* lesion. These results indicate that PIOC originating from odontogenic cysts have a better prognosis than the *de novo* lesions. At the time of writing, the survival time for the presented *de novo* PIOC patient was 18 months after the initial diagnosis.

Radical surgery with/without post-operative radiotherapy is recommended for management of *de novo* PIOC.¹⁷ Other treatment modalities, such as radiotherapy or chemotherapy, should be considered only for lesions that cannot be surgically controlled.¹⁷ For our patient, treatment consisted of segmental mandibular resection plus post-operative radiotherapy. Despite local recurrence, our patient was alive with controlled disease at the time of writing.

Since PIOC essentially occurs only in the tooth-bearing areas of the jawbone, the hypothesis of odontogenic epithelial origin is theoretically acceptable, except in the the maxillary incisive canal.¹⁸ At termination of the odontogenesis, remnants of the odontogenic epithelium, derived from different origins such as the tooth germ, reduced enamel epithelium, Hertwig's sheath and the dental lamina, remain in the oral tissues as epithelial rests. Occasionally, owing to some unknown stimuli, these epithelial rests are activated and, either alone or in conjunction with mesodermal tissues, they then proliferate and develop into odontogenic cysts or carcinomas.^{6,8} In contrast to the classic oral mucosa squamous cell carcinomas, the risk factors of alcohol, tobacco or betel-quid abuse are usually not present in PIOC patients. The most common risk factor for inducing neoplastic formation of PIOC is assumed to be a reactive inflammatory stimulus, with/without a predisposing genetic cofactor.¹⁹

In the most recent review of PIOC by Swei *et al*,²⁰ it was suggested that the tumour may involve not only the bone marrow space, but also the periodontal and the subepithelial soft-tissue analogues as epithelial rests may exist in all three. To account for the possibility that a squamous cell carcinoma of odontogenic origin could also arise in the periodontal and subepithelial soft-tissue spaces, therefore the term odontogenic squamous cell carcinoma was proposed as a replacement for PIOC, whereas the term intraosseous would be used to denote origin only in the bone-marrow space.²⁰ Since the presented example was found in the edentulous mandible of our patient, this excluded involvement of the periodontal space, and indicated association with both the bone marrow and subepithelial soft-tissue analogues.

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