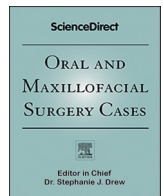




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PIC developing from odontogenic cysts: Clinical and radiological considerations on a series of 6 cases

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ABSTRACT

Purpose: The purpose of this work is to describe the peculiarities of clinical and radiological behavior in SCCs arising from odontogenic cyst (PIO SCC).

Material & methods: Our computer based records were retrospectively reviewed looking for patients who underwent radical surgery for PIO SCC from December 2001 to January 2016 with a minimum post-operative follow-up of 2 years. Information obtained from radiological findings and treatment outcome were collected.

Results: From 2001 to 2016, 6 out of 560 SCC's patients (1,07%) were diagnosed PIO SCC. 5 females and 1 male, mean age was 55,2 years (range, 28–82 years). 4 PIO SCC were located in the mandible while 2 in the maxilla. Orthopantomography (OPT) has not given specific signs of malignancy. CT methods (msCT/CONE BEAM-CT/contrast-enhanced CTs) provided more information: unilocular lesions with multiple and excessive cortical interruptions, periosteal reaction far beyond the lesion in all directions, dislocation or disappearance of the IAN, intense peripheral remineralization. In all cases, the treatment involved incisional biopsy of the suspect lesions and subsequent surgical excision of the primary tumor with neck dissection in continuity in the mandibular PIO SCC and in discontinuity in PIO SCC of the maxilla. Recurrence or distant metastases was not observed until now (follow-up from 48 months to 168 months)

Conclusions: Carcinomas on cysts have radiological “red flag” characteristics (bone erosion, large dimension, involvement of IAN..) that must be taken into consideration in order to perform an early diagnosis and a correct treatment. Accurate radiological study can reduce misdiagnosis and improper treatment. PIO SCC have a progression of the disease and a different prognosis from real intraosseus carcinomas (PIC) and although it is a rare entity it must be considered in the differential diagnosis of larger osteolytic lesions.

Introduction

Primary odontogenic intraosseous carcinoma is a rare malignant lesion affecting the jaw bone [1]. The aetiology seems to be related to the malignant degeneration of embryological remnants. Epithelial rest of Malassez, dental lamina and dental follicle epithelium represent potential suspects [2].

Its nomenclature and definition have changed over time: “intraosseous epidermoid carcinoma” [3], “primary intraosseous odontogenic carcinoma” [4], “primary intraosseous squamous cell carcinoma” (PIO SCC) [2,5].

The former WHO classification (2005) that divided PIO SCC into 3 subtypes (solid, originated from a cyst or associated with other benign epithelial odontogenic tumors) has been revised: actually primary intraosseous carcinoma (PIC) appeared in the 4th edition of the World Health Organization Classification of Head and Neck tumors as a single diagnostic entity in 2017 [6].

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Despite the few cases described in the literature (about 250 cases), SCCs arising from an odontogenic cyst have their own clinical and radiological peculiarities distinct from the solid intraosseous carcinomas. Furthermore, there is a lack of literature on this type of pathology.

The purpose of this work is to describe the peculiarities of clinical and radiological behaviour in a serie of cases treated at our institution, in order to characterize the aspects useful for a correct diagnosis.

Materials and methods

The authors retrospectively reviewed the records of patients who underwent radical surgery for PIOSCC from December 2001 to January 2016 with a follow-up of at least 2 years.

This study was approved by the independent ethics committee of the author's hospital.

Tumor stage was classified according to the TNM classification of the International Union Against Cancer (AJCC) [7] and histologic differentiation according to the WHO classification [8].

The diagnostic criteria of primary intraosseous odontogenic squamous cell carcinoma (PIOSCC) included the absence of a primary lesion of the overlying mucosa or skin and the exclusion of metastasis from a distant primary site. Moreover cases of the solid type of intraosseous cell carcinoma (PIC) were excluded from the study.

All patients underwent extensive pre-operative evaluation (Orthopantomography, msCT, CBCT, CT with contrast, and in selected cases MRI). Information obtained from radiological findings were collected and thoroughly evaluated.

Results

Patient characteristic

The clinicopathological characteristics of the patients are presented in Table 1. In the period from 2001 to 2016, 6 of 560 patients (1,07%) were diagnosed PIOSCC. (5 females and 1 male). The mean age was 55,2 years (range, 28–82 years) (see Table 2).

Four PIOSCC were located in the mandible and 2 were located in the maxilla.

The main complaints included swelling, pain, pathological fracture and sensory disturbance of the region in the IAN or infraorbital nerves territory. In maxillary lesions nasal obstruction symptoms were sometimes present.

In all the cases, the primary diagnostic hypothesis was different from that of a cancerous cyst. The previous hypotheses were of infected residual cysts for the two maxillary cases (cases 1 and 6). In the mandibular localizations, the hypotheses prior to the final diagnosis were of complicated and infected follicular cysts (cases 2 and 3) and of infected residual cysts (case 4). The case n°5 was diagnosed and treated at an other institution as a cutaneous fistula secondary to a dental abscess. In this last case, radiological investigations had not been performed and a plastic of the fistula had been attempted three times.

All the reported cases had incongruous diagnosis and interventions before the definitive diagnosis (dental extractions, FESS, cystectomies with an iatrogenic fracture of the jaw, extraction of teeth included and corrections of cutaneous fistula. The average

Table 1
Clinical Characteristic of 6 patients with pioscc

N	age	gender	primary site	chief complaints	previous hypothesis	treatment before diagnosis	duration after treatment (mo)	Hystology
1	28	female	maxillary molar and sisus	- swelling - pain - sensory disturbance area infraorbital nerve - nasal obstruction	residual cyst	tooth extraction FESS	3	PIOSCC well differentiated
2	40	female	mandible angle-angle-ramus	- swelling - pain - sensory disturbance area of the NAI	TMJ problems infected follicular cyst	MRI TMJ cystectomy	6	PIOSCC well differentiated
3	52	female	mandible angle-ramus	- swelling - pain - sensory disturbance area of the NAI	infected follicular cyst	cystectomy with fracture of the mandible	3	PIOSCC moderately differentiated
4	57	male	mandible ramus	- swelling - pain - sensory disturbance of the NAI	residual cyst	tooth extraction and cystectomy	3	PIOSCC moderately differentiated
5	82	female	mandible angle-ramus	- swelling - pain - oro-cutaneous fistula	teeth infection	extraction and fistula closure	12	PIOSCC moderately differentiated
6	72	female	maxillary molar and sinuses	- swelling - sensory disturbance infraorbital nerve - nasal obstruction	infected radicular cyst	extraction	6	PIOSCC well differentiated

Table 2
Radiological characteristic of 6 patients with piosec

N	age	gender	primary site	radiologic findings (panoramic)	MRI	Radiologic findings (MSCT or CBCT)	Radiologic findings CT with contrast
1	28	female	maxillary molar and sisus	radiolucent lesion (Hypothesis residual cyst)	no	bony erosion the sinus	expansive lesion with parenchymatous appearance, poorly vascularized, with a maximum diameter about 3 cm with calcifications inside tissue with intense and irregular enhancement, widely involving the left in infratemporal fossa
2	40	female	mandible angle-angle-ramus	voluminous radiolucent lesion of the left mandibular ramus with an impacted 3.8 tooth (hypothesis follicular cyst)	alteration of the signal: irregular inhomogeneous hypointensity in the T1-weighted sequences and irregular hyperintensity in the weighted T2-STIR sequences	expansive lesion with widespread periosteal reaction, extensive peripheral remineralization and cortical disruptions	tissue with intense and irregular enhancement, widely involving the right masseter e medial pterigoid muscle
3	52	female	mandible angle-ramus	radiolucent lesion in the right mandibular ramus in correspondence with the crown of 4.8 included (hypothesis follicular cyst)	no	osteolytic lesion, 3 cm in his maximum diameter interruption of the cortical bone areas of peripheral remineralization involvement of the NAI channel	tissue with intense and irregular enhancement, widely involving the right masseter e medial pterigoid muscle
4	57	male	mandible ramus	radiolucent lesion in the right mandibular ramus (hypothesis residual cyst)	no	expansive lesion in the right mandibular body with a larger size of 3 cm Interruption of the cortical bone Areas of peripheral remineralization Involvement of the NAI	perimandibilar tissue with intense and irregular enhancement, widely involving the right masseter e myloyd muscle
5	82	female	mandible angle-ramus	radiolucent lesion in the right mandibular ramus in correspondence with 3.8 included (hypothesis residual cyst)	no	expansive lesion in the right mandibular body with a larger size of 4 cm Interruption of the cortical bone Involvement of the NAI	tissue with intense and irregular enhancement, widely involving the right masseter e medial pterigoid muscle
6	72	female	maxillary molar and sinuses	radiolucent lesion (Hypothesis residual cyst)	alteration of the signal: irregular inhomogeneous hypointensity in the T1-weighted sequences and irregular hyperintensity in the weighted T2-STIR sequences,	bony erosion the sinus	solid lesion involving the alveolar process at the maxillary level that determines root wear, thinning of the maxillary corticals. its occupied a good part of the maxillary sinus and is surrounded by thin calcified walls. the radiological finding is suspect due to a neo-productive intracistic lesion

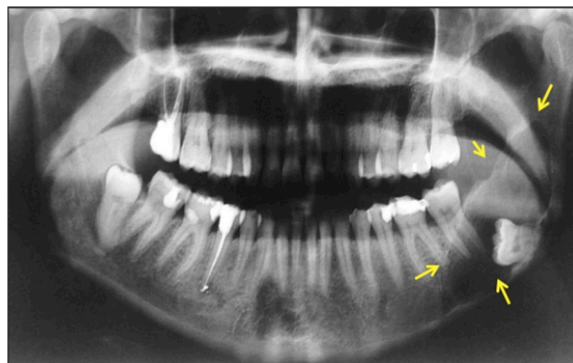


Fig. 1. A panoramic showing a great ovalar radiolucent lesion with well-defined margins including an impacted third molar referable as a follicular lesion.

diagnostic delay was 5.5 months since the onset of the symptomatology (from 3 months to 12 months as extreme).

Radiodiagnostic characteristics

Orthopantomography (OPT) has not given specific signs, which differentiate cystic lesions from cancerous cystic lesions. Only in three cases (case 2, case 3 and 5), we could detect the lack of sclerotic edge typical of odontogenic cysts. From this type of examination, it appears difficult to strap down further significant or specific data (Fig. 1).

The various TC methods (MSCT/CONE BEAM) have allowed a more thorough evaluation.

In the expansive lesions of the maxilla, the erosive characteristics with diffuse cortical discontinuity and the presence of multiple calcifications inside the lesion were evident. With the administration of the contrast medium, the same expansive lesions had a parenchymatous appearance with disohomogenous contrast enhancement, they were not very vascularized and the internal calcifications were more evident.

For PIOSCs of the mandible, some results of MSCT and CBCT appear interesting. Normally traditional radiology in a dentigerous cyst, which originates from the crown of a non-erupted tooth, shows a unilocular radiolucency that arises from the AJC of a non-erupted tooth. With CBCT or MSCT, dislocations of the IAN channel, expansions and erosions of the mandibular cortex can be made evident in these cases.

In two cases (case 2 and 3), some radiological signs were more evident. In particular, an intense periosteum reaction, which extended far beyond the radiolucent site was present. Another sign noted was an intense peripheral remineralization. Another sign is the dislocation of the IAN channel and its difficult location along the entire course of the lesion. Finally, multiple erosive interruptions of the mandibular cortex have become more evident.

In one case (case 5), which presented as residual cysts at the level of the horizontal branch of the jaw, at the CBCT exam, the unilocular radiolucency extended to the lower edge of the mandible, dislocating and eroding the lingual and vestibular cortical. The cortical interruptions were excessive compared to the signs of erosion present in a simple residual cyst. In addition, there were areas of redevelopment within the lesion and there was an important periosteum reaction far beyond the lesion in all directions. Although suspicious the forementioned findings were not specific but led to a more cautious approach and to an incisional biopsy in order to provide definite histological definition.

In contrast-enhanced CTs, an important peri-lesional and far distant contrast was evident. Together with the periosteal reaction, this latter evidence demonstrates a significant inflammatory component, confirmed by the histological examination of the surgical specimen. (Figs. 2 and 3) (see Fig. 4).

In the two maxillary cases (case 1 and 6) the lesions were studied with MRI: the two lesions exhibited heterogeneous density, invading and damaging the left lateral nasal wall and left bottom edge of the left maxillary sinus. Axial MRI showing a high-density on a T2-weighted image, indicating expansion of the tumors to the other's structure. The lesions exhibited gadolinium enhancement (Fig. 5).

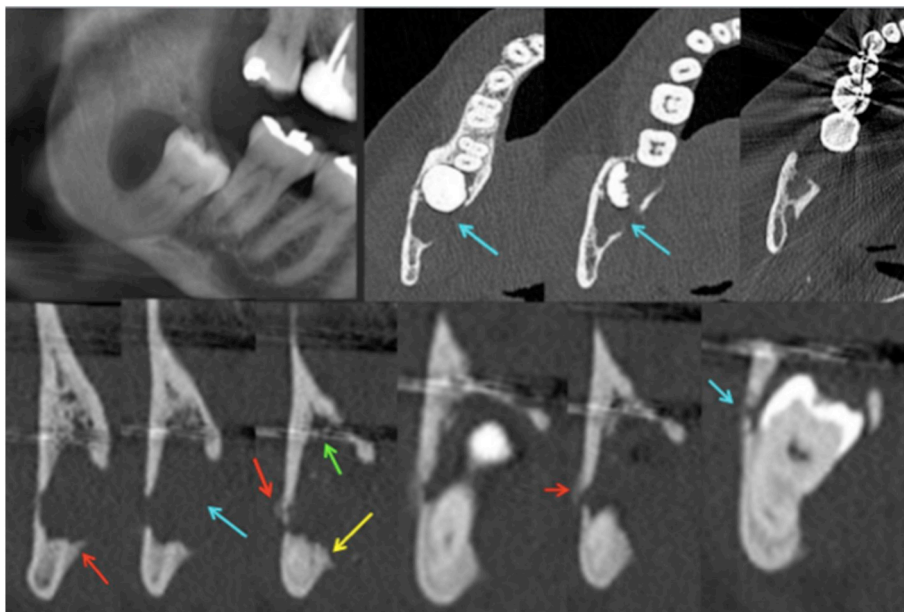


Fig. 2. CT notices more data report to OPT, in particular: a) osteolytic mandibular lesion associated with 4.8. b) blue arrow shows cortical bone interruption, red arrow outlines a periosteal reaction. c) red arrow shows periosteal reaction while green arrow peripheral remineralization. Moreover yellow arrow show a dislocation of mandibular canal.

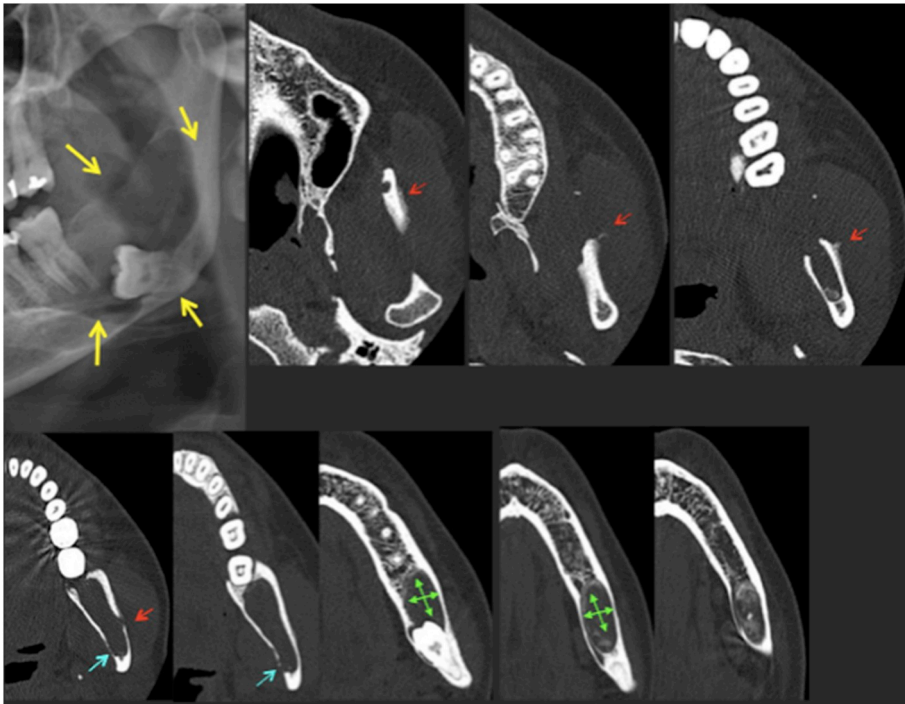


Fig. 3. a) MSCT demonstrating a great osteolytic lesion at the left mandibular angle. B) red arrow: periosteal reaction. C) blue arrow: cortical bone interruption D) green arrow: peripheral remineralization.

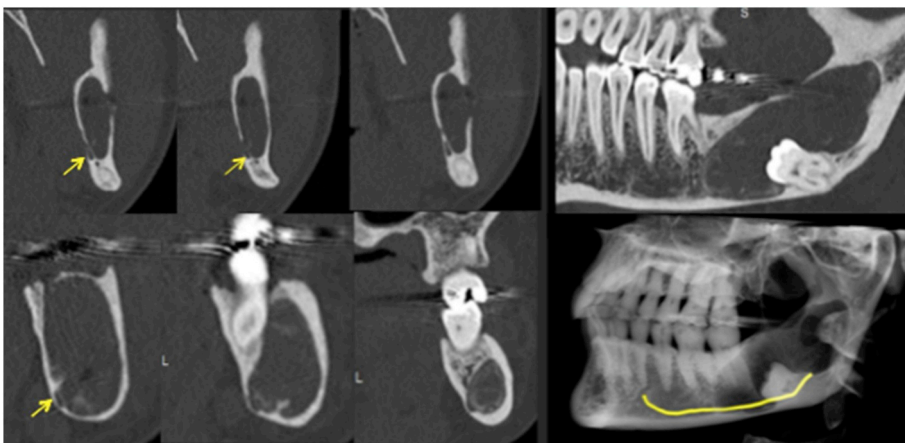


Fig. 4. MSCT detecting the dislocation of the mandibular canal, it's not possible to detect it. It shows expansive lesion with widespread periosteal reaction, extensive peripheral remineralization and cortical disruptions.

Treatment outcome

The treatment outcome is presented in [Table 3](#).

In all cases, the treatment involved surgical excision of the primary tumor with neck dissection.

The reconstruction of the mandible and soft tissues was obtained with a free fibular flap in all but one case ([Fig. 6](#)).

Only one case, in consideration of the age and comorbidities of the patient, the reconstruction was achieved with a locking 2.4 reconstructive plate and pectoralis major flap ([Fig. 7](#)).

The two maxillary cases were extensive and required a Type 4b resection according to Brown classification [9] and a concomitant prophylactic neck dissection. The reconstruction of the orbital floor in both cases was achieved with the positioning of a titanium mesh. The reconstruction of the maxilla was obtained in one case with a free fibular flap and a temporalis myofascial flap and in the other case with a free ALT flap, without bone reconstruction.

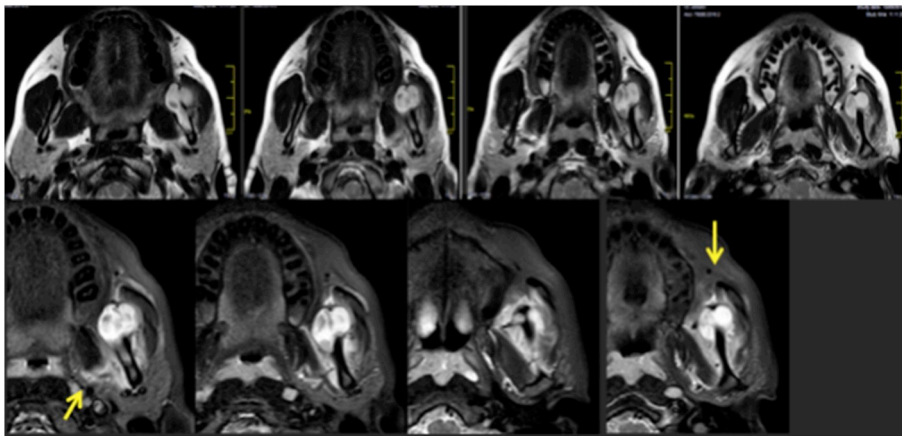


Fig. 5. MR lesion studied with MR demonstrated a signal alteration in the left mandibular angle with patchy hypointensity in T1 weighted sequences and irregular hyperintensity in T2-shir weighted sequences matching for complicated follicular cyst.

Table 3

Treatment course of 6 patients with pioscc

N	initial treatment	histopathology of the specimen	adjuvant post surgery therapy	pN	ECS	Recurrence	prognosis
1	- type IV c maxillectomy - RND omolateral - Fibula free flap e TMF	PIO SCC well differentiated with negative margins, bony erosion	RT (66Gy)+ CDPP 240mg/m2	1	no	no	NED 48 mo
2	- segmental resection of the mandible with condyle disarticulation - mRND - Free fibula Flap	PIO SCC well differentiated with negative margins, bony erosion	RT (66Gy)	0	no	no	NED 48 mo
3	- segmental resection of the mandible - mRND - Free fibula Flap	PIO SCC moderately differentiated with negative margins, bony erosion	no	1	no	no	36 mo
4	- segmental resection of the mandible - mRND - Pectoralis major flap (PMF) and surgical plate	PIO SCC moderately differentiated with negative margins, bony erosion	RT (66Gy)+CDPP 240mg/m2	2	no	no	168 mo
5	segmental resection of the mandible mRND Free fibula Flap and ALT	PIO SCC moderately differentiated with negative margins, bony erosion and cuteness infiltration	RT (66Gy)+CDPP 240mg/m2	3	no	no	108 mo
6	- type IV c matillectomy - RND omolateral - ALT	PIO SCC well differentiated with negative margins, bony erosion	no	0	0	no	36 mo



Fig. 6. Post operative RX OPT oulining resection of the right mandible reconstructed with free fibular flap.



Fig. 7. In this case post operative RX OPT showing resection of the right mandibular reconstructed with a surgical plate and pectoralis major-flap (PMF).

Post-operative adjuvant radiotherapy (66 Gy total) with or without concurrent chemotherapy (cisplatin or carboplatin) was performed in 4 cases, according to with NCCN clinical practice guideline. Pathologic lymphnodes without extracapsular spread were reported in 3 patients. Recurrence or distant metastases were not observed during follow-up (follow-up ranging from 48 to 168 months).

Discussion

Primary intraosseous carcinoma (PIC) appears as a single diagnostic entity, in the 4th edition of the World Health Organization Classification of Head and Neck tumors in 2017 [6]. This new edition recognizes that some PIC may arise from pre-existing cysts, but designation as specific subtypes was neither necessary nor justified on clinicopathological grounds.

More than 70% of PIC develop from a pre-existing cyst [10–12].

The aim of this paper is to report a serie of cases of squamous cell carcinoma originating from the lining of an odontogenic cyst (PIO SCC).

The incidence of PIO SCC represents less than 1% of oral carcinomas (OSCC or Mucoepidermoid carcinomas).

PIO SCC represent 1.7% of squamous carcinomas of the oral cavity (OSCC), according to data collected in ten years [13].

The pathogenesis of this subtype of PIC is not known yet. However, the presence of long-lasting inflammation and/or infection seems to be related to the onset of the SCC [14]. A long period of chronic inflammation has been suggested as a predisposing factor to the malignant transformation of the cystic epithelium [15,16].

Some authors have found a higher incidence of PIO SCC arising on radicular cyst (inflammatory type) [17], others have found a greater incidence on follicular cysts (non-inflammatory type) [18,19].

In the current serie, the PIO SCC originated from residual cysts in three cases (typically of inflammatory origin) and from follicular cysts in the remaining three (typically of non-inflammatory origin). However, all the cases reported in our serie presented multiple inflammation/infection episodes, both in the residual cysts and in the follicular forms.

The absence of an inflammation may involve a pathogenetic mechanism correlated with oncogenesis. In the end, some authors [20] have suggested that the presence of keratinization in the epithelial lining could be a risk factor. Keratinization was generally found only in 15–18% of odontogenic cysts. Most SCC that originates from cysts are keratinized and well differentiated [21].

Epidemiological data are few and fragmented in literature.

The largest series of published clinical cases consist of 116 cases [23]. The average age was 60.2 years and the male to female ratio was 2.22:1. The prevalence of male patients is also confirmed in a recent literature review [12] and probably the highest incidence of odontogenic cysts in males explains it.

In literature, PIO SCC seems to have a higher prevalence in the mandible compared to the maxilla, with a clear prevalence of localization to the mandibular ramus [12,16,18]. Our cases are in line with the literature with four cases located in the mandible and two in the maxilla.

When PIO SCC is located in mandibular branch/angle region the most common symptoms are pain and swelling followed by dental mobility, and paresthesia of the inferior alveolar nerve [14,18,22–26].

A history of chronic painful sinus and resistance to medical therapy is often present in PIO SCC of the upper jaw. A paresthesia of the infraorbital nerve innervation territory is sometimes reported [18].

In all our cases, the initial diagnostic hypothesis was different from that of a PIO SCC. (see Table 1). The average diagnostic delay was 5.5 months (from 3 months to 12 months as extreme). This diagnostic delay occurs because the malignant transformation of an odontogenic cyst may not be clinically or radiologically well distinguished in the initial cases.

We strongly believe that the early and correct diagnosis of PIOSCC must necessarily pass through a correct and accurate radiological study.

Unfortunately no specific radiological pattern for the diagnosis of PIOSCC is reported in literature. Many lesions are removed as simple cystic lesions with a late histological diagnosis of carcinoma because the radiological information usually is based on an orthopantomography (OPT). In our case serie, all the cases were initially incorrectly treated elsewhere because the diagnosis was based on first level X-ray examination.

PIOSCC generally is presented radiologically as a radiolucent unilocular lacunar image with scalloped and poorly defined edges; these radiological aspects suggest invasive development, especially if the cortical bone is eroded [13–16,21–23,27–29].

This radiological aspect was suggestive in at least 1 case of our case series (case 2).

However, Borrás-Ferreres [15] reported a similar percentage of corticated (37.7%) or poorly defined margins (33.9%) of the unilocular lesion in the radiological study.

Langlais et al. [34] suggested that PIOSCC growth is too fast to produce such features.

More detailed information is supplied by Multi-Slice Computed Tomography (MSCT) and Cone Beam Computed Tomography (CBCT). In our experience CBCT, compared to OPT, showed more accurate information concerning periosteal reaction, peripheral remineralization and cortical bone disruption; all these were suspect features of two cases of mandibular PIOSCC (case 1 and 2). Moreover, MSCT was even more detailed than CBCT, showing also dislocation of the mandibular canal. In some of our cases, both the dislocation of the IAN channel and its disappearance were evident.

In our opinion retrospectively these radiological findings although constant, are not specific enough. However, they can lead to the decision to perform a preoperative biopsy.

The contrast-enhanced CTs completes the diagnosis and is useful for staging. Our cases of PIOSCCs are characterized by the presence of intense and irregular enhancement. In general, this finding is congruent with the presence of a peritumoral inflammatory infiltrate that extends far beyond the lesion and that is often reported by the anatomopathological evaluation of the surgical specimens (Fig. 8).

In the contrast-enhanced CTs study, the PIOSCCs located in the maxilla appeared as expansive lesions, that led to discontinuity and thinning of the maxillary corticals with parenchymatous appearance, poorly vascularized and with intense and irregular enhancement.

Staging of the SCC on odontogenic cysts is important for pre-operative assessment, although due to their nature these lesions are always considered as T4 [31]. Positive node metastases are one of the main prognostic features for PIOSCC.

In the largest published case series, the treatment adopted was similar to that adopted for an OSCC with a large bone invasion. Borrás-Ferreres [15] reported a serie of 56 cases: 53 cases were treated with aggressive surgery procedures. In 18 out of 53 patients adjuvant RT was performed and in 8 cases adjuvant radio-chemotherapy was adopted. Chantravekin et al., 2008 [15] (n = 56) and of Bodner et al., 2011 [23] (n = 116) reported an aggressive surgical behavior with extensive resections and neck dissections.

In line with the literature, our cases underwent extensive resection of the primary tumor and prophylactic neck dissection. The type of the neck dissection was chosen according to the radiological N stage. All patients had mRND. 4 patients in our study underwent postoperative adjuvant radiotherapy. All patients but one were suitable for microvascular reconstruction.

The totality of our patients (100%) is disease free after a period of time more than 2 years. Other authors [12] reported that the majority of patients (73.1%) are still alive after a period of time between 4 months and 10 years. Likewise, the largest case series published by Chantravekin et al. [21] and Bodner et al. [23] had similar high percentages of patient survival, 85.3% and 62% at 2 years, respectively.

The cases of SCC that arise from cysts have a better prognosis compared to cases which do not originate from pre-existing lesions [18]. The rate of metastasis in cases of PIC is reported, in literature, to be 18.1–51% [32], with marked differences between de novo tumors (36.5%) and cystic origin tumors (4.4%) [33].

Conclusions

Primary intraosseous carcinoma (PIC) appears, in the 4th edition of the World Health Organization Classification of Head and Neck tumors, as a single diagnostic entity in 2017: the primary intraosseous carcinoma was framed as a single entity collecting under this

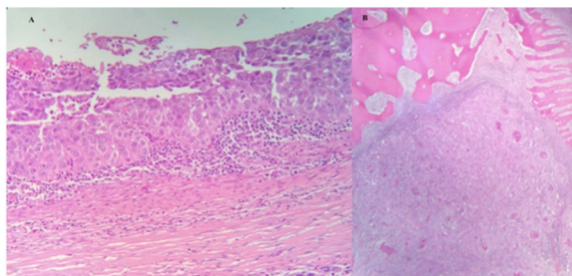


Fig. 8. Representative histopathologic features of PIOSCC. A) the surface of the tumor is covered with non cancerous oral mucosa with severe dysplasia (hematoxylin and eosine stain, original magnification 40×9. B). Growth of tumor cells in bone marrow of the jaw with intense inflammatory infiltrate (hematoxylin and eosine stain, original magnification 40×.).

heading the carcinomas “de novo” intraosseus tumors and those originated from a pre-existing cyst. Carcinomas arising on cysts may have typical radiological characteristics that can be interpreted as red flags and lead to decision to perform a biopsy prior to enucleation which may allow an early correct diagnosis. The radiological study can avoid the accidental removal of carcinomas on cysts and then the neoplastic diffusion. Finally, carcinomas on cysts have a different progression of the disease and a different prognosis from real intraosseus carcinomas. For these reasons, the authors think that squamous cell carcinoma originated from the lining of odontogenic cysts should be considered as a separated pathological entity.

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