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A rare case of secondary ameloblastic carcinoma in a young Man

Ameloblastic carcinoma is a rare and aggressive malignant odontogenic tumour that can arise de novo or from a pre-existing benign lesion. It most frequently involves the mandible, and its clinical course is aggressive with extensive local destruction. Although rare, these lesions have been known to metastasize, mostly to regional lymph nodes or lungs. Surgical therapy, eventually followed by radiotherapy, is the treatment modality most frequently used, while the role of chemotherapy remains unclear. Here we present a case of secondary ameloblastic carcinoma of the mandible in a 33-year-old male patient with typical aggressiveness and extensive local destruction and metastasis with a follow-up period of 93 months.

KEY WORDS: Ameloblastic Carcinoma, Head and Neck Cancer, Maxillofacial Surgery, Oncological Surgery

Introduction

Odontogenic tumours are a heterogeneous group of lesions that in most cases are benign. They are malignant only in 0-6% of cases [1] and, the most known are malignant ameloblastoma (MA) and ameloblastic carcinoma (AC). According to the most recent classification of the World Health Organization (WHO) published in 2005: MA is a tumour showing the characteristics of benign ameloblastoma associated with metastases, however, AC has malignant cytological features regardless of the presence of metastases. AC is sub-categorized into primary type when it develops de novo or secondary type (intraosseous or peripheral form) if it results from a previous central or peripheral ameloblastoma [2-3]. The incidence of AC is not precisely defined as few cases have been reported in the literature as the treatment modalities are still debated. The present study reports the clinical, histological, immunohistochemical, and therapeutic characteristics of a case of secondary mandibular AC affecting a 33-year-old male patient with a follow-up period of 93 months.

Case Presentation

A 33-year-old male presented to the Maxillofacial Unit of University Hospital "Magna Graecia", Catanzaro, Italy, in January 2013 with a swelling on the right side of the face associated with severe pain for 4 months (Fig. 1A). In anamnesis, the patient reported having undergone Hemi-mandibulectomy and reconstruction with a bone graft from the right iliac crest for solid ameloblastoma mixed type (follicular and plexiform) in 2008. The patient was a non-smoker, reported no alcohol consumption, and had no other diseases. Clinical examination revealed facial asymmetry with swelling of the right cheek with no alterations in the surrounding cutaneous tissue and cervical lymph nodes; paraesthesia of the right lower lip was noticed. On intraoral examination, there was a swollen area extending from the right retromolar region to the upper jaw involving masticatory space. The orto-panoramic radiograph (RX-OPT) showed the pres-

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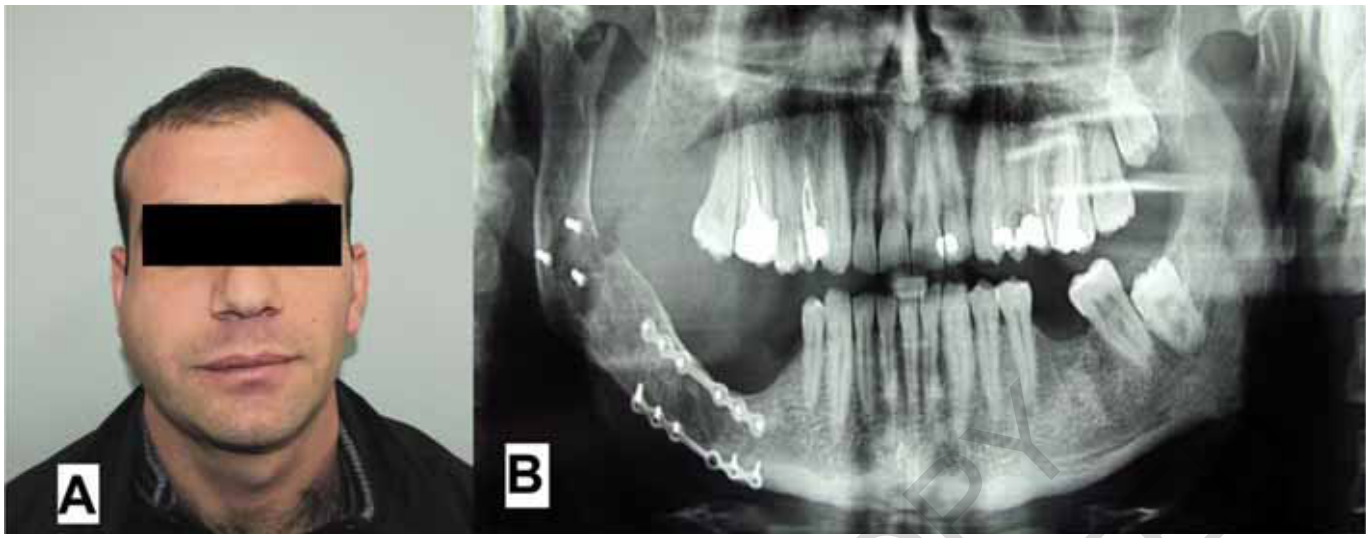

Fig. 1: (A) Preoperative view, showing expansive swelling in the right half face. (B) RX-OPT showing bone graft fixation with a radiolucent image in the posterior area of the body and ascending ramus of the right mandible.

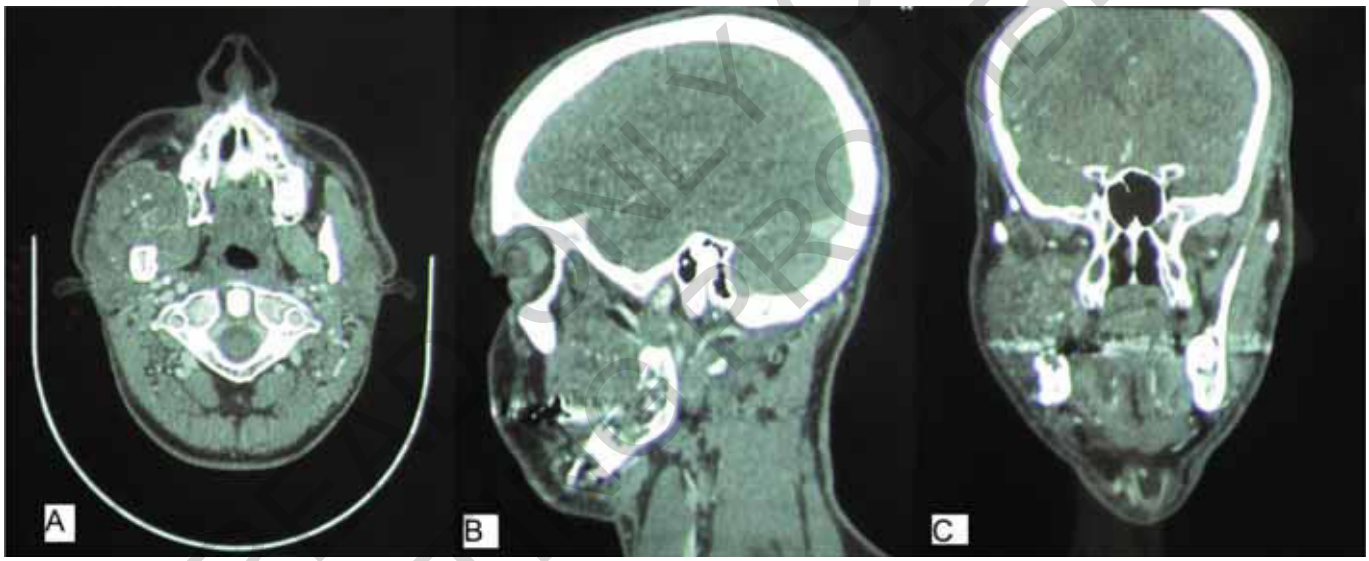

Fig. 2: Axial (A), sagittal (B), and coronal (C) sections of CT reveal a neoplastic lesion with compression and infiltration of both adjacent muscles both the right angular region and ascending ramus of the mandible.

ence of bone graft fixation means on the right mandible with a non-well-defined radiolucent image in the posterior area of the body and ascending ramus (Fig.1B).
Contrast-enhanced computer tomography (CT) revealed a neoplastic lesion that was uniformly internally contrast-enhanced with compression and infiltration of both adjacent muscles both the right angular region and ascending ramus of the mandible (Fig. 2).
No lymphadenopathy was evident in the submandibular and cervical areas.
An incisional biopsy was performed under local anaesthesia and revealed areas consistent with an ameloblastic lesion but with evident cellular pleomorphism and mitotic activity. So, the patient underwent tumour resection (including the previous bone graft) under general anaesthesia and the defect was temporarily reconstructed with the placement of a 2.7 mm titanium reconstruction plate with condyle (Fig. 3A-B).
Histologically, the tumour largely demonstrated the same appearance as the biopsy (Fig. 4).
Immunohistochemical investigations showed positivity for p53 for which the final diagnosis was AC. Post-operative recovery was smooth and uneventful, and the patient was discharged on the seventh day after surgery. Radiotherapy was not required because the resection margins were free and there was no metastasis. The patient underwent follow-up visits and RX-OPT every 6 months which revealed no recurrence of the disease (Fig. 5A-B).
After three years the patient complained of headaches and diplopia, for this reason, a cranial MRI

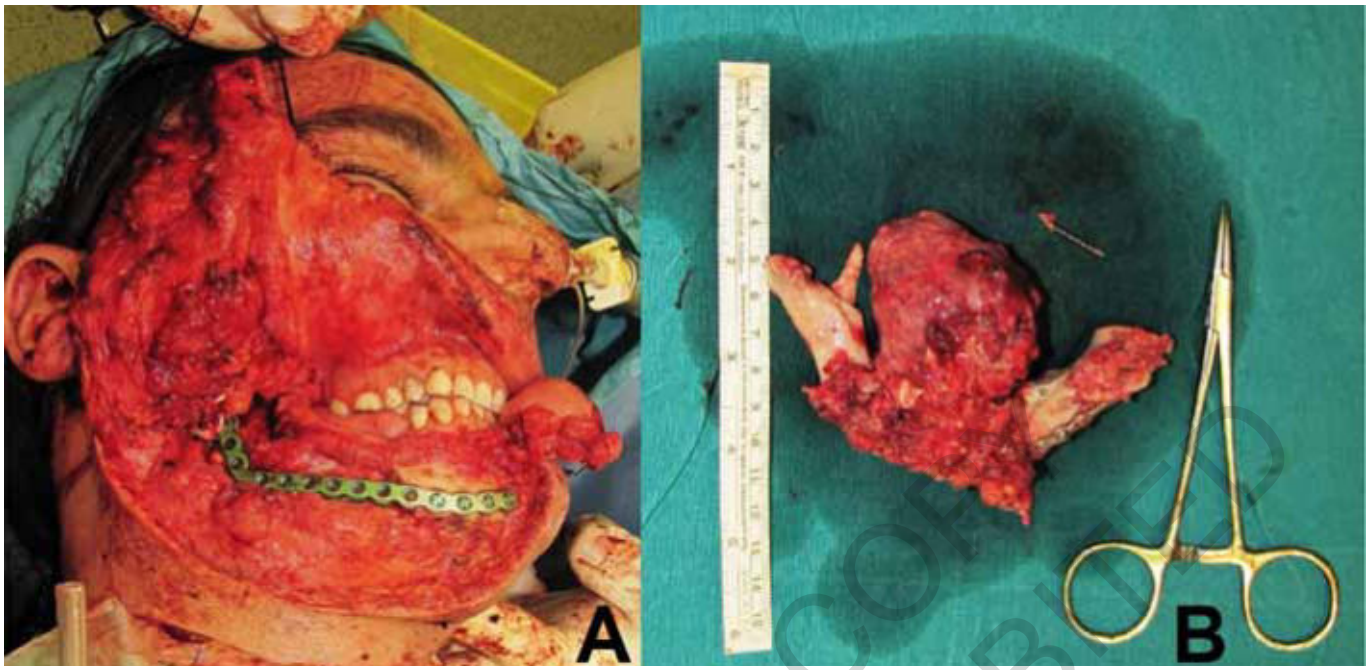

Fig. 3: Intraoperative views. (A) Patient surgical view showing Hemi-mandibulectomy and plate placement. (B) Tumorectomy with safe margin removal, including the previous bone graft.

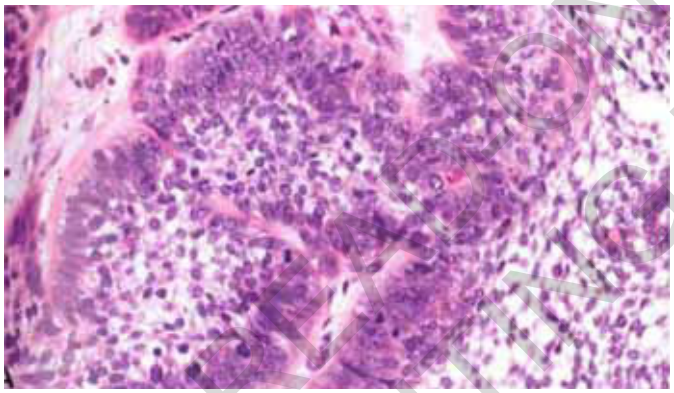

Fig. 4: Architectural feature of AC: A peripheral basaloid layer and stellate reticulum-like central epithelium, with frequent mitotic figures and atypia.

Review Board Statement

The study was conducted following the Declaration of Helsinki; the Ethics Committee of the Magna Graecia University of Catanzaro, Italy, was ordered which revealed a mass of soft tissue occupying the left infratemporal cavity and ethmoid cells with intracranial extension. A CT-angiography was performed to rule out any vascular involvement such as internal carotid arteries (ICAs) and to identify the vascularity of the tumour. On CT angiography, the tumour was significantly vascularized, and the left ICA showed tumour displacement and involvement.

In addition, a neurologic physical examination showed nonfunction of the left sixth cranial nerve and left optic neuropathy. For all these reasons, a multidisciplinary team was set up, and high-dose carbon ion therapy (60 GyE) was recommended.

The treatment was performed in 4 weekly fractions (3 GyE/fraction) for a total of 5 weeks. The first follow-up examination including clinical examination and diagnostic MRI with contrast medium was performed 3 months after the completion of the radiation treatment. MRI showed a significant reduction in tumour size and the presence of right lymph node metastases. A cytological sample was taken from the right submandibular region and showed the presence of atypical epithelial cells, suggestive of AC. In March 2017, a lymphadenectomy of the I-II-III-IV-V lymph node stations was performed.

In July 2018, on MRI, a cystic area with necrosis of the left infratemporal fossa (ITF) appeared. In April 2019 the MRI is repeated: the above area appears to have increased in size, causing a mass effect on the orbital apex, and extending towards the temporal pole (Fig. 6). It was agreed to carry out a combined surgery between neurosurgeons and ENT (intranasal and transcranial approach): cystic lesions were drained, and histological mapping was performed.

Histological examination confirmed the recurrence of ameloblastic carcinoma. After that, the patient underwent many close clinical and instrumental follow-ups (Fig. 7). He died in November 2020.

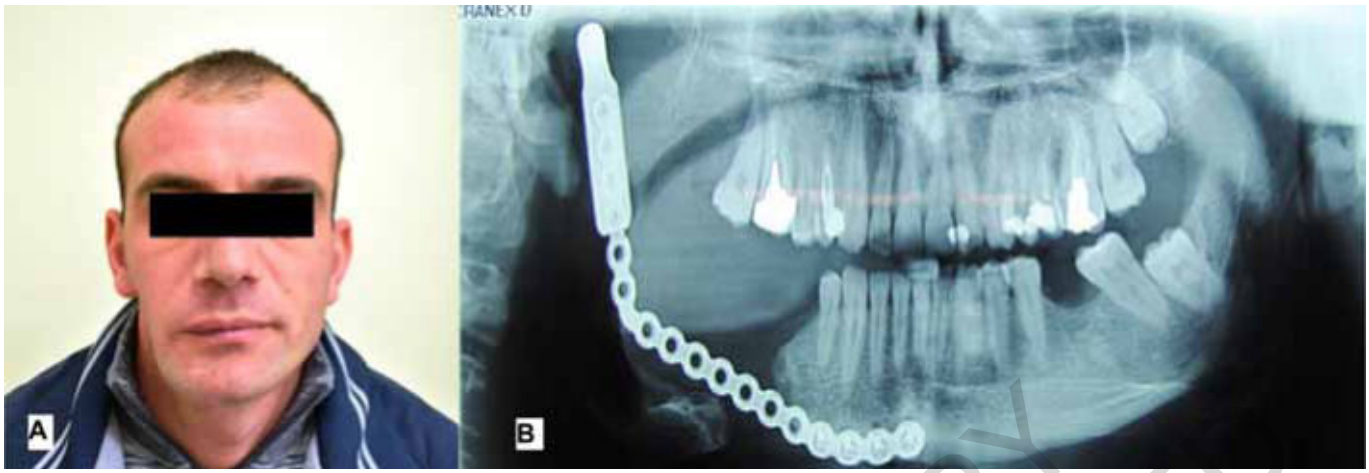

Fig. 5: Post-operative views. (A) clinical image a few months after surgery. (B) Orto-panoramic radiograph showing 2.7 mm titanium reconstruction plate with condyle on the right mandibula.

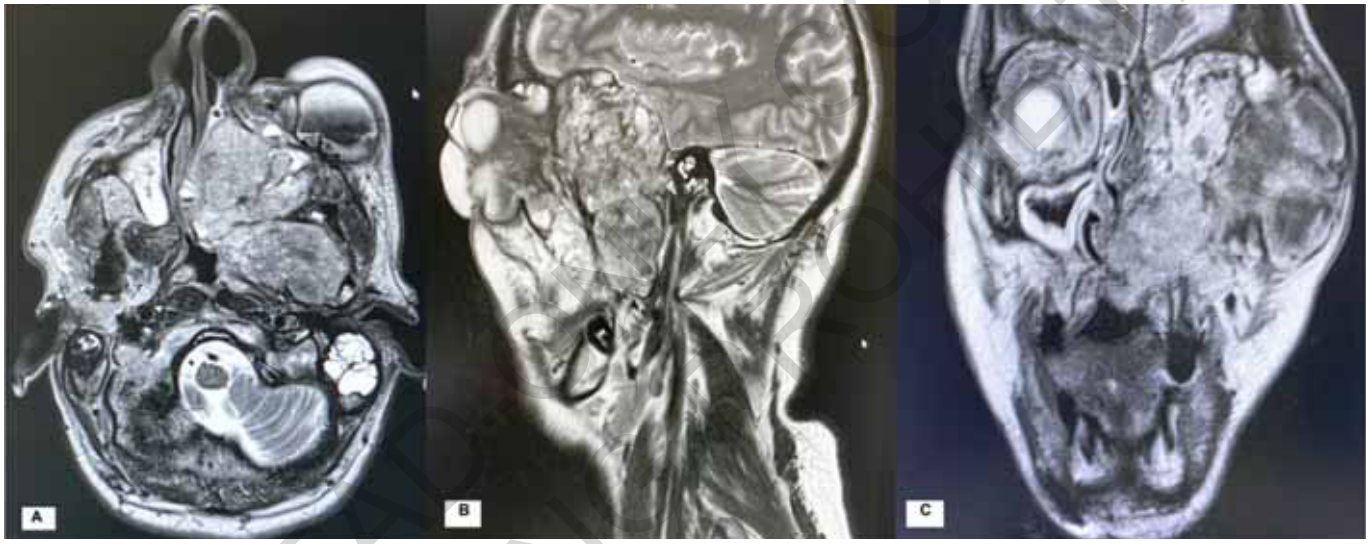

Fig. 6: Axial (A), sagittal (B), and coronal (C) sections of MRI reveal a mass of soft tissue occupying the left infratemporal cavity and ethmoid cells with intracranial extension.

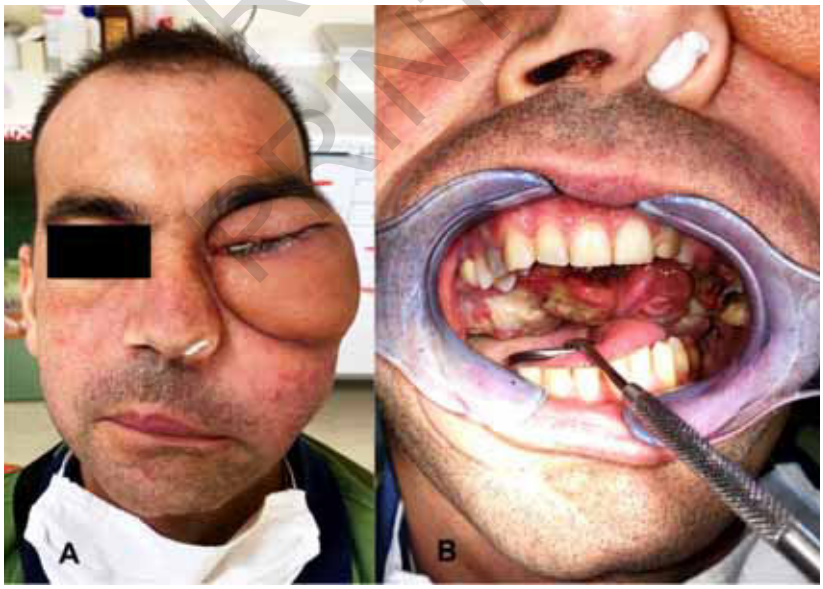

Fig. 7: Last clinical views: Diffuse swelling in the left half-face (A) with intraoral expansion (B).

Discussion

Ameloblastic carcinoma is an extremely rare odontogenic epithelial malignant tumour first described in 1927 by Risak et al. In 1972 the WHO drafted for the first time a classification of odontogenic tumours, recognizing malignant ameloblastoma as the malignant counterpart of benign ameloblastoma [4]. Numerous classifications were proposed in the following years, until 2005 when the WHO defined AC as an odontogenic malignant tumour [5] in which the histopathological features of ameloblastoma and malignancy coexist. It can develop de novo as the "Primary type", or by malignant transformation of the epithelial cells of ameloblastoma as the "Secondary type". The classifications of AC are still under revision. It appears more frequently in men and the most common site is the mandible. The clinical presentation is quite heterogeneous, it can range from a cystic lesion with benign clinical features to a large tissue mass [6] associated with ulceration, bone resorption or tooth mobility, extensive locoregional invasion, and distant metastatic spread (major prognostic factor). The path of diffusion includes both the hematogenous one and the lymphatic one. The most common presenting symptoms are swelling, pain and headache.

AC can determine a locoregional involvement or generate regional and distant metastases; these lesions have been known to metastasize mostly to the lung or regional lymph nodes 7,8. Generally, the first exam required is the ortho-panoramic. AC appears as a radiolucent lesion with defined margins (mimicking ameloblastoma) or poorly defined (with an invasion of the surrounding bone); the possible presence of focal radiopacities, which reflect dystrophic calcifications, can help in the differential diagnosis [6]. However, these radiological features are not specific to ACs.

The wide variety of histological features of this type of tumour creates a certain complexity in the interpretation of conventional radiographs, CT, and MRI [9-10]. According to many authors, MRI is the best technique for evaluating lesions with the simultaneous presence of solid and mixed cystic patterns [11-13]. Therefore, only the histological examination with immunohistochemical methods can be decisive and allow a diagnosis of certainty to be made. The main differential diagnosis of AC is ameloblastoma: both are characterized by a central epithelium resembling a star lattice and a peripheral basal layer of palisade cells with reverse nuclear polarity. Almost always, AC has cytological atypia, high mitotic index, reverse polarization, peripheral palisade and necrosis, and neural and vascular invasion. In doubtful cases, immunohistochemistry is essential; in fact, AC significantly expresses cytokeratin 18, parenchymal matrix metalloproteinase-2 (MMP-2), stromal MMP-9, and Ki-67[14]. In the sample under examination, a significant positivity was found for cytokeratin 18 and ki-67; it also showed positive p53 reactivity in 75% of cancer cells. The mean Ki-67 proliferation rate was 16.31% (range 9.30% - 22.9%) indicating highly proliferative activity than ameloblastoma. Immunoreactivities for vimentin, desmin, neuron-specific enolase, common leukocyte antigen, CD99, and protein S-100 were negative.

Immunohistochemistry makes it possible to discriminate between AC and all neoplastic lesions (both benign and malignant) that mimic their histological and clinical characteristics such as primary intra-alveolar .epidermoid carcinoma [6,15-16], ameloblastoma acanthoma Tous and kerato-ameloblastoma [6,15,17-18] mandibular odontogenic myxoma [19], odontogenic squamous tumour [20], ghost cell tumour [21], metastatic carcinoma of the lungs, sinus and gastrointestinal tract [6,15,18] and intraosseous manifestations of extranodal lymphomas [22].

Due to this rarity of AC, there is no standard therapeutic approach; the most used method is radical surgical excision to obtain negative margins [23-25]. Cervical lymph node dissection should only be considered in the presence of obvious lymphadenopathy. Radiation therapy should be considered in case of locally advanced or metastatic disease not amenable to surgical resection [26-27]. Another method proposed for AC is carbon ion therapy [28-30]; in this case report, carbon ion therapy of 60 GyE has been reported to be associated with excellent outcomes with acceptable morbidity indicating the possible beneficial role of this therapy. The efficacy of chemotherapy in patients with metastatic AC is still debated. These tumours are also subject to numerous relapses which justify a long follow-up.

Conclusions

Ameloblastic carcinoma is an exceptionally rare and aggressive malignant variant of ameloblastoma. It is characterized by a quite varied clinical and instrumental presentation which makes diagnosis difficult and late. No standard treatment has been established for this rare tumour. There is no sufficient clinical data to establish the prognosis of AC, but available information suggests a modest 5-year overall survival of 69% [9]. Further study of AC is encouraged to clearly define its biological and clinical features, its molecular pathogenesis, and its long-term prognosis. This could play a key role in the development of treatment protocols, including personalized therapy.

Riassunto

I tumori odontogeni sono un gruppo eterogeneo di lesioni che nella maggior parte dei casi sono benigne; sono maligni solo nello 0-6% dei casi. Il carcinoma ameloblastico (AC) è un tumore odontogeno maligno raro e aggressivo che può sorgere de novo o da una lesione benigna preesistente.

AC può essere suddiviso in: tipo primario, quando si sviluppa de novo; tipo secondario (forma intraossea o periferica) se deriva da un precedente ameloblastoma centrale o periferico. La sua incidenza non è definita precisamente poiché solo pochi casi sono stati segnalati nella letteratura; inoltre, ancora oggi le modalità del trattamento sono dibattute.
Il più delle volte coinvolge la mandibola e il suo decorso clinico è aggressivo con una vasta distruzione locale. Sebbene rare, queste lesioni sono state conosciute per la metastasi, principalmente ai linfonodi regionali o ai polmoni.
La terapia chirurgica, seguita alla fine dalla radioterapia, è la modalità di trattamento più utilizzata, mentre il ruolo della chemioterapia rimane poco chiaro.
Qui presentiamo un caso di Carcinoma ameloblastico secondario della mandibola in un paziente maschio di 33 anni con aggressività tipica e ampia distruzione locale e metastasi con un periodo di follow-up di 93 mesi.

References

1. Martinez MM, Mosqueda-Taylor A, Carlos R, Delgado-Azanero W, Almeida OP: *Malignant odontogenic tumours: A multicentric Latin American study of 25 cases*. Oral Dis, 2014; 20:380-85.

2. Barnes L, Eveson JW, Reichart P, Sidransky D: *Odontogenic tumours pathology and genetics of head and neck tumours*. Lyon, France IARC Press, 2005; 163-75.

3. Akrish S, Buchner A, Shoshani Y, Vered M, Dayan D: *A myeloblastic carcinoma: Report a new case, literature review and comparison to ameloblastoma.* J Oral Maxillofac Surg, 2007; 65:777-83.

4. Pindborg JJ, Kramer IRH and Torloni H (eds): *Histological typing of odontogenic tumours, jaw cysts and allied lesions*. World Health Organisation, 1972; Geneva 35-36.

5. Barnes L, Eveson JW, Reichart P, Sidransky D, *Editors, world health organization classification of tumours. Pathology and genetics of head and neck tumours. IARC Press Lyon.* Odontogenic carcinomas, 2005; 287-93.

6. Benlyazid A, Lacroix-Triki M, Aziza R, Gomez-Brouchet A, Guichard M, Sarini J: *Ameloblastic carcinoma of the maxilla: Case report and review of the literature*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2007; 104(6):e17-24.

7. Kar IB, Subramanyam RV, Mishra N, Singh AK: *Ameloblastic carcinoma: A clinicopathologic dilemma - Report of two cases with total review of literature from 1984 to 2012*. Ann Maxillofac Surg, 2014; 4(1):70-7.

8. Eversole LR: *Malignant epithelial odontogenic tumors*. Semin Diagn Pathol, 1999; 16:317-24.

9. Smitha T, Priya NS, Hema KN, Franklin R: *Ameloblastic carcinoma: A rare case with diagnostic dilemma*. J Oral Maxillofac Pathol, 2019; 23(Suppl 1):69-73.

10. Sancheti S, Somal PK, Sarkar S: *Ameloblastic carcinoma: A diagnostic dilemma*. Indian J Pathol Microbiol, 2019; 62(3):501-03.

11. Yukimori A, Tsuchiya M, Wada A, Michi Y, Kayamori K, Sakamoto K, Ikeda T: *Genetic and histopathological analysis of a case of primary intraosseous carcinoma, NOS with features of both ameloblastic carcinoma and squamous cell carcinoma*. World J Surg Oncol, 2020; 29:18(1):45.

12. Ueta E, Yoneda K, Ohno A, Osaki T: *Intraosseous carcinoma arising from mandibular ameloblastoma with progressive invasion and pulmonary metastasis*. Int J Oral Maxillofac Surg, 1996; 25:370-2.

13. Khoozestani NK, Mosavat F, Shirkhoda M, Azar R: *Ameloblastic carcinoma with calcification: A rare case report in the mandible and literature review*. Case Rep Dent, 2020; 13:4216489.

14. Sandra F, Mitsuyasu T, Nakamura N, Shiratsuchi Y, Ohishi M: *Immunohistochemical evaluation of PCNA and Ki-67 in ameloblastoma*. Oral Oncol, 2001; 37:193-8.

15. Corio RL, Goldblatt LI, Edwards PA, Hartman KS: *Ameloblastic carcinoma: A clinicopathologic study and assessment of eight cases*. Oral Surg Oral Med Oral Pathol, 1987; 64(5):570-76.

16. Shear M: *Primary intra-alveolar epidermoid carcinoma of the jaw.* J Pathol, 1969; 97:645-51.

17. Pindborg JJ: *Copenhagen: Munksgaard*. Pathology of the Dental Hard Tissues, 1970; 371-77.

18. Gandy SR, Keller EE, Unni KK: *Ameloblastic carcinoma: Report of two cases*. J Oral Maxillofac Surg, 1992; 50(10):1097-102.

19. Albanese M, Nocini PF, Fior A, Rizzato A, Cristofaro MG, Sancassani G, Procacci P: *Mandibular reconstruction using fresh frozen bone allograft after conservative enucleation of a mandibular odontogenic myxoma*. J Craniofac Surg, 2012; 23(3):831-5, doi: 10.1097/SCS.0b013e31824dbff6.

20. Infante-Cossio P, Hernandez-Guisado JM, Fernandez-Machin P, Garcia-Perla A, Rollon-Mayordomo A, Gutierrez-Perez JL: *Ameloblastic carcinoma of the maxilla: A report of 3 cases.* J Craniomaxillofac Surg, 1998; 26:159-62.

21. Novembre D, Giofrè E, Barca I, Ferragina F, Cristofaro MG: *A rare case of mandibular dentinogenic ghost cell tumor: Histopathological, clinical and surgical management*. J Oral Maxillofac Pathol, 2021; 25(1):206, doi: 10.4103/jomfp.JOMFP_185_20.

22. Sorrentino A, Ferragina F, Barca I, Arrotta A, Cristofaro MG: *Extra-nodal lymphomas of the head and neck and oral cavity: A retrospective study*. Curr Oncol, 2022; 29(10):7189-97, doi: 10.3390/curroncol 29100566.

23. Giridhar P, Mallick S, Upadhyay AD, Rath GK: *Pattern of care and impact of prognostic factors in the outcome of ameloblastic carcinoma: A systematic review and individual patient data analysis of 199 cases*. Eur Arch Otorhinolaryngol, 2017; 274(10):3803-810.

24. Goldenberg D, Sciubba J, Koch W, Tufano RP: *Malignant odontogenic tumors: A 22-year experience*. Laryngoscope, 2004; 114:1770-74.

25. Vu NB, Le NT, Chaisuparat R, Thunyakitpisal P, Tran NM: *Ameloblastic carcinoma in a 2-year-old child: A case report and review of the literature*. Case Rep Dent, 2020; 22:2020:4072890.

26. Tarle M, Müller D, Tarle A, Blivajs I, Aljinović Ratković N, Knežević P: *Challenges in the diagnostics and treatment of ectopic ameloblastic carcinoma: A case report*. Croat Med J, 2020; 5:61(3):271-75.

27. Mahmoud SAM, Amer HW, Mohamed SI: *Primary ameloblas-*

tic carcinoma: Literature review with case series. Pol J Pathol, 2018; 69(3):243-53.

28. Jensen AD, Ecker S, Ellerbrock M, Nikoghosyan A, Debus J, Münter MW: *Carbon ion therapy for ameloblastic carcinoma*. Radiat Oncol, 2011; 6:13.

29. Takayama K, Nakamura T, Takada A, Kato T, Sakuma H, Mitsudo K, Fuwa N, Murakami M: *Proton beam therapy combined with retrograde intra-arterial infusion chemotherapy for an extremely rapid growing recurrent ameloblastic carcinoma: A case report*. Mol Clin Oncol, 2020;13(4):34.

30. Yamagata K, Ishikawa H, Saito T, Bukawa H: *Proton beam therapy for ameloblastic carcinoma of the maxilla: Report of a rare case*. J Oral Maxillofac Surg, 2019; 77(1):227.e1-227.e5.