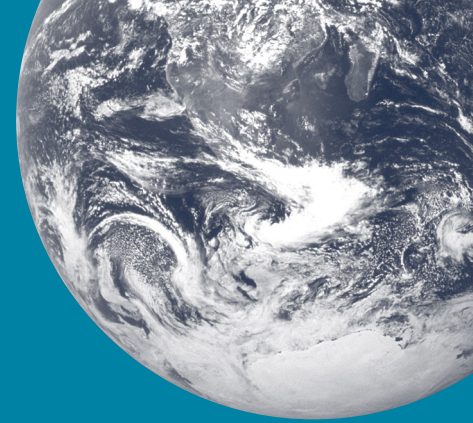




ORAL AND MAXILLOFACIAL METASTASIS OF BREAST CANCER: A CASE REPORT AND LITERATURE REVIEW

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Abstract – Objective: Oral metastases are relatively rare. In women, the most common oral metastases originate from breast cancer, most diagnosed malignancy and the second leading cause of death. The aim of this study was to review the literature regarding oral metastases from breast cancer with the help of a case report, with a focus on clinical and radiographical features and differential diagnosis.

Materials and Methods: The English-language literature between 1980 and 2020 was searched for cases of metastatic lesions to the oral cavity, including bone and soft tissue. Clinical and histopathological data were collected from selected articles.

Results: 81 studies were included in the analysis, with a total of 191 affected patients. 97% were women (mean age 54.6) and the remaining 3% were men (mean age 65.2). Adenocarcinoma was the most frequent histotype (33%) followed by ductal carcinoma (17%). In 102 patients (51.5%), oral metastases were intra-osseous and the remaining 96 patients (48.5%) showed metastases to soft tissues. The primary breast tumor was already known before the onset of the oral metastatic lesion (76.4%). The average time between primary tumor diagnosis and appearance of the oral metastases was 3.8 years. 73% of the patients died, the mean survival time from oral metastasis diagnosis was 21.6 months.

Conclusions: Oral metastases can present both clinically and radiographically very similar to other benign lesions frequently encountered in clinical dental practice. In most cases, the patient has developed the primary neoplasm before oral metastasis, therefore, a complete anamnesis is decisive. Once the diagnostic hypothesis and the differential diagnosis have been established, the histopathological examination is fundamental; therefore, it must always be performed.

KEYWORDS: Breast cancer, Case report, Gingiva, Jaw bone, Literature review, Metastasis, Oral cavity.

INTRODUCTION

The oral cavity is a rare site for metastatic dissemination, representing 1-1.5% of all tumors in this anatomical region^{1,2}. It's relevant to underline that in women, the most common oral metastases both in the mandibular bone (41%) and in the soft tissues (24.3%) originate from breast cancer^{3,4}. Glob-

ally, breast cancer has caused 1.9 million cases and 601,000 deaths^{5,6}. In the USA, it's the most diagnosed cancer and the second leading cause of death⁷. Being one of the most frequent cancers, oral metastases from breast tumors should be included in the differential diagnosis of both osteolytic and exophytic soft tissue lesions of the jaws. The aim of this work is to report a case of an oral metastases



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from breast cancer and to carry out a systematic review on oral metastases originating from this primary tumor, with a focus on clinical and radiographical features and differential diagnosis.

MATERIALS AND METHODS

An extensive search in the electronic databases of the PubMed/ MEDLINE was performed for articles published between January 1980 and October 2020. Second, the reference lists of related review articles and publications were systematically screened. The specific keywords searched were “oral”, “metastasis”, “breast”, “cancer” in various combinations. All types of English-language articles (case reports, retrospective studies and reviews) that reported oral breast cancer metastases, published in the last 40 years were included. Ar-

ticles not accessible and not in English have been excluded. Data were extracted by two reviewers independently (MMS and CC). Items that did not meet the inclusion criteria were excluded. Any disagreement between the authors regarding the inclusion of a particular article and the extraction of the data was resolved by discussion. The PRISMA flow diagram shows the flow of information through the different phases of the review process (Figure 1). A total of 2265 records were identified through the electronic and manual search. After exclusion of duplicates and screening of titles and abstracts, 102 studies were left for full-text assessment. At last, 81 studies were included in the qualitative and in the quantitative analysis, with a total of 198 affected patients. Clinical data (number of patients, gender, age, symptoms, oral site, type of lesion, previous history of malignancy, presence of other metastases and treatment)

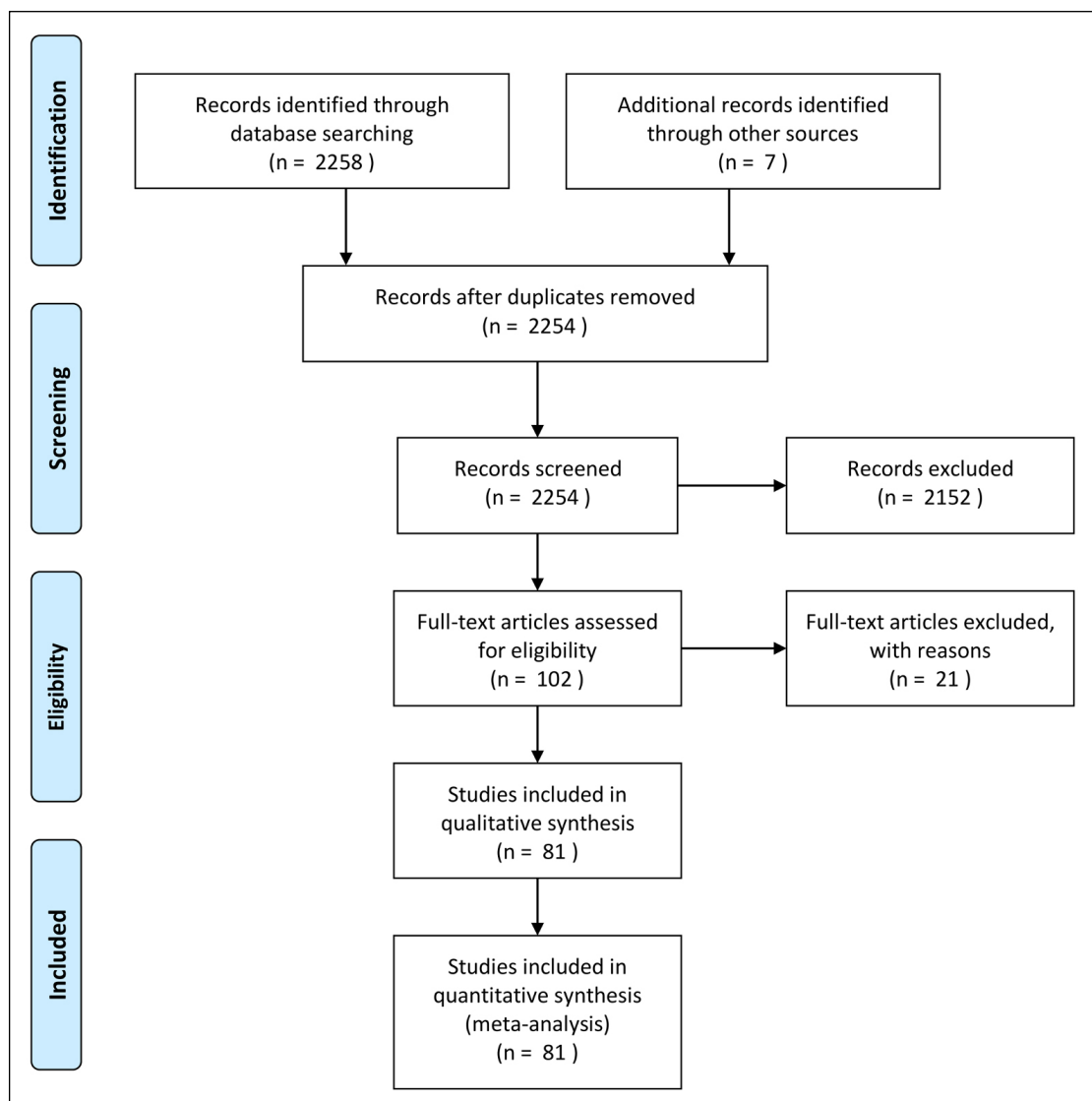


Fig. 1. Flow chart of the search strategy performed.

TABLE 1. Clinicopathological features of the oral metastases (n=198).

Site of oral metastasis		Number of cases	%
<i>Intraosseous</i>	Jaw bone (unspecified)	9	4.5
	Mandible bone	72	36.4
	Condyle	12	6
	Maxillary bone	2	1
	Mandible and maxilla	7	3.5
<i>Soft tissues</i>	Gingiva (unspecified in which jaw bone)	26	13
	Mandibular gingiva	11	5.5
	Maxillary gingiva	9	4.5
	Tongue	16	8
	Parotid gland	13	6.6
	Oral floor	1	0.5
	ATM	10	5
	Others	10	5

and histopathological data (site of primary tumor, histotype of breast cancer) were collected from selected articles. The selected studies were divided into two categories based on the most involved oral anatomical areas (Table 1).

RESULTS

191 patients were analyzed, mean age at diagnosis and gender are described in Table 2 and Figure 2. The age range was 25–88 years, with a mean of 54.6 years for women and 67.6 for men. Only 1 patient was under 30 years, the remaining clustered were predominantly in the 50-59 years age group (Figure 3). The most frequent histological types of primary breast cancers are described in the Figure 4. In 102 patients (51.5%), oral metastases were intra-osseous and the remaining 96 patients (48.5%) showed metastases to soft tissues (Table 1). In most cases, the primary breast tumor was already known before the onset of the oral metastatic lesion (76.4%). In fact, the average time between the diagnosis of the primary tumor and the appearance of the oral metastasis was 3.8 years. However, in 34 patients (23.6%) the oral lesion was diagnosed before the primary tumor. 73% of the patients died, particularly, the mean survival time from oral metastasis diagnosis was 21.6 months. The remaining 26% survived the diagnosis and treatment of oral metastasis, with a mean follow-up time of 19.7

months. As regards the most affected sites, the anatomical areas and their respective clinical, radiological and diagnostic features are described below in order of frequency.

INTRAOSSEOUS METASTASIS

Mandibular and maxillary bone

As regards mandibular metastases, the results found in this review are similar with the data in the literature⁸. Clinically they can be completely undetectable⁹, can mimic a periodontal abscess¹⁰ or periapical inflammatory disease¹¹. More frequently, swelling of the jaw is noticeable, especially following palpation of the contralateral area¹²⁻¹⁵, even in the absence of alterations of the overlying mucosa¹⁶. In addition, tooth mobility can often be detected^{17,18}. More rarely, it can lead to necrotic bone exposure, in which case, if the drug history is positive, it can be mistaken for medication-related osteonecrosis of the jaws (MRONJ)¹⁹.

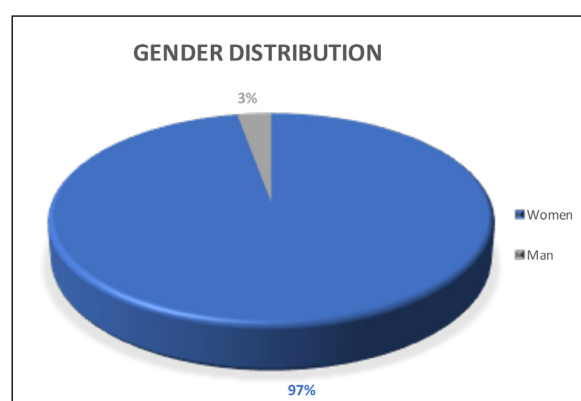

Fig. 2. Gender distribution of patients with oral metastatic tumors.

TABLE 2. Standard deviation and average age of the patients included in the review.

Women	Men	
<i>Middle age</i>	54.6	67.25
<i>Standard deviation</i>	12.5	17.2

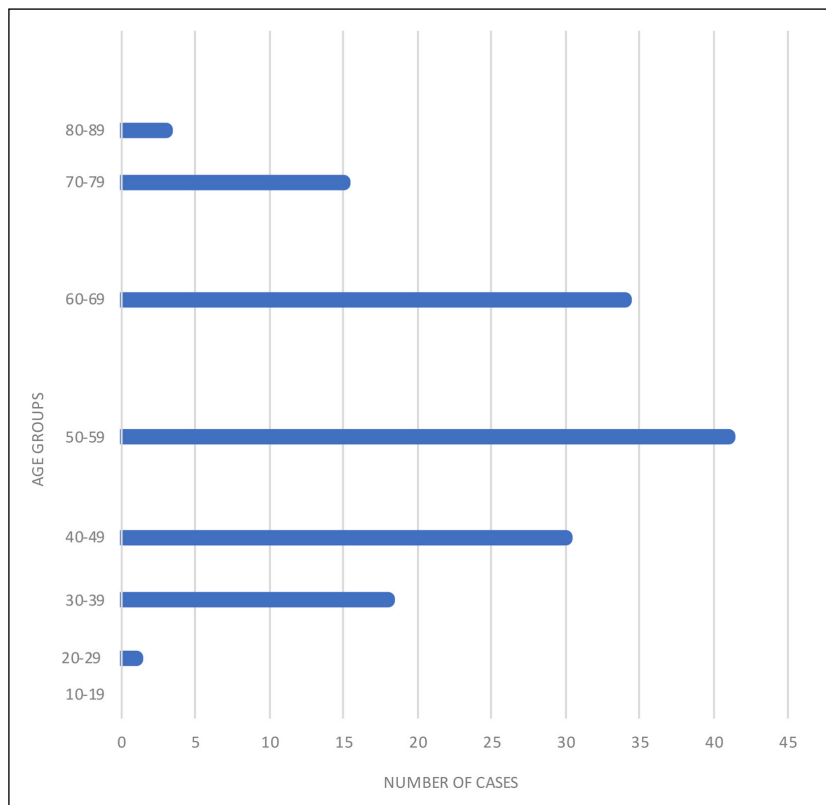
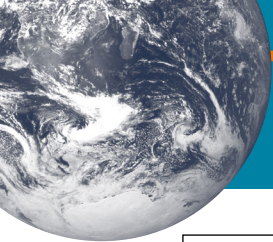


Fig. 3. Age distribution of patients with oral metastasis from breast cancer.

For this reason, histopathological examination is decisive. Regarding the symptoms reported by patients, pain is often present^{12,13,20} but also lip and chin hypoesthesia can be detected^{10,15}. This last symptomatology, known as numb chin syndrome, must be carefully considered, as it's statistically significantly correlated to metastatic lesions in the orofacial area²¹⁻²⁵. Radiographically, mandibular metastases appear as a radiolucent osteolytic lesion with or without resorption of cortical bone and dental roots^{18,26-28}. The less common

maxillary intraosseous metastases have clinical and radiographic features similar to mandibular ones^{29,30}. In the literature, we have found an interesting case of a maxillary metastasis that was initially misdiagnosed for a periapical lesion³¹.

Condyle

Condyle metastasis typically cause temporomandibular joint disorders, trismus, reduced mouth

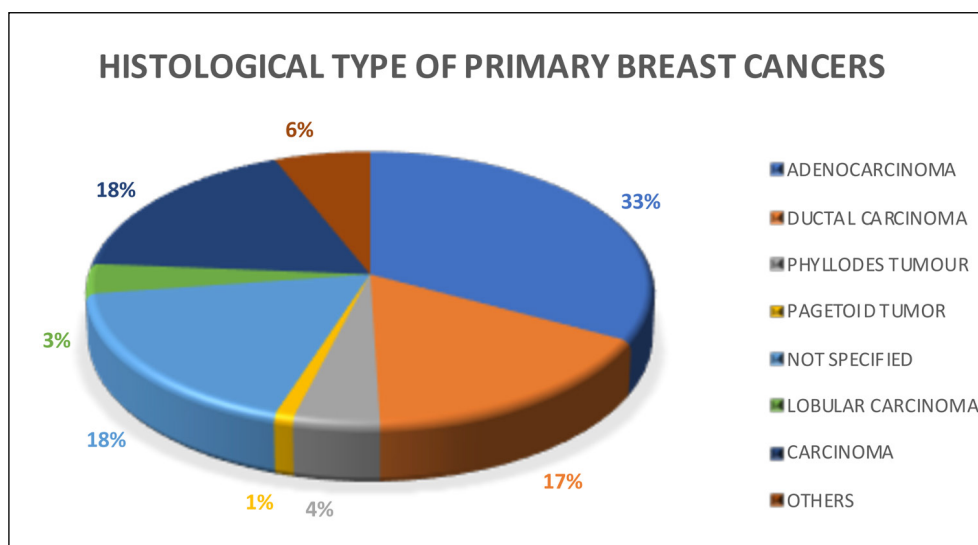


Fig. 4. Histopathological distribution of primary breast tumors found.



Fig. 5. Oral metastasis from ductal carcinoma of the present case reported.

opening and spontaneous pain or on palpation of the temporomandibular joint (TMJ)^{32,33}. In addition, swelling in the TMJ region may be found on extraoral clinical examination³⁴. Also in this case, changes in sensitivity are often reported by the patient³⁵. Radiographically they appear as lithic and radiolucent lesions with circumscribed margins in the condylar region^{33,35}. No pathological changes are evident on intraoral clinical examination³⁵. A condylectomy or hemi-condylectomy is opted in most of the studies included in this review^{33,36}.

SOFT TISSUE METASTASIS

Gingiva

Clinically, gingival metastases, like our case, appear as edematous, erythematous, exophytic and hypertrophic masses³⁷⁻⁴². Maxillary and mandibular gingival metastases share the same clinical features. Also in this case, pain and hypoesthesia are often present⁴³⁻⁴⁵. Often, the surface of the lesion is ulcerated^{46,47} and radiographic signs of erosion of the underlying bone are present⁴⁶. Gingival metastases can be mistaken for exophytic, hyperplastic, and reactive lesions⁴⁸ such as pyogenic granuloma, fibrous epulis, peripheral giant cell granuloma, peripheral fibroma, hemangioma^{49,50} or dental abscess⁵¹. Therefore, the biopsy examination with histopathological analysis is mandatory for all gingival lesions that may suggest a benign inflammatory etiology⁴⁴.

Tongue

Lingual metastatic lesions appear as submucosal nodular masses⁵² or exophytic nodular lesion^{53,54}. Tongue metastasis is usually asymptomatic^{52,55,56}. One study included in this review indeed reported no pain, dysphagia or impaired speech ability⁵⁷; however, weakness of the tongue and difficulty handling food in the back of the mouth were found. On intraoral physical examination there was marked right-sided hemi-atrophy of the tongue with deviation of the tongue towards the right side⁵⁷. In these cases, magnetic resonance is considered the exam of choice. In severe and advanced cases, blood-tinged sputum, dysphagia and dyspnea can appear⁵⁴.

Parotid gland

Clinically, parotid gland metastatic lesions appear as painless nodules⁵⁸⁻⁶¹. A study included in the review reports a case in which the patient reported only flu symptoms in the previous weeks⁶² and another reported peripheral facial paralysis⁶³. On extraoral clinical examination, swelling of the involved parotid gland may be found⁶²⁻⁶⁵. In these cases, the fine needle aspiration biopsy (FNAC)^{62,64} and PET/CT⁶³ can be critical in the diagnosis.

TMJ

The main symptom reported by the affected patients was pain localized in the TMJ area⁶⁶. On clinical examination, swelling, trismus, TMJ dysfunction, malocclusion and more rarely pathological fracture were found⁶⁶. Adenocarcinoma was the histotype most frequently detected following histopathological analysis⁶⁶. Another case included in the review experienced pain for 6 weeks in the right preauricular area, clicks and difficulty in chewing⁶⁷. Initial maxillofacial examination showed tenderness in the area of the right TMJ, temporalis and masseter muscles. Oral and pharyngeal examination was unremarkable and an orthopantomogram failed to show any abnormality⁶⁷.

Oral floor

This case describes a lesion of the oral floor initially mistaken for a neoplasm of the minor salivary glands. The histological analysis gave the result of a metastatic lobular carcinoma of the breast. The final diagnosis was based on comparison with a primary tumor removed 13 years earlier and on immunohistochemical reactivity with antibodies against steroid receptors⁶⁸.



Others oral sites

A completely asymptomatic case with no clinical signs of Pagetoid breast carcinoma metastasized to the palatine tonsils is included in this section, whose diagnosis was made by PET scan³⁷. Another interesting case concerns a metastasis from ductal carcinoma in the masticator space anterior to masseter muscle⁶⁹. The patient reported a painful lesion, hard on palpation in the context of the cheek⁶⁹. Another case reported an oral metastasis from metaplastic breast carcinoma with an unusual clinical presentation: physical examination showed a large mass with necrotic surface in the left retromolar area, measuring approximately 5 centimeters, which caused important trismus and tooth mobility⁷⁰. The patient had type 1 neurofibromatosis, had been diagnosed primary neoplasm one month earlier and died two weeks after oral metastasis⁷⁰. Another case came to attention due to the appearance of an ulcer in the hard palate⁷¹. Reported symptoms were suggestive of acute right sinusitis, followed by headache, nasal obstruction, right exophthalmos, decreased right visual acuity and consequent right eye blindness. TC scan showed irregular augmentation of the right maxillary and sphenoid sinuses, osteolysis of the right pterygoid process, medial and posterior wall of the right maxillary sinus and ethmoid cells, finally erosion of the hard palate and infiltration of periorbital adipose tissue. A biopsy of the palatal ulcer was performed and the histological examination showed a poorly differentiated adenocarcinoma⁷¹. Another case, included in the present review, concerned an oral sign as the first manifestation of ductal carcinoma metastasis: the patient in fact reported hyper sialorrhea and bilateral facial palsy⁷².

Case report

A 77-year-old Sardinian woman was diagnosed in 2016 with a pT2 (2.9 × 2.4 cm) M0 N0 moderately differentiated infiltrating ductal carcinoma (G2) of the left breast. The primary cancer treatment consisted of XII cycles of neoadjuvant chemotherapy. At the end of the last cycle, the patient came to our observation for the appearance of a lesion in the gingival area. The patient reported no history of tobacco or alcohol use. Extraoral examination showed no asymmetry of the face. Intraorally, there was a well circumscribed, round, sessile nodule measuring 2 × 2 cm located in the gingival mucosa of the right hemi-mandible which was covered by smooth red mucosa (Figure 5). The lesion was asymptomatic, fibroelastic in consistency and there

was no hardening of surrounding tissues. On palpation, submandibular lymph nodes were involved. Following the diagnostic suspicion of oral metastases, a total body PET/TC was prescribed. The examination, after intravenous administration of 18F-FDG, revealed the presence of marked accumulation of the metabolic tracer in correspondence with the osteolytic lesion with apparent interruption of the cortical bone in the right hemi-mandible, of the tubercle and of the medial portion of the body of the mandible adjacent segment, indicative of hypermetabolic localization of disease. No other metastatic lesions in the body are evident from the PET/TC. An incisional biopsy of the exophytic lesion was performed and the histological examination showed a ductal adenocarcinoma metastasis. Following the diagnosis, the patient was referred to an oral oncology hospital ward.

DISCUSSION

Gingival metastatic lesions are less frequent than those in the jaw bones^{3,40,55,73,74}. It's now proven that oral metastases from breast tumors primarily affect women, although some cases in men are described^{38,75}. According to Murgod et al⁷⁶ in a careful literature review, in women, breast cancer is responsible for 25% of all oral metastases. Furthermore, in the literature, there are no systematic reviews regarding only oral metastases from breast cancer; however, some features and information can be drawn from the reviews that also include other primary cancers. As for the average age at diagnosis, in most cases, breast neoplasms arise around the fifth decade of life⁴⁰, although they can appear at any age; for example, in this series the age ranged from 25 to 88 years, according to the results of van der Waal et al⁴⁰. The mean age found in this study was 61.1 years, in agreement with that obtained by Seoane et al⁴⁴, equal to 58.5 years. Furthermore, according to the results obtained, the primary tumor is known in most cases when the metastatic lesion is diagnosed, although in some cases, it may be the first manifestation of the primary tumor⁷⁶. In fact, Hirshberg et al⁵⁵ found that in 67% of cases, oral metastases were diagnosed synchronously with the primary tumor while only 20% were the first manifestation. Regarding the mucosal site involved, according to the others works present in the literature, the adherent gingiva, as in our case, is the preferred site of soft tissue metastases in the oral cavity^{3,50,56,74}. Indeed, Zachariades et al⁷⁷ analyzed 422 metastatic lesions to the oral cavity, of which only 12 (2.8%) involved soft tissues, primarily the adherent gingiva followed by the tongue⁴⁴. Therefore,

the early manifestation of a gingival metastasis may resemble a hyperplastic or reactive lesion, as previously stated. Kanazawa and Sato⁷⁸ have proposed that rapid growth is more associated to gingival metastasis; however, Neville et al⁷⁹ pointed out that this feature can also be found also in pyogenic granulomas. Regarding the breast cancer's histotype, several authors agree that adenocarcinoma is the one that most frequently metastasizes in the oral cavity^{40,44,80,81}. According to the results obtained and the data in the literature, most of the patients who presented an oral metastatic tumor also had other metastases in other sites, for which the prognosis is often poor⁴⁰. Particularly, in the present review, the median survival time was 21.6 months, slightly higher than that reported by other reviews which also included metastases from other primary sites, suggesting a longer survival for primary breast tumors. Van der Waal et al⁴⁰, in fact, reported a median survival time of 6 months. As regards our clinical case, it presents a feature that strongly disagrees with the cases described in the literature. Particularly, our case differs from the other ones because our patient was totally edentulous. In fact, Allon et al⁵⁶ showed a statistically significant association between gingival metastases and the presence of teeth ($p < .001$; odds ratio = 8.2). This appears to be related to the conditions of the gingival microenvironment in a chronic state of inflammation. The inflammatory hypervascularization would favor the processes of adhesion, angiogenesis of metastatic cells and consequent formation of the support stroma^{56,82-84}. Indeed, according to Hirshberg et al⁸⁵ some proinflammatory cytokines such as IL-1 β , IL-6, TNF- α , which are localized in inflamed gingival tissue⁸⁶⁻⁸⁸, stimulate and facilitate tumor angiogenesis and attract macrophages associated with metastasis^{89,90}. In the literature, a rationale for the gingival metastases' etiopathogenesis in the absence of dental elements has not been found. Furthermore, although jaw bone metastases are more frequent than those on soft tissues, our clinical case involves the oral mucosa, although other gingival metastases from breast cancer have largely been found in literature^{30,42,51}. As for the clinical features, most of the gingival metastases appear as an exophytic lesion^{37-42,49,85,91-93}, as in our case. Unlike other studies in the literature⁴²⁻⁴⁷, our patient had no symptoms and the surface was not ulcerated. In addition, the reported metastasis derives from adenocarcinoma, the most frequent histotype described in the literature. Finally, it's the authors' opinion that this review and particularly this case report reinforce the significance of gingival metastases as a sign of a neoplastic pathology with a poor prognosis.

CONCLUSIONS

It's important to underline that very often oral metastases can present both clinically and radiographically very similar to other benign lesions frequently encountered in clinical dental practice. In most cases, the patient has developed the primary neoplasm before oral metastasis; therefore, a correct and complete anamnesis, with focus on the remote pathological one, is decisive. The detailed history of any past malignancies can provide critical information. Once the diagnostic hypothesis and the differential diagnosis have been established, the histopathological examination is fundamental; therefore it must always be performed (even after the removal of apparently benign lesions). Finally, immunohistochemistry can be a valuable aid in difficult cases.

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INFORMED CONSENT:

The participant in this study signed the informed consent.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

REFERENCES

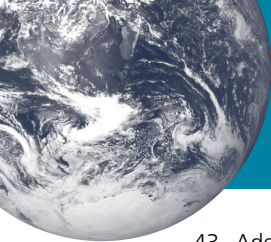
1. Servato JP, de Paulo LF, de Faria PR, Cardoso SV, Loyola AM. Metastatic tumours to the head and neck: retrospective analysis from a Brazilian tertiary referral centre. *Int J Oral Maxillofac Surg* 2013; 42: 1391-1396.
2. Irani S. Metastasis to the oral soft tissues: a review of 412 cases. *J Int Soc Prev Community Dent* 2016; 6: 393-401.
3. Hirshberg A, Shnaiderman-Shapiro A, Kaplan I, Berger R. Metastatic tumours to the oral cavity - pathogenesis and analysis of 673 cases. *Oral Oncol* 2008; 44: 743-752.
4. Kaplan I, Raiser V, Shuster A, Shlomi B, Rosenfeld E, Greenberg A, Hirshberg A, Yahalom R, Shnaiderman-Shapiro A, Vered M. Metastatic tumors in oral mucosa and jawbones: Unusual primary origins and unusual oral locations. *Acta Histochem* 2019; 121: 151448.
5. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I, Abdulle ASM, Abebe ND, Abraha HN,



Abu-Raddad LJ, Abualhasan A, Adedeji IA, Advani SM, Afarideh M, Afshari M, Aghaali M, Agius D, Agrawal S, Ahmadi A, Ahmadian E, Ahmadvanpour E, Ahmed MB, Akbari ME, Akinyemiju T, Al-Aly Z, AlAbdulKader AM, Alahdab F, Alam T, Alamene GM, Alemnew BTT, Alene KA, Alinia C, Alipour V, Aljunid SM, Bakeshei FA, Almadi MAH, Almasi-Hashiani A, Alsharif U, Alsowaidi S, Alvis-Guzman N, Amini E, Amini S, Amoako YA, Anbari Z, Anber NH, Andrei CL, Anjomshoa M, Ansari F, Ansariadi A, Appiah SCY, Arab-Zozani M, Arabloo J, Arefi Z, Aremu O, Areri HA, Artaman A, Asayesh H, Asfaw ET, Ashagre AF, Assadi R, Ataeinia B, Atalay HT, Ataro Z, Atique S, Ausloos M, Avila-Burgos L, Avokpa-ho EFGA, Awasthi A, Awoke N, Ayala Quintanilla BP, Ayanore MA, Ayele HT, Babaee E, Bacha U, Badawi A, Bagherzadeh M, Bagli E, Balakrishnan S, Balouchi A, Bärnighausen TW, Battista RJ, Behzadifar M, Behzadifar M, Bekele BB, Belay YB, Belayneh YM, Berfield KKS, Berhane A, Bernabe E, Beuran M, Bhakta N, Bhattacharyya K, Biadgo B, Bijani A, Bin Sayeed MS, Birungi C, Bisignano C, Bitew H, Bjørge T, Bleyer A, Bogale KA, Bojia HA, Borzi AM, Bosetti C, Bou-Orm IR, Brenner H, Brewer JD, Briko AM, Briko NI, Bustamante-Teixeira MT, Butt ZA, Carreras G, Carrero JJ, Carvalho F, Castro C, Castro F, Catalá-López F, Cerin E, Chaiah Y, Chanie WF, Chattu VK, Chaturvedi P, Chauhan NS, Chehrizi M, Chiang PP, Chichiabellu TY, Chido-Amajuoyi OG, Chimed-Ochir O, Choi JJ, Christopher DJ, Chu DT, Constantin MM, Costa VM, Crocetti E, Crowe CS, Curado MP, Dahlawi SMA, Damiani G, Darwish AH, Daryani A, das Neves J, Demeke FM, Demis AB, Demissie BW, Demoz GT, Denova-Gutiérrez E, Derakhshani A, Deribe KS, Desai R, Desalegn BB, Desta M, Dey S, Dharmaratne SD, Dhimal M, Diaz D, Dinberu MTT, Djalalinia S, Doku DT, Drake TM, Dubey M, Dublinian E, Duken EE, Ebrahimi H, Effiong A, Eftekhari A, El Sayed I, Zaki MES, El-Jaafary SI, El-Khatib Z, Elemineh DA, Elkout H, Ellenbogen RG, Elsharkawy A, Emamian MH, Endalew DA, Endries AY, Eshtrati B, Fadhlil I, Fallah Omrani V, Faramarzi M, Farhangi MA, Farioli A, Farzadfar F, Fentahun N, Fernandes E, Feyissa GT, Filip I, Fischer F, Fisher JL, Force LM, Foroutan M, Freitas M, Fukumoto T, Futran ND, Gallus S, Gankpe FG, Gayesa RT, Gebrehiwot TT, Gebremeskel GG, Gedefaw GA, Gelaw BK, Geta B, Getachew S, Gezae KE, Ghafourifard M, Ghajar A, Ghashghaee A, Gholamian A, Gill PS, Ginindza TT, Girmay A, Gizaw M, Gomez RS, Gopalani SV, Gorini G, Goulart BNG, Grada A, Ribeiro Guerra M, Guimaraes ALS, Gupta PC, Gupta R, Hadkhale K, Haj-Mirzaian A, Haj-Mirzaian A, Hamadeh RR, Hamidi S, Hanfore LK, Haro JM, Hasankhani M, Hasanazadeh A, Hassen HY, Hay RJ, Hay SI, Henok A, Henry NJ, Herteliu C, Hidru HD, Hoang CL, Hole MK, Hoogar P, Horita N, Hosgood HD, Hosseini M, Hosseinzadeh M, Hostiuc M, Hostiuc S, Househ M, Hussen MM, Ileanu B, Ilic MD, Innos K, Irvani SSN, Iseh KR, Islam SMS, Islami F, Jafari Balalami N, Jafarinia M, Jahangiry L, Jahani MA, Jahanmehr N, Jakovljevic M, James SL, Javanbakht M, Jayaraman S, Jee SH, Jenabi E, Jha RP, Jonas JB, Jonnagaddala J, Joo T, Jungari SB, Jürisson M, Kabir A, Kamangar F, Karch A, Karimi N, Karimian A, Kasaeian A, Kasahun GG, Kassa B, Kassa TD, Kassaw MW, Kaul A, Keiyoro PN, Kelbore AG, Kerbo AA, Khader YS, Khalilarjmandi M, Khan EA, Khan G, Khang YH, Khatab K, Khater A, Khayamzadeh M, Khazaei-Pool M, Khazaei S, Khoja AT, Khosravi MH, Khubchandani J, Kianipour N, Kim D, Kim YJ, Kisa A, Kisa S, Kissimova-Skarbek K, Komaki H, Koyanagi A, Krohn KJ, Bicer BK, Kugbey N, Kumar V, Kuupiel D, La Vecchia C, Lad DP, Lake EA, Lakew AM, Lal DK, Lami

FH, Lan Q, Lasrado S, Lauriola P, Lazarus JV, Leigh J, Leshargie CT, Liao Y, Limenih MA, Listl S, Lopez AD, Lopukhov PD, Lunevicius R, Madadin M, Magdeldin S, El Razek HMA, Majeed A, Maleki A, Malekzadeh R, Manafi A, Manafi N, Manamo WA, Mansourian M, Mansournia MA, Mantovani LG, Maroufizadeh S, Martini SMS, Mashamba-Thompson TP, Massenburg BB, Maswabi MT, Mathur MR, McAlinden C, McKee M, Meheretu HAA, Mehrotra R, Mehta V, Meier T, Melaku YA, Meles GG, Meles HG, Melese A, Melku M, Memiah PTN, Mendoza W, Menezes RG, Merat S, Meretoja TJ, Mestrovic T, Miazgowski B, Miazgowski T, Mihretie KMM, Miller TR, Mills EJ, Mir SM, Mirzaei H, Mirzaei HR, Mishra R, Moazen B, Mohammad DK, Mohammad KA, Mohammad Y, Darwesh AM, Mohammadbeigi A, Mohammadi H, Mohammadi M, Mohammadian M, Mohammadian-Hafshejani A, Mohammadoo-Khorasani M, Mohammadpourhodki R, Mohammed AS, Mohammed JA, Mohammed S, Mohebi F, Mokdad AH, Monasta L, Moodley Y, Moosazadeh M, Moossavi M, Moradi G, Moradi-Joo M, Moradi-Lakeh M, Moradpour F, Morawska L, Morgado-da-Costa J, Morisaki N, Morrison SD, Mosapour A, Mousavi SM, Mucche AA, Muhammed OSS, Musa J, Nabhan AF, Naderi M, Nagarajan AJ, Nagel G, Nahvijou A, Naik G, Najafi F, Naldi L, Nam HS, Nasiri N, Nazari J, Negoii I, Neupane S, Newcomb PA, Nggada HA, Ngunjiri JW, Nguyen CT, Nikniaz L, Ningrum DNA, Nirayo YL, Nixon MR, Njaji CA, Nojomi M, Nosratnejad S, Shideh MN, Obsa MS, Ofori-Asenso R, Ogbo FA, Oh IH, Olagunju AT, Olagunju TO, Oluwasanu MM, Omonisi AE, Onwujekwe OE, Oommen AM, Oren E, Ortega-Altamirano DDV, Ota E, Otstavnov SS, Owolabi MO, P A M, Padubidri JR, Pakhale S, Pakpour AH, Pana A, Park EK, Parsian H, Pashaei T, Patel S, Patil ST, Pennini A, Pereira DM, Piccinelli C, Pillay JD, Pirestani M, Pishgar F, Postma MJ, Pourjafar H, Pourmalek F, Pourshams A, Prakash S, Prasad N, Qorbani M, Rabiee M, Rabiee N, Radfar A, Rafiei A, Rahim F, Rahimi M, Rahman MA, Rajati F, Rana SM, Raoofi S, Rath GK, Rawaf DL, Rawaf S, Reiner RC, Renzaho AMN, Rezaei N, Rezapour A, Ribeiro AI, Ribeiro D, Ronfani L, Roro EM, Roshandel G, Rostami A, Saad RS, Sabbagh P, Sabour S, Saddik B, Safiri S, Sahebkar A, Salahshoor MR, Salehi F, Salem H, Salem MR, Salimzadeh H, Salomon JA, Samy AM, Sanabria J, Santric Milicevic MM, Sartorius B, Sarveazad A, Sathian B, Satpathy M, Savic M, Sawhney M, Sayyah M, Schneider IJC, Schöttker B, Sekerija M, Sepanlou SG, Sepehrimanesh M, Seyedmousavi S, Shaahmadi F, Shabaninejad H, Shahbaz M, Shaikh MA, Shamsheirani A, Shamsizadeh M, Sharafi H, Sharafi Z, Sharif M, Sharifi A, Sharifi H, Sharma R, Sheikh A, Shirkoobi R, Shukla SR, Si S, Siabani S, Silva DAS, Silveira DGA, Singh A, Singh JA, Sisay S, Sitas F, Sobngwi E, Soofi M, Soriano JB, Stathopoulou V, Sufiyan MB, Tabarés-Seisdedos R, Tabuchi T, Takahashi K, Tamtaji OR, Tarawneh MR, Tassew SG, Taymoori P, Tehrani-Banihashemi A, Temsah MH, Temsah O, Tesfay BE, Tesfay FH, Teshale MY, Tessema GA, Thapa S, Tlaye KG, Topor-Madry R, Tovani-Palome MR, Traini E, Tran BX, Tran KB, Tsadik AG, Ullah I, Uthman OA, Vacante M, Vaezi M, Varona Pérez P, Veisani Y, Vidale S, Violante FS, Vlassov V, Vollset SE, Vos T, Vosoughi K, Vu GT, Vujcic IS, Wabinga H, Wachamo TM, Wagnew FS, Waheed Y, Weldegebreel F, Weldesamuel GT, Wijeratne T, Wondafrash DZ, Wonde TE, Wondmieneh AB, Workie HM, Yadav R, Yadegar A, Yadollahpour A, Yaseri M, Yazdi-Feyzabadi V, Yeshaneh A, Yimam MA, Yimer EM, Yisma E, Yonemoto N, Younis MZ, Yousefi B, Yousefifard M, Yu C, Zabeh E,

- Zadnik V, Moghadam TZ, Zaidi Z, Zamani M, Zandian H, Zangeneh A, Zaki L, Zendehdel K, Zenebe ZM, Zewale TA, Ziapour A, Zodpey S, Murray CJL. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2019; 5: 1749-1768.
6. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Housami N, Poortmans P, Ruddy K, Tsang J, Cardoso F. Breast cancer. *Nat Rev Dis Primers* 2019; 5: 66.
7. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A, Siegel RL. *CA Cancer J Clin* 2019; 69: 438-451.
8. Liu Y, Vargo RJ, Bilodeau EA. Analytic survey of 57 cases of oral metastases. *J Oral Pathol Med* 2018; 47: 275-280.
9. Choukas C, Toto PD, Choukas NC. Metastatic breast carcinoma mandible in gynecomastia gynecomastic. Case report. *Oral Surg Oral Med Oral Pathol* 1993; 76: 757-759.
10. Poulas E, Melakopoulos I, Tosios K. Metastatic breast carcinoma in the mandible presenting as a periodontal abscess: a case report. *J Med Case Rep* 2011; 5: 265.
11. Daley T, Darling MR. Metastases to the mouth and jaws: a contemporary Canadian experience. *J Can Dent Assoc* 2011; 77: b67.
12. Kalaitidou IG, Astreidis IT, Kontos KI, Lazaridou MN, Bourlidou ET, Gerasimidou DK, Vladika NP, Mangoudi DL. Metastatic tumours to the oral cavity: report of three cases. *J Oral Maxillofac Res* 2015; 6: e5.
13. Thorawat A, Naikmasur VG, Patil P, Perumal P. Secondary metastasis to the mandible from breast carcinoma -a rare case report. *J Clin Diagn Res* 2015; 9: ZD25-26.
14. Gonzalez-Perez LM, Infante-Cossio P, Crespo-Torres S, Sanchez-Gallego F. Mandibular metastases as first clinical sign of an occult male breast cancer. *Int J Oral Maxillofac Surg* 2012; 41: 1211-1214.
15. Sánchez Aniceto G, García Peñín A, de la Mata Pages R, Montalvo Moreno JJ. Tumors metastatic to the mandible: analysis of nine cases and review of the literature. *J Oral Maxillofac Surg* 1990; 48: 246-251.
16. Varghese G, Singh SP, Sreela LS. A rare case of breast carcinoma metastasis to mandible and vertebrae. *Natl J Maxillofac Surg* 2014; 5: 184-187.
17. Ehlinger P, Peeters LC, Servais J, Fossion E. Hormonal therapy in the treatment of mandibular metastasis of breast carcinoma. Report of a case. *Int J Oral Maxillofac Surg* 1993; 22: 108-109.
18. Lu SY, Huang SH, Chen YH. Numb chin with mandibular pain or masticatory weakness as indicator for systemic malignancy - a case series study. *J Formos Med Assoc* 2017; 116: 897-906.
19. Favia G, Tempesta A, Limongelli L, Crincoli V, Piattelli A, Maiorano E. Metastatic Breast Cancer in Medication-Related Osteonecrosis Around Mandibular Implants. *Am J Case Rep* 2015; 16: 621-626.
20. Ogütçen-Toller M, Metin M, Yildiz L. Metastatic breast carcinoma mimicking periodontal disease on radiographs. *J Clin Periodontol* 2002; 29: 269-271.
21. Ryba F, Rice S, Hutchison IL. Numb chin syndrome: an ominous clinical sign. *Br Dent J* 2010; 208: 283-285.
22. Aerden T, Grisar K, Neven P, Hauben E, Politis C. Numb chin syndrome as a sign of mandibular metastasis: a case report. *Int J Surg Case Rep* 2017; 31: 68-71.
23. Fortunato L, Amato M, Simeone M, Bennardo F, Barone S, Giudice A. Numb chin syndrome: A reflection of malignancy or a harbinger of MRONJ? A multicenter experience. *J Stomatol Oral Maxillofac Surg* 2018; 119: 389-394.
24. Carbone M, Della Ferrera F, Carbone L, Gatti G, Carrozzo M. Numb chin syndrome as first symptom of diffuse large B-cell lymphoma. *Case Rep Dent* 2014; 2014: 413162.
25. Orhan K, Bayındır H, Aksoy S, Seker BK, Berberoğlu A, Ozan O. Numb chin syndrome as a manifestation of possible breast cancer metastasis around dental implants. *J Craniofac Surg* 2011; 22: 942-945.
26. Cooney BM, Ruth GJ, Behrman DA, Bova GS, Behrman SJ. Malignant cystosarcoma phyllodes of the breast metastatic to the oral cavity: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol* 1988; 66: 599-604.
27. Guimarães AL, Perdigão PF, Siqueira FM, Castro WH, Gomez RS. Oral metastasis of breast carcinoma diagnosed by fine needle aspiration cytology. A case report. *Acta Cytol* 2003; 47: 1074-1076.
28. Lee YH, Lee JI. Metastatic carcinoma of the oral region: An analysis of 21 cases. *Med Oral Patol Oral Cir Bucal* 2017; 22: e359-e365.
29. Ertas U, Yalcin E, Erdogan F. Invasive ductal carcinoma with multiple metastases to facial and cranial bones: a case report. *Eur J Dent* 2010; 4: 334-337.
30. Dib LL, Soares AL, Sandoval RL, Nannmark U. Breast metastasis around dental implants: a case report. *Clin Implant Dent Relat Res* 2007; 9: 112-115.
31. Spott RJ. Metastatic breast carcinoma disguised as periapical disease in the maxilla. *Oral Surg Oral Med Oral Pathol* 1985; 60: 327-328.
32. Jham BC, Salama AR, McClure SA, Ord RA. Metastatic tumors to the oral cavity: a clinical study of 18 cases. *Head Neck Pathol* 2011; 5: 355-358.
33. Qiu YT, Yang C, Chen MJ, Qiu WL. Metastatic spread to the mandibular condyle as initial clinical presentation: radiographic diagnosis and surgical experience. *J Oral Maxillofac Surg* 2013; 71: 809-820.
34. Ram H, Singhai A, Kumar S, Singh R. Carcinoma of breast metastasising to mandible. *BMJ Case Rep* 2015; 2015: bcr2014206571.
35. Magat G, Sener SO, Cetmili H. Metastatic breast cancer to bilateral mandibular ramus regions. *J Cancer Res Ther* 2019; 15: 1177-1180.
36. McClure SA, Movahed R, Salama A, Ord RA. Maxillofacial metastases: a retrospective review of one institution's 15-year experience. *J Oral Maxillofac Surg* 2013; 71: 178-188.
37. Gondim DD, Chernock R, El-Mofty S, Lewis JS Jr. The great mimicker: metastatic breast carcinoma to the head and neck with emphasis on unusual clinical and pathologic features. *Head Neck Pathol* 2017; 11: 306-313.
38. de Almeida Freire N, de Andrade BAB, Silva Canedo NH, Agostini M, Románach MJ. Oral and maxillofacial metastasis of male breast cancer: Report of a rare case and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2019; 127: e18-e22.
39. Malhotra G, Nair N, Awasare S. F-18 FDG PET scan findings in a case of carcinoma of the breast with a rare site of metastases to the gingival region. *Clin Nucl Med* 2006; 31: 820-821.
40. van der Waal RI, Buter J, van der Waal I. Oral metastases: report of 24 cases. *Br J Oral Maxillofac Surg* 2003; 41: 3-6.
41. Andabak Rogulj A, Tomasovic Loncaric C, Muller D, Blivajs I, Andabak M, Vucicevic Boras V, Sekerija M. Solid malignant metastases in the jaw bones. *Br J Oral Maxillofac Surg* 2018; 56: 705-708.
42. Scipio JE, Murti PR, Al-Bayat HF, Matthews R, Scully C. Metastasis of breast carcinoma to mandibular gingiva. *Oral Oncol* 2001; 37: 393-396.



43. Adelson RT, DeFatta RJ, Miles BA, Hoblitt SL, Ducic Y. Metastatic breast cancer of the oral cavity. *Am J Otolaryngol* 2005; 26: 279-281.
44. Seoane J, Van der Waal I, Van der Waal RI, Cameselle-Teijeiro J, Antón I, Tardío A, Alcázar-Otero JJ, Varela-Centelles P, Diz P. Metastatic tumours to the oral cavity: a survival study with a special focus on gingival metastases. *J Clin Periodontol* 2009; 36: 488-492.
45. Pouloupoulos AK, Antoniadis K, Kiziridou A. Bilateral metastatic breast angiosarcoma to the mandibular gingiva: case report. *Oral Oncol* 2001; 37: 199-201.
46. Yoshida S, Saotome T, Mikogami T, Shiota T. Metastasis of mammary gland malignant phyllodes tumor to the mandibular region: a case report and review of the literature. *J Oral Maxillofac Surg* 2017; 75: 440.e1-440.e9.
47. McCarty MJ, Vukelja SJ. Atypical medullary carcinoma of the breast metastatic to the oral cavity. *Am J Otolaryngol* 1994; 15: 289-291.
48. Guerrieri P, Oliveira A, Arosio F, Murgia MS, Viganò L, Casu C. Exophytic soft tissue traumatic lesions in dentistry: a systematic review. *Int J Appl Dent Sci* 2020; 6: 387-392.
49. Shah MY, Mehta AR. Metastasis from breast cancer presenting as an epulis in the upper gingiva. *J Oral Maxillofac Pathol* 2009; 13: 38-40.
50. Hirshberg A, Buchner A. Metastatic tumours to the oral region. An overview. *Eur J Cancer B Oral Oncol* 1995; 31B: 355-360.
51. Kechagias N, Ntomouchtsis A, Patrikidou A, Christoforidou B, Andreadis C, Vahtsevanos K. Metastasis of a ductal breast carcinoma to the buccal mucosa of the mandible with tooth involvement. *Oral Maxillofac Surg* 2012; 16: 377-381.
52. Owosho AA, Xu B, Kadempour A, Yom SK, Randazzo J, Ghossein RA, Huryñ JM, Estilo CL. Metastatic solid tumors to the jaw and oral soft tissue: A retrospective clinical analysis of 44 patients from a single institution. *J Craniomaxillofac Surg* 2016; 44: 1047-1053.
53. Suárez Roa Mde L, Ruiz Godoy Rivera LM, Vela Chávez T, Pérez Sánchez M, Meneses García A. Breast malignant phyllodes tumour metastasising to soft tissues of oral cavity. *Clin Transl Oncol* 2007; 9: 258-261.
54. Billan S, Abdah-Bortnyak R, Stein ME, Kuten A. Base of the tongue metastasis: aggressive behavior of triple-negative breast carcinoma. *Isr Med Assoc J* 2009; 11: 250.
55. Hirshberg A, Leibovich P, Buchner A. Metastases to the oral mucosa: analysis of 157 cases. *J Oral Pathol Med* 1993; 22: 385-390.
56. Allon I, Pessing A, Kaplan I, Allon DM, Hirshberg A. Metastatic tumors to the gingiva and the presence of teeth as a contributing factor: a literature analysis. *J Periodontol* 2014; 85: 132-139.
57. Fernandes R. Metastatic disease causing unilateral isolated hypoglossal nerve palsy. *BMJ Case Rep* 2010; 2010: bcr0520102998.
58. Jakharia-Shah A, Wheatley H, Beesley M. Reminder of an important clinical lesson: breast cancer metastasis to the parotid gland. *BMJ Case Rep* 2019; 12: e226494.
59. Nuyens M, Schüpbach J, Stauffer E, Zbären P. Metastatic disease to the parotid gland. *Otolaryngol Head Neck Surg* 2006; 135: 844-848.
60. Perez-Fidalgo JA, Chirivella I, Laforga J, Colio JM, Blanes MD, Baydal R, Roselló S, De-la-Morena E, Lluch A. Parotid gland metastasis of a breast cancer. *Clin Transl Oncol* 2007; 9: 264-265.
61. Duncan M, Monteiro M, Quante M. Bilateral parotid gland metastases from carcinoma of the breast that presented 25 years after initial treatment. *Br J Oral Maxillofac Surg* 2015; 53: 94-96.
62. Zhang JZ, Gu M. Malignant phyllodes tumor of the breast metastatic to the parotid gland diagnosed by fine needle aspiration biopsy. A case report. *Acta Cytol* 2003; 47: 253-258.
63. Cao XS, Cong BB, Yu ZY. Parotid gland metastasis from carcinoma of the breast detected by PET/CT: Case report and review. *Medicine (Baltimore)* 2018; 97: e10616.
64. Agarwal R, Rana D, Gupta L, Singh M, Jain S, Rath AK. Mucinous breast carcinoma metastatic to parotid gland: Report of a case diagnosed by fine needle aspiration. *Cytopathology* 2019; 30: 128-130.
65. Dangore-Khasbage SB, Degwekar SS, Bhowate RR, Bhake A. Metastatic involvement of parotid from carcinoma of the breast--a case report. *Oral Maxillofac Surg* 2009; 13: 49-53.
66. Kruse AL, Luebbbers HT, Obwegeser JA, Edelmann L, Graetz KW. Temporomandibular disorders associated with metastases to the temporomandibular joint: a review of the literature and 3 additional cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; 110: e21-e28.
67. Deeming G, Divakaran R, Butterworth D, Foster M. Temporomandibular region metastasis from cystosarcoma phyllodes: a case report and review of the literature. *J Craniomaxillofac Surg* 2003; 31: 325-328.
68. Nicol KK, Iskandar SS. Lobular carcinoma of the breast metastatic to the oral cavity mimicking polymorphous low-grade adenocarcinoma of the minor salivary glands. *Arch Pathol Lab Med* 2000; 124: 157-159.
69. Jain S, Kadian M, Khandelwal R, Agarwal U, Bhowmik KT. Buccal metastasis in a case of carcinoma breast: A rare case report with review of literature. *Int J Surg Case Rep* 2013; 4: 406-408.
70. Vivas AP, Bomfin LE, Pinto CA, Nicolau UR, Alves FA. Oral metastasis of metaplastic breast carcinoma in a patient with neurofibromatosis 1. *Case Rep Oncol Med* 2014; 2014: 719061.
71. Pittoni P, Di Lascio S, Conti-Beltraminelli M, Valli MC, Espeli V, Bongiovanni M, Richetti A, Pagani O. Paranasal sinus metastasis of breast cancer. *BMJ Case Rep* 2014; 2014: bcr2014205171.
72. Jain A, Vats M, Neogi S, Khwaja GA. Paraneoplastic cerebellar degeneration with bilateral facial palsy: a rare primary presentation of breast cancer. *BMJ Case Rep* 2018; 2018: bcr2018224996.
73. Wu YT. Metastatic carcinoma to the oral tissues and jaws: a study of 25 cases. *Zhonghua Kou Qiang Yi Xue Za Zhi* 1990; 25: 258-261.
74. D'Silva NJ, Summerlin DJ, Cordell KG, Abdelsayed RA, Tomich CE, Hanks CT, Fear D, Meyrowitz S. Metastatic tumors in the jaws: a retrospective study of 114 cases. *J Am Dent Assoc* 2006; 137: 1667-1672.
75. Franklin CD, Kunkler IH. Carcinoma of the male breast metastatic to the mandible. *Clin Oncol* 1992; 4: 62-63.
76. Murgod S, Girish HC, Shyamala K, Savita JK. Metastatic tumors of the oral region: a review. *Res J Pharm Biol Chem Sci* 2015; 6: 1779.
77. Zachariades N. Neoplasms metastatic to the mouth, jaws and surrounding tissues. *J Craniomaxillofac Surg* 1989; 17: 283-290.
78. Kanazawa H, Sato K. Gingival metastasis from primary hepatocellular carcinoma: report of a case and review of literature. *J Oral Maxillofac Surg* 1989; 47: 987-990.
79. Neville B, Damm D, Allen C, Chi A. *Neville Oral and Maxillofacial Pathology*, 4ed.; 2016.
80. Epstein JB, Knowling MA, Le Riche JC. Multiple gingival metastases from angiosarcoma of the breast. *Oral Surg Oral Med Oral Pathol* 1987; 64: 554-557.

81. Eckardt A, Nommels R. Breast carcinoma metastatic to the gingiva. *J Oral Maxillofac Surg* 1986; 44: 902-905.
82. Nelson D, Ganss R. Tumor growth or regression: powered by inflammation. *J Leukoc Biol* 2006; 80: 685-690.
83. Kaplan RN, Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, MacDonald DD, Jin DK, Shido K, Kerns SA, Zhu Z, Hicklin D, Wu Y, Port JL, Altorki N, Port ER, Ruggero D, Shmelkov SV, Jensen KK, Rafii S, Lyden D. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature* 2005; 438: 820-827.
84. Allavena P, Sica A, Solinas G, Porta C, Mantovani A. The inflammatory micro-environment in tumor progression: the role of tumor-associated macrophages. *Crit Rev Oncol Hematol* 2008; 66: 1-9.
85. Hirshberg A, Berger R, Allon I, Kaplan I. Metastatic tumors to the jaws and mouth. *Head Neck Pathol* 2014; 8: 463-474.
86. Otenio CC, Fonseca I, Martins MF, Ribeiro LC, Assis NM, Ferreira AP, Ribeiro RA. Expression of IL-1 β , IL-6, TNF- α , and iNOS in pregnant women with periodontal disease. *Genet Mol Res* 2012 Dec 17; 11: 4468-4478.
87. Zheng XY, Mao CY, Qiao H, Zhang X, Yu L, Wang TY, Lu EY. Plumbagin suppresses chronic periodontitis in rats via down-regulation of TNF- α , IL-1 β and IL-6 expression. *Acta Pharmacol Sin* 2017; 38: 1150-1160.
88. Bickel M, Axtelius B, Solioz C, Attström R. Cytokine gene expression in chronic periodontitis. *J Clin Periodontol* 2001; 28: 840-847.
89. Kim J, Bae JS. Tumor-associated macrophages and neutrophils in tumor microenvironment. *Mediators Inflamm* 2016; 2016: 6058147.
90. Solinas G, Germano G, Mantovani A, Allavena P. Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation. *J Leukoc Biol* 2009; 86: 1065-1073.
91. Giunta G, Casu C, Manfredi M, Giovannacci I, Mergoni G, Sarraj A, Bonannini M, Vescovi P, Meleti M. Metastasis of the oral cavity: report of 11 cases and review of the literature. *Abstract Minerva Stomatol* 2016; 65: 206.
92. Casu C, Viganò L. Oral metastasis on the floor of the mouth and on the cheek: a short review. *Curr Anal Dent* 2018; 05-06.
93. Casu C, Viganò L, Fanuli M. Lip metastasis: an overview of the last 30 years. *J Rare Disord Diagn Ther* 2018; 3: 13.