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\(^3,4\). Globally, 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 death\(^7\). 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
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. Articles 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)
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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 literature. Clinically they can be completely undetectable, can mimic a periodontal abscess or periapical inflammatory disease. More frequently, swelling of the jaw is noticeable, especially following palpation of the contralateral area, even in the absence of alterations of the overlying mucosa. In addition, tooth mobility can often be detected. More rarely, it can lead to necrotic bone exposure, in which case, if the drug history is positive, it can be mistaken for medicated-related osteonecrosis of the jaws (MRONJ).

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

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

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

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle age</td>
<td>54.6</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Fig. 2. Gender distribution of patients with oral metastatic tumors.
maxillary intraosseous metastases have clinical and radiographic features similar to mandibular ones. In the literature, we have found an interesting case of a maxillary metastasis that was initially misdiagnosed for a periapical lesion.

**Condyle**

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

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

Parotid gland

Clinically, parotid gland metastatic lesions appear as painless nodules. A study included in the review reports a case in which the patient reported only flu symptoms in the previous weeks and another reported peripheral facial paralysis. On extraoral clinical examination, swelling of the involved parotid gland may be found. In these cases, the fine needle aspiration biopsy (FNAC) and PET/CT can be critical in the diagnosis.

TMJ

The main symptom reported by the affected patients was pain localized in the TMJ area. On clinical examination, swelling, trismus, TMJ dysfunction, malocclusion and more rarely pathological fracture were found. Adenocarcinoma was the histotype most frequently detected following histopathological analysis. Another case included in the review experienced pain for 6 weeks in the right preauricular area, clicks and difficulty in chewing. 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 abnormality.

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 receptors.

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

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

SOFT TISSUE METASTASIS

Gingiva

Clinically, gingival metastases, like our case, appear as edematous, erythematous, exophytic and hypertrophic masses. Maxillary and mandibular gingival metastases share the same clinical features. Also in this case, pain and hypoesthesia are often present. Often, the surface of the lesion is ulcerated and radiographic signs of erosion of the underlying bone are present. Gingival metastases can be mistaken for exophytic, hyperplastic, and reactive lesions such as pyogenic granuloma, fibrous epulis, peripheral giant cell granuloma, peripheral fibroma, hemangioma or dental abscess. Therefore, the biopsy examination with histopathological analysis is mandatory for all gingival lesions that may suggest a benign inflammatory etiology.
Others oral sites

A completely asymptomatic case with no clinical signs of Pagetoid breast carcinoma metastasized to the palate tonsils is included in this section, whose diagnosis was made by PET scan\(^7\). Another interesting case concerns a metastasis from ductal carcinoma in the masticator space anterior to masseter muscle\(^69\). The patient reported a painful lesion, hard on palpation in the context of the cheek\(^69\). Another case reported an oral metastasis from metastatic 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 trismus and tooth mobility\(^37\). The patient had type 1 neurofibromatosis, had been diagnosed primary neoplasm one month earlier and died two weeks after oral metastasis\(^70\). Another case came to attention due to the appearance of an ulcer in the hard palate\(^71\). 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 adenocarcinoma\(^71\). 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 palsy\(^72\).

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\(^5,40,55,73,74\). 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 al\(^76\) 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 life\(^40\), 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 al\(^40\). The mean age found in this study was 61.1 years, in agreement with that obtained by Seoane et al\(^44\), 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 tumor\(^76\). In fact, Hirshberg et al\(^55\) 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\(^5,50,56,74\). Indeed, Zachariades et al\(^77\) analyzed 422 metastatic lesions to the oral cavity, of which only 12 (2.8%) involved soft tissues, primarily the adherent gingiva followed by the tongue\(^44\). Therefore,
the early manifestation of a gingival metastasis may resemble a hyperplastic or reactive lesion, as previously stated. Kanazawa and Sato\(^9\) have proposed that rapid growth is more associated to gingival metastasis; however, Neville et al\(^9\) 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 poor\(^40\). 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 al\(^40\), 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 al\(^56\) 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\(^6,82-84\). Indeed, according to Hirshberg et al\(^85\) some proinflammatory cytokines such as IL-1\(\beta\), IL-6, TNF-\(\alpha\), which are localized in inflamed gingival tissue\(^86-88\), 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 literature\(^42-47\), 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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**CONFLICT OF INTEREST:**

The authors declare that there is no conflict of interest.

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