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Differential Diagnosis of Oral Metastases

Diagnóstico Diferencial de las Metástasis Orales

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ABSTRACT: Metastatic lesions in the mouth can resemble common inflammatory lesions. Therefore, we set out to investigate oral metastases whose clinical and imaging characteristics mimicked those of harmless lesions, confusing and delaying the diagnosis. For this, a systematic review was carried out from case reports, case series, and cross-sectional studies in the PubMed/Medline, Scopus, Embase-via Elsevier, Virtual Health Library, Web of Science, and gray literature, using PICO strategy without period restriction. We assessed the quality of studies using the Joanna Briggs Institute assessment tool. A narrative synthesis of the data was carried out. Association analyses using chi-square and Fisher's exact tests were performed, with statistical significance at $p<0.05$. Most of the lesions came from the lung, breast, kidneys, liver, and thyroid. They affected mainly the mandibles of men, between the fifth and seventh decades of life, causing osteolysis. In soft tissue, there were firm swellings, associated with bleeding. Limitations regarding the heterogeneity of the included studies and the absence of clinic pathological descriptions of the tumors substantially reduced the chance of statistical analysis of the data. Knowing the different possibilities of clinical presentation of oral and maxillofacial metastases is important for the diagnostic suspicion to occur and diagnostic errors to be avoided. Thus, treatment is instituted and survival can be extended. Protocol registration: PROSPERO CRD42020200696

KEY WORDS: mouth neoplasms, neoplasm metastasis, differential diagnosis, oral manifestations, systematic review.

INTRODUCTION

Cancer is a disease characterized mainly by the disordered proliferation of poorly differentiated cells with the ability to invade nearby and distant tissues (Hirshberg *et al*., 2014). It is considered one of the main causes of death in Brazil and in the world, with more than 600,000 new cases recorded each year, according to data from the National Cancer Institute (INCA, 2020).

Morbidity and mortality are mainly due to the dissemination process (Hirshberg *et al*., 2014). In the mouth and jaws, metastatic tumors are rare, representing only 1 % of all malignancies that affect this region (Van der Waal *et al*., 2006; Seoane *et al*., 2009; Shen *et al*., 2009; Hirshberg *et al*., 2014; Kirschnick *et al*., 2020). The jaws are more affected than the soft tissues, with a predilection for the mandible, in a proportion that can reach 3:1 (Hirshberg & Buchner, 1995; Piattelli *et al*., 2000; Van der Waal *et al*., 2006; Shen *et al*., 2009; Kumar & Manjunatha, 2013; Hirshberg *et al*., 2014).

Oral and maxillofacial metastases (OMFM) are considered late complications. They compromise quality of life as they grow rapidly, causing pain, difficulty in chewing, dysphagia and disfigurement (Hirshberg *et al*., 2008; Kumar & Manjunatha, 2013; Hirshberg *et al*., 2014).

The definitive diagnosis is made based on the microscopic features, which should be the same as the original tumor (Shen *et al*., 2009). As the primary site is often still hidden, immunohistochemical evaluation can be useful in identifying the cell lineage (Rajappa *et al*., 2005; Shen *et al*., 2009).

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It is necessary to realize the need to perform biopsy and subsequent microscopic investigation. Metastatic lesions, however, are poorly known, their clinical-radiographic picture is variable, and common inflammatory and reactive lesions can be mimicked (Kumar & Manjunatha, 2013; Allon *et al*., 2014; Hirshberg *et al*., 2014; Melgaço-Costa *et al*., 2020). Some of them are treated based on clinical judgment and the suspicion of a mistake only arises when the therapeutic response does not come.

Therefore, it is important for dentists to be aware of the most commonly associated features, especially those that can lead to diagnostic confusion. This will enable them to raise more plausible hypotheses and make earlier diagnoses.

The aim of this work was to conduct a systematic review of OMFM cases with emphasis on the differential diagnosis with common oral lesions. Based on "PICOS", the review question was: "In patients with metastatic dissemination in the mouth, both in soft tissues and in the maxillary bones, which lesions make up the spectrum of differential diagnosis?".

MATERIAL AND METHOD

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Page *et al*., 2021).

Eligibility Criteria. Metastatic tumors located in oral mucosa and submucosa, and also in maxillary bones, major salivary glands, and palatine tonsils were included. All of the included lesions were histopathologically diagnosed as the spread of a distant primary tumor that mimics common oral lesions. The articles were published in the form of case reports, case series and cross-sectional studies, in English, Portuguese, Spanish, and French. The exclusion criteria were as follows: articles with (1) unavailable full version, (2) insufficient clinical-pathological data, (3) oral and maxillofacial metastases (3.1) discovered during autopsies, (3.2) from hematological malignant tumors, and (3.3) from primary malignant tumors of the head and neck region, and (4) cases with differential diagnosis not reported or explored.

Sources of Information and Search Strategy. The following databases were searched: PubMed/Medline, Scopus, Embase, Virtual Health Library, Web of Science, and gray literature (Google Scholar and Brazilian Digital Library of Theses and Dissertations). The reference lists of the selected articles were manually tracked to detect any relevant studies not retrieved through the electronic search. The search strategy is summarized in Table S1, Supporting Information. The references found in the databases were exported to a reference manager, EndNote Web® (Thomson Reuters, New York, USA).

Study Selection. The selection process was performed in two phases. In phase 1, two authors (FANH and TCK) worked independently and used titles and abstracts to identify any eligible articles. In phase 2, the same authors read the full texts and excluded those that did not meet the inclusion criteria. Any disagreements between the two authors were resolved by discussion until consensus. When there was no consensus, a third author (VCV) was consulted, whose decision was final. The inter-examiner kappa value was greater than 0.80 in both phases.

Data Collection Process and Data Extracted. Data collection for the selected studies was performed by the first reviewer (FANH). The second reviewer (TCK) confirmed the accuracy of the data collected. Any disagreements were resolved by consulting the third reviewer (VCV). The following information was extracted from each study: author, demographic data (sex and age), location of the lesion, evolution time, symptomatology, past or current history of malignancy, clinical appearance, imaging appearance (if applicable), differential diagnosis, previous treatments, microscopic appearance, primary site, treatment, and prognosis.

The cases were grouped according to similarity to oral and maxillofacial common lesions from three different groups: 1) inflammatory; 2) neoplastic; 3) undefined nature.

Risk of Bias Within Studies. The risk of bias was assessed using the modified Joanna Briggs Institute's critical assessment tools, for case reports, case series, and cross-sectional studies (Moola *et al*., 2017). Each question was answered with "yes", "no", "unclear" or "not applicable".

Two reviewers (FANH and TCK.) analyzed the risk of bias separately and classified the articles as "high risk" (when the study reached up to 49 % "yes" to the considered parameters), "moderate risk" (50–69 %

"yes"), and "low risk" (greater than 70 % "yes"). A conference was held between the two reviewers, and disagreements were resolved by consensus. The numbers were generated using RevMan 5.4 software (Review Manager 5.4, Cochrane Collaboration).

Analysis of Evidence and Statistics. A database covering the variables and classifications was organized in a Microsoft Office Excel 2016 spreadsheet (Microsoft Corporation, Redmond, WA, USA) to tabulate the statistical data. The information gathered was analyzed using Jamovi, 1.6.15 version (Jamovi Project 2021, Sydney, NSW, Austrália). A descriptive study of the results was conducted. Moreover, association analyses were developed between SITE OF THE PRIMARY TUMOR (as an independent variable) and: 1. Demographic data (sex and age), 2. Lesion location (bone tissue, soft tissue, palatine tonsils and salivary gland), 3. Signs and symptoms (symptomatology, paresthesia, dysphagia, bleeding, dental mobility, and impairment of mandibular movements), 4. Previous treatment (extraction, root canal treatment and antibiotic therapy), 5. Knowledge of the primary tumor, 6. Multiplicity of metastases (only in oral and maxillofacial regions or at multiple sites), 7. Clinical features (surface, consistency, size, color, clinical appearance, and evolution time), 8. Imaging features (radiolucid, radiopaque, and mixed), 10. Diagnostic hypothesis (metastatic, primary malignant, inflammatory, benign neoplastic, and lesion of undefined nature). Another association analysis was performed between LESION LOCATION (bone tissue and soft tissue - as an independent variable) and the same dependent variables mentioned above. For the nominal qualitative variables, chi-square and Fisher's exact tests were used. In all tests, statistical significance was set at $p<0.05$.

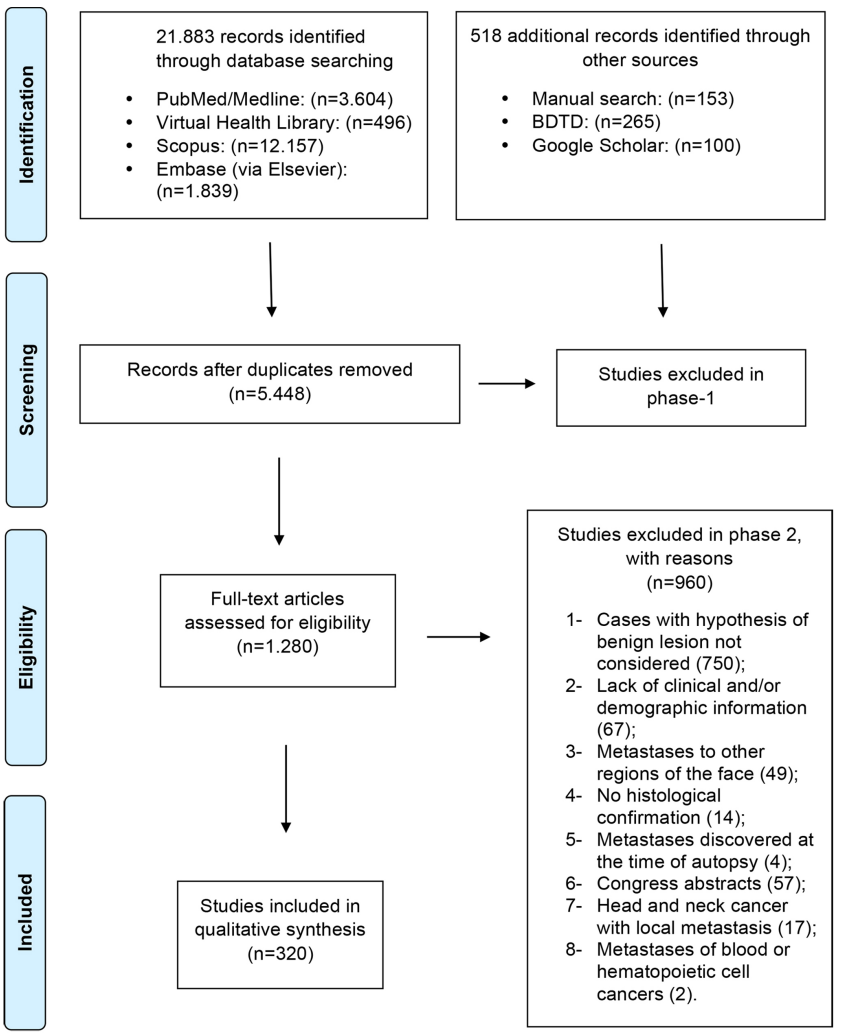

Fig. 1.The PRISMA flow chart.

RESULTS

Selection and Characteristics of the Studies. A total of 21.883 articles were initially identified in the databases. However, 5.448 were removed as they were duplicates and 15.673 were considered not relevant, after reading the titles and abstracts. All 1.280 remaining articles were read in full. Of these, 960 were excluded after applying the inclusion criteria (Table S2, Supporting information). Finally, 320 papers were included for quality analysis. The PRISMA flow chart summarizes the selection process, including the reasons for exclusions (Fig. 1). Of the 320 studies analyzed, 309, 8, and 3 were case reports, case series, and cross-sectional studies, respectively, with references available in the Supporting information. In total, 341 patients were included. The studies were published from 1928 to 2022.

Synthesis of Studies

General characteristics of OMFM. The general features (Table I) of the 341 patients in the sample are

Table I. Demographic and clinical features.

Variable	N (%)
Sex (n=340)	
Male	182 (53.5)
Female	158 (46.5)
Male-to-Female	1.1:1
Age (n=336)	Mean: 57.5 (±14.8) Range: 5-89 y
Lesion location (n=341)	
Bone tissue	179 (52.5)
Soft tissue	162 (47.5)
Bone tissue (n=179)	
Mandible	140 (78.2)
Maxilla	26 (14.5)
Maxilla and mandible	2 (1.1)
TMJ	11 (6.2)
Soft tissue (n=162)	
Alveolar mucosa	8 (4.9)
Cheek	2 (1.2)
Gingiva	114 (70.4)
Lip	3 (1.9)
Oral mucosa	6 (3.7)
Palatine tonsils	4 (2.5)
Salivary gland	11(6.8)
Tongue	11 (6.8)
Soft palate	2 (1.2)
Floor of the mouth	1 (0.6)
Evolution time (n=213)	
Up to 1 month	69 (32.4)
Up to 3 months	89 (41.8)
Up to 6 months	30 (14.1)
Over 6 months	25 (11.8)
Symptoms	
Pain (n=226)	
No	72 (31.9)
Yes	154 (68.1)
Teeth mobility (n=61)	
No	5 (8.2)
Yes	56 (91.8)
Bleeding (n=63)	
No	4 (6.3)
Yes	59 (93.7)
Numbness (n=79)	
No	3 (3.8)
Yes	76 (96.2)
Dysphagia and dysphonia (n=35)	
No	4 (11.4)
Yes	31 (88.6)
TMJ restrict movements (n=43)	
No	4 (9.3)
Yes	39 (90.7)
Weight loss (n=57)	
No	24 (42.1)
Yes	33 (57.9)
Fever (n=37)	
No	25 (67.6)
Yes	12 (32.4)

Variable	N (%)
Primary site (n=341)	
Known	176 (51.6)
Unknow	165 (48.4)
Metastases (n=341)	
Multiple metastases	220 (64.5)
OMF region without confirmation	68 (19.9)
Only OMF region	53 (15.5)

summarized in Table S3, Supporting information. OMFM were more prevalent in men (53.5 %, 182 of 340), with a mean age of 57.5 years (±14.8). Hard tissue was slightly more impacted than soft tissue (52.5 % x 47.5 %). The mandible was the most common site (78.2 %, 140 of 179) for intraosseous lesions (52.5 %, 179 of 341). In 162 of 341 patients (47.5 %), the lesion was found in soft tissue, with a strong preference for the gingiva (70.4 %, 114 of 162). In terms of oral hygiene, 70.17 % of the patients whose gingiva was affected had poor oral hygiene, and 91.06 % had at least one tooth in the mouth. 165 of 341 patients (48.4 %) had no idea there was a primary malignancy when they were diagnosed with OMFM. Of 121 cases in which the oral and maxillofacial lesion was said to be the only focus of dissemination (35.4 %, 121 of 341), in 53 this information was confirmed with complementary exams, while in the remaining 68 cases, there was only the author's report.

Pain was the most common local sign/symptom (68.1 %, 154 of 226), followed by paresthesia (96.2 %, 76 of 79), bleeding (93.7 %, 59 of 63), and tooth mobility (91.8 %, 56 of 61). The most common systemic sign/symptom was weight loss (57.9 %, 33 of 57), followed by fever (32.4 %, 12 of 37). Most lesions had a short evolution time in both male and female: from 1 to 3 months (74.2 %, 158 of 213). The clinical appearance (Table II) was variable, but the description most mentioned was mass (34.9 %, 119 of 341), with red color (57.7 %, 71 of 123), firm consistency (52.3 %, 70 of 134), ulcerate surface (52.8 %, 66 of 125), and no cervical lymphadenopathy (69.9 %, 79 of 113).

There was a history of tooth extraction in 46.04 % of the cases (93 of 202). Previous antibiotic therapy was found in 58 patients (28.71 %, 58 of 202). The most common radiographic description (Table II) was of an osteolytic/radiolucent area (74.16 %, 155 of 209), unilocular (83.9 %, 26 of 31), with imprecise limits (66.7 %, 38 of 57). Radiopaque or mixed injuries were rarely mentioned (8.13 %, 17 of 209). Detailed information about CT and PET-CT is provided in the Table S3, Supporting information.

The most frequently considered clinical hypotheses (Table II) were of benign lesions (73.92 %, 394 of 533). Among the benign diagnostic hypotheses considered, 266 (67.51 %) were of inflammatory nature (48.12 % soft tissue and 51.88 % bone tissue), 49 (12.44 %) neoplastic (44.90 % soft tissue and 55.10 % bone tissue) and 79 (20.05 %) undefined. Pyogenic granuloma (17.26 %, 68 of 394) was the most common, followed by abscess (9.90 % 39 of 394), infection (9.64 %, 38 of 394), osteomyelitis (6.60 %, 26 of 394), periodontal disease (5.08 %, 20 of 394), TMJ lesion (4.31 %, 17 of 394), epulis (4.06 %, 16 of 394), ameloblastoma (3.04 % ,12 of 394), and osteonecrosis (2.54 %, 10 of 394).

Table II. Clinical and image features.

Variable	N (%)
Clinical manifestation (n=341)	
Lesion	45 (13.2)
Mass	119 (34.9)
Necrotic bone	3 (0.9)
Nodule	29 (8.5)
Non-healing extraction socket	4 (1.2)
Swelling	112 (32.8)
Symptoms only	27 (7.9)
Ulcer	2 (0.6)
Color (n=123)	
Black	2 (1.6)
Blue	1 (0.8)
Brown	1 (0.8)
Grey	4 (3.2)
Normal	28 (22.8)
Pink	8 (6.5)
Purple	5 (4.1)
Red	71 (57.7)
White	3 (2.4)
Size (n=172)	
Up to 1 cm	10 (5.8)
Up to 2 cm	46 (26.7)
Up to 3 cm	52 (30.2)
Over 3 cm	64 (37.2)
Consistency (n=134)	
Firm	66 (49.3)
Hard	28 (20.9)
Soft	36 (26.9)
Soft to firm	4 (3.0)
Tenderness (n=72)	
No	29 (40.3)
Yes	43 (59.7)
Limits (n=33)	
Ill-defined	20 (60.6)
Well-defined	13 (39.4)
Shape (n=32)	
Elliptic	1 (3.1)
Hemispherical	2 (6.3)
Irregular	4 (12.5)
Lobulated	10 (31.3)
Nodular	1 (3.1)
Oval	12 (37.5)
Polypoid	2 (6.3)
Base (n=41)	
Pedunculated	22 (53.7)
Sessile	19 (46.3)
Surface (n=125)	
Corrugated	1 (0.8)
Granulomatous	8 (6.4)
Irregular	9 (7.2)
Lobulated	2 (1.6)
Regular/Normal	39 (31.2)
Ulcerated	66 (52.8)
Cervical lymphadenopathy (n=113)	
No	79 (69.9)
Yes	34 (30.1)
Previous treatment (n=202)	
Extraction	93 (46.0)
Antibiotic therapy	58 (28.7)
Endodontic treatment	18 (8.9)
Treatment for TMJ symptoms	7 (3.5)
Other treatment	26 (12.9)
Image features (n=209)	
Radiolucent/Hypodense	155 (74.2)
Radiopaque/Hyperdense	8 (3.8)
Mixed/Isodense	9 (4.3)
Normal	37 (17.7)
Limits (n=57)	
Ill-defined	38 (66.7)
Well-defined	19 (33.3)
Uni/Multi (n=31)	
Multilocular	5 (16.1)
Unilocular	26 (83.9)
Hypothesis of diagnosis (n=533)	
Metastatic lesion	67 (12.6)
Primary malignant	72 (13.5)
Inflammatory lesion	266 (49.9)
Neoplastic lesion	49 (9.2)
Undefined	79 (14.8)
Benign hypothesis (n=394)	
Abscess	39 (9.9)
Ameloblastoma	12 (3.0)
Epulis	16 (4.1)
Infection	38 (9.6)
Periodontal disease	20 (5.1)
Pyogenic granuloma	68 (17.3)
Osteonecrosis	10 (2.5)
Osteomyelitis	26 (6.6)
TMJ lesion	17 (4.3)
Others	148 (37.6)

The most evident primary sites (Table III) were the lungs (20.2 %, 69 of 341), breast (13.8 %, 47 of 341), kidneys (11.4 %, 39 of 341), liver (10.3 %, 35 of 341), and thyroid (7.0 %, 24 of 341). Adenocarcinoma (32.8 %, 112 of 341) was the most prevalent histological type, followed by no specified carcinoma (13.2 %, 45 of 341), hepatocellular carcinoma (7.0 %, 24 of 341), renal cell carcinoma (5.6 %, 19 of 341), ductal carcinoma (5.0 %, 17 of 341), and follicular carcinoma (4.7 %, 16 of 341). Female patients had a higher predilection for the two most common histological types of thyroid carcinomas: follicular and ductal (28 of 33 cases), compared to male patients who had a higher predilection for adenocarcinomas (68 of 111 cases), hepatocellular carcinomas (21 of 24 cases), and renal cell carcinomas (13 of 19 cases).

Table III. Primay tumor, treatment, and outcome

Variable	N (%)
Primary site (n=341)	
Breast	47 (13.8)
Colum/Rectum	17 (5.0)
Kidney	39 (11.4)
Liver	35 (10.3)
Lung	69 (20.2)
Others	52 (15.2)
Ovarian/Uterus	16 (4.7)
Prostate	18 (5.3)
Stomach	12 (3.5)
Thyroid	24 (7.0)
Unknow primary site	12 (3.5)
Diagnosis (n=341)	
Adenocarcinoma	112 (32.8)
Carcinoma	45 (13.2)
Clear cell carcinoma	12 (3.5)
Ductal carcinoma	17 (5.0)
Follicular carcinoma	16 (4.7)
Hepatocellular carcinoma	24 (7.0)
Melanoma	15 (4.4)
Others	68 (20.0)
Renal cell carcinoma	19 (5.6)
Squamous cell carcinoma	13 (3.8)
Received treatment (n=284)	
Died before	4 (1.4)
No	17 (6.0)
Yes	263 (92.6)
Types of treatment (n=416)	
Chemotherapy	120 (28.8)
Palliative treatment	47 (11.3)
Radiotherapy	113 (27.2)
Referral to oncologist	30 (7.2)
Surgical excision	93 (22.4)
Others	13 (3.1)
Follow-up (n=248)	
Alive	76 (30.6)
Dead	172 (69.4)
Survival time (n=151)	
Up to 3 months	67 (44.4)
Up to 6 months	40 (26.5)
Up to 12 months	23 (15.2)
Up to 24 months	15 (10.0)
Up to 36 months	4 (2.6)
Over 36 months	2 (1.3)

Among the 263 patients who received treatment (92.6 %, 263 of 284), summarized in Table III, chemotherapy was the most used (28.85 %, 120 of 416), followed by radiotherapy (27.16 %, 113 of 416). In most cases, the prognosis was obscure, with 172 patients dying (69.4 %, 172 or 248), with a median survival of less than 3 months for 44.4 % of them (67 of 151).

Analysis of the Association of Variables

In the analysis of the association of variables, using the chi-squared test and Fisher exact test, we observed a strong association ($p<0.001$) between the SITE OF THE PRIMARY TUMOR (breast, kidney, liver, lung, ovarian/uterus, prostate, stomach, thyroid) and the sex of the patient, and also some data of the metastatic lesion, such as knowledge of cancer, oral lesion location, soft tissue location, complaint of pain, prognosis and diagnostic hypothesis (inflammatory soft and bone tissue lesion), the association table is provided in the Table S4, Supporting information.

Breast and thyroid were affected more frequently in female patients (93.6 % and 79.2 %, respectively), while lung and liver were affected more frequently in male patients (75.4 % and 85.7 %, respectively). Breast tumors (89.4 %, 42 of 47) corresponded to the cases in which more patients were already conscious to have malignancy, at the moment of metastatic diagnosis; unlike lung tumors, in which patients were surprised in most cases (71.0 %, 49 of 69).

Bone tissue lesions were more frequently observed in patients with prostate (94.4 %, 17 of 18), thyroid (87.5 %, 21 of 24), and breast (66.0 %, 31 of 47) tumors; while soft tissue lesions were more frequently observed in patients with stomach (75.0 %, 9 of 12), ovary/uterus (68.8 %, 11 of 16), and kidney (66.7 %, 26 of 39) tumors. The gingiva (70.37 %, 114 of 162) was the most affected soft tissue, with a preference for lung (21.2 %, 31 of 114) and liver (16.7 %, 19 of 114), as primary sites. Pain was the most prevalent symptom in metastatic lesions from breast (87.5 % 28 of 32) and prostate (85.7 %, 12 of 14). The lung tumors had the worst prognosis, reaching 41 deaths among the 50 patients (82.0 %). The primary tumor site was lung, kidney, and liver (20.3 %, 17.9 % and 14.1 %, respectively) among the 128 lesions with inflammatory nature suspicion located in soft tissue; while lung, breast and prostate (24.6 %, 21.7 % and 8.7 %, respectively) were the primary sites for the 138 lesions in bone tissue with the same suspicion.

The following data also showed a positive association with the site of the primary tumor, although the reliability was lower: multiplicity of metastases ($p=0.022$), and age of the patient ($p=0.003$). Metastatic lesions originating from the ovary/uterus (81.3 %, 13 of 16), breast (76.6 % 36 of 47), kidney (76.9 %, 30 of 39), and lung (62.3 %, 43 of 69) were more likely to

have multiple metastases; while lesions from thyroid (66.7 %, 16 of 24) and liver (57.1 %, 20 of 35) used to have metastases only in maxillofacial region. Of the 341 patients in the sample, 122 (35.8 %) were in the age group of 51-60 years.

The association of variables, again analyzed using the chi-squared test and Fisher exact test, was used also to determine whether some features of the oral metastatic tumors were related to the LESION LOCATION (if bone or soft tissue). There was a notable positive association for pain, bleeding, and clinical appearance ($p<0.001$), the association table is provided in the Table S5, Supporting information.

The presence of pain was characteristically common in bone tissue tumors (73.38 %, 113 of 154), as well as bleeding was in soft tissue ones (76.27 %, 45 of 59). Of the 179 cases affecting bone tissue, with available information about clinical appearance, swelling was the most prevalent sign (49.72 %); while mass/nodule was the majority (63.58 %) for the 162 cases in soft tissue.

Past history of tooth extraction did not show a positive association with the lesion location. However, this procedure was observed in 35.75 % of the cases affecting bone tissue and in 17.90 % of the cases affecting soft tissue. Unfortunately, many articles possibly omitted information about misdiagnosis or mistreatments.

The following associations did not present statistically significant positive results ($p>0.05$): bone tissue location vs. site of the primary tumor; time of death vs. site of the primary tumor; neoplastic nature lesion vs. site of the primary tumor; imaging features vs. site of the primary tumor; tooth mobility vs. lesion location; metastases (multiple or only OMF region) vs. lesion location; imaging features vs lesion location.

Risk of Bias Among Studies. Following the Joanna Briggs Institute risk of bias classification15, 222, 60, and 38 studies had low, moderate, and high risk of bias, respectively. Details are shown in Tables S6, S7, and S8, of supporting information. In general, case reports and series do not provide high-quality scientific evidence. However, as it is a very rare entity, there are no other types of study. We extended our search to include a considerable number of cases (341), extracted from the 320 articles available in literature, and the risk of bias, fortunately, was low in most of them.

DISCUSSION

This study reveals a substantial association ($p < 0.05$) between specific parameters and the diagnosis of metastases in the oral and maxillofacial region, including location of the primary tumor, sex of the patient, and some features of the metastatic lesions (location, nature of the diagnostic hypothesis, previous treatment, symptomatology, clinical appearance, knowledge of the primary tumor and prognosis).

The metastatic process is not a random event, but is a regulated site-specific process, based on the "seed and soil" hypothesis (Paget, 1889). The metastasis "seed" has a predilection for growing up in an organ/environment that, in some proportion, provides a suitable "soil" (Hirshberg *et al*., 2008). It is also known as the metastatic tropism. In our sample, the lungs, breast, kidneys, liver, and thyroid were most evident primary sites, as evidenced by the findings of the systematic review of Labrador *et al*. (2021). However, the literature indicates the involvement of all, except the thyroid (Hirshberg *et al*., 2008; Kumar & Manjunatha, 2013; Allon *et al*., 2014; Hirshberg *et al*., 2014; Gupta *et al*., 2017; Kirschnick *et al*., 2020). The specific relationship between these organs and the maxillofacial area has not yet been determined.

The dissemination process, known as "metastatic cascade", involves a sequence of steps, from the progression of the primary tumor and ends with the dispersal of metastatic tumor cells (MTCs) through lymphatic and/or blood vessels (Rai, 2010). It is well understood that metastatic lesions of the oral and maxillofacial region usually arise from hematogenous spread from a primary or secondary tumor, as in the case of the lung, where the spread proceed once the pulmonary filter is passed and the MTCs achieve any portion of the body (Maschino *et al*., 2013; Kirschnick *et al*., 2020). In the present study, the lungs were the primary site of the OMFM that had the worst prognosis. Most cases of lung metastasis in our study had diffused metastasis, and only a few cases were discovered as a solitary metastatic site, probably due to the hematogenous route disseminating metastatic cells. Despite that, the Batson plexus is another route of dissemination that might explain the absence of lung cancer as the primary site (Kirschnick *et al*., 2020). In this trail, the heart and lungs are not involved in the venous network that runs up and down the spine. There are several connections that provide a vehicle for the elucidation of "aberrant" metastatic

models and eliminates the stumbling barrier of lung involvement (Batson, 1940; Kirschnick *et al*., 2020).

In our study, the patient profile was male, with a mean age of 57.4 years. Despite the search restriction (cases involving individuals who had OMFM that looks like common oral lesions), the literature indicates that OMFM follows the same pattern (Hirshberg *et al*., 2008; Kaplan *et al*., 2019; Kirschnick *et al*., 2020; Labrador *et al*., 2021; Kimura *et al*., 2022). According to Nolen *et al*. (2017), cancer risk increases with advancing age and a plausible explanation for it is that multiple mechanisms are related to aging, such as immune response, cell survival and signaling, stress and frailty (Torre *et al*., 2015). Likewise, cancer affects more males than females, and men are almost 40 % more likely to die from cancer (Peate, 2011). This could explain a predominance of older male individuals with OMFM.

For metastatic lesions from the liver, we observed, in our sample of only positive cases, a marked predilection for males (88.23 %), a result consistent with that of Wu *et al*. (2018), in which, behavioral and metabolic aspects support this conclusion. In contrast, females seemed to be more likely to be affected by thyroid tumors (82.61 %) and breast (93.61 %) than males, as also reported by Irani (2017). This high tendency toward females is associated with the high incidence of thyroid and breast carcinomas in women (Araújo *et al*., 2010; Gholami *et al*., 2020). The high incidence of this type of cancer, as well as the numerous educational campaigns presented, primarily through television and health programs, can explain the fact that women are more concerned about the possibility of developing breast cancer, and this restlessness drives them to seek out prevention methods (Araújo *et al*., 2010). On other hand, lung cancer patients expressed the highest frequency of occult primary malignancy until the time they were diagnosed with maxillofacial metastases. This could be explained because lung cancer is heterogeneous, aggressive, silent and its diagnosis is frequently done at an advanced stage (Woodman *et al*., 2020).

In the hard tissue, the mandible was the most affected site (Aniceto *et al*., 1990; Sánchez-Jiménez *et al*., 2005; Hirshberg *et al*., 2008; Barnes, 2009; Kumar & Manjunatha, 2013; Kirschnick *et al*., 2020; Labrador *et al*., 2021) probably because of the higher content of hematopoietic marrow (Van der Kwast & Van der Waal, 1974; Zachariades, 1989; Aniceto *et al*., 1990). Solid organ tumors target certain organs as secondary foci, such as cancers originating from the breast, prostate gland and thyroid have a high tropism for bone tissues, and as a result they have a larger propensity to affect the jaws (Jeon *et al*., 2019). The presence of pain and swelling could be explained by the endothelin axis, a pathway composed of the endothelin A and B receptors. The activation of the first and the silencing of the second result in increased pain. This occurs by tumor cells and inflammatory (immune) cells that stimulate chemical mediators, such as prostaglandins (PGE2), nerve growth factor (NGF), endothelins (ET-1) and bradykinin (BK) (Labrador *et al*., 2021). In addition, metastatic bone lesions produce a variability of radiographic images. A lytic/radiolucent image with ill-defined margins is frequently observed (Kirschnick *et al*., 2020). This is because the osteolytic response of cancer cells stimulates proteases, which then activate RANKL, causing an increase in osteoclast activity (Labrador *et al*., 2021). Osteoblast deposition, however, can occur in metastasis of prostate tumors, resulting in a mixed or radiopaque image (Shen *et al*., 2009; McClure *et al*., 2013; Cai *et al*., 2016; Kirschnick *et al*., 2020).

Periodontal disease is characterized by microbial-associated and host-mediated inflammation that results in periodontal attachment loss and bone resorption. A metastatic process that leads to an osteolytic response, even around the teeth, should not be considered a periodontitis, but dental clinician would reasonably consider periodontal or periapical inflammatory disease as the prime diagnostic choice (Allen & Duckworth, 1985). In this area, the metastatic tumor generates tooth loosening, pain, and edema (Hirshberg *et al*., 2008). These signals/symptoms lead the clinician to extract the affected tooth. However, OMFM should be considered in patients with a radiolucent image with ill-defined margins, developing in a short period of time, that lead to tooth loosening, and with no history of poor dental hygiene or periodontal disease in the past or present status. This hypothesis needs to be raised even if the patient's medical history does not report malignancies, since in 25 % of the cases in the literature the OMFM was found before the primary origin was diagnosed (Hirshberg *et al*., 2008).

Soft tissue metastasis will appear as an exophytic lesion with a variable rate of growth, whether due to the metastatic tumor breaking out of bone or metastasis to the soft tissue itself. Such lesions are frequently friable, painless, and easily bleeding when stimulated (Allen & Duckworth, 1985; Curien *et al*., 2007). These are typical characteristics of hyperplastic,

reactive conditions like pyogenic granuloma. In our sample, inflammatory nature lesions were the most frequent diagnostic hypothesis. This could be explained by the dense capillary network of chronically inflamed gingiva that may retain MTCs, allowing them to easily extravasate through the leaky blood vessels (Allon *et al*., 2014; Labrador *et al*., 2021). Soluble cytokines found in chronically inflamed gingiva, such as interleukin-1 and tumor necrosis factor-a, have been shown to assist metastatic spread by increasing angiogenesis and accelerating the production of extracellular matrix required for tumor stroma (Seoane *et al*., 2009; Peinado *et al*., 2011; Allon *et al*., 2014; Hirshberg *et al*., 2014; Landskron *et al*., 2014; Stockmann *et al*., 2014).

Gingival metastatic lesions are highly vascularized, rapid and expansive growth, which explains why the lesion is edematous and bleeding in clinical appearance. Such features are also found in pyogenic granuloma, corroborating the mimicry between the lesions (Curien *et al*., 2007; Seoane *et al*., 2009; Dhawad & Nimonkar, 2011). The friability is another mimetized characteristic, and a plausible explanation for this is because tumor cells adhering to the extracellular matrix and degrading it with tumor proteolytic enzymes, particularly collagenase (Taicher *et al*., 1991). It's possible that cancer cells interact with fibroblasts and other mesenchymal cells in the host and stimulate them to produce collagenases (Taicher *et al*., 1991). Patients with primary tumor in kidney, stomach, and ovary/uterus were the ones with predominance metastases in soft tissues, in accordance with the literature (Hirshberg *et al*., 2008; Kim *et al*., 2009; Kirschnick *et al*., 2020). Special care should be taken in patients with past history of these malignancies and the presence of “benign” lesions in soft tissues.

In terms of oral hygiene, 76.11 % of the patients had poor oral hygiene, and 90.26 % had more than one tooth in the mouth. The presence of teeth seemed to be significantly related to the progress of gingival metastases, according to the literature (Curien *et al*., 2007; Allon *et al*., 2014; Labrador *et al*., 2021), since several researches have also suggested a possible association between periodontal disease and the risk to develop cancer in different tissues (Velly *et al*., 1998; Abnet *et al*., 2001; Hujoel *et al*., 2003; Stolzenberg-Solomon *et al*., 2003; Abnet *et al*., 2005; Rosenquist *et al*., 2005; Michaud *et al*., 2007; Pendyala *et al*., 2014). In some cases, tooth extraction and wound area could attract circulating tumor cells (Allen & Duckworth, 1985; Irani, 2017). Therefore, it seems recommendable that patients with a previous history of malignancy (particularly in lung, breast, kidneys, liver, and thyroid), which also present periodontal disease,should have six-month periodontal evaluations to prevent metastatic progression to the oral and maxillofacial region.

The clinical appearance of an OMFM might be deceiving. Histopathologic studies may not be ordered since these lesions do not show clinical or radiographic symptoms of malignancy, and the clinical diagnosis is usually that of a benign reactive lesion, which delays appropriate diagnosis (Kirschnick *et al*., 2020). We must be alert and prepared to consider subtle clinical and radiographic presentations in order to establish an early diagnosis. The clinical appearance of lesions in patients with known malignant disease may favor the diagnosis of metastases (Allon *et al*., 2014). For a proper diagnosis, a detailed review of the patient's past medical and dental histories, physical examination, clinical symptoms, laboratory testing, and histopathologic evaluation using immunohistochemical analysis and imaging modalities should all be part of a standard diagnostic evaluation (Allon *et al*., 2014). Considering these aspects, it is possible to reduce the amount of diagnostic confusion (Pontes *et al*., 2014).

When periodontal disease or other benign lesions are suspected on the initial examination, but since periodontal treatment, antibiotic therapy or other conservative treatment measures were not effective and the lesion continues to grow, a biopsy is mandatory. The association of other local symptoms such as paresthesia, bleeding, and systemic symptoms like weight loss, fever, and pain, should arouse the suspicion of a metastatic lesion. Oral metastases are uncommon in the natural history of malignant tumors, but periodontists must be aware of them in order to handle local and systemic oncology problems quickly (Alández *et al*., 1995). The differences between a gingivitis or periodontitis, compared to a OMFM, can be subtle. Differences in relation to time and amount of bleeding, in bone resorptive processes, patterns of teeth loosening and expected time to evaluate periodontal treatments without resolution, all have not yet been evaluated.

Describing the clinicopathological data of each case report, case series, and cross-sectional studies, the publications included in this investigation revealed limitations. As already explained, case reports and case series offer inherent publication bias. The variation in clinical and imaging descriptions and the frequent lack

of some information can affect the results. For this reason, it is important to emphasize the importance of publishing original papers with well-characterized methodologies on detailing epidemiologic, clinical, imaging aspects, and the patient's outcome. However, because these descriptive observational studies provided the greatest evidence for this topic, we worked around the limitations by connecting multiple factors in search of plausible relationships and carefully analyzing the data. Moreover, even with a comprehensive search, which spanned almost 100 years of publications, language restrictions may have prevented some studies from being included.

CONCLUSION

Oral and maxillofacial metastases have a wide range of clinical and imaging characteristics, and they can even look like common inflammatory and reactive lesions, which might be misleading. Clinicians should be aware of this possibility and include it in their differential diagnosis spectrum, even when clinical and radiological features, indicate of a malignancy were very subtle. Mistakes in diagnosis and, as a result, in therapeutic strategy, leads to metastatic spread and compromise the prognosis.

Registration and protocol

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020200696) and available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=200696

HENSCHEL, F. A. N.; KIMURA, T. C. & VELTRINI, V. C. Diagnóstico diferencial de las metástasis orales. *Int. J. Odontostomat., 17(3)*:300-311, 2023.

RESUMEN: Las lesiones metastásicas en la cavidad oral pueden parecer similares a lesiones inflamatorias comunes. Por ello, nos propusimos investigar metástasis orales cuyas características clínicas e imagenológicas simularan las de lesiones inofensivas, confundiendo y retrasando el diagnóstico. Para ello, se realizó una revisión sistemática a partir de reportes de casos, series de casos y estudios transversales en PubMed/Medline, Scopus, Embase-vía Elsevier, Virtual Health Library, Web of Science y literatura gris, utilizando la estrategia PICO sin restricción de periodo. La calidad de los estudios se evaluó mediante la herramienta de evaluación del Instituto Joanna Briggs. Se realizó una síntesis narrativa de los datos. Se realizaron análisis de asociación mediante chi-cuadrado y prueba exacta de Fisher, con significancia estadística en p<0,05. La mayoría de las lesiones procedían de pulmón, mama, riñones, hígado y tiroides. Afectan principalmente a las mandíbulas de los hombres, entre la quinta y la séptima década de la vida, provocando osteólisis. En los tejidos blandos, había hinchazones firmes, asociadas con sangrado. Las limitaciones con respecto a la heterogeneidad de los estudios incluidos y la ausencia de descripciones clinicopatológicas de los tumores redujeron sustancialmente la posibilidad de realizar un análisis estadístico de los datos. Conocer las diferentes posibilidades de presentación clínica de las metástasis orales y maxilofaciales es importante para que se produzca la sospecha diagnóstica y se eviten errores diagnósticos. Por lo tanto, se instituye el tratamiento y se puede prolongar la supervivencia. Registro de protocolo: PROSPERO CRD42020200696

PALABRAS CLAVE: neoplasias orales, metástasis de neoplasias, diagnóstico diferencial, manifestaciones orales, revisión sistemática.

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