

Gingival exophytic lesions as first oral manifestation of primary lung adenocarcinomas: Systematic review

ABSTRACT

Metastases from malignant tumors in the oral cavity are rare and comprise approximately 1% of all oral neoplasms, being more frequent in the jaws than in the soft tissues. The presentation of a gingival metastasis as the first manifestation of a primary tumor in the oral cavity is extremely rare. The objective of this review is to update the diagnosis and management of oral metastasis being the first clinical manifestation of the tumor and review all the cases published to date, providing a new original clinical case with very specific histopathological characteristics. We systematically reviewed the literature in order to find all the cases of primary lung tumors that appeared with a gingival metastasis as the first manifestation. The search process involved a total of 1916 articles. After reading the latter, 15 (one of them with two different cases) met the inclusion criteria. Of the 15 articles, 6 were rated as medium quality (40%) and 9 as high quality (60%). We present a lung adenocarcinoma that first manifested as a metastasis in the gum, simulating a benign lesion. The unusually high growth rate of this lesion should conduct to have other diagnostic possibilities, and histopathological confirmation is essential.

Keywords: Differential diagnosis, exophytic lesion, gingival metastases, lung tumor, primary tumors

INTRODUCTION

Metastases from malignant tumors in the oral cavity are rare and comprise approximately 1% of all oral neoplasms, being more frequent in the jaws than in the soft tissues.^[1] The most common origin of primary tumors in males is the lung, followed by the kidney, liver, and prostate. In women, the most common primary location is the breast, followed by the female genital tract, liver, and colon.^[2] The presentation of a gingival metastasis as the first manifestation of a primary tumor in the oral cavity occurs in 30% of cases and is usually associated with advanced-stage tumor disease with the possible presence of several metastases.^[3] In soft tissues, the most common location is on the gingiva (54%), followed by the tongue (25%).^[4] Hirshberg *et al.* suggested that chronic inflammation in soft tissues may be a determining factor in attracting metastatic cells.^[1] This chronic inflammation may be related to greater permeability of blood vessels and the presence of adhesive molecules.^[5] These types of


lesions run the risk of being underdiagnosed due to the similarity of their clinical characteristics with other entities

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such as pyogenic granuloma, periodontal abscess, gingival hyperplasia, giant cell granuloma, or hemangioma.^[6]

The prognosis for metastases in the oral cavity is very poor. Survival for soft-tissue metastases is slightly higher than bone metastases.^[4] The time between the diagnosis of a gingival metastasis and the death of the patient varies from a few weeks to a year, with the maximum survival being 5 years.^[3]

The objective of this work is to update by a systematic review the diagnosis and management of oral metastases in soft tissue, being the first clinical manifestation from other tumors, review all the cases published to date, and provide a new original clinical case with very specific histopathological characteristics.

METHODS

Protocol and registration

The design of this study was carried out by SPD and is registered in PROSPERO (Reference: CRD42018103692). The review was carried out following PRISMA guidelines and the PICO method:^[7,8] patients with primary lung tumor with gingival metastasis (P = patient), gingival metastasis as the first manifestation (I = intervention), late manifestation of gingival metastasis (C = comparison), and number of cases of primary lung tumors that debut as gingival metastasis (O = outcome). All of the procedures performed in this study complied with the ethical standards established by the institutional and research committee and with the Declaration of Helsinki of 1964 and its subsequent amendments. The patients gave written or verbal consent to participate in the study and likewise they granted their permission for the research results to be published anonymously. This study is exempted of the ethics committee.

Eligibility criteria, information sources, and search

The exclusion criteria were the following: (1) articles that describe cases of hard tissue metastases in the oral cavity, (2) primary tumors of non-pulmonary origin, (3) full text not available or written in a language other than English/Spanish, (3) Absent or unspecified data in relation to age, sex, location and histological type of the primary lung tumor. We carried out a literature search in PubMed, Embase, and Web of Science to identify all the cases of primary lung tumors that appeared with a gingival metastasis as the first manifestation written in English between September 1975 and November 2019 using the terms (gingival metastasis OR oral metastasis) AND (lung cancer OR lung adenocarcinoma). Medical Subject Headings terms and free search were also used.

Study selection

From the results obtained from the search, two independent researchers (MPS and SPD) analyzed abstracts that met the search criteria, that is, abstracts that mentioned cases of primary lung tumors that appeared with a gingival metastasis as the first manifestation. Then, both researchers read the complete article and determined whether it met the following inclusion criteria: Articles written in English / Spanish, with access to the full text available and with detailed information on: age, sex, location of metastasis, and description of the histological type of the primary lung tumor. A third investigator (AGG) acted as a mediator in cases of dispute. Agreement was calculated using Cohen's kappa coefficient, with $k = 0.92$.

Data collection process

Data retrieved from all articles were collected by both researchers (in duplicate) independently and corroborated by the third party, who acted as a mediator in cases of discrepancy or lacked agreement.

Data items

The following information was extracted from each study: first author, year of publication, sex and age of the patient, clinical aspect of lesion, and location and type of primary tumor.

Risk of bias in individual studies

The methodological quality of the included studies and the possibility of bias were assessed using the modified Newcastle-Ottawa, Pierson, and Bradford Hill scales for case series and "in relation to a case" studies.^[9] The authors of this scale recommend assessing the quality of the studies according to four categories, selection, ascertainment, causality, and reporting, with eight specific questions to answer giving low (1–3 questions), medium (4–6 questions), and high (7–8 questions) quality values. This analysis was carried out independently by each of the two investigators, and in cases of disagreement, the third acted as a mediator.

RESULTS

The search process involved a total of 1916 articles, of which 1901 were excluded because they were not articles based on cases of primary lung tumors that appeared with a gingival metastasis as the first manifestation. After reading the latter, 15 articles (one of them with two different cases) met the aforementioned inclusion criteria [Table 1]. Of the 15 articles, 6 were rated as medium quality (40%) and 9 as high quality (60%).

The results obtained in our review are described [Table 2] on a population of 17 patients (included our own case) with

an average age of 59.56 years, standard deviation of 10.62, and range between 40 and 84 years. We have observed a greater presence of the male sex, with 14 men (82.4%) compared to 3 women (17.6%). Regarding the clinical aspect of the lesion, the exophytic manifestation was the most frequent (76.5%), above the ulcerated form (23.5%). In 7 out of 17 cases, the lesions of gingival metastasis were located in the maxilla (41.15%), another 7 cases out of 17 the location was in the mandible (41.15%), 1/17 was located in the tongue (5.9%) and another 1 out of 17 in the palatine tonsil (5.9%). Only 1 case was found where the location of the lesions was multiple (5.9%). The definitive diagnosis of the most frequent primary tumor was adenocarcinoma (52.9%), followed by undifferentiated carcinoma (23.5%), sarcomatoid carcinoma (5.9%), small cell carcinoma (5.9%), anaplastic carcinoma of nonsmall cells (5.9%), and malignant fibrous histiocytoma (5.9%).

Description of the proposed case

A 73-year-old male patient had a consultation for a gum injury with approximately 1 month of rapid growth. The patient was a smoker of 20 cigarettes a day until he quit smoking 1 year prior to his visit, was a moderate drinker (approximately 20–25 g of alcohol/day), and had a removable prosthesis. Weight loss was reported to be related to the impossibility of using said prosthesis. The examination revealed an asymptomatic exophytic lesion with a broad base that presented a firm-soft consistency depending on the area. The lesion was located in the second quadrant at the level of the radicular remnant of 24, extending through the vestibule and covering the incisal surface of 23 [Figure 1]. After performing a radiographic study by means of orthopantomography, we observed that there was no bone involvement and proceeded to perform a biopsy. Clinical suspicions included pyogenic granuloma or other reactive gingival processes, squamous cell carcinoma or, less likely, another type of neoplasm.

The histological study revealed a dense malignant neoplastic proliferation, which ulcerated the epithelium but showed no transition with it. It was solid, with focal glandular

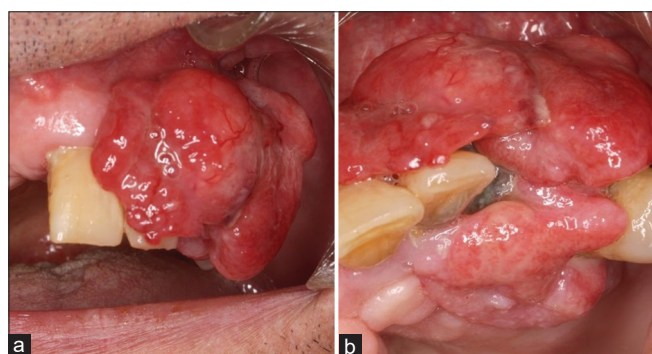


Figure 1: Clinical situation of the lesion. (a) Facial view. (b) Occlusal view

differentiation and mucus production. There were areas of necrosis in the center of some of the nests. The immunohistochemical study (EnVision Detection System, Antibodies Ready-to-Use, DAKO Glostrup, Denmark) showed positivity for cytokeratins AE1/AE3, 19, 8/18, and 7 in practically all of the tumor cells as well as for EMA. On the other hand, staining for PGFA, p40, CK20, TTF-1, napsin, vimentin, and smooth muscle actin was negative. The proliferative index measured with the Mib-1 antibody was very high. The lesion was diagnosed as a poorly differentiated adenocarcinoma, probably metastatic of unknown origin [Figure 2].

Subsequent studies of the patient included a chest radiograph showing a nodular radiopacity in the right hemithorax and a contrast-enhanced body computed tomography scan showing a 12-mm spiculated solid nodule in the anterior subpleural location of the right upper lobe, accompanied by a right hilar mass that infiltrated the mediastinum and encompassed the pulmonary artery, as well as homolateral intermediary bronchial and mediastinal adenopathies. Metastatic lesions were also seen in the soft parts of the neck, cervical spine, and central nervous system. There was diffused enlargement of the adrenal glands, but there were no alterations in the liver, spleen, pancreas, or kidneys or evidence of abdominopelvic adenopathies.

The patient was diagnosed with Stage IV lung adenocarcinoma and died a few weeks after the definitive diagnosis was confirmed. No EGFR or B-RAF mutations were detected, and the “*in situ*” hybridization study for ALK and ROS-1 was negative, as was the immunohistochemical study for PDL1; therefore, the possibility of oncological treatment was ruled out.

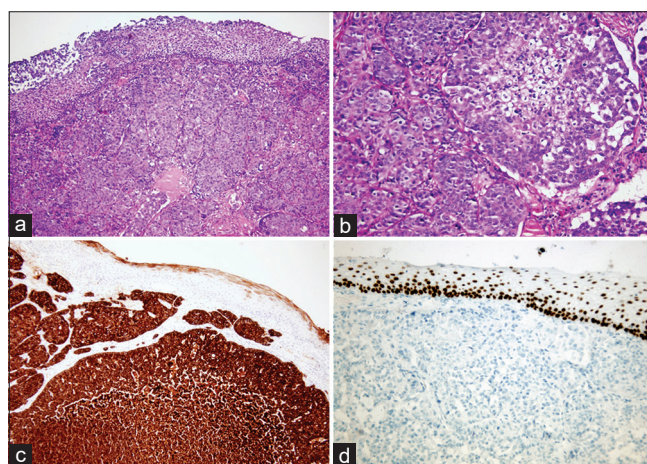
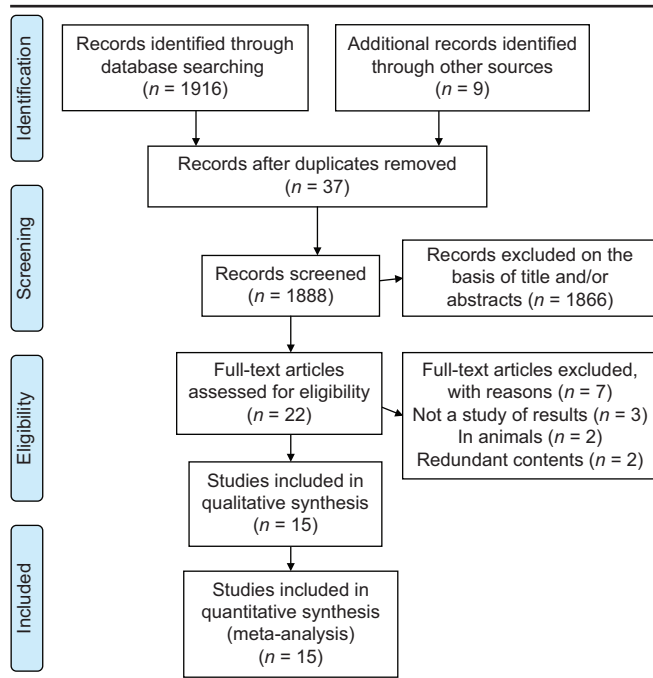


Figure 2: The histological study demonstrates an infiltrative, solid, extensively ulcerate lesion (a). The cells showed marked pleomorphism and glandular differentiation was difficult to appreciate (b). The immunohistochemical study showed positivity for CK7 (c) and was negative for p40 (d)

DISCUSSION

Metastases of malignant tumors in the oral cavity are rare, accounting for only 1% of all oral neoplasms, and more

Table 1: PRISMA 2009 flow diagram



frequently affect the maxillae than the soft tissues and of the latter, especially the gum and tongue.^[1,2,10,11] In a 2008 review, Hirshberg *et al.* conducted a study of 673 cases of oral metastases, of which 112 were primary lung tumors, and in turn, 58 affected the jaws and 54 affected the soft tissues.^[2] In another more recent study, Lee and Lee reviewed 21 cases of oral metastases, of which 18 affected the jaws and the remaining three affected the soft tissues.^[10]

Oral metastases are more common in men than in women, with a ratio of 1.61:1. However, the proportion changes when oral metastases specifically affect the soft tissues, being more frequent in females, with a 2:1 ratio. The mean age at which oral metastasis affecting the soft tissues is diagnosed is 59 years.^[9]

In a third of the cases, metastasis may be the first manifestation of the disease.^[12] These lesions can manifest with different clinical appearances, which causes great difficulties when establishing a diagnosis. Clinically, they are observed as exophytic lesions with a high growth rate, there may be ulcers on the surface with a tendency to bleed, and the lesions may be asymptomatic or with pain and with poor delimitation of the edges.^[10]

Before the appearance of this type of lesion, the clinician must develop a differential diagnosis that includes both benign

Table 2: Clinical and histopathological aspects of gingival metastasis as the first manifestation of a distant tumor

| Authors | Age | Sex | Clinical aspect | Location | Primary tumor |
|--------------------------------------|-----|--------|--|---|--|
| Peris K <i>et al.</i> (1994) | 68 | Male | Deep red, nonulcerated mass | Upper right gingival fornix | Undifferentiated carcinoma |
| Aoe K <i>et al.</i> (2003) | 84 | Male | Deep red, ulcerated mass | Left lower gingival fornix | Small cell carcinoma |
| Park JY <i>et al.</i> (2006) | 55 | Male | Exophytic pedunculated mass | Gingiva from the left lower second molar to the left lower canine | Sarcomatoid carcinoma |
| Pozzi EC <i>et al.</i> (2008) | 57 | Female | Exophytic gingival soft-tissue mass | Region of the lower left canine to the first molar | Adenocarcinoma |
| Califano L <i>et al.</i> (2008) | 60 | Male | Red-grayish fungiform centrally ulcerated mass | Right lower mandibular gingiva | Non-small cell anaplastic carcinoma |
| Moharil RB <i>et al.</i> (2010) | 40 | Male | Reddish-pink pedunculated growth | Vestibular gingiva mucosa on the lower left posterior side of the jaw | Undifferentiated epithelial malignancy |
| Orlandi A <i>et al.</i> (2011) | 74 | Female | Exophytic lesion | Vestibular gingival mucosa on the lower right incisors | Adenocarcinoma |
| Ravi Prakash SM <i>et al.</i> (2012) | 57 | Male | Multiple exophytic tumefaction | Maxillary and Mandibular gingiva | Adenocarcinoma |
| Maschino <i>et al.</i> (2013) | 65 | Male | Exophytic mass and bleeding | Maxillary gingiva | Adenocarcinoma |
| | 62 | Male | Ulcerated and slightly painful mucous mass | Maxillary gingiva | Adenocarcinoma |
| Thomas ME and Koshi R (2013) | 47 | Male | Swelling on the gingiva | Labial aspect of the upper right incisor | Malignant fibrous histiocytoma |
| Rajini Kanth M <i>et al.</i> (2015) | 62 | Male | Polypoid exophytic lesion with an ulcerated growth | Right mandibular premolar-molar region | Adenocarcinoma |
| Nuyen BA and Tang CG (2016) | 59 | Male | Marked indurated swelling | Left alveolar ridge of tooth 11 | Adenocarcinoma |
| Sawheny E <i>et al.</i> (2016) | 52 | Male | Ulcerated swelling | Maxillary gingiva | Poorly differentiated carcinoma |
| Jeba J <i>et al.</i> (2016) | 45 | Male | Swelling with no ulceration | Left side of the tongue | Adenocarcinoma |
| Piñero <i>et al.</i> (2018) | 73 | Male | Exophytic lesion | Maxillary gingiva | Adenocarcinoma |
| Zaubitzer L <i>et al.</i> (2018) | 66 | Female | Asymmetrical palatine tonsils with induration | Right palatine tonsil | Adenocarcinoma |

reactive lesions and the suspicion of malignancy, whether primary or metastatic. The main types of lesions that can mimic gingival metastasis are gingival hyperplasia, pyogenic granuloma, epulis, or giant cell granuloma, especially peripheral cells.^[13]

Metastatic lesions presented in this review^[4,14-27] occurred in a wide age range (40–84 years), although they were more common in the fifth and sixth decades of life and only 3 of the 14 occurred in women (17.6%). Clinically, they corresponded to exophytic lesions (76.5%), more frequent in the lower jaw than the superior; histologically, the lesions corresponded to poorly differentiated adenocarcinomas (52.9%), followed by undifferentiated carcinomas (23.5%).

The treatment of oral metastasis depends on its presentation, depending on whether it is the first manifestation of the primary cancer or if they appear later in the evolution of the disease. The main modalities of treatment are radiotherapy, chemotherapy, and surgical exeresis of the lesion.^[23] The prognosis of patients with metastasis in the oral cavity is always bad because it corresponds to tumors in advanced stages,^[2] and in the case of metastatic lung adenocarcinomas, the average survival ranges from 4 months to a maximum of 5 years.^[28] In those cases that first appeared as a metastasis in the oral cavity, the survival of the patient was specified in 13 of the 16 cases, with a range from the 1st week to 9 months.

We present a case of pulmonary adenocarcinoma that first appeared as a metastasis in the gum. The sex of the patient is male, and the age is higher than the average, 73 years old. The exophytic form was the clinical presentation of our patient, in which the first diagnostic suspicion was a pyogenic granuloma. The rapid growth rate, in addition to the size reached by the lesion, advised taking a biopsy to confirm this impression. Conversely, this confirmed the presence of a poorly differentiated adenocarcinoma, which made us suspect a possible metastasis. The immunohistochemical study confirmed the nature of the tumor, with positivity for low molecular weight cytokeratins and negativity for p40, but the pulmonary origin could not be confirmed because the stains for both TTF-1 and napsin were negative.

Probably, the poor differentiation of the neoplasm explains this previously reviewed extreme.^[16] Our patient died 4 weeks after the definitive diagnosis was confirmed.

We consider the role of the dentist in the early diagnosis of oral neoplasms to be fundamental, through a thorough examination of the oral mucosa, both in healthy patients and in those with symptomatic lesions. We want to emphasize that this type of pathology can present itself as the first

manifestation in the oral cavity, and its early diagnosis can be a determining factor in assessing the evolution and prognosis of the patient.

In summary, we present a lung adenocarcinoma that first manifested as a metastasis in the gum, simulating a benign lesion. The unusually high growth rate should make other diagnostic possibilities valued, and histopathological confirmation is essential.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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