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CASE REPORT

Metastatic ductal breast carcinoma to the mandible: case report and review of the literature

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Abstract:

Mandibular metastasis is uncommon, representing about 1% of all head and neck metastatic bone tumors. Diagnosis is challenging due to variable clinicopathological and radiographic features. Immunohistochemistry can assist in identifying the tumor's primary origin. We report on a 78-year-old woman with a history of left breast invasive ductal carcinoma (TXNXM0, Stage IIB, ER 100%, PR 5%, HER2-negative) and right ductal carcinoma in situ. A comprehensive diagnostic workup, including immunohistochemistry analysis, confirmed a metastatic ductal breast carcinoma to the mandible. The patient received chemotherapy at the Hospital Universitario Nacional de Colombia. Despite treatment, she passed away in December 2022 due to advanced systemic disease. This case illustrates the importance of a thorough diagnostic approach in maxillofacial metastasis to confirm origin, guide prognosis, and initiate timely treatment. Currently, multidisciplinary management is essential to reduce morbidity and improve patient's quality of life.

Keywords: Breast cancer; Metastasis; Bone metastasis; Mandible; Immunohistochemistry.

INTRODUCTION

Metastasis accounts for 90% of cancer-related deaths in advanced stages[1]. This process is characterized by the spread of tumor cells to distant organs (e.g., lungs, liver, brain, and skeleton) via hematogenous or lymphatic routes[2]. Metastatic spread is facilitated by the epithelial-mesenchymal transition (EMT), a process through which an epithelial cell transforms into a mesenchymal cell by losing its polarity and adhesion to other cells, acquiring the ability to degrade the extracellular matrix, and gaining cellular plasticity, motility, invasiveness, microenvironment modulation, and the ability to colonize[1,2]. In contrast, the mesenchymal-epithelial transition (MET) enables cells to reactivate the cell cycle and form micrometastases, a process associated with metastatic growth[1,2].

Bone is the most common site of metastasis for many cancers, particularly those affecting bones rich in hematopoietic bone marrow, such as the hips, ribs, and long bones[3]. Disseminated tumor cells reach the bone marrow, disrupting normal bone metabolism by producing IL-1, IL-6, IL-11, and parathyroid hormone-related peptide (PTHrP), which alters the balance between OPG, RANK, and RANKL[3]. In osteolytic metastasis, bone resorption releases components such as calcium, which contributes to oncological hypercalcemia, phosphorus, and growth factors like IGFs, TGF-β, and BMPs[3]. On the other hand, osteoblastic metastatic tumors, such as those originating from metastatic prostate cancer, involve endothelin-1 (ET-1)[3]. ET-1 promotes the synthesis of immature bone by blocking DKK-1, inhibiting osteoclast activity, and activating the Wnt-β-catenin pathway, helping promote osteoblastic differentiation[3].

Statement of Clinical Significance
Metastasis to the oral and maxillofacial region is rare but is associated with increased morbidity and mortality. This case report highlights the importance of a comprehensive diagnostic workup to facilitate early detection and optimize therapeutic strategies.

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Additionally, some tumors may present a mix of osteolytic and osteoblastic metastases[3].

Less than 1% of metastases develop in the jawbones[4]. The mandible is the most predisposed site due to the presence of remnants of hematopoietic bone marrow in the posterior region (body and ramus)[4,5]. Given the biological complexity of mandibular metastasis, diagnosing this condition is challenging and requires a detailed medical history, integration of clinical and radiographic findings, histopathological analysis, and the use of immunohistochemical techniques. This article presents a case of metastatic breast carcinoma in the mandible, along with a review of the literature.

CASE REPORT

A 78-year-old woman was referred in May 2022 to the Head and Neck Surgery Service at the Hospital Universitario Nacional de Colombia (HUN) due to a symptomatic, aggressive, and rapidly growing mass located in the right mandibular region, present for one year (Figure 1). Clinical examination revealed tenderness to palpation (dysesthesia), trismus, cervical distention, and an asymptomatic enlargement of the right thyroid lobe (Figure 1). The patient's medical history included hypertension, type II diabetes mellitus, stage III chronic kidney disease, chronic smoking (16 years, 25 pack-years), left thyroidectomy (2013), left breast carcinoma (2017) (TXNXM0, stage IIB, ER 100%, PR 5%, HER2 negative, Ki67 10%), and ductal carcinoma in situ of the right breast (2019). Treatment for the latter included bilateral quadrantectomy, lymphadenectomy, radiotherapy (16 sessions in 2017 and 16 sessions in 2019), and chemotherapy (anastrozole for 2 years).

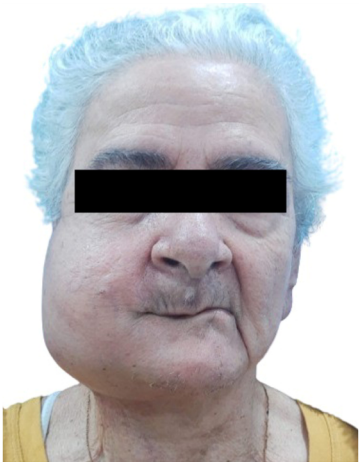

Figure 1. Clinical features. Facial asymmetry due to a large tumoral mass in the right mandibular region (body and ramus).

A contrast-enhanced computed tomography (CT) scan revealed a lytic lesion in the right mandibular ramus and angle, with cortical destruction and central necrotic foci. The lesion involved the mandibular condyle, coronoid process, ramus, angle, body, and symphysis of the right mandible, with infiltration into the temporomandibular joint, right masticatory and buccal spaces, as well as the floor of the mouth and the right parotid gland area (34 x 38 x 48 mm), with loss of fat planes (Figure 2A–D). Additionally, magnetic resonance imaging (MRI) showed a solid mass in the right mandible that was hyperintense on T2-weighted, with central necrotic areas and involvement of the right facial and external carotid arteries (Figure 2E–F).

An incisional biopsy was performed in the right retromolar trigone along the external oblique line of the mandible. The lesion was described as solid, fibrous, hemorrhagic, and friable, involving the base of the right mandibular body and ramus. The specimen was fixed in formalin and sent to the Pathology Service of the Hospital Universitario Nacional de Colombia (HUN) for histopathological examination. Macroscopically, the specimen was described as a light brown fragment measuring 1.5 x 1 x 0.5 cm, with hemorrhagic areas and a firm, homogeneous texture on the longitudinal section.

Histopathological analysis revealed a malignant, infiltrative tumor composed of small, round, basaloid cells with fine chromatin, large hyperchromatic nuclei, inconspicuous nucleoli, numerous atypical mitoses, and cells arranged in cords, trabeculae, and nests, forming a rosette-like pattern with clear spaces, pink material in the center, fibrohyalinized stroma, isolated calcified bone spicules, dilated vascular spaces, and a mild mononuclear inflammatory infiltrate (Figure 3A–C). Given the patient's history of bilateral breast carcinoma and the histological findings of ductal spaces, tubular formations, and pseudorosette structures, the presumptive diagnosis was consistent with metastatic breast carcinoma in the mandible. On July 27, 2022, the Head and Neck Service reported, based on the CT scan with contrast (TACAR) results, the presence of pulmonary lesions suggestive of metastasis.

The immunohistochemical markers used were CKAE1/AE3 and EMA, which were positive, confirming the epithelial nature of the tumor. CK7 was positive, while CK20 was negative, suggesting a metastatic tumor of either breast or lung origin. However, negativity for TTF-1 excluded a pulmonary origin. GATA3 and hormone receptors were also tested. Estrogen receptors (ER) showed strong nuclear positivity (Allred score:

8/8, 100%), while progesterone receptors (PR) were negative in all tumor cells (Allred score: 0/8), and HER2 was negative. Synaptophysin showed granular positivity in the cytoplasm, while chromogranin and CD56 were negative. The cellular proliferation index, Ki67, was 90% (Figure 3D–L). Based on these histopathological and immunohistochemical findings, the definitive diagnosis was metastatic carcinoma with a CK7(+)/CK20(-)/TTF-1(-)/GATA3(+) profile, favoring an origin from non-specialized (ductal) breast carcinoma with estrogen receptor-positive (ER) (Allred 8/8), progesterone receptor-negative (PR) (Allred 0/8), and HER2-negative status (Figure 3D-–L).

The patient was treated by the Oncology Service, where a palliative chemotherapy regimen was chosen, consisting of Fulvestrant 250 mg (IM), Denosumab 120 mg (SubQ), and Ribociclib 600 mg every three weeks. During treatment, the patient showed a positive clinical response, with a reduction in tumor burden and improvement in both clinical and radiological parameters, such as mass size. However, the patient passed away in December 2022 due to multiorgan involvement caused by the disease.

DISCUSSION

According to the 2022 *World Health Organization Classification of Head and Neck Tumors* (5th edition)[4], mandibular metastasis accounts for only 1% of all head and neck metastatic bone tumors and are most frequently observed in individuals aged 50 to 70 years[4–6]. Metastatic tumors in the oral and maxillofacial region typically involve the jawbones and soft tissues (e.g., gingiva and tongue), with the mandible — especially its posterior region (body and ramus) — being the most affected site[4–6]. In some cases, mandibular involvement is associated with hematopoietic remnants in osteoporotic defects[5]. Dissemination to this region may occur through hematogenous spread

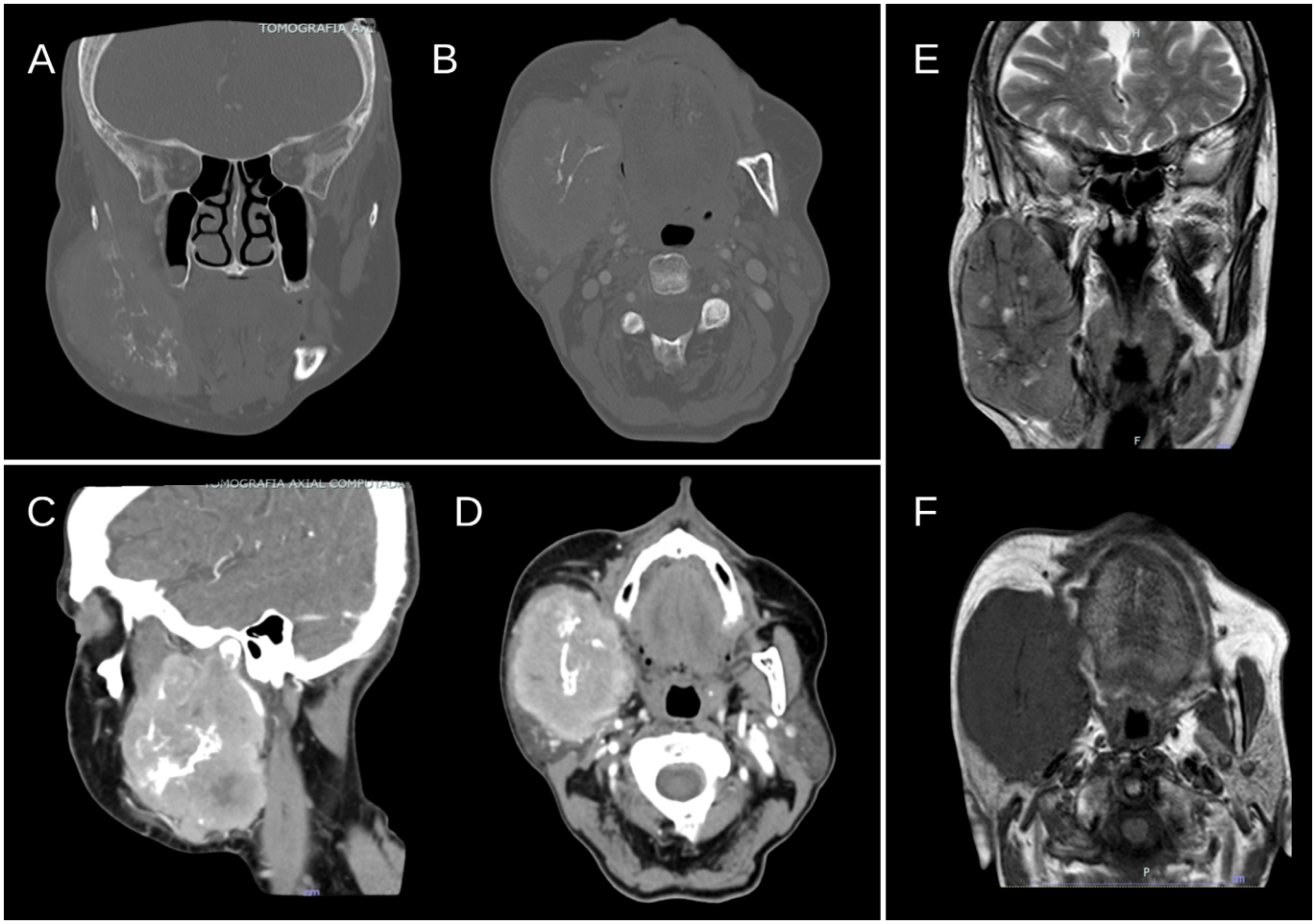

Figure 2. Radiological features. A-D. Contrast-enhanced CT scan of the head and neck (A-B: T1-weighted, C-D: T2-weighted). E-F. MRI of the head and neck. E: T2-weighted, F: T1-weighted. Higher signal uptake on T2-weighted is a characteristic radiological finding in osteolytic metastatic bone tumors.

by the pulmonary circulation or Batson's plexus, or via lymphatic spread[4,5,7], as seen in papillary thyroid and breast carcinomas[4,8]. Metastases to the oral and maxillofacial region (MOMR) may reflect an advanced-stage primary malignancy[6]. In some instances, MOMR may be the first clinical sign of an occult primary tumor, thereby

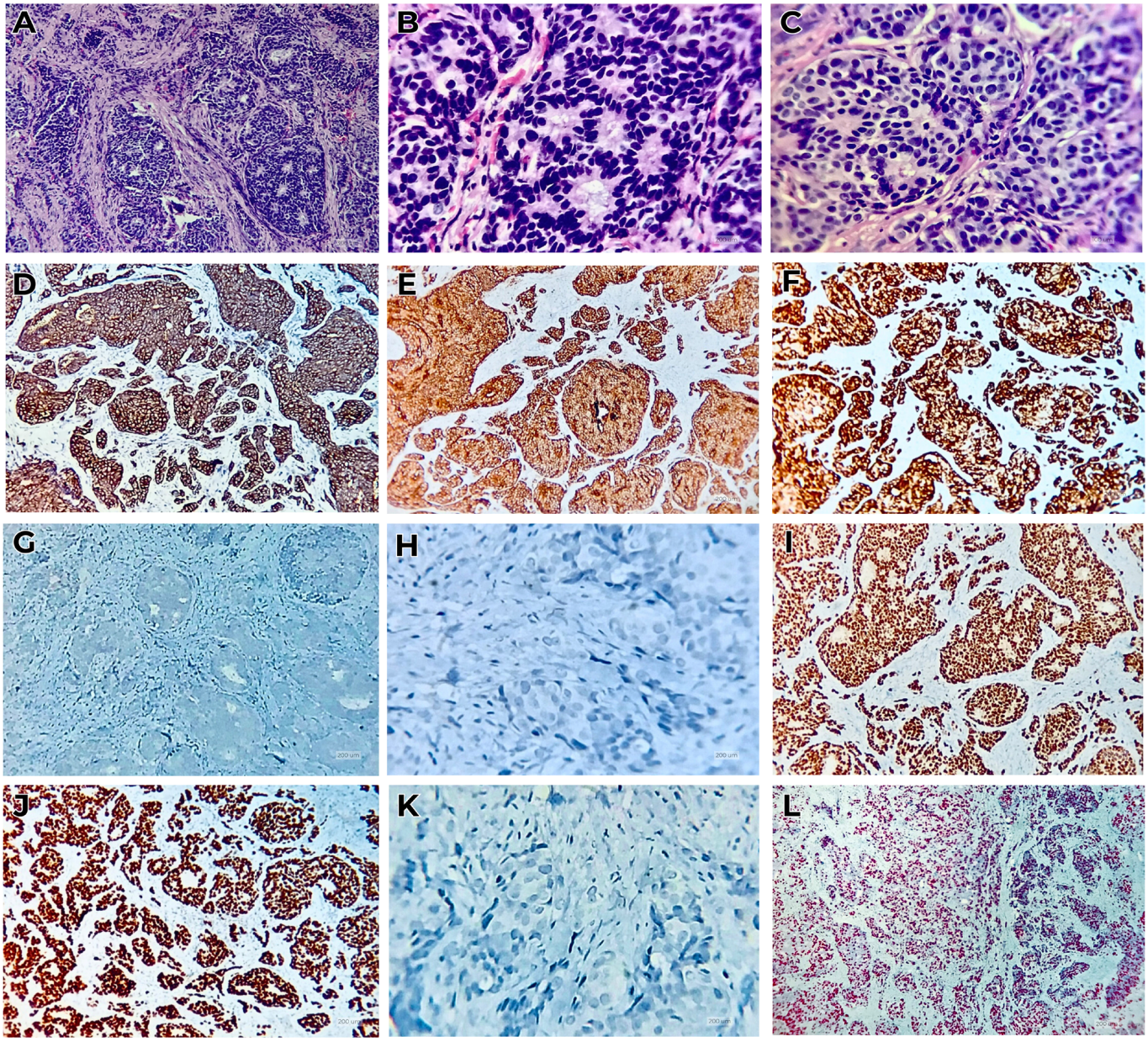

Figure 3. Histopathological Features and Immunohistochemical Markers of Metastatic Breast Carcinoma (Ductal) in the Mandible. A-C. Malignant tumor-like lesion with a dense population of small, round, basaloid cells with fine chromatin, large hyperchromatic nuclei, inconspicuous nucleoli, numerous atypical mitoses, arranged in cords, trabeculae, and nests, forming a rosette-like pattern with clear spaces, pink material in the center, fibrohyalinized stroma, isolated calcified bone spicules, dilated vascular spaces, and mild mononuclear inflammatory infiltrate (hematoxylin and eosin [H&E], original magnification: A: X4, B: X10, C: X40). D. CKAE1/AE3 positive, defining the epithelial lineage of the tumor cell nests (original magnification, X10). E. EMA (+), a predictive marker for the epithelial origin of the tumor cells (original magnification, X10). F. Cytokeratin 7 (CK7) strongly positive in the tumor cell population (original magnification, X10). G. Cytokeratin 20 (CK20) negative (original magnification, X10). H. TTF1 negative, which excludes the pulmonary origin of the metastasis (original magnification, X10). I. GATA3 strongly positive, confirming the mammary origin of the tumor cells (original magnification, X10). J. Estrogen receptor (ER) strongly positive in the tumor cell nests (original magnification, X10). K. Human epidermal growth factor receptor 2 (HER2) negative, a predictive marker for breast cancer prognosis (original magnification, X10). L. Ki67 cell proliferation index of 90% (original magnification, X10).

correlating with a poorer prognosis[6]. Hence, a detailed medical history and standardized workup are relevant to guide the diagnosis and identification of the primary neoplasm when the origin is unknown[5].

The clinical signs and symptoms of MOMR are variable, sometimes including chronic pain, tooth mobility, facial contour deformity, discomfort, trismus, tenderness, and numb chin syndrome; although these features could be particularly associated with mandibular metastasis, they are not pathognomonic[5,6]. Radiographically, mandibular metastases can exhibit osteolytic, osteoblastic, or mixed radiologic patterns[4–7]. Osteolytic lesions are most commonly observed[6], while less than 10% present with osteoblastic features. In up to 5% of cases, radiologic abnormalities are absent[5,7]. Advanced imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), bone scintigraphy, and positron emission tomography (PET) are essential for detecting and characterizing metastatic bone tumors[9,10], and play a critical role in the diagnosis of mandibular metastasis. MRI typically demonstrates hyperintense signals in osteolytic lesions on T2-weighted images, whereas osteoblastic lesions may not[10]. PET imaging is particularly useful for assessing multi-organ metastases but may yield false-positive results[9,10].

The prevalence of oral and maxillofacial metastases varies by tumor type and patient sex[5,6,11,12]. Adenocarcinoma is the most frequent histological subtype associated with mandibular metastases, typically originating from primary tumors of the breast, lung, thyroid, kidney, or prostate[5,6,11,12]. Metastatic bone lesions generally retain the phenotypic profile of the primary tumor, although some degree of dedifferentiation may occur[13]. On the other hand, when metastatic carcinoma infiltrates the bone marrow, it may induce architectural changes in the trabecular bone, a phenomenon known as osteocarcinomatous dysplasia[14]. This may be observed in histopathological analysis as distinct patterns of bone destruction, including osteolytic, osteosclerotic, and mixed types[14]. Osteolytic patterns are further subclassified into uniform rarefaction, lacunar osteolysis, and fragmentation, the latter of which was observed in the current case report. While osteosclerotic patterns are divided into layered, sprouting, and network types[14].

Certain metastatic bone tumors may histologically resemble small round cell tumors, while others exhibit large undifferentiated or spindle cell morphologies, complicating the differential diagnosis[13]. In the present case, the initial differential diagnoses included small round cell tumors and primary adenocarcinoma, due to the observation of pseudorosette-like structures. However, a comprehensive evaluation that integrated the patient's medical history and findings from contrast-enhanced computed tomography (CT), which revealed pulmonary lesions suggestive of metastasis, effectively ruled out these diagnostic possibilities. These clinical and radiological findings subsequently guided the selection of immunohistochemical markers, which ultimately facilitated the definitive diagnosis of metastatic disease.

Immunohistochemistry and molecular pathology are essential tools for identifying the tumor origin[5]. CK1/AE3 and EMA support an epithelial origin [11], while CK7 and CK20 profiles guide metastatic classification[5,11]. CK7(+)/CK20(–) pattern, when TTF-1 is negative, suggests a breast origin, as lung and breast carcinomas share the same CK7/CK20 pattern[5,11] (Table 1). GATA3 and Mammaglobin are reliable markers for confirming metastatic breast carcinoma[5,6,11]. Hormonal receptor status (ER, PR) and HER2 expression are used to further classify breast carcinoma into molecular subtypes: luminal A (ER+/–, PR+/–, HER2–), luminal B (ER+/–, PR+/–, HER2+), HER2-enriched (ER–, PR–, HER2+), and triple-negative (ER–, PR–, HER2–)[15]. This classification is critical for prognosis and therapeutic decision-making. In the current case, the ER/PR/HER2 profile was instrumental in guiding palliative management, underscoring the crucial role of

Table 1. Possible Primary Origins Based on CK20/CK7 immunoreactivity.

Immunoreactivity	Possible primary origin
CK20(+)/CK7(+)	Mucinous ovarian carcinoma
	Pancreatic carcinoma
	Merkel cell carcinoma (skin)
	Transitional cell carcinoma (bladder)
CK20(-)/CK7(+)	Lung adenocarcinoma
	Endometrial adenocarcinoma
	Non-small cell lung carcinoma
	Non-mucinous ovarian carcinoma
	Ductal breast carcinoma
	Lobular breast carcinoma
	Mesothelioma (lung)
CK20(+)/CK7(-)	Colorectal adenocarcinoma
CK20(-)/CK7(-)	Squamous cell lung carcinoma
	Prostate adenocarcinoma
	Small cell lung carcinoma
	Renal cell carcinoma
	Hepatoma

pathology in multidisciplinary cancer care. Additionally, the Ki-67 index of 90%, which is markedly higher than that observed in the primary tumor, may reflect tumor progression and a high degree of malignancy.

A systematic review conducted by Labrador et al.[6] reported an average time to metastasis diagnosis of 10.8 months, with a progression period of 6.9 months in men and 16.2 months in women[6]. This timeframe aligns with the one-year progression observed in the metastatic tumor of the present case. The prognosis of metastatic tumors is poor, with a survival rate of less than one year[6,7]. Treatment is primarily palliative and is tailored according to the characteristics of the primary tumor (e.g. Radiotherapy, chemotherapy, or both)[5-7,12]. Management of bone metastases — especially from breast cancer — includes denosumab (a monoclonal antibody against RANKL) and bisphosphonates such as zoledronic acid. These agents reduce hypercalcemia, pain, disability, and other skeletal-related events, thereby decreasing associated morbidity[15].

A surgical approach may be considered in selected patients with solitary, localized lesions[16]. In our view, radical surgery should be evaluated based on factors such as patient age, comorbidities, tumor progression, previous oncologic treatments, and the feasibility of long-term reconstruction and rehabilitation. In the present case, hemimandibulectomy with free flap reconstruction was not feasible due to the advanced stage of the disease. Ultimately, a comprehensive and multidisciplinary approach is essential to confirm the diagnosis of mandibular metastasis, assess prognosis, and guide treatment strategies aimed at improving the patient's quality of life.

CONCLUSION

Here, we emphasize the critical role of early and accurate diagnosis, highlighting the need for timely intervention to address both the oncological and functional aspects of patient care. Hence, a comprehensive and multidisciplinary approach involving different physicians such as oncologists, oral and maxillofacial surgeons, head and neck surgeons, plastic and reconstructive surgeons, pathologists, andradiologists is essential to confirm the diagnosis, assess prognosis, and guide treatmentstrategies aimed at improving the oncology patient's quality of life.

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AUTHORS' CONTRIBUTIONS

JPRM: conceptualization, investigation, methodology, writing – original draft, writing – review & editing. **LMZL:** data curation, investigation. **AKSL:** conceptualization, investigation, methodology, writing – original draft, writing – review & editing. **CPPV:** conceptualization, investigation, methodology, writing – original draft, writing – review & editing

CONFLICT OF INTEREST STATEMENT

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