

1-1-2024

## Oral Manifestations of Metastatic Diseases: A Clinical and Histologic Analysis Of 7 Cases

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### Recommended Citation

Zheng, Zeming DDS and Philipone, Elizabeth DMD (2024) "Oral Manifestations of Metastatic Diseases: A Clinical and Histologic Analysis Of 7 Cases," *The New York State Dental Journal*: Vol. 90: No. 1, Article 4. Available at: <https://commons.ada.org/nysdj/vol90/iss1/4>

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# Oral Manifestations of Metastatic Diseases

## A Clinical and Histologic Analysis of Seven Cases

Zeming Zheng, D.D.S.; Elizabeth Philipone, D.M.D.

### ABSTRACT

**Metastatic diseases comprise 1% to 3% of malignant oral neoplasms, with nearly one-third of patients unaware of having a primary cancer.<sup>[1-4,9]</sup> This retrospective analysis identified all oral lesions diagnosed as metastatic disease in the Columbia College of Dental Medicine Department of Oral Pathology's oral biopsy database from 2015-2020 and recorded patient demographics, clinical presentation and diagnosis, origin of the primary, and whether the patient had known history of the disease. From 17,500 total cases, seven cases were identified as metastatic disease and described in detail. Clinicians' recognition and awareness of these lesions' often evasive, ambiguous oral presentations may help facilitate diagnosis, treatment and prognosis.**

Metastatic disease to the oral cavity is uncommon, representing only 1% to 3% of all malignant oral neoplasms. These metastatic lesions can affect the bones, soft tissues or both.<sup>[1-3]</sup> However, lesions are two-times more likely to affect bone than oral soft tissue.<sup>[4,5]</sup> In particular, the molar region of the mandible is the most commonly affected osseous location.<sup>[1-3,6,7]</sup> With regards to soft tissue, the gingiva is the most common site for occurrence.<sup>[2-5,8]</sup> Oral metastases are more common in males and occur most frequently in middle-aged and older adults.

Metastasis to the oral cavity usually suggests end-stage disease, with a poor prognosis of 3.7- to 8.25-month survival time.<sup>[4,8-10]</sup> Oral metastases develop late in the disease

process, with the majority of patients already having an established diagnosis of the malignancy.<sup>[9]</sup> However, in up to 30% of patients, the malignancy remains undetected until it presents in the oral cavity.<sup>[2,4,9]</sup>

Clinical presentation of metastatic disease in the oral cavity is dependent on the site of involvement. Patients with metastatic disease to the jaws report symptoms that include pain, swelling, paresthesia, numbness, toothache and loose teeth.<sup>[1,5,10,11]</sup> These signs and symptoms are non-specific and can often mimic other common inflammatory conditions, such as periodontal disease or osteomyelitis.<sup>[12,13]</sup> Unfortunately, extracting the tooth in these cases may further promote metastasis of the cancer. Chronic inflammation, in itself, has also been linked to metastasis. Inflammatory chemokines may promote tumor cell proliferation and dissemination, and many common oral immunoinflammatory processes are associated with an increased chance of malignant transformation.<sup>[14]</sup>

Radiographic presentation of jaw metastases is often described as ill-defined or "moth-eaten" radiolucency, but metastatic prostate and breast carcinomas may present as radiopaque or mixed lesions. Periodontal ligament space widening, fracture and cortical erosion can also be observed.<sup>[15]</sup>

For soft-tissue lesions, an exophytic nodular mass is the most common clinical presentation.<sup>[15]</sup> These lesions often resemble commonly occurring benign or reactive lesions, such as pyogenic granuloma, peripheral giant cell granuloma or fibrous epulis.<sup>[8]</sup>

In this retrospective analysis, we present epidemiologic and diagnostic data on a cohort of patients whose oral biopsy reports confirmed manifestations of metastatic diseases of known and unknown primary origins.

## Methods

This study received approval from the institutional review board. The Department of Oral Pathology's biopsy service database was searched from 2015 to 2020 to identify all biopsied oral lesions that were diagnosed as metastatic disease. Recorded data included patient sex and age at diagnosis, location of biopsy, description of clinical presentation, clinical diagnosis, histologic/biopsy diagnosis and whether the patient had a prior known history of the disease.

## Results

Through the search of the oral biopsy database, out of 17,500 total cases, seven cases were histopathologically identified metastatic disease. These patients included five females and two males from 44 to 88 years old, with a mean age of 67.6 years at diagnosis. Three cases represented intraosseous lesions, all of which involved the left mandible. Three cases manifested in the soft tissue, including the maxillary gingiva, mandibular gingiva and mandibular retromolar area. One case involved both soft and hard tissue—presenting as a mandibular radiolucency with adjacent vestibular soft-tissue swelling (Table 1).

The intraosseous metastases presented in various ways, including “a destructive lytic lesion” and an unresolving periapical radiolucency. For two of the cases, the clinical diagnoses of metastatic breast carcinoma and met-

astatic prostate cancer were correct. These cases presented with clinical descriptions of a “destructive lytic lesion of the left mandible” and “pain and unresolving periapical radiolucency #19, #20,” respectively. Both patients were known to have metastatic disease to other sites prior to the oral biopsies. In one case that presented as a “persistent swelling of left posterior mandible #19,” an incorrect clinical diagnosis of reactive periostitis post root canal therapy was suspected. Upon biopsy this case was diagnosed as metastatic lung carcinoma. The patient was unaware of having lung cancer (Table 1).

As for the three metastases presenting in the oral soft tissues, two cases included the correct clinical diagnosis on the provided differential. The remaining case had incorrect clinical diagnosis of pyogenic granuloma.

For the one case that presented with involvement of bone and adjacent soft tissue, the clinical presentation was of a firm vestibular swelling with adjacent periapical radiolucency that was unresponsive to root canal therapy. A persistent infection was favored by the submitting clinician, with a comment to rule out neoplasm (Table 1).

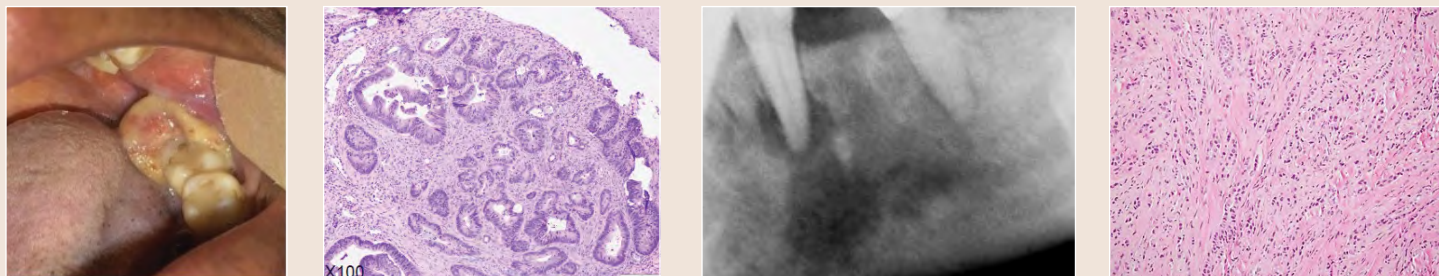
In five of the seven cases, the patient was known to have a prior diagnosis of malignancy. Thus, in the remaining two cases, the initial manifestation of the disease was within the oral cavity and diagnosed at the time of the biopsy.

**TABLE 1.** Summary of recorded data, including patient sex and age at diagnosis, location of biopsy, description of clinical presentation, clinical diagnosis, histologic/biopsy diagnosis, and whether patient had prior known history of disease.

Case	Age	Sex	Site	Clinical Presentation	Clinical Diagnosis	Microscopic Diagnosis	Known History of Primary Disease
1	44	F	Soft tissue, left mandibular retromolar area	Ulcerated soft-tissue swelling	Squamous cell carcinoma vs metastasis	Metastatic adenocarcinoma of colon	Yes
2	56	F	Intraosseous, left mandible	Destructive lytic lesion	Metastatic breast cancer	Metastatic ductal adenocarcinoma of breast	Yes
3	73	F	Intraosseous, left mandible	Persistent radiolucency with expansion #19	Reactive periostitis post root canal therapy	Metastatic carcinoma of lung	No
4	76	F	Intraosseous and soft tissue, right mandible and vestibule	Firm swelling and infection unresponsive to root canal therapy #28 periapical pathology #28	Persistent infection, r/o neoplasm	Metastatic carcinoma of lung	Yes
5	74	M	Intraosseous, left mandible	Periapical radiolucency #19-20 with pain, unresolving to endodontic treatment	R/o metastatic prostate	Metastatic prostate carcinoma	Yes
6	47	M	Soft tissue, right posterior maxillary gingiva	Ulcerated soft-tissue mass distal to #2	Squamous cell carcinoma vs metastatic renal	Metastatic renal cell carcinoma	Yes
7	88	F	Soft tissue, left mandibular gingiva	Red, ulcerated soft-tissue mass	Pyogenic granuloma	Metastatic carcinoma of unknown primary	No

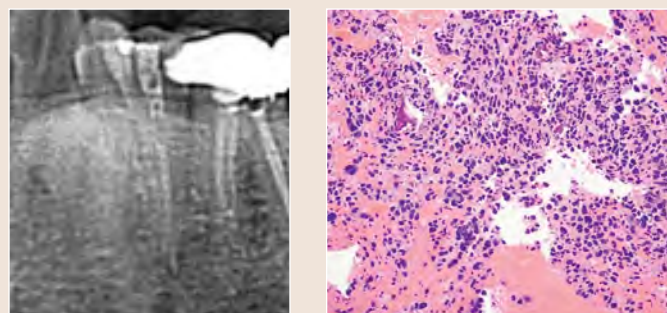


**Figure 1.** Representative clinical photos, radiographic images and histologic H&E slides of metastatic diseases presented.



(a) Case 1. Ulcerated tan mass of retromolar pad area and histologically diagnosed as metastatic adenocarcinoma, colon.

(b) Case 2. Irregular radiolucency of left mandible with ill-defined and somewhat moth-eaten borders. Histologic diagnosis of metastatic breast carcinoma.

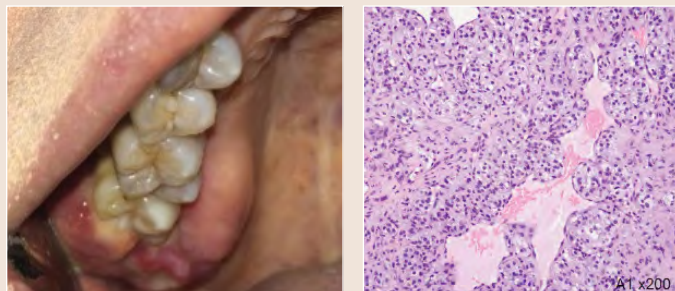


(c) Case 3. Subtle radiolucency that did not resolve with endodontic treatment. Clinically, some expansion was present at site of left mandibular first molar (#19). Clinical diagnosis was of reactive periostitis. Intraosseous curetting (H&E x400) revealed atypical, hyperchromatic epithelioid cells admixed with inflammatory cells and for hard-tissue fragments. Immunohistochemical staining profile of metastatic lung cancer.

(d) Case 5. Histologic slide of metastatic prostate carcinoma.

The microscopic diagnoses of these seven cases included colon adenocarcinoma (one case), ductal breast adenocarcinoma (one case), lung carcinoma (two cases), prostate carcinoma (one case) and renal cell carcinoma (one case).

**Figure 1.** Representative clinical photos, radiographic images and histologic H&E slides of metastatic diseases presented.



(e) Case 6. Ulcerated mass of right posterior maxillary gingiva. Histologically diagnosed as metastatic renal cell carcinoma.

(f) Different case of metastatic renal carcinoma presenting instead as swelling of gingiva resembling peripheral giant cell granuloma and pyogenic granuloma.

The seventh case could not be further classified from the oral biopsy sample and was, therefore, diagnosed as poorly differentiated metastatic disease of unknown primary. This patient was subsequently found to have multiple metastatic deposits throughout the body, including the brain.

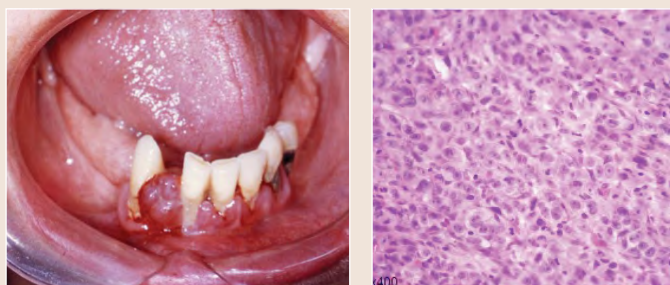
Table 1 presents a summary of recorded data, including patient sex and age at diagnosis, location of biopsy, description of clinical presentation, clinical diagnosis, histologic/biopsy diagnosis and whether the patient had a prior known history of the disease. Figure 1 presents representative clinical, histologic and radiographic images of these cases.

## Discussion

In this retrospective study, we identified seven cases with oral metastases out of a total of 17,500 biopsy reports (0.046%) over the past five years. This is consistent with the literature reporting that metastatic disease presenting in the oral cavity is very rare.<sup>[1]</sup>

In terms of site distribution, all three cases of bony metastases presented in the mandible, which is the most commonly affected bony location.<sup>[1-3,6,7]</sup> For the three cases of soft-tissue metastases, the gingiva was the most common site. This is, again, consistent with what is cited in the literature as the most commonly affected soft-tissue location.<sup>[2-5,8]</sup> Ninety percent of oral metastases are reported to present in the bone.<sup>[1]</sup> However, we found an equal distribution of cases presenting in the soft tissue (n=3) and in bone

**Figure 1.** Representative clinical photos, radiographic images and histologic H&E slides of metastatic diseases presented.



(g) Case 7. Growth of right mandibular gingiva thought to be pyogenic granuloma. Histologic diagnosis was of poorly differentiated metastatic carcinoma of unknown origin.

(n=3). One case presented in both the bone and adjacent soft tissue. Murillo et al. also reported a slight variation in distribution, with a predominance of mixed metastatic presentation, followed by soft-tissue and then bony lesions.<sup>[10]</sup>

Hirshberg et al. found that gender distribution differed for metastases presenting in bone vs. soft tissue, with an equal gender distribution in jaw bone metastases and 2:1 male predilection for soft-tissue metastases.<sup>[4]</sup> Although Murillo et al. found that there was a male predominance for all metastases, they stated that oral metastases are often found in similar proportions in male and female patients.<sup>[10]</sup>

Aniceto et al. reported a female-to-male ratio of 3:2 in a similar study of nine oral metastases presenting in the mandible, with breast adenocarcinoma being the most common primary tumor. Our results may be more in alignment with the findings of Aniceto et al. because of the similar cohort size with all bony metastases presenting in the mandible and a case of invasive ductal carcinoma of the breast that rarely presents in men. Although lung and colon cancer are both more common in men, the two cases of lung cancer and one case of colon cancer in our study presented in females, which may have further contributed to the female predilection.<sup>[16]</sup>

Although oral metastases can affect patients of all ages, the greatest prevalence occurs around 50 to 60 years of age:

51.5 years in men and 47.1 years in women; 52 years for bony metastases and 42 years for soft-tissue metastases.<sup>[4]</sup> In this study, patients ranged from 44 to 88 years old, with a mean age of 67.6 years at diagnosis: 60.5 years for males and 70 years for females; 67.7 years for bony metastases and 56.3 years for soft-tissue metastases. Therefore, in general, our cohort was slightly older in age.

The common sites of primary disease metastasizing to the oral cavity include breast, lung, kidney, liver and thyroid gland.<sup>[1-3,7,17]</sup> In the U.S., breast cancer is the most common primary malignancy to metastasize to the oral cavity in females, followed by lung and colorectal carcinoma. In males, prostate cancer is most common, followed by lung, colorectal and bladder cancer.<sup>[18,19]</sup> Sites of the primary disease in our patients included colon (n=1), breast (n=1), lung (n=2), prostate (n=1) and kidney (n=1). These were all among the most commonly reported sites of primary disease metastasizing to the oral cavity in the U.S. Lung cancer most often metastasizes to the gingiva, but in our case, presented in the mandible and mandibular vestibule.<sup>[21]</sup> Breast cancer mostly has been reported to more frequently metastasize to the gingiva, but in our study was found in the mandible.<sup>[21]</sup> The majority of prostate (80% to 90%) and colorectal cancer have been sited to metastasize to the bone, particularly the mandible, as consistent with our findings.<sup>[22,23]</sup>

Although oral metastases usually suggest advanced stage disease that has been previously diagnosed elsewhere in the body, in 22% to 30% of patients, the oral cavity is the initial site of diagnosis.<sup>[2,4,9]</sup> Two patients (28.6%) did not have prior history of a primary cancer before the oral biopsy.

It is important to note that oral metastases can mimic more common reactive lesions, infections, or benign tumors, and without a history of primary malignancy, an oral metastatic lesion would not be clinically suspected (Figure 2). Similar presentations and differential diagnosis



**Figure 2.** Clinical photos of benign entities that are common differential diagnoses for metastatic diseases presented. (a) Ulcerated mass of mandibular gingiva microscopically diagnosed as peripheral giant cell granuloma. (b) Erythematous growth of anterior maxillary gingiva microscopically diagnosed as pyogenic granuloma. (c) Large erythematous and ulcerated gingival mass microscopically diagnosed as pyogenic granuloma.



ses have been reported in the literature as was provided by our group of submitting clinicians.<sup>[1,5,8,10,11]</sup> In patients with known primary disease, it may be helpful for clinicians to recognize some clinically differentiating signs of metastatic disease, such as a rapidly evolving lesion; tendency to bleed; changes caused by tumor growth, such as root resorption; ulcers; and necrosis.<sup>[23]</sup> Even then, oral metastases can remain a challenge to diagnose with only clinical signs and symptoms.

Despite the poor prognosis associated with oral metastatic disease, newer treatment options, such as anti-angiogenic agents, for example, Bevacizumab (anti-VEGF), have shown promise in treating metastatic colorectal cancer, non-small cell lung cancer, and renal cell carcinoma. Finally, new developments in next-generation sequencing could develop more personalized treatment plans that target specific mutations and offer better prognosis for patients.<sup>[24,25]</sup>

## Conclusion

Metastatic diseases can present at various sites within the oral cavity in males and females of all ages. Their clinical presentation is often evasive and ambiguous, which complicates diagnosis, treatment and, potentially, prognosis. It is important for clinicians to be aware of the variety of possible clinical presentations of metastatic disease to the oral cavity and to be cognizant that the oral lesion is the initial presentation of the cancer in up to 30% of patients. ✍

*The authors report they have no conflicts of interest to disclose. Their research was supported by a College of Dental Medicine Summer Research Fellowship and received approval from the Columbia University institutional review board. Queries about his article can be directed to Zeming Zheng at zz2640@cumc.columbia.edu.*

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