Case Report

Oral Gingival Metastasis: A Diagnostic Dilemma

Abstract
Oral cavity is a rare target for metastasis with an incidence of 1% among all oral cancers. In 24% of such cases, oral metastasis is the first indication of an undiagnosed primary. Metastatic oral malignancies have been reported in the mandible, tongue, and gingiva. Although gingival metastasis has been reported from lung, prostate, rectal carcinoma in men and carcinoma of breast, adrenal glands, and genitalia in females, gingival metastasis from carcinoma of the penis has not been reported. Herein, a case of metastatic gingival carcinoma that developed after extraction of teeth from primary carcinoma of the penis is presented. An extensive literature search revealed no such similar case reports.

Keywords: Gingiva, metastatic carcinoma, penis, primary tumor

Introduction
Metastasis is a complex biological course that occurs due to the detachment of tumor cells from primary tumor through the blood, lymph, or serosal surfaces. Metastasis to the oral cavity is rare, accounting to about 1% among all oral malignancies.[1] Most oral metastases involve the jawbones, the mandible being the most common site. Involvement of oral soft tissues is rare and mostly located in the gingiva and tongue.[2,3] The most common primary sources in decreasing order of frequency are breast, lung, kidney, prostate, and colorectum.[2] The breast is the most common primary site for tumors metastasizing to the jawbones, whereas the lung is the most common source for metastases to the oral soft tissues.[4]

The primary site of metastases differs between genders. The lung is the most common primary site in males, followed by the kidney, bone, and colorectum, whereas in females, the most frequent primary sites are breast, followed by genital organs and kidneys.[4]

The diagnosis of a metastatic lesion to the oral region is challenging, both to the clinician and to the pathologist. The clinician must recognize the possibility that a lesion may represent a metastasis, and the pathologist must determine the site of tumor origin.[5] Although various cases of cancer metastasizing to gingiva have been previously reported, oral gingival metastasis from primary penile cancer is rare and has not been reported. Herein, we report an unusual case.

Case Report
A 57-year-old male presented to the Department of Oral Medicine and Radiology of Sree Balaji Dental College and Hospital with chief complaints of pain in the gums and mobility of teeth in the upper and lower jaw for the past 2 months. History revealed that the patient developed ulcers in the oral cavity following extraction of the left lower posterior teeth 2 months ago that spread subsequently to involve other areas of the jaw. On general examination, the patient had progressive loss of weight. Medical history revealed pain in the genital organ for the past 4 months. On examination, intraorally burrowing type of ulcer was seen in the attached gingival region of the left lower molars [Figure 1, A-1] and in the region of the right and left upper molars; [Figure 2, A-3, A-4]submandibular lymph nodes were palpable measuring 2 cm × 3 cm, which were nontender, fixed, and firm in consistency. On genital examination, the penis was curved nodular and hard in consistency. The left testis was found to be enlarged [Figure 1, A-2]. Left inguinal lymph node was swollen measuring 2 cm × 3 cm, which was nontender, fixed, and firm in texture. A provisional diagnosis of malignant tumor/granulomatous lesion of the gingiva was made.

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Scanty material was aspirated from the inguinal node which showed pleomorphic cells with atypical hyperchromatic nuclei, atypical bizarre-shaped cells in the background of lymphocytes [Figure 3, B-1], and tumor giant cells. Picture was that of secondary deposits suggestive of poorly differentiated squamous cell carcinoma.

Computed tomography (CT) - whole abdomen showed multiple hypodense lesions in the liver and spleen [Figure 4 C-1]. Ovoid well-defined lesions with coarse rim calcifications were seen in the left testis and right epididymis [Figure 4, C-2]. Bulky penile corpus cavernosum noted. A radiological diagnosis of metastasis/disseminated granulomatous lesion was done.

Histopathological examination of the punch biopsies of oral lesions with H- and E-stained sections showed parakeratinized stratified squamous epithelium with no features of dysplasia. Numerous atypical cells, bizarre-shaped cells with nuclear hyperchromatism [Figure 3, B-2], and numerous malignant cells were seen throughout the connective tissue highly suggestive of poorly differentiated malignancy.

Immunohistochemistry (IHC) was done for the histopathological typing. IHC for pan cytokeratin was negative [Figure 5, D-1]. However, the normal appearing surface epithelium showed positivity. IHC for vimentin was done and it was negative [Figure 5, D-2]. IHC for p53 showed positive staining in few cells [Figure 6, E-1]. Ki67 was positive in more than 75% of the cells [Figure 6, E-2]. Correlating the IHC findings and histopathological findings, diagnosis of poorly differentiated carcinoma was given.

As the fine-needle aspiration cytology (FNAC) report from the inguinal region had revealed secondary deposits suggestive of poorly differentiated carcinoma probably from the penis and correlating the radiological as well as histopathological findings of oral lesion that had revealed atypical bizarre-shaped cells which is not of nativity from the oral site, the final diagnosis of metastatic carcinoma of the gingiva was made. Tumor, node, and metastasis staging is T2N1M1.

Palliative therapy was given initially to alleviate pain. Later, a combination therapy of surgery, radiation, and chemotherapy was suggested. Unfortunately, the patient succumbed to his disease before reassessment and treatment of his metastatic disease.

Discussion

Cancer cells must possess some characteristics that will allow them to survive in new environment. Thus, a
successful metastatic area/focus depends on the ability of cancer cells to sustain suitable distinct microenvironments in the metastatic cascade such as the nature of the primary tumor, systemic circulation, and the metastatic destination.\textsuperscript{6,7} Further, the tumor progression depends on angiogenesis and revascularization.\textsuperscript{8}

The oral region is not a preferred site for metastatic colonization and is usually the result of secondary spread from other metastatic lesions, mainly from the lungs. Hirshberg et al.\textsuperscript{9} suggested that inflammation plays an important role in attracting metastatic cells to the gingiva. A recent literature review showed that the jawbones, particularly the mandible, were more frequently affected than the oral soft tissues at a ratio of 2:1. In about 54% cases, the attached gingiva was the most commonly affected in the oral soft tissue site.\textsuperscript{10} Oral metastasis can grow rapidly causing pain, difficulty in chewing, dysphagia, disfigurement, and intermittent bleeding, leading to poor quality of life. Analysis of the literature by Hirshberg et al. revealed 56 cases in which tooth extraction preceded the discovery of the metastases. Tooth extraction can serve as a promoting factor in the metastatic process.\textsuperscript{2,10} The “seed-soil” theory proposed by Paget explains the basic mechanism of cancer metastasis. It is that the potential of a tumor cell to metastasize depends on its interactions with the homeostatic factors that promote tumor cell growth, survival, angiogenesis, invasion, and metastasis.\textsuperscript{11}

In the present case, the tooth extraction preceded the oral metastatic process. The patient did not have any adverse oral habits, occlusal discrepancies. Primary tumor site was found to be penis, and CT demonstrated secondaries in the liver and spleen. The oral cavity metastases could have been possibly due to the secondary metastatic colonization. Moreover, inguinal node FNAC and biopsy from the oral ulcer revealed similar atypical spindle-shaped cells, malignant cells with nuclear hyperchromatism. Histopathologically, the epithelial–mesenchymal transformation (EMT) in the high-grade epithelial tumors is a well-known phenomenon. During EMT, the epithelial cells lose their polygonal shape and desmosomal cell junctions. They gain the shape of mesenchymal cells (flattened, elongated cell) and motility. Ramaekers et al. reported the presence of vimentin positivity in carcinoma which can be demonstrated in the metastatic cells, and the expression is transient.\textsuperscript{12} This may explain the loss of vimentin positivity in our case.

The loss and appearances of specific cytokeratins are reported in the literature during the process of EMT. In our case because it was secondary from a high-grade primary tumor, there may be a loss of pan cytokeratin.\textsuperscript{13} However, we could not confirm the presence of other specific cytokeratins due to limited available specimen in the paraffin wax block. However, looking at the morphology of the cells in the H and E slides, p53 positivity, origin of the primary, and similar cells in the cytology from inguinal node, we diagnosed it as poorly differentiated carcinoma.

The treatment and prognosis is primarily based on the site of origin and the degree of metastatic spread.\textsuperscript{14} Unfortunately, the identification of a metastatic tumor usually represents a poor overall prognosis.

**Conclusion**

The diagnosis of a metastatic lesion in the oral region is challenging, both to the clinician and to the pathologist. The prognosis of metastatic lesions to the oral cavity is very poor, and combination chemotherapy to alleviate the symptoms is the only preferred therapeutic modality. Hence, careful clinical and histopathological assessment leads to definitive diagnosis of the metastatic lesion and its origin which could help in improving the prognosis.

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Conflicts of interest

There are no conflicts of interest.

References

1. Meyer I, Shklar G. Malignant tumors metastatic to mouth and jaws. Oral Surg Oral Med Oral Pathol 1965;20:350-62.
2. Hirshberg A, Buchner A. Metastatic tumours to the oral region. An overview. Eur J Cancer B Oral Oncol 1995;31B: 355-60.
3. van der Waal RI, Buter J, van der Waal I. Oral metastases: Report of 24 cases. Br J Oral Maxillofac Surg 2003;41:3-6.
4. Cantero R, Diez L, Pérez JCG, Gómez F, Sierra E, Sastre J, et al. Gingival metastasis as first sign of a rectal cancer. Coloproctology 1998;20:229-32.
5. Bodner L, Sion-Vardy N, Geffen DB, Nash M. Metastatic tumors to the jaws: A report of eight new cases. Med Oral Patol Oral Cir Bucal 2006;11:E132-5.
6. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nat Rev Cancer 2009;9:239-52.
7. Nguyen DX, Bos PD, Massagué J. Metastasis: From dissemination to organ-specific colonization. Nat Rev Cancer 2009;9:274-84.
8. Folkman J. Role of angiogenesis in tumor growth and metastasis. Semin Oncol 2002;29 6 Suppl 16:15-8.
9. Hirshberg A, Leibovich P, Buchner A. Metastases to the oral mucosa: Analysis of 157 cases. J Oral Pathol Med 1993;22:385-90.
10. Hirshberg A, Shnaiderman-Shapiro A, Kaplan I, Berger R. Metastatic tumours to the oral cavity – Pathogenesis and analysis of 673 cases. Oral Oncol 2008;44:743-52.
11. Fidler IJ. The pathogenesis of cancer metastasis: The ‘seed and soil’ hypothesis revisited. Nat Rev Cancer 2003;3:453-8.
12. Ramaekers FC, Haag D, Kant A, Moesker O, Jap PH, Vooijs GP. Coexpression of keratin- and vimentin-type intermediate filaments in human metastatic carcinoma cells. Proc Natl Acad Sci U S A 1983;80:2618-22.
13. Fillies T, Werkmeister R, Packeisen J, Brandt B, Morin P, Weingart D, et al. Cytokeratin 8/18 expression indicates a poor prognosis in squamous cell carcinomas of the oral cavity. BMC Cancer 2006;6:10.
14. Sánchez Aniceto G, García Peñín A, de la Mata Pages R, Montalvo Moreno JJ. Tumors metastatic to the mandible: Analysis of nine cases and review of the literature. J Oral Maxillofac Surg 1990;48:246-51.