Aggressive Gingival Metastasis of Adenocarcinoma of Unknown Origin: Case Report

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Abstract

A case of localized soft tissue growth located on the lingual aspect of the left mandibular gingiva is reported in a 61-year-old male patient in whom excisional biopsy of the lesion was performed. The histopathologic diagnosis was adenocarcinoma. Further clinical and biopsy examinations taken from several organs indicated the presence of metastatic adenocarcinomas in the brain, spleen, lymph nodes, and liver. The oral tumor recurred after repeated surgical removal. Based on histopathological examination and immunoprofiling analysis the primary tumor probably originated in the gastrointestinal tract.

Key words: Adenocarcinoma, localized gingival growth, metastasis

Introduction

Oral cancers are malignant neoplasms that affect the structures of the mouth. They may be a primary lesion that originated in the mouth, a metastasis from a distant site, or an extension from an adjoining site. Metastasis is the culmination of a multistage process; in this process malignant tumor cells detach themselves from the primary tumor, moving into lymphatic or vascular systems until they become lodged in the capillary bed and invade surrounding tissues (Ravi Prakash *et al.*, 2012). Oral metastatic tumors are rare, constituting about 1% of malignant oral neoplasms and often have secondarily spread from other metastatic lesions (Van der Waal *et al.*, 2003). Initially, metastatic tumors of the oral cavity might invade oral soft tissues or jawbones. The most common primary sources of tumors metastasizing to male jawbones are the lungs and to female jawbones are the breasts (Hirshberg and Buchner, 1995; Van der Waal *et al.*, 2003). The gingiva is the most commonly involved oral soft tissue site (Hirshberg *et al.*, 1993). Such metastasis has been reported for various tumors, including adenocarcinoma of the colon, lung, liver, kidney, and testis (Fantasia and Chen, 1979; Wedgwood *et al.*, 1979; Buchner and Begleiter, 1980; Alvarez *et al.*, 2006; Ravi Prakash *et al.*, 2012). This report describes the clinical and histopathological features of a fast growing invasive metastatic adenocarcinoma of unknown origin affecting the gingiva.

Materials and methods

A 61-year-old, non-smoker male patient was referred to King Husain Medical Center, Department of Periodontics in Jordan on February 2015, due to the month-long presence of a rapidly growing, painless mass in the lower left part of the mouth (*Figure1*). Medical history revealed that the patient was admitted on November 2014 to the Department of General Surgery as a case of multiple lymph nodes enlargement, abdominal pain and weight loss in the last six months. Laparoscopic excision of intraperitoneal lymph nodes was performed and histopathologic examination revealed metastatic adenocarcinoma. Positron emission tomography/computed tomography (PET/CT) nuclear medicine for the whole body was performed and disclosed a hyper-metabolic malignant process involving multiple lymph nodes, brain, spleen, and an abdominal mass. Brain magnetic resonance imaging (MRI) showed metastatic deposits in the left cerebral hemisphere, left occipital and parietal lobes, and a lacunar infarction of the right thalamus, in addition to preventricular and sub-cortical white matter ischemia. Based on the histopathologic diagnosis of the intraperitoneal lymph nodes the patient was referred to the Oncology Department as a case of metastatic adenocarcinoma for chemotherapy and palliative radiotherapy for the brain.

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Intraoral examination showed a firm, irregular, creamy-colored mass measuring 2.5 x 3.0 x 0.5 cm in diameter (*Figure* 1). The mass was painless and appeared as a localized sessile growth in the lingual gingiva between the distal surface of the left mandibular lateral incisor tooth and the mesial aspect of the left permanent first premolar. The involved teeth were non-mobile; no other related abnormality was found in the oral mucosa. Panoramic X-ray showed generalized horizontal moderate alveolar bone loss (*Figure* 2) compatible with chronic moderate periodontitis. Excisional biopsy of the lesion was performed. The histopathologic diagnosis was adenocarcinoma. Three weeks later, the patient returned complaining of difficulty in chewing due to recurrence of the mass. The mass was excised for the second time; a biopsy confirmed the diagnosis of metastatic adenocarcinoma. From February until May 2015, the mass recurred and was excised four times. On the third visit, the bone involved caused mobility of the premolars, which had to be extracted. On the fourth visit the patient looked pale and the medical report indicated liver metastasis. Intraoral view of the fourth recurrence of the gingival mass is shown in *Figure 3*. We have not obtained any further information since the last biopsy.

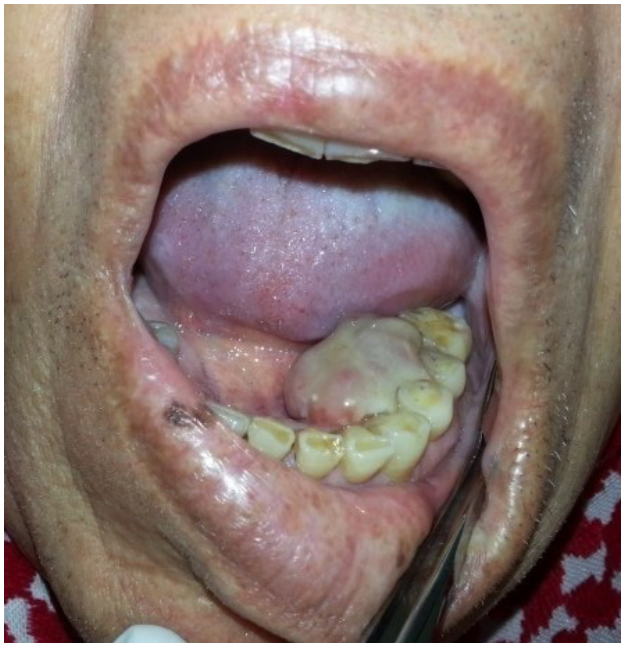

Figure 1. Intraoral view of the swelling in the lower left gingiva. Note the irregular creamy-colored mass on the lingual gingiva that extends from the distal surface of the mandibular lateral incisor to the mesial aspect of the mandibular first molar.

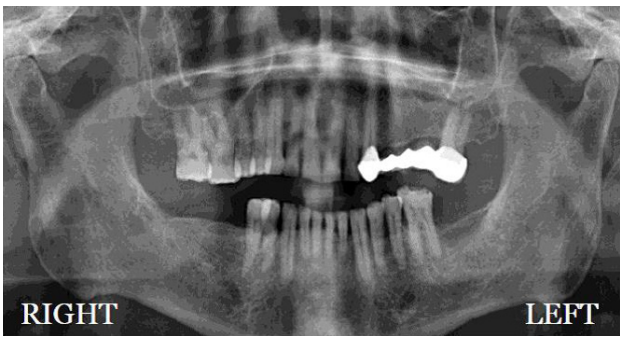

Figure 2. An orthopantomogram view showing generalized, moderate bone loss around the remaining teeth. There are no radiographic changes in the bone associated with the lesion in the lower left posterior area.

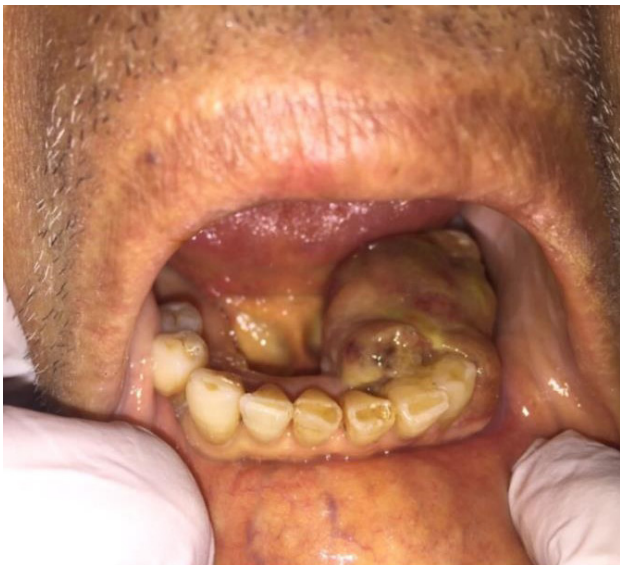

Figure 3. Fourth recurrence of the gingival mass following removal. Note the irregular re-growth of the yellowish mass from the distal aspect of the mandibular left lateral incisor to the ascending ramus and buccal extension.

Results

An excisional biopsy revealed extensive ulceration of the mucosa. The subepithelial stroma was infiltrated by an adenocarcinoma composed of variable-sized glands surrounded by desmoplastic fibrous tissue. Some of these glands showed central necrosis. The cells of the glands were highly anaplastic with numerous mitoses (*Figure 4A* and *4B*). Immunohistochemical staining, including monoclonal antibodies for cytokeratins, were positive for CK20 but negative for CK7 in the tumor cells (*Figure 5A* and *5B*). This suggests that the primary tumor most likely originated from the gastrointestinal tract.

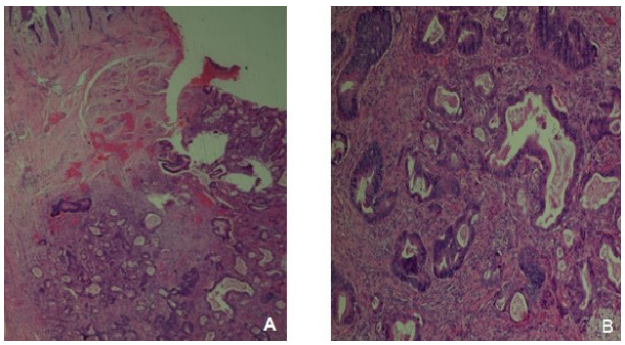

Figure 4. Low (A) and high (B) magnification of the tumor showing ulceration of the outer surface of the gingiva and infiltration of the subepithelial stroma by malignant cells of variable sized glands surrounded by a desmoplastic fibrous tissue and central necrosis. The cells of the glands were highly anaplastic with numerous divisions (hematoxylin and esosin, 100 x and 200 x).

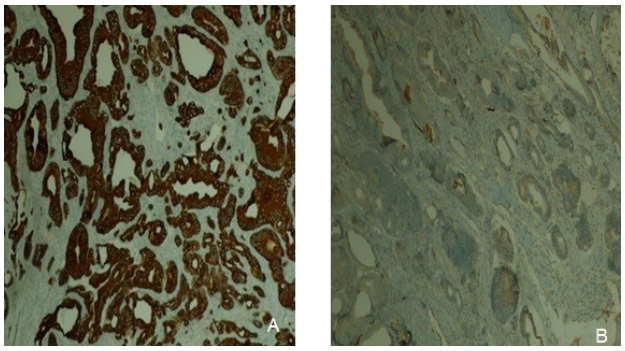

Figure 5. Immunohistochemical staining positive for (A) cytokeratin CK20 and negative for (B) cytokeratin CK7 (200 x).

Discussion

This report examines a case of aggressive gingival metastasis of adenocarcinoma in a 61-year-old male. Hirshberg *et al.* (1993) reported 157 cases of metastasis to the oral soft tissues with a male to female predilection ratio of 1.6:1. The patient was referred with the diagnosis of metastatic adenocarcinoma with gingival overgrowth that developed rapidly. He had a hypermetabolic malignant process that involved multiple lymph nodes, brain, spleen, and an abdominal mass with no definite origin. Systemic neoplastic spread is a late event in tumor progression. However, rapidly invasive cancers are sometimes diagnosed because of the appearance of metastatic lesions in the absence of a clearly detectable primary mass, which is referred to as "cancer of unknown primary origin" (CUP), accounting for 3-5% of all cancer diagnoses (Stella *et al.*, 2012). Metastasis of unknown primary tumors is difficult to distinguish histopathologically, especially for poorly differentiated adenocarcinomas (Aksoy *et al.*, 2014). Identification of the primary tumor site is important because of its prognostic and therapeutic significance. In order to determine the primary site, monoclonal antibodies, specifically cytokeratin (CK) subtypes, may be used to classify tumors according to the site of origin. The two most common CK stains are CK20 and CK7. CK20 is a protein that is expressed primarily in the gastric and intestinal epithelium, urothelium, and Merkel cells. CK20 is expressed in adenocarcinomas of the colon, stomach, pancreas, and biliary system (Soares *et al.*, 2011). The expression of CK7 was seen in the majority of cases of carcinoma, with the exception of those carcinomas arising from the colon, prostate, kidney, and thymus; carcinoid tumors of the lung and gastrointestinal tract origin; and Merkel cell tumor of the skin (Chu *et al.*, 2000).

The combination of CK7 and CK20 immunoprofiling has been helpful in identifying primary tumor sites (Varadhachary *et al.*, 2004). In the present case, the immunoprofile favored a gastrointestinal origin because the tumor cells were positive for CK20 and negative for CK7. According to Chu *et al.* (2000) and Wang *et al.* (1995), in a high percentage of adenocarcinomas originating from the gastrointestinal system, CK20 is positive whereas CK7 is negative.

Metastatic oral malignancy rarely occurs in the attached gingiva. When metastasis occurs in the jawbones, the mandible premolar region is the most common site (Van der Waal *et al.*, 2003; Hirshberg *et al.*, 2008). In our case, the metastatic lesion occurred in the lingual gingiva at the canine/premolar region. It involved the marginal and attached gingiva with early extension to the interdental papillae. Ellis *et al.* (1977) and Ramirez *et al.* (2003) have shown that metastasis to oral soft tissues develops as a rapidly and expansive growing mass that tends to be ulcerated and hemorrhagic. These lesions often resemble reactive soft tissue lesions such as pyogenic granuloma or peripheral giant cell. When a lesion grows rapidly, it is advisable to include the possibility of a metastatic tumor in the differential diagnosis even though there is no identification of a primary tumor (Soares *et al.*, 2011). The definitive diagnosis depends on the biopsy result.

In addition to progressive discomfort, symptoms of oral metastatic tumors consist mainly of pain, swelling, bleeding, neuroparalysis, and drifting of teeth (Rusthoven *et al.*, 1984). Metastasis to the gingiva may also affect speech and nutrition (Rajini Kanth *et al.*, 2015). In the present case, the patient's only complaint was his inability to tolerate the presence of the mass inside his mouth. As a result, he sought to have it removed as soon as possible. The oncologist referred the patient to have the tumor conservatively excised because of the patient's deteriorating medical condition. Since the patient could not tolerate extensive surgery, palliative radiotherapy and chemotherapy were recommended as alternatives (Shimoyama *et al.*, 2004).

In the present case, the oral metastasis of the primary tumor was so rapid and aggressive that it recurred four times and invaded the underlying jawbone in a period of less than three months. During the fourth month the tumor metastasized to the liver. We were unable to follow the patient because of his declining health. Oral metastasis often is indicative of a poor prognosis with an average survival time of approximately six months following diagnosis (Van der Waal *et al*., 2003).

Appropriate medical and dental history is critical to determine if there is a tumor metastasis of unknown primary origin, as in the case presented in this report. Definitive diagnosis is confirmed by histopathological and immunohistochemical examination. Immunoprofiling may be helpful in identifying the primary tumor site.

References

Aksoy S, Orhan K, Kursun S, Kolsuz ME and Celikten B. Metastasis of prostate carcinoma in the mandible manifesting as numb chin syndrome. *World Journal of Surgical Oncology* 2014; 12:401.

Alvarez-Alvarez C, Iglesias-Rodriguez B, Pazo-Irazu S and Delgado-Sánchez-Gracián C. Colonic adenocarcinoma with metastasis to the gingiva. *Medicina Oral Patologia Ora ly Cirugia Bucal* 2006; 11:E85-87.

Buchner A and Begleiter A. Metastatic renal cell carcinoma in the gingiva mimicking hyperplastic lesion. *Journal of Periodontology* 1980; 51:413-415.

Chu P, Wu E and Weiss LM. Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. *Modern Pathology* 2000; 13:962-972.

Ellis GL, Jensen JL, Reingold IM and Barr RJ. Malignant neoplasms metastatic to gingivae. *Oral Surgery Oral Medicine Oral Pathol*ogy 1977; 44:238-245.

Fantasia JE and Chen A. A testicular tumor with gingival metastasis. *Oral Surgery* 1979; 48:64-68.

Hirshberg A, Leibovich P and Buchnar A. Metastasis to the oral mucosa: analysis of 157 cases. *Journal of Oral Pathology and Medicine* 1993; 22:385-390.

Hirshberg A and Buchner A. Metastatic tumours to the oral region. An overview. *European Journal of Cancer part B: Oral Oncology* 1995; 31B:355-360.

Hirshberg A, Shnaiderman-Shapiro A, Kaplan I and Berger R. Metastatic tumours to the oral cavity - pathogenesis and analysis of 673 cases. *Oral Oncology* 2008; 44:743-752.

Rajini Kanth M, Ravi Prakash A, Raghavendra Reddy Y, Sonia Bai JK and Ravindra Babu M. Metastasis of lung adenocarcinoma to the gingiva: A rare case report. *Iran Journal of Medical Science* 2015; 40:287-291.

Ramirez JR, Seoane J, Montero J, Esparza Gómez GC and Cerero R. Isolated gingival metastasis from hepatocellular carcinoma mimicking a pyogenic granuloma. *Journal of Clinical Periodontology* 2003; 30:926-929.

Ravi Prakash SM, Verma S, Gill N and Malik V. Multiple gingival metastasis of adenocarcinoma of the lung. *Indian Journal of Dental Research* 2012; 23:558-559.

Rusthoven JJ, Fine S and Thomas G. Adenocarcinoma of the rectum metastatic to the oral cavity. Two cases and a review of the literature. *Cancer* 1984; 54:1110-1112.

Shimoyama S, Seto Y and Aoki F. Gastric cancer with metastasis to the gingiva. *Journal of Gastroenterology and Hepatology* 2004; 19:831-835.

Soares AB, Thomaz LA, Duarte MT, de Camargo de Moraes P and de Araujo VC. Metastatic adenocarcinoma of the colon: Early manifestation in gingival tissue. *Head and Neck Pathology* 2011; 5:140-143.

Stella GM, Senetta R, Cassenti A, Ronco M and Cassoni P. Cancers of unknown primary origin: Current perspectives and future therapeutic strategies. *Journal of Translational Medicine* 2012; 10:12.

Van Der Waal RI, Buter J and Van Der Waal I. Oral metastasis: Report of 24 cases. *British Journal of Oral and Maxillofacial Surgery* 2003; 41:3-6.

Varadhachary GR, Abbruzzese JL and Lenzi R. Diagnostic strategies for unknown primary cancer. *Cancer* 2004; 100:1776-1785.

Wang NP, Zee S, Zarbo RJ, Bacchi CE and Gown AM. Coordinate expression of cytokeratins 7 and 20 defines unique subsets of carcinomas. *Applied Immunohistochemistry* 1995; 3:99-107.

Wedgwood D, Rusen D and Balk S. Gingival metastasis from primary hepatocellular carcinoma. *Oral Surgery* 1979; 47:263-266.