Gingival metastasis of ovarian carcinoma: report of a case and review of the literature

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Abstract. Diagnosing gingival metastases is difficult because clinically they can mimic benign oral lesions. The authors report an unusual case of metastatic ovarian carcinoma in the gingiva of a 46-year-old woman 5 years after ovariectomy. The tumor presented as an exophytic growth at the molar region of the mandible. Histological examination showed invasive proliferation of atypical glandular structures composed of mucin-producing cells laying in a fibrous stroma. Tumor cells were immunopositive for carcinoembryonic antigen, MUC1 mucin, and lysozyme, while stromal fibroblasts were immunopositive for vimentin and estrogen receptor. The diagnosis of metastatic ovarian mucinous cystadenocarcinoma was made. A review of the English literature revealed this to be the first report of gingival metastasis of an ovarian carcinoma.

Keywords: estrogen receptor; gingiva; mucinous cystadenocarcinoma; oral metastasis; ovarian carcinoma.

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Metastatic tumors in the oral cavity are rare and comprise less than 1% of all malignant oral neoplasms. Almost 90% of these metastases involve the jawbones, particularly the mandible, and only 10% involve the oral soft tissues, predominantly the gingiva. In about 33% of cases, the oral metastasis is the first sign of distant undiagnosed malignancy. Metastasis in the oral cavity is difficult to diagnose and the prognosis for these patients is generally poor.

Distant metastasis from primary epithelial ovarian cancer is commonly observed as nodal and intraperitoneal spread. It may spread to distant sites, such as the lung and liver, but metastasis to the oral region is rare. The authors describe a case of metastatic ovarian carcinoma presented as a mass involving the gingiva and discuss the possible pathogenesis of the gingival metastasis of an ovarian carcinoma. Based on a review of the literature, the authors determine the frequencies of gingival metastases from malignancies of distant organs.

Case Report
A 46-year-old woman was admitted to the Department of Oral and Maxillofacial Surgery, Ojiya General Hospital complaining of swelling in the left side of the mandible. The patient had had stage IV, well-differentiated, ovarian mucinous cystadenocarcinoma, which was treated by total hysterectomy and bilateral ovariectomy, as well as a gallbladder adenocarcinoma, which was independent of the ovarian cancer and was treated by cholecystectomy. An extraoral examination showed a hen’s egg-sized swelling in her left cervical region, suggesting a lymph node metastasis. Intraorally, a polypoid lesion, measuring 3.8 x 2.5 x 2.0 cm, was seen protruding from the mandibular gingiva in the area of the left second molar tooth. The lump was soft with a hemorrhagic and ulcerated surface.
Gingiva and cervical lymph node metastases of the ovarian or gallbladder carcinomas were suspected because of the patient’s history, and an incisional biopsy from the gingival mass was carried out to confirm the diagnosis. A computerized tomography (CT) scan of the whole body revealed additional metastases to the lungs and liver. A good prognosis was not expected, but the gingival tumor was surgically excised 2 weeks after presentation to relieve the patient’s oral dysfunction. 18 days after the operation, the patient died from acute renal failure.

Microscopically, the gingival mass comprised an invasive and dense proliferation of tubular structures in a fibrous stroma. The tubules were lined by tall columnar cells that contained mucin at their luminal ends and the cells showed features of atypia (Fig. 1B). The tumor cells were immunoreactive for CEA (C), MUC1 (D), and the stromal fibroblasts were strongly positive for vimentin (E), and some of them expressed estrogen receptor (F).

Fig. 1. Histopathology of metastatic ovarian carcinoma of the gingiva. (A, B) Haematoxylin and eosin stain; (C–F) immunohistochemical stains for CEA, MUC1, vimentin, and estrogen receptor, respectively. (A) x 100, (B-F) x 200. The tumor comprised a dense proliferation of tubular structures with papillary projections and cystic dilatations in a fibrous stroma (A). The tubules were lined by columnar cells that contained mucin at their luminal ends and the cells showed features of atypia (B). The tumor cells were immunoreactive for CEA (C), MUC1 (D), and the stromal fibroblasts were strongly positive for vimentin (E), and some of them expressed estrogen receptor (F).
nuclear hyperchromatism and frequent mitotic figures. The cells contained cytoplasmic mucin, especially in the luminal end (Fig. 1B); the mucin was positive for PAS, alcian blue, colloidal iron and mucicarmine. Mucinous material was also retained in the tubular and cystic lumina. When compared with the histological findings from the patient’s two previous tumors, these features matched the ovarian mucinous cystadenocarcinoma and were different from those of the cholecystic adenocarcinoma.

Immunohistochemical stainings were performed using the streptavidin-biotin complex method (Histofine SAB-PO kit, Nichirei Co. Ltd., Tokyo, Japan) of Hsu et al. Antibodies against carcinoembryonic antigen (CEA; 1:100, DAKO, Glostrup, Denmark), MUC1 mucin (1:100, Toray-Fuji Bionics, Inc., Tokyo, Japan), lysozyme (1:100, DAKO), vimentin (1:100, DAKO) and estrogen receptor (1:100, DAKO) were used. The tumor cells lining the tubular structures and cystic spaces, particularly their luminal cytoplasm, were positive for CEA (Fig. 1C) and lysozyme, while their luminal cell surfaces were positive for the transmembrane glycoprotein MUC1 (Fig. 1D). The stromal fibroblasts showed immunoreactivity to vimentin (Fig. 1E), and their stromal fibroblasts showed immunoreactivity to estrogen receptor (Fig. 1F).

Discussion

This is the first report of gingival metastasis from an ovarian carcinoma. Primary epithelial carcinomas constitute 90-95% of ovarian malignancies, and of these epithelial tumors, serous carcinomas are the most common; representing more than 50%, whereas mucinous carcinomas are rare and constitute less than 10%. Ovarian carcinoma cells are typically exfoliated into the peritoneal cavity, and death usually occurs due to ascites and chronic bowel obstruction. Dauplat et al. reviewed 225 patients with primary epithelial ovarian carcinomas and found that distant metastases through lymphatic or haematogenous routes occurred in 38% of patients. Of the patients who had distant metastases, 78% had serous adenocarcinoma, 6% endometrioid carcinoma, 4% mucinous adenocarcinoma, 7% clear cell carcinoma and 4% had undifferentiated carcinomas. Metastases were mostly in the pleura, liver, lung, distant lymph nodes, skin, pericardium, CNS and bone, but no tumor metastasized to the oral cavity. An extensive review of the English literature revealed only four cases of metastatic ovarian tumors to the oral region. Two of these cases were metastases to jaw bones (one embryonal carcinoma and one not specified), and the other two were to the oral soft tissues; one diagnosed as granulosa cell tumor metastasized to the palate and one diagnosed as adenocarcinoma (not otherwise specified) metastasized to the lip. This report presents the third case of metastatic ovarian carcinoma to the oral soft tissues and the first case of metastatic ovarian carcinoma to the gingiva. Most ovarian malignancies are of epithelial origin, including the present case, but two of the four cases with known histological types were not purely epithelial.

There have been no case reports in the literature of metastatic ovarian tumor to the oral cavity since 1973, showing that oral metastases of ovarian cancers are rare. In 1928, Brown and O’Keefe reported a ‘sarcoma of the ovary with unusual oral metastases’, but their case has been reviewed and microscopic examination of the original biopsy revealed a histological appearance characteristic of Burkitt’s lymphoma.

A review of the literature revealed that metastatic tumors in the oral region were rare, and the most common sources of metastases were the breast, lung, kidney, thyroid, prostate and colon. The breast is the most common primary site for metastasis to the jawbones while the lung is the most common site for metastasis to the soft tissues. When tumors metastasize to the oral cavity, they usually localize in the jawbones rather than in the oral soft tissues. Hirschberg et al. reviewed the English literature from 1916 to 1991 and found 157 well-documented cases of metastatic tumors to the oral mucosa. The gingiva was found to be the most common site of involvement (86 cases; 55%) followed by the tongue (43 cases; 27%) and with much less frequency, the tonsils, palate, lips, buccal mucosa and floor of the mouth. Elkhoury et al. reviewed the English literature from 1991 to October 2003 and found an additional 22 cases of reported metastases to the gingiva. A review of the English literature from October 2003 to November 2007 revealed an additional 8 cases of metastases to the gingiva to bring the total number since 1916, including the present case, to 117 cases. These 117 cases, listed according to the primary site of metastases, are summarized in Table 1. During the last 91 years, the five most common sites of metastases to the gingiva have been the lung (21%), breast (11%), kidney (11%), liver (9%), and bone (9%). In most of the reports, gingival metastases usually occurred in patients with advanced stages of malignancies and were most often associated with metastatic deposits in other organs, as in the present case.

Many factors can lead to difficulty in diagnosing gingival metastases. Metastases can mimic benign oral lesions clinically and may manifest before primary tumors. The history of malignant tumors can assist in suggesting a metastasis, but

<table>
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<th>Primary site</th>
<th>Hirschberg et al.11*</th>
<th>Elkhoury et al.7</th>
<th>2003–2007</th>
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*Includes metastases to alveolar mucosa. †Includes vagina, cervix, uterus, ovaries. §Present case. §Abdominal mass but no definite diagnosis obtained.
late metastasis is difficult to diagnose. In this case, gingival metastasis occurred 5 years after the treatment of the primary tumor. The diagnosis becomes more complicated when the secondary tumor acquires some histopathological variations compared with the primary tumor. When compared with the primary mucinous cystadenocarcinoma, the gingival tumor in the present case showed less prominent mucous production. By using special stains and immunostainings for CEA and MUC1, the authors were able to identify the intracellular and intraluminal localization of the mucinous material and the simultaneous immunopositivity of carcinoma cells to lysozyme was helpful in confirming the diagnosis. The gingival tumor also showed more fibrous stroma. The stromal fibroblasts were clearly immunopositive for vimentin and estrogen receptor. The vimentin immunopositivity is explained by the enhanced activity of estrogen receptors on these cells. Previous studies have indicated a close relationship between ovarian hormones and dimensional changes of the gingiva. Estrogen stimulates the proliferation of gingival fibroblasts and maturates connective tissues by blocking collagen degradation. Consequently, the stromal fibrosis seen in the gingival secondary tumor could be explained by the enhanced activity of the gingival fibroblasts by estrogen released by the local and distant tumors.

References


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