Oral metastasis of uterine carcinoma: Case report and 83-year review of this uncommon occurrence

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SUMMARY

Uterine cervix cancer is the second most common female cancer and the third most common cause of female cancer mortality. The disease spreads into the surrounding tissues by direct infiltration, whereas, spread by hematogenous dissemination is relatively unusual and the involvement of oral and maxillofacial region is extremely rare in gynecological cancer. A 72-year-old Chinese woman was referred to our dental clinic with a 4-month history of a painful and gradually expanding swelling in oral cavity associated with a severe limitation of mouth opening. The submucosa was fibro-elastic with normal mucosal covering on the left side of the soft palate that extended up to the palatoglossal arch, measuring 2.5 cm in maximum diameter. Fine needle aspiration cytology was performed on the nodule and the cytological diagnosis was consistent with undifferentiated carcinoma. An incisional biopsy was performed and the diagnosis of undifferentiated carcinoma of primary unspecified location was made. The patient's son reported that his mother had been experiencing the return of her "menstrual cycle" so we referred her to the gynecologist who detected a lesion in the cervix uteri, bigger than the one in the oral cavity. Both lesions had the same histological and immunohistochemical profile prompting us to report this case as carcinoma of the cervix uteri that metastasized to the oral cavity. Unfortunately, the patient died 24 months after the initial diagnosis of the oral metastasis. The patient received sessions of radiotherapy exclusively in both lesions. The review of literature showed that oral metastasis from uterine cervix carcinoma is rare, indicating poor prognosis and that the correlation of clinical medical history, laboratory, imagenological, cytological, histopathological and immunohistochemical exams are essential for achievement of the precise diagnosis.

Key words: *Uterine Cervical Neoplasms; Neoplasm Metastasis; Mouth Neoplasms; Prognosis*

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INTRODUCTION

Uterine cervix cancer affects about 500,000 women worldwide per year, thereby making it the second most common female cancer. In addition, it is the third most common cause of female cancer mortality (1). The disease usually spreads into the surrounding tissues by local extension and lymphatic dissemination and the commonest sites are pelvis and abdomen (2-4). Spread by hematogenous dissemination is relatively unusual, and most commonly involves distant regions, such as lungs, bones, liver, and extrapelvic lymph nodes. Rare metastases to brain, breast, thyroid, skin spinal cord, kidney, adrenal gland and oral and maxillofacial region have also been reported (3-6). They are usually seen late in the course of the disease and have poor prognosis (7-9). Oral cavity metastases from cervix uterine cancer seem to be an extremely rare event. The aims of this study are to report an additional case of cervix uterine carcinoma metastasizing to the oral cavity and to review the similar cases reported in the English literature from 1928-2011.

CASE REPORT

A 72-year-old Chinese woman was referred to the Piracicaba Dental School, Oral Diagnosis Clinic, with a 4-month history of a painful and gradually expanding swelling in oral cavity associated with a severe limitation of mouth opening. Anamnesis was difficult because the patient did not speak Brazilian Portuguese, only being able to mumble a few words. Initially, the patient's medical history had been obtained from her son, who also was not fluent in Brazilian Portuguese language, but was able to contribute with a reasonable translation of the patient's complaints. Medical history at this point was unremarkable. At the first intra-oral examination, we could observe a 2.5×2.0 cm fibro-elastic submucosal nodule with normal mucosal covering on the left side of the soft palate that extended up to the palatoglossal arch. The patient had trismus (Figure 1), which made the clinical examination difficult. Differential diagnosis included inflammatory nodule of infectious origin versus neoplasm. Fine needle aspiration cytology (FNAC) was performed on the nodule. The material was smeared on 5 glass slides and fixed in 95% ethanol for Papanicolaou and Panotico® staining. Cytological smears showed pleomorphic, hyperchromatic cells, atypical mitotic figures, increased number of nucleoli and prominent nucleoli and the diagnosis was consistent with undifferentiated carcinoma (Figures 2a and 2b). She returned after one week showing little improvement of her clinical condition and a slightly wider mouth opening, which allowed us to perform an incisional biopsy of the nodule. The specimen was fixed in 10% formalin and paraffin-embedded following a routine staining technique using hematoxylin and eosin. Microscopically, the mucosa was covered by normal epithelium and the connective tissue was infiltrated by undifferentiated neoplastic cells (Figure 2c). Immunohistochemical analysis demonstrated positivity for pan cytokeratin AE1/AE3 and epithelial membrane antigen (EMA), while no immunoreactivity was observed for markers as vimentin, cytokeratin 7 (CK7), CD56 and progesterone receptor (PR) (Figure 3a1-3f1). Diagnosis was established as undifferentiated carcinoma of primary unspecified location. Urinalysis showed high levels of erythrocytes (260,000/ml) and leukocytes (410,000/ml). Besides, the patient's son reported that his mother had been experiencing the return of her "menstrual cycle" for the last couple of months. The patient was referred to the Oncology Clinic for treatment of the oral neoplasia and was sent to the gynecologist. An examination revealed tumor of the cer-

vix stage IIIb according to FIGO (International Federation of Gynecology and Obstetrics). A computed tomography (CT) scan of the abdomen confirmed the presence of the tumor mass, replacing the cervix measuring 8x6x4 cm (Figure 4a) and a head computed tomography scan disclosed the presence of a mass with extension to the parapharyngeal space (Figure 4b). A cervical biopsy showed undifferentiated carcinoma of the cervix with morphology similar to the oral neoplasm (Figure 2d). Immunohistochemical analysis of the uterine lesion showed the same pattern as that presented by the oral lesion (Figure 3a2-3f2). Based on these findings, it was concluded that the oral lesion represented a metastasis from the uterine cervix carcinoma. The treatment protocol to the oral lesion involved radiotherapy exclusively (4.054 cGy/8 sessions). The uterine lesion treatment protocol involved radiotherapy (665 cGy/25 sessions) for uterus and brachytherapy for rectum and bladder (628 cGy and 1000 cGy, respectively). After 18 months of the follow-up, there was an apparent reduction in size of the cervix tumor and the oral metastasis in a CT scan (Figures 4c and 4d) with improvement of all of the symptoms. However, the patient died 24 months after the initial diagnosis of the oral metastasis.

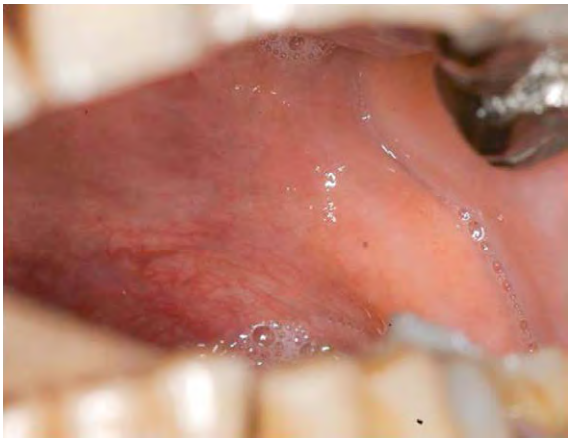

Figure 1. Submucosal nodule with normal mucosal covering on the left side of the soft palate that extended up to the palatoglossal arch. Observation was made difficult because of the marked trismus.

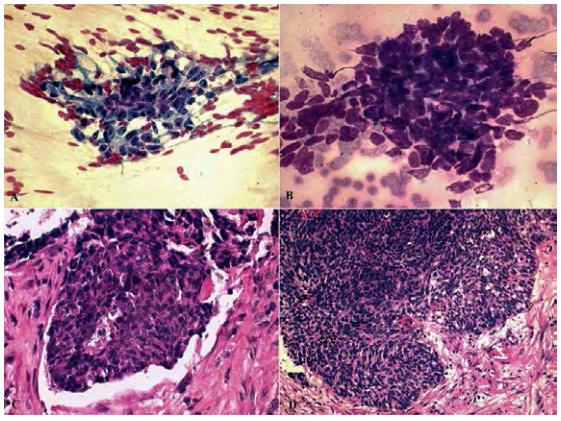

Figure 2. Photomicrographs of the cytological smears of the oral cavity lesion showing pleomorphic and hyperchromatic epithelial cells with atypical mitotic figures, increased number of nucleoli and prominent nucleoli a) Papanicolaou, ×400; b) Panotico®, ×400; c) Photomicrograph showing undifferentiated carcinoma of the oral cavity and d) of the uterine cervix (HE, ×400 and 200, respectively). Note the morphological similarities of both lesions

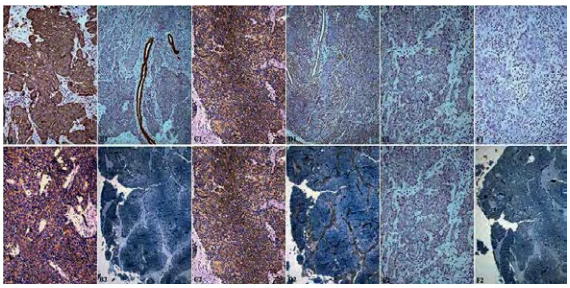

Figure 3. Photomicrograph showing immunoreactivity for a1) AE1/AE3 and b1) EMA, while no immunoreactivity was observed for c1) vimentin, d1) CK7, e1) CD56 and f1) PR of the oral cavity and for a2) AE1/AE3 and b2) EMA, while no immunoreactivity was observed for c2) vimentin, d2) CK7, e2) CD56 and f2) PR of the uterine cervix (Immunoperoxidase, ×40) Note the phenotypic similarity of both lesions

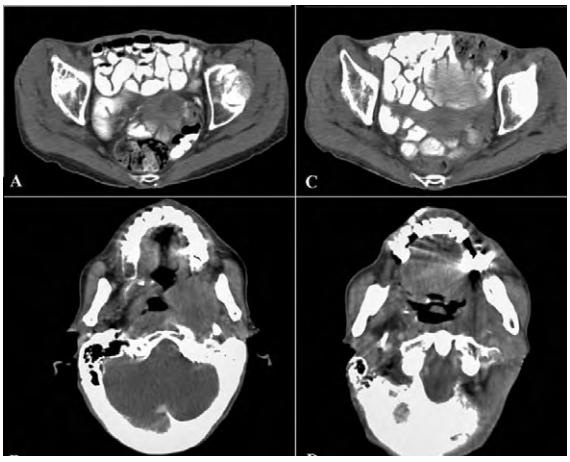

Figure 4. a) CT scan showing the presence of a tumor mass, replacing the cervix b) CT scan demonstrating a soft tissue mass with extension to the parapharyngeal space c) CT scan demonstrating apparent reduction in size of the tumor mass the cervix and d) oral cavity after 18-month follow-up

DISCUSSION

Oral metastatic tumors account for approximately 1% of oral malignancies (7, 8, 10, 11). The most common primary malignant tumors that metastasize to oral region in women are, in order of frequency, breast, female genital organs (FGO), kidney, and colorectum (9). According to the English literature (1928-2011) only 34 cases of FGO were reported metastasizing to the oral cavity (Table 1). The most common FGO site was the uterus (n=19), followed by the ovary (n=8), fallopian tube (n=1) and vagina (n=1). In five cases the FGO site was not specified. In the uterus, the most common site was the endometrium, and the present study reported a rare case of oral metastasis from cervix uteri.

The jawbones are more affected by metastases than the oral soft tissues (2:1) (9, 12-15). Table 1 displayed that 16 cases of FGO metastasized to jawbones but in the current case, cervix uteri carcinoma affected the oral soft tissue.

The attached gingiva is the most common site for the metastatic colonization in the oral soft tissue and the clinical presentation of the metastatic lesions differed between the oral sites (10, 14, 16). Table 1 showed that the most common location was the gingiva (n=6), followed by the tongue (n=4), palate (n=2), lips (n=2) and floor of the mouth (n=1). The

Table 1. Summary of oral metastases cases of female genital organs' neoplasms

	Author	Age	FGO site	Oral site	Histologic type	Clinical presentation	First sign	Other metastases	Size (cm)	Follow-up (months)	Died
OK	Brown and O'Keefe (1928)[35]	16	Ovary	Gingiva	Sarcoma	Swelling, pain and loose teeth	yes	yes	2	N/A	yes
OK	Huysen and Wallace (1932)	50	Ovary	Mandible	Carcinoma	Numbness and swelling	yes	yes	N/A	2	yes
OK	Kostrubala et al (1950)[37]	16	Ovary	Mandible	Dysgerminoma	Pain and numbness	yes	yes	N/A	6	yes
OK	Holland (1953)[38]	61	Uterus, cervix	Mandible	Carcinoma	Numbness	no	yes	N/A	8	yes
OK?	Salman and Langel (1954)[39]	64	Uterus, unspecified	Mandible	Carcinoma	Swelling extraoral	no	yes	N/A	3	yes
OK	Wheelock et al (1962)[40]	N/A	Ovary	Mandible	Dysgerminoma	N/A	N/A	N/A	N/A	N/A	N/A
OK	Meyer and Shklar (1965)[41]	53	Ovary	Lip, mucolabial sulcus	Adenocarcinoma	N/A	N/A	yes	N/A	N/A	N/A
OK	Uhler et al (1972)[28]	41	Uterus, cervix	Mandible	Carcinoma	Pain and swelling extraoral	no	yes	N/A	3	yes
OK	Hatziotis et al (1973)[42]	27	Ovary	Palate	Carcinoma	Swelling, surface ulcerated and bled easily	no	yes	N/A	N/A	N/A
OK	Orlian (1977)[43]	62	Uterus, endometrium	Maxilla	Adenocarcinoma	Swelling (supporting bone loss	no	N/A	1,7	3	yes
OK	Carl (1980)[44]	44	Vagina	Palate	Adenocarcinoma	Swelling, surface ulcerated	no	yes	4	N/A	N/A
OK	Kaziro (1981)[33]	59	Uterus, unspecified	Tongue (dorsum)	Leiomyosarcoma	Polyp	no	yes	1,2	N/A	N/A
OK	Curtin and Radden (1985)[45]	44	Fallopian tube	Mandible	Adenocarcinoma	Numbness	no	yes	2	9	no
OK	Tsounias (1988)[46]	67	Uterus, unspecified	Mandible	Leiomyosarcoma	Pain	no	yes	N/A	2	yes
OK	Davidson and Moyo (1991)[16]	44	Uterus, cervix	Gingiva	Carcinoma	Ulcerating lesion	no	yes	N/A	6	yes
OK	Maxymiw et al (1991)[47]	63	Uterus, endometrium	Mandible	Carcinoma	Swelling extraoral	no	yes	2,5	3	yes
OK	Baden et al. (1992)[25]	78	Uterus, endometrium	Tongue	Carcinoma	Swelling hypesthesia	no	yes	3	6.5	yes
OK	Allen et al (1993)[19]	65	Uterus, unspecified	Lower lip	Leiomyosarcoma	Nodule	no	yes	0,8	16	no
	Saiz et al (1998)[29]	49	Uterus, unspecified	Floor of mouth and parotid gland	Leiomyosarcoma	N/A	N/A	N/A	N/A	N/A	N/A
OK	Galen (1998)[48]	55	Uterus, endometrium	Mandible	Adenocarcinoma	Swelling intraoral	yes	yes	N/A	N/A	N/A
OK	Persson et al (1998)[26]	55	Uterus, unspecified	Tongue	Leiomyosarcoma	Nodule	no	N/A	N/A	N/A	N/A
OK	Dosortez et al (1999)[49]	71	Uterus, endometrium	Mandible	Adenocarcinoma	Swelling intraoral (ulcerated)	no	yes	3	15	no
OK	Rocha et al (2000)[11]	67	Uterus, endometrium	Mandible	Adenocarcinoma	Swelling extraoral (pain)	no	yes	3	9	yes
OK	Medina et al (2001)[50]	67	Uterus, corpus	Gingiva	Angiosarcoma	Sessile mass (lobulated, nonulcerated, and had a violaceous hue)	yes	yes	3	15	yes
OK	Vora e Levin (2003)[31]	62	Uterus, unspecified	Tongue	Leiomyosarcoma	Swelling	no	yes	1	N/A	yes
	Bodner et al (2006)[51]	75	Uterus, unspecified	Mandible	Adenocarcinoma	Swelling	N/A	N/A	N/A	21	yes
OK	D´Silva et al (2006)[27]	N/A	FGO, unspecified	Jaws, unspecified	N/A	N/A	no	N/A	N/A	N/A	N/A
OK		N/A	FGO, unspecified	Jaws, unspecified	N/A	N/A	no	N/A	N/A	N/A	N/A
OK	Lim et al (2006)[8]	N/A	FGO, unspecified	Oral region, unspecified	Leiomyosarcoma	N/A	N/A	N/A	N/A	N/A	N/A
OK		N/A	FGO, unspecified	Oral region, unspecified	Dysgerminoma	N/A	N/A	N/A	N/A	N/A	N/A
OK		N/A	FGO, unspecified	Oral region, unspecified	Melanoma	N/A	N/A	N/A	N/A	3	yes
OK	Sasaki et al (2008)[17]	54	Ovary	Gingiva	Adenocarcinoma	Swelling	yes	yes	N/A	N/A	no
OK	Munakata et al (2009)[52]	46	Ovary	Gingiva	Adenocarcinoma	Polypoid lesion and swelling (ulcerated)	no	yes	3,8	1	yes
OK	Kim et al. (2009)[34]	56	Uterus, unspecified	Gingiva	Leiomyosarcoma	Swelling	no	yes	4	3	yes
	Present case	72	Uterus, cervix	Palate	Carcinoma	Nodule and pain	yes	N/A	2,5	24	yes

Legend: N/A – not available

location of metastatic tumor was unspecified in 3 cases but was defined as rising in the oral region. The early manifestation of oral soft tissue metastases in gingiva, may resemble a hyperplastic or a reactive lesion, such as a pyogenic granuloma, peripheral giant cell granuloma or fibrous hyperplasia (10, 14, 16). In other locations in the oral soft tissues, the clinical presentation is a submucosal mass (9). In the current case, the patient showed submucosal nodule in soft palate measuring 2.5 cm in maximum diameter and the lesion was associated to severe limitation of mouth opening (trismus) and pain. In addition, other clinical presentations of the metastatic lesions include ulcer, hemorrhage and paresthesia (3, 8, 17). The metastatic tumor size ranged from 0.8 to 3.8 cm, with a mean of 2.5 cm (Table 1).

The clinical differential diagnosis of such lesions may be lengthy. Pain, trismus and swelling could not only suggest a malignant process but also a variety of infectious lesions and reactive processes (3, 18, 19). FNAC has been used for diagnosing tumors, infectious diseases and reactive disorders (20-22), and is frequently used as a helpful diagnostic tool in soft tissue masses located in the head and neck, and its use in salivary glands, oral cavity, lymph nodes, thyroid glands, as well as bone lesions in the jaws is well documented (20-24). Baden (25) and Persson and Domanski (26) made diagnosis of the tongue metastasis from uterus by FNAC. In the present case, FNAC was employed to diagnose the oral metastasis as well. The cytological smears showed features of malignant neoplasm and the diagnosis was consistent with undifferentiated carcinoma.

The histologic appearance of metastatic disease is often poorly differentiated, making it challenging to determine the location of the primary lesion. Taking a thorough medical history can assist the diagnosis, and conducting a screening using a panel of immunohistochemical stains may facilitate the diagnosis (27). In the present case, the cytological diagnosis was confirmed by incisional biopsy and immunohistochemical findings, which were compatible with undifferentiated carcinoma. In the review, the majority of cases were adenocarcinomas and the diagnosis of some oral metastases was based on a combination of the histologic and immunohistochemical findings between oral and uterine specimens (17, 28, 29). Similar morphology and immunoreactivity was observed in both specimens.

In patients with a known malignant disease, the clinical presentation may favor the pre-operative diagnosis of metastasis (7, 9). However, in 24%-37% of patients, the metastatic lesion in the oral region is the first indication of an undiscovered malignancy at a distant site (8-10, 30). Table 1 shows similar results to previous reports, where in 22.22% of the cases (in seven cases this information was not available) and the current case, the oral lesion was the first sign of metastasis originating from the FGO, which had not been discovered yet. The current suspicion was based on patient's clinical features, clinical medical history, laboratory exams, CT and FNAC. It was confirmed by histopathological and immunohistochemical analyses, which were similar for oral and uterus lesions. The primary site was distant from the oral cavity which suggests hematogenous spread (19, 31). In an attempt to explain metastases to the oral region from a primary tumor in FGO, the valveless vertebral venous plexus (Batson's plexus) has been proposed as a mechanism for bypassing filtration through the lungs; an increase in intrathoracic pressure directs blood flow into this system from the caval and azygous venous system and accounts for the increased distribution of axial skeleton and head and neck metastases (32). However, all the cases available in this review (n=24) had other metastases diagnosed before or shortly after the diagnosis of oral metastases. Thus, Batson's theory may not apply to these cases and the diagnosis of metastatic oral tumor is usually the evidence of a widespread disease (8, 9).

Age at presentation is an important clinical parameter when the diagnosis of a lesion is being formulated. It has been reported that most metastatic oral tumors are found in patients in their eighth, seventh and sixth decades of life (8,13,14). In the present case, the patient was 72-year-old at the moment of the diagnosis. In the current review, there was a highest occurrence in the seventh (n=9), sixth (n=7) and fifth (n=6) decades and the mean age was 56.9 years.

The prognosis of oral metastases is generally poor, and the majority of patients did not survive more than two years after the initial diagnosis of intraoral metastatic lesion (19,31,33,34). In the present review, eighteen patients died after diagnosis of the oral metastases. Sixteen patients were followed up for an average of 5.9 months (range 1- 21 months), which represents the time period between the discovery of the oral metastases and their death; in two cases, follow-up information was not available and in four cases the patients were alive. The cause of death was widespread metastatic disease in the most of cases. Due to poor prognosis, patients should be treated in order to improve quality of life (7,9,16), and local resection, radiotherapy or chemotherapy even in a widespread disease should be performed (9). The choice of therapy is based on the location and number of metastatic lesions, tumor size and clinical condition (4,6). In the present case, according to FIGO classification, the tumor was defined as IIIb. The health status and the patient's age did not allow for resection and chemotherapy. Treatment with radiotherapy could give excellent palliation (16), thus, palliative radiotherapy was instituted for the current patient. After 18 months of the follow-up, a reduction in tumor size was detected as shown in the CT scan, as well as the improvement in the patient's symptoms and the quality of life. Unfortunately, after 24 months of follow-up, the patient of the present case died.

Early detection of metastases is very important, especially in oral metastases where prognosis is usually poor (8, 11). Though a rare finding, the possibility of presence of oral metastatic disease during the diagnosis of primary tumors involving a distant site should always be considered, because almost all types of malignancies may metastasize to the mouth (7, 10).

Clinicians should keep in mind that soft tissues' masses mimicking benign lesions may represent an initial sign of oral metastatic lesion. Additionally, a complete history and physical examination should be performed. In conclusion, the correlation of clinical medical history, laboratory, imagenological, cytological, histopathological and immunohistochemical exams were essential for achieving of the precise diagnosis of the oral metastasis.

Conflict of interest

We declare no conflicts of interest.

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