

REVIEW ARTICLE

Metastatic tumors to the jaws and oral cavity

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ABSTRACT

Cancer is a disease involving complex multiple sequential irreversible dysregulated processes showing metastasis that results in morbidity and mortality. Metastasis is a complex biological course that begins with detachment of tumor cells from the primary tumor, spreading into the distant tissues and/or organs, invading through the lymphovascular structures followed by their survival in the circulation. Metastatic tumors to the oro-facial region are uncommon and may occur in the oral soft tissues or jawbones. The clinical presentation of metastatic tumors can be variable, which may lead to erroneous diagnosis or may create diagnostic dilemma. Therefore, they should be considered in the differential diagnosis of inflammatory and reactive lesions that are common to the oral region. Most of the literature on oral metastases involves either single case reports or reviews of these reported cases from scattered geographical areas. Hence this present article is an attempt to provide a detailed review of pathogenesis, epidemiological details including clinical and radiographic presentations, microscopic features and treatment of metastatic tumors to the jaws and oral cavity.

Key words: Metastasis, metastatic tumors, primary cancers

BACKGROUND

Metastatic tumors (MT) to the oral region are uncommon, comprising only 1-3% of all malignant oral neoplasms. Metastatic lesions may occur in the oral soft tissues, in the jawbones or in both osseous and soft tissues. The common primary sources of tumors metastatic to the oral region are the breast, lung and kidney. Mandible is the most common location for metastases, with the molar area being the most frequently involved site.^[1-4] Frequently, they show non-aggressive clinical findings mimicking a reactive or benign lesions or even simple odontogenic infections.

The diagnosis of a metastatic lesion in 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] However, these tumors are of great clinical significance, as their appearance may be the first

indication of an undiscovered malignancy at a distant primary site, or the first evidence of dissemination of a known tumor from its primary site.

PATHOGENESIS

Metastasis involves sequential progression of the primary tumor towards invasion and dispersion/spreading of cancer cells through the lymphatic or blood vessels. Circulating cancer cells survive and settle in the microvasculature of the target organ and extravasate through the vessel wall. These cancer cells gain access, advance towards evident metastasis with or without an intervening period of latency. These steps are supported by functions of the cancer cells themselves or of the tumor microenvironment.^[6] 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 by the following steps.^[6,7]

- The primary tumor,
- Systemic circulation, and
- The final metastatic destination.

Further, the tumor progression depends on angiogenesis and revascularization, the formation of new blood vessels which is a must for tumor development.^[8] It is a well established fact that the growth and size of tumor is angiogenesis

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dependent. The development of the tumor vasculature is dependent on a variety of proangiogenic and antiangiogenic, inflammatory, and coagulation factors.^[9,10] Hypoxia in the tumor mass is the critical stimulus for angiogenesis in the growing tumor at initial stages. Hypoxia directs the up-regulation of few transcription factors which regulate proangiogenic signals, mainly the vascular endothelial cell growth factors (VEGFs).^[9-12] Significant data indicates that metastasis of various cancers to distant organs is a regulated, site-specific process and not a random event.^[7] Numerous studies indicate that diverse molecular pathways are involved in the lymphatic and hematogenous dissemination of several cancers. The oral region is not a preferred site for metastatic colonization and are usually the result of secondary spread from other metastatic lesions, mainly from the lungs. In such cases, tumor cells bypass the filtration of the lungs and accounts for the increased circulation to axial skeleton leading to head and neck metastasis.

However, the pathogenesis of the metastatic tumors in the jawbones is not clear. A number of primary malignancies particularly cancers from the breast, prostate, lungs and kidneys prefer bone for the metastatic process. Within the skeleton, bones with red marrow are the favored sites for metastatic deposits. In contrast, jawbones have little active marrow, mainly in elderly persons. However, remnants of hematopoietic active marrow can be detected in the posterior areas of the mandible and the hematopoietically active sites attract metastatic tumor cells. The oral soft tissues have a rich network of capillaries which can entrap malignant cells. Chronic inflammation has been linked to various steps involved in tumor genesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis.^[4] The proliferating capillaries show uneven basement membrane and the tumor cells can penetrate more easily. Hirshberg^[13] suggested that inflammation plays an important role in attracting metastatic cells to the gingiva.

Epidemiological details

Metastatic tumors to the oro-facial region are uncommon and account for approximately 1-1.5% of all malignant oral tumors.^[14] Most metastatic tumors to the oro-facial region are seen in patients aged between 40-70 years. In younger patients, metastases is common in jaw bones compared to soft tissues. There was almost equal gender distribution in jawbone metastases and a male to female ratio of 2:1 in oral soft tissues. The nature of primary tumor and the site of metastases within the oral cavity differ between the sexes.^[15-17] The most common sources of metastatic tumors to the oral region are primary cancers from the lung, breast, kidney and bone. The breast is the most common primary site for tumors that metastasize to the jawbones, whereas the lung is the most common source for cancers that metastasize to the oral soft tissues. 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 tissues site.^[16]

The most common primary tumor in male patients is from the lungs and is followed by kidneys, prostate, liver, bone, thyroid and skin.^[18,19] In female patients, the most common primary cancers are those in the breasts and less frequently from the female genital organs, bone and kidneys.^[13,16,20]

Clinical presentation

Oral metastasis is considered as a late complication and frequently associated with multiple organ metastases. Oral metastases can grow rapidly causing pain, difficulty in chewing, dysphagia, disfigurement and intermittent bleeding, leading to poor quality of life.

The clinical presentation of metastatic tumors can be variable, which may lead to erroneous diagnosis or may create diagnostic dilemma.^[1] Presence of teeth seems to be an important determinant on oral site preference for metastases. In the soft tissues, the attached gingiva is the most frequently involved site preceded by the tongue.^[20] In the early stages, gingival metastases resemble hyperplastic or reactive lesions such as pyogenic granuloma, peripheral giant cell granuloma, fibrous epulis and periodontal abscesses.^[21,22] Gingival metastases are shown to be polypoid or exophytic, highly vascularized, and hemorrhagic.^[23]

The metastatic lesion in other locations of the oral soft tissues manifests as a sub-mucosal mass particularly in the tongue with few cases presenting as ulcers.^[16] With the progression of the disease, oral metastatic lesions, especially those located in the soft tissues, cause progressive discomfort. Pain, bleeding, superinfection, dysphagia, interference with mastication, and disfigurement are some of the main complaints of patients. In the edentulous patients, metastatic lesions are spread evenly between the tongue and alveolar mucosa. In the jaws, the mandibular molar area is the most common location of the metastatic lesion. The clinical manifestations of the metastatic lesions include a bony swelling with tenderness, pain, ulcer, hemorrhage, paresthesia, and pathological fracture.^[16,24] Sometimes, tooth mobility and trismus are also present. Paresthesia in the mandibular metastasis is reported to be located in the area innervated by the mandibular alveolar dental nerve.^[25]

In some cases, metastases are discovered after a recent dental extraction at the site. Analysis of the literature by Hirshberg revealed 56 cases in which tooth extraction preceded the discovery of the metastases. In many of these cases the metastatic tumor was assumed to be present in the area before extraction. A soft tissue mass extruding from a recent extraction wound accompanied by pain are the main symptoms. In many of these cases the metastatic tumor is present in the area before

the extraction causing pain, swelling and loosening of teeth. These symptoms lead the clinician to extract the affected tooth. However, in some cases, metastasis probably develops after extraction. Tooth extraction can serve as a promoting factor in the metastatic process.^[15,16,20,26,27] Metastatic lesions may mimic odontogenic infections and other disease conditions leading to late diagnosis by the unwary clinician. However, in 24% of patients, the metastatic lesion in the oro-facial region may be the first indication of an undiscovered malignancy at a distant site.^[20,27]

Patient complaining of numb chin or mental nerve neuropathy should always raise the possibility of a metastatic disease in the mandible, signifies deep invasion of the tumor into the bone and involvement of the inferior dental or mental nerves. These features when seen in a patient with a known malignancy, it is termed as 'mental nerve neuropathy' or the "numb chin syndrome".^[4,28-30]

Radiological findings

Metastatic tumors do not possess a pathognomonic radiographic appearance.^[31] Radiographic findings in metastatic tumors to the jaw may range from the absence of any manifestation to a lytic or opaque lesion with ill-defined margins. In general, the balance between osteoblastic and osteoclastic activity determines the phenotype of metastatic bone lesions. Metastases from prostate cancer nearly always form osteoblastic lesions in bone. In contrast, bone metastases from kidney, lung, or breast cancers are more often osteolytic.^[32-34] Sometimes, they may also occur as a solitary radiolucency of the jawbone which may simulate an infected cyst or osteomyelitis. The entire mandible may also have a moth-eaten appearance.^[35,36] The cortical bone of adjacent structures such as the mandibular canal, maxillary sinus and nasal floor is resorbed. Extension through the cortical plate of the jaws may stimulate a spiculated periosteal reaction.^[37]

Histological findings

The diagnosis of metastatic tumors in the oral region is difficult due to their rare occurrence. Jaw lesions more commonly present with a known or previously treated primary. An intraoral incisional biopsy and histopathologic examination is the means to confirm and identify a malignant tumor and potentially its metastatic origin.

The pathologist may not provide an exact diagnosis, since metastatic lesion does not represent a single disease and histological appearance is variable. If any history of a previous tumor exists; the microscopic findings of the metastatic lesion should be compared with that of the primary tumor. Usually a distinction of a metastatic tumor from a primary malignancy can be made. In some cases, special staining, immunohistochemical procedure, and electron microscopy may be performed to identify the nature of primary tumor.^[27,28,38]

Once a metastatic tumor is suspected an appropriate referral for an oncologic work up is required. Advanced imaging, scintigraphy and regional investigations based on the suspected source should be done to find out or confirm the origin and identify any other areas of secondary spread.

Treatment and prognosis

The treatment and prognosis is primarily based on the site of origin and the degree of metastatic spread.^[28] Unfortunately, the identification of a metastatic tumor usually represents a poor overall prognosis. The time from the appearance of the metastasis to death is several months. If the primary tumor was successfully treated and the patient's medical condition permits, the metastatic lesion should be aggressively treated. Management may involve surgical resection, radiation, chemotherapy or a combination of these techniques. If the primary is recurrent or there are widespread metastases, the jaw lesion should be managed conservatively. This goal of palliative treatment is to reduce the patient's pain and preserve oral function. This may involve reducing the size of the tumor through radiotherapy, chemotherapy or local surgical excision.^[39] Oral metastases usually are evidence of a widespread disease and indicate a grave prognosis.

SUMMARY

Metastases in the mouth are extremely rare, comprising 1% of all malignant mouth neoplasms. They are located in the mandible in 80 to 90% of cases; maxillary metastases are less common. Many types of primary malignancies can produce oral metastases; the most of these tumors are located in breast, prostate, lungs, thyroid gland and kidneys; these primary tumors give rise to most bone metastases.^[24]

Metastasis to jaw bone, although rare, is a possible cause of jaw swelling. Age and sex can provide important clue to possible location of primary lesion. Most metastatic jaw lesions involve one oral site, and only a few occur in two or three sites. There are variations in the predominant primary sites across the globe, giving rise to jaw metastases.^[40] Because of its rarity, the diagnosis of metastatic lesions in the oral cavity is very often missed. Besides, it may simulate a benign process.^[41] Metastasis to the jaw bone occurs due to hematogenous route of the spread of malignant tumor and this requires the presence of hematopoietically active bone marrow well connected with sinusoidal vascular spaces at the site of deposition of malignant cells. The posterior mandible and focal osteoporotic bone marrow defects in the edentulous mandible have been shown to be the hematopoietically active sites that may attract metastatic tumor cells.^[42-45] Though both bone and soft tissues of the oral and maxillofacial region share a common blood-supply, a different tissue environment exists. A hypothesis by Fidler says that metastatic tumor cells select a favorable environment to anchor and proliferate creating an individual tissue/organ specificity of cancer metastasis.

The 'seed-soil' theory proposed by Paget is accepted as the basic mechanism for cancer metastasis. Many studies have proved the 'seed-soil theory' 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.^[46,47]

Sometimes, metastatic lesions to jaws may show vague pain and misdiagnosed as pathologic entities of dental origin such as pulp/periapical disease.^[48] Recently, a case of a metastatic breast carcinoma mimicking as periodontal abscess in the mandible has been reported.^[49] In few cases tooth extraction preceded the discovery of the metastasis. The role of trauma to the oral mucosa, especially from ill-fitting dentures, sharp tooth or restorations, poor oral hygiene and tooth extraction trauma, in the causation of oral metastasis needs further investigation.^[50] So, diligent clinical and histopathological investigations and the use of immunohistochemical techniques are utilized to diagnose the metastatic lesion and its origin. However, it is important to note that majority of the jaw bone metastasis have a high tendency to go undetected. Sometimes, the discovery of an oral metastasis leads to the detection of an occult primary malignancy elsewhere in the body. Majority of the cases have micrometastasis and hence have poor prognosis. Terminal stage of the disease leads to loss of follow-up or in some instances mortality of the patients.

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, combination chemotherapy to alleviate the symptoms is the only preferred therapeutic modality.^[41] Hence, careful clinical and histopathological assessment lead to definitive diagnosis of the metastatic lesion and its origin.

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