



AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: <http://www.ajptr.com/>

Metastatic Tumors to Jaw Bone and Oral Cavity- A Bird View

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ABSTRACT

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 account for approximately 1- 1.5% of all malignant oral tumors. Metastatic lesions can be found anywhere in the oral cavity, however, the jawbones with the molar area is the most frequently involved site. In the oral soft tissues, the gingival is the most common site, suggesting the possible role of inflammation in the attraction of metastatic deposits. Metastatic carcinomas in oral region can be the first clinical manifestation of an undiagnosed primary systemic tumor. The symptoms of metastatic carcinoma depend on the location of the tumor and 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 case reports; 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 jaw bones and oral cavity.

Key words: metastatic tumors, jawbones, oral soft tissue.

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Received 03 August 2018, Accepted 29 August 2018

Please cite this article as: Kamala KA *et al.*, Metastatic Tumors to Jaw Bone and Oral Cavity- A Bird View. American Journal of PharmTech Research 2018.

INTRODUCTION

Cancer is a disease involving complex multiple sequential irreversible dysregulated processes includes sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis, that results in morbidity and mortality.^{1,2}

Metastasis begins with detachment of tumor cells from the primary tumor, spreading into the distant tissues and/or organs, invading through the lymphatic or blood vessels followed by their survival in the circulation.² Metastatic tumors to the oro- facial region are uncommon and account for approximately 1- 1.5% of all malignant oral tumors. 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.³

Pathophysiology

The metastatic process is complex process and involves several sequential steps. Tumor cells must detach from the primary tumor, spread in the tissues, invade blood vessels, and survive their travel in the circulation. Then, the metastatic cells settle in the microvasculature of the target organ, extravasate through the vessel wall, and proliferate within the recipient tissue.^{4,5}

The most basic feature is cell movement away from the primary tumor through the extracellular matrix (ECM). Cell motility involves remodeling of the cytoskeleton, cell-matrix interactions, localized proteolysis, actin-myosin contractions which leads to the loss of cell-to –cell contacts and the gain of cell motility. This is achieved via a process known as epithelial-to-mesenchymal transition (EMT). The EMT program dissociates the cells within epithelial cell sheets into individual cells that exhibit multiple mesenchymal attributes. Extrinsic factors in the tumor microenvironment can promote the motility of cancer cells.⁶ Direct invasion by carcinoma cells of the stromal compartment involves active proteolysis effected principally by matrix metalloproteinases (MMPs), while degrading the basement membrane and other ECM that lie in the path of invading tumor cells, MMP-expressing cells also liberate growth factors that are sequestered there, thereby fostering cancer cell proliferation.⁷

Tumor progression depends on the formation of new blood vessels (angiogenesis) and is a prerequisite for tumor outgrowth.⁸ The development of the tumor vasculature is dependent on the homeostatic balance between a variety of proangiogenic and antiangiogenic (vascular endothelial growth factor (VEGF) and thrombospondin, respectively), inflammatory, and coagulation factors.^{9,10} The critical initial stimulus for angiogenesis is hypoxia in the growing tumor. Hypoxia

leads to the up-regulation of hypoxia-induced transcription factors (HIF)- α and HIF-2 α , which are the master regulators of proangiogenic signals, mainly VEGFs. The new blood vessels formed are largely immature leaky and tortuous, allowing tumor cells to intravasate easily into the vasculature.⁷⁻¹⁰

Pathogenesis of the metastatic process in the jawbones is not clear. In the skeleton, bones with red marrow are the preferred sites for metastatic deposits.¹¹ Hematopoietically active marrow represent an attractive site of metastatic involvement because the vascular space are sinusoidal in nature and present a relatively easy barrier for tumor cells to penetrate.¹² Jawbones have little active marrow, especially in elderly persons; however, remnants of hematopoietic active marrow can be detected in the posterior areas of the mandible, especially in cases of focal osteoporotic bone marrow defects. These hematopoietically active sites may attract metastatic tumor cells.³ Expression of CXCR4 chemokine receptor and its ligand are known to be involved in cancer metastasis and is highly expressed in bone marrow.¹³ In addition marrow contains growth factors which may enhance colonization of some metastatic tumors.¹² Hasimoto *et al*¹⁴, from a study of autopsy cases, suggested that hematopoietic areas in the mandible favor the early deposition of tumor cells.

In the oral soft tissues, the gingiva is the most common site for metastases with strong association to the presence of teeth. The rich capillary network of chronically inflamed gingiva can entrap malignant cells. The proliferating capillaries have a fragmented basement membrane through which tumor cells can more easily penetrate. The inflammatory environment present in the gingiva may provide a permissive niche for metastatic cells, allowing them to perform the essential tasks of angiogenesis, formation of supportive stroma, and immune evasion. The same pathogenesis can be attributed to metastatic deposits in post extraction sites.^{3,15} Soluble cytokines such as IL-1 and TNF- α which are present in the chronically inflamed gingival are known to facilitate metastatic progression by stimulating angiogenesis and accelerating the generation of ECM necessary for tumor stroma and also may attract or induce the tumor associated macrophages.¹⁶⁻¹⁸

Epidemiological Details

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.¹⁹ For men, the most common primary sites are the lung, kidney, liver, and prostate, and for women the breast, female genital organs, kidney, and colo-rectum.¹

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 (table 1 and

2). A recent literature review showed that the jawbones, particularly the mandible were more frequently affected than the oral soft tissues at a ratio of 2:1.¹⁹

Table 1 Percentage of origin of metastasis to oral mucosa and jaw bone in males.³

Gender	Metastasis to oral mucosa	%	Metastasis to Jaw bones	%
Male	Lung	31	Lung	25
	Kidney	14	Kidney	10.8
	Skin	12	Liver	8.6
	Liver	7.5	Prostate	7.5
	Colorectum	5.2	Bone	7.5
	Bone	5.2	Adrenal gland	5.3
	Testis	4.5	Colorectum	4.7
	Esophagus	4.5	Testis	4.4
	Stomach	3.7	Esophagus	3.6
	Rare tumors	12.4	Stomach	2.5
			Bladder	2.5
Rare tumors			17.6	

Table 2. Percentage of origin of metastasis to oral mucosa and jaw bone in females.³

Gender	Metastasis to oral mucosa	%	Metastasis to Jaw bones	%
Female	Beast	24	Beast	36
	Genital organ	14.8	Genital organ	9.5
	Kidney	12	Kidney	8.5
	Lung	9.4	Colorectum	7.1
	Bone	9.4	Bone	6.7
	Skin	6.8	Adrenal gland	5.8
	Colorectum	6.8	Thyroid	5.4
	Rare tumors	16.8	Rare tumors	20.4

In the jawbones, the mandible was more frequently involved than the maxilla, with the molar area being the most frequent site (50%) followed by the premolar area (38%) and the angle-ramus (29%).^{12, 15 20} In the oral soft tissues the attached gingiva is the most commonly affected site (60%) followed by the tongue (18%).^{20,21} The gingiva is the most common site for metastatic colonization to oral mucosa.^{13,22} In about 54% cases, the attached gingiva was the most commonly affected in the oral soft tissues site.¹⁹

Clinical Presentation

A rapidly progressing swelling accompanied by pain and paraesthesia are the classic symptoms of a metastatic tumor in the jawbones. Symptoms may vary according to location: for example, trismus in lesions located in the condyle and symptoms related to the sinus and exophthalmos in maxillary lesions. Mental nerve neuropathy or the so-called the “numb chin syndrome” is the consequence of loss of function of the terminal sensory division of the mandibular branch of the trigeminal nerve.^{1,3,4} Any pathological process involving the mental nerve, the mandibular nerve,

and even the mandibular trunk of the fifth nerve may produce this loss of function. The appearance of a mental nerve neuropathy should always raise the possibility of a metastatic disease in the mandible.²³ Similar symptoms can be the result of odontogenic infection, trauma, benign odontogenic tumors, systemic diseases such as amyloidosis, sarcoidosis multiple sclerosis or as neurological manifestation of a non-metastatic malignancy. In most cases, the physical examination reveals a bony swelling with tenderness over the affected area.^{24, 25}

In oral soft tissue gingival is the most frequently involved site preceded by tongue. An exophytic, highly vascularized and hemorrhagic, sometimes ulcerated lesion is the most common clinical presentation of metastatic lesions in the oral soft tissues. Early lesions, mainly those located in the gingiva may resemble a hyperplastic or reactive lesion, such as pyogenic granuloma, peripheral giant cell granuloma, fibrous epulis and periodontal abscess.¹³ With the progression of the disease, oral metastatic lesions, especially those located in the soft tissues, may cause progressive discomfort, pain, bleeding, super-infection, dysphasia, interference with mastication, and disfigurement.^{13,15} In some cases, especially those of metastatic hepatocellular carcinoma, severe post-biopsy hemorrhagic episodes had been reported.^{19, 26}

Radiographic Features

An oral radiography survey (periapical and panoramic radiographs), use of technetium -99 m-phosphonate bone sintigraphy, CT scans, and MRIs can be obtained to evaluate the extent of the metastatic process to the jaw bones may be helpful. The most common radiographic presentation is that of a lytic lesion with ill-defined margins and occasionally osteoblastic lesions are observed.²⁷ Prostate and breast tumors are often associated with radiopaque metastatic lesions. The areas appear as patchy sclerosis due to new bone formation, arising from the stimulation of surrounding normal bone. In contrast, bone metastases from kidney, lung, or breast cancers are more often osteolytic.^{28,29}

Mandible is most commonly affected followed by maxillary sinus, anterior hard palate and mandibular condyle. 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.^{30,31} 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.^{19, 32}

Multiple myeloma may be confused with metastatic tumors; however, the border of multiple myeloma is usually better defined than in metastatic disease. When a lesion starts within the periodontal ligament space of a tooth, the appearance may be identical to that of a periapical

inflammatory lesion. A point of differentiation is that the periodontal ligament space widening from inflammation is at its greatest width and centered about the apex of the root. In contrast, the malignant tumor usually causes irregular widening, which may extend up the side of the root. An odontogenic cyst, if secondarily infected, may have an ill-defined border, giving a similar appearance to a metastatic lesion. Invasion of the jaws by primary tumors of the overlying epithelium such as squamous cell carcinoma may be indistinguishable from metastatic disease but can be differentiated by clinical examination.³³

Investigations

A details of investigatory procedures listed in table 3 and 4 and standardized workup for malignancy of undefined primary origin has been described by Amela et al.³⁴ 1. Extensive physical exam (including head and neck, rectal and pelvic examination); Basic blood and biochemistry survey; CT-scan of chest, abdomen, and pelvis; a-fetal-protein and b-HCG in both sexes; Prostate specific antigen in men; Mammography in women. 2. Oriented workup: Breast MRI for women with inaugural axillary lymph nodes; [18F] fluoro-2-deoxy-Dglucose positron emission tomography; Symptom oriented endoscopies. 3. Histopathological evaluation: Immunohistochemical analysis.¹ 4. Deregulated bone metabolism is associated with the release of biochemical markers amenable to noninvasive measurement in blood or urine. Examples are the amino [N]- and carboxy [C]-terminal cross-linked telopeptides of type I collagen, or NTX and CTX, which reflect osteolysis and the bone-specific alkaline phosphatase (BSAP) levels in serum reflecting the rates of osteogenesis.^{1, 35}

Table 3 Investigatory procedures to be followed in metastatic tumors.^{3, 34}

S.No	Tests	Details of tests
1	Review the clinical history	<ul style="list-style-type: none"> a. Physical exam (including head and neck, rectal and pelvic examination) b. If history of previous tumors exists, obtain the slides nad reports for review
2	Complete blood cell count	
3	Liver function test	<ul style="list-style-type: none"> a. Including calcium level b. Serum creatinine value
4	Imaging studies	<ul style="list-style-type: none"> a. Periapical And Panoramic Radiographs b. Chest Radiographs c. CT Scans of chest, pelvis and abdomen d. MRI Scans (breast MRI for women with inaugural axillary lymph nodes) e. Bone Scintigraphy f. Ultrasound For Male Patients g. Mammography For Female Patients h. Positron electron transmission scanning with

		fluorodeoxyglucose- to identify primary tumor
5	Cervical papanicola smear	for female patient
6	a-fetal-protein and b-HCG in both sexes	
7	Serum prostate specific antigen and transaminase	for male patients
8	Symptom oriented endoscopies.	
9	Detection of biochemical markers	Deregulated bone metabolism is associated with the release of biochemical markers like <ol style="list-style-type: none"> amino [N]- and carboxy [C]-terminal cross-linked telopeptides of type I collagen, NTX and CTX, which reflect osteolysis Bone-specific alkaline phosphatase (BSAP) levels in serum reflecting the rates of osteogenesis.
10	Perform biopsy of the lesion	<ol style="list-style-type: none"> Evaluate the light microscopic features of neoplasm Histological staining Immunohistochemical tests Electronic microscopy

Table 4 Immunohistochemical markers used to diagnose the most common malignancies metastasizing to the jaws and mouth.^{1,3,34,38, 39}

S.No	Origin	CK7/CK20	Additional markers
1	Breast	7+/20-	ER/PR, GCDFP-15, Mammaglobin
2	FGO	7+/20-	PAX8, WT-1
3	Prostate	7-/20-	PSA, PSAPa, Prostein, PSMA, NKX3.1, AMACR, Cam 5.2?/CK903-
4	Lung	7+/20-	TTF-1 (adenocarcinoma),nNaspin A, Surfactant
5	Thyroid (papillaryand follicular)	7+/20-	TTF-1, Thyroglobulin, PAX8
6	Thyroid medullary	7+/20-	TTF-1, Calcitonin
7	Kidney	7-/20-	EMA, PAX2, PAX8, CAIX, RCC, CD10, Vimentin
8	Bladder	7+/20-	P63, Thrombomodulin (not specific), Uroplakin, GATA3
9	Colorectal	7-/20+	CEA, CDX2,Villin, SATB2
10	Liver	7-/20-	Hep-Par1, canalicular CD10, Bile duct specific CEA, aFP,
11	Adrenal	7-/20-	Inhibin, MelanA, negative AE1
12	Squamous cell carcinoma	7b-/20-	P63

FGO-Female genital organ

^bCK7 positive in cervical carcinoma

Treatment and Prognosis

The treatment and prognosis is primarily based on the site of origin and the degree of metastatic spread.³⁶ 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.³⁷ Oral metastases usually are evidence of a widespread disease and indicate a grave prognosis.¹⁹

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