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Metastatic Tumors of the Oral Region: A Review.

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ABSTRACT

Metastatic tumors of the oral region constitute a rare entity with very few reported cases and exhibiting symptoms that may mimic common dental and periodontal infections and benign lesions and are often diagnosed at an advanced stage of disease leading to a poor and unfavorable prognosis. This article seeks to review existing literature regarding the metastatic lesions in order to increase awareness of the occurrence in order to help in early detection, diagnosis and better prognosis.

Keywords: Metastasis, jaw tumors, malignancy, oral region.

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INTRODUCTION

Neoplasms of the oral region may be of varied origin and presentation and among malignant neoplasms, metastases constitute a very small percentage [1%]. Such metastases may be either in the soft tissues or bone. A majority of them occur in the mandible and the most common locations from which they metastasize, are the breast, lung, thyroid, prostate and the kidneys. A majority of metastatic tumors to the oral soft tissues are found in the attached gingiva in case of dentulous patients, whereas in edentulous patients they are equally distributed between the tongue and alveolar mucosa. Neuroblastoma of adrenal gland is the most common primary site in the first decade of life with bone malignancies being the most common primary site in the second decade [1]. Autopsy studies have shown that two thirds of breast carcinomas, half of prostate carcinomas, and a third of lung and kidney carcinomas spread to one or more bones before proving fatal.

Carcinomas to the jaws usually spread by the hematogenous route whereas sarcomas arising in soft tissues and bones rarely metastasize to the jaws. Primary malignancies from the adjacent tissues may spread by a lymphatic route which may not be the case for tumors from lower parts of the body, which tend to disseminate through blood and should be filtered out by the lungs. One possible explanation may be, *Batson's plexus*, a valveless vertebral venous plexus that might allow retrograde spread of tumor cells, bypassing filtration through the lungs [2].

Pathogenesis

Metastasis is not a random process but involves specific events that include tumor cell detachment from the primary site, surrounding tissue invasion, intravasation, transport to the site of metastasis, extravasation and either bone degradation or bone formation. Prognosis of the primary growth has been shown to correlate with loss of cellular cohesion and detachment of neoplastic cells from the primary site at the advancing front of oral squamous cell carcinoma. Poor prognosis has correlated with loss of E-cadherin [transmembrane glycoproteins] and β -catenin. Migration of neoplastic cells from the tumor primary as well as the metastatic site requires tumor cell motility. The factors which enhance tumor cell motility include cytokines such as autotoxin and hepatocyte growth factor and also other extracellular matrix proteins such as laminin, fibronectin and collagen IV. Cell-matrix interactions are mediated by a class of receptors called Integrins. Local invasion and movement in and out of the vascular tree is facilitated by tumor cell adhesion to integrins. The bone-homing capacity of tumor cells and ability to invade is enhanced through mediation by integrin receptors of adhesive interaction between tumor cells and bone. Capability of producing enzymes influences the ability of tumor cells to breach extracellular matrix. The most studied enzyme systems are metalloproteinases [MP] and the urokinase plasminogen activator system [uPA]. Tumor progression in bone is linked to MPs according to available literature [3].

Adherence of tumor cells to endothelium is facilitated by certain members of the immunoglobulin and selectin families. Tumor cell mobility is enhanced by chemotactic factors released by endothelial cells. The bone-homing characteristics of multiple myeloma and prostate carcinoma cell lines may be influenced by expression of CD44 and VLA-4 by bone marrow endothelium. Both these malignancies have an affinity for bone [3].

The interaction between bone microenvironment and tumor cells may result in osteolytic or osteoblastic metastasis. Most malignancies are characterized by osteolytic metastases. The ability of tumor cells to stimulate bone resorption is emphasized by their close proximity to bone resorbing cells. This process may be through either direct cell to cell contact or by release of soluble mediators which may cause differentiation of osteoclast precursors or through activation of osteoclasts themselves. The microenvironment may be enriched by bone derived growth factors that enhance tumor survival during bone resorption. Osteolytic metastasis is generally associated with pathologic fractures, displacement of hematologic precursor cells and hypercalcemia. Parathyroid hormone-related protein [PTHrP] and TGF- β are the most studied chemical mediators of bone resorption. Several studies have shown a relation between PTHrP and development of bone metastasis and hypercalcemia. Hodgkin's lymphoma patients show detectable levels of plasma PTHrP concentration. Hypercalcemia of malignancy differs from that secondary to hyperparathyroidism in that there is an increase of both osteoblasts and osteoclasts in hyperparathyroidism whereas in patients with hypercalcemia of malignancy there is an increase of osteoclasts only.

Bisphosphonates are used as an antiresorptive agent for the treatment of hypercalcemia due to malignancy by selectively inhibiting osteoclasts. The suppression of bone remodeling by bisphosphonates which may cause extensive bony sequestration in Osteomyelitis [3].

TGF- β which is expressed by differentiated osteoblasts and osteoclasts, induces PTHrP activity, acts as chemoattractant for breast carcinoma cells and may either inhibit or promote growth of neoplastic cell lines. IGF-I [insulin-like growth factor], IGF-II, fibroblast growth factors 1 & 2, bone morphogenetic protein [BMP] and platelet-derived growth factor are also present in mineralized bone matrix and released during breakdown of bone [3].

Osteoblastic metastases which may appear radiodense on the radiograph may be caused by neoplastic cells in bone and are characterised microscopically by bone formation. This is typical in carcinoma of the prostate and may cause hypocalcemia. Pathologic fractures may occur due to the low strength of the newly formed bone. The factors implicated in this process include TGF- β , IGF-I & II, PSA [prostate specific antigen], FGF-I & II, BMP and ET-I [endothelin] [3].

Clinical features

Individuals affected by metastatic carcinoma are usually in the older age groups, mostly between the fifth and seventh decades with an average age of 45 years [4]. Patients with metastases to the jawbones are younger than those with metastases to the oral soft tissues. Oral soft tissue metastases are most commonly seen in the gingiva [50%] followed by the tongue[25%]². The lesion may be a nodular mass resembling a reactive growth or a surface ulceration [2]. Underlying destruction of alveolar bone may cause loosening of adjacent teeth. Malignant cells, on reaching the oral cavity may take advantage of the rich vascular network of inflamed gingival tissues for further growth [2].

Lung cancer is responsible for more than one third of all oral soft tissue metastases in men followed by renal carcinoma and melanoma. Metastases from prostate cancer have an affinity for bone². In women, breast cancer causes 25% of all metastases, followed by malignancies of genital organs, lung bone and kidney. Even though the primary tumor is known in most cases when the metastatic lesion is discovered, it may be the first sign of malignant disease in a few cases [2].

Table 1: Metastatic tumors to the oral region in men [1]

Metastatic site and origin	Percentage
Oral Mucosa	
Lung	35
Kidney	16
Skin	15
Liver	7
Colorectum	5.5
Testis	5.5
Bone	3
Stomach	3
Rare tumors	10
Jawbones	
Lung	22
Prostate	12
Kidney	10
Bone	9
Adrenal Gland	9
Liver	7
Testis	5.5
Colorectum	4
Rare tumors	21.5

Metastases to the maxilla are rare with 80% of reported instances occurring in the mandible. Within the jaw, the premolar-molar region, the angle and the body of the mandible are more commonly involved. Metastatic lesions of the jaw may be completely asymptomatic. Bone pain, loosening of teeth, lip paresthesia, bone swelling, gingival mass and pathologic fracture may be evident [1]. *Numb-chin syndrome* is caused by

mandibular metastasis with involvement of inferior alveolar nerve producing a distinctive pattern of anesthesia in which there is an unexplained loss of sensation of the lower lip and chin. These symptoms may also be associated with primary inflammatory or neoplastic diseases of the jaws. In some cases the patient may be completely asymptomatic and the lesion may be discovered on radiographic examination. Rarely, an osseous metastasis may be discovered at a nonhealing extraction site from which the tooth was recently removed due to complaints of local pain or mobility.

Table 2: Metastatic tumors to the oral region in women [1]

Metastatic site and origin	Percentage
Oral Mucosa	
Breast	24
Genital organs	17
Lung	12
Kidney	10
Bone	10
Skin	7
Rare tumors	20
Jawbones	
Breast	42
Adrenal gland	8.5
Colorectum	8
Kidney	6
Bone	6
Thyroid	6
Rare tumors	23.5

Radiographic features

Metastatic deposits in the jaws appear as radiolucent defects [4]. Most jaw metastases show poor margins on the radiograph with a ‘moth-eaten’ appearance and are radiolucent while some tumors may be radiopaque [4]. Sometimes a metastatic tumor may cause widening of the periodontal ligament. Some carcinomas, particularly from the prostate and breast, may stimulate new bone formation resulting in radiopaque or mixed radiolucent and radiopaque lesions.

Patients with gnathic metastases may have symptoms at a time when conventional radiographs fail to demonstrate detectable alterations. Bone scintigraphy is used in such instances because it has a higher sensitivity and a greater ability to detect subtle osseous metastases.

Histopathologic features

The lesion, in case of soft tissue metastases resembles the tumor of origin, most cases are carcinomas with metastatic sarcomas being rare [2]. It can be variable, reflecting the tumor type and grade of tumor differentiation. Metastatic carcinomas are poorly differentiated and histopathologic study gives little clue as to the primary site of tumor. A prominent desmoplastic stromal response may be present. Poorly differentiated metastatic carcinoma may be difficult to differentiate from anaplastic small cell sarcomas, malignant lymphomas and malignant melanoma. The diagnosis can be verified with an immunoperoxidase stain for cytokeratin, which is present in all carcinoma cells [4]. Although microscopic examination can usually determine diagnosis of metastatic carcinoma, final diagnosis depends on medical history and complete physical examination, with appropriate laboratory studies [4].

Prognosis

Generalized skeletal metastases are usually an ominous event and the prognosis for patients with metastatic carcinoma of the jaws is poor because, by definition, osseous metastasis automatically places the patient in stage IV disease. Jaw involvement is almost always associated with widely disseminated disease. Five year survival after detection of metastatic carcinoma involving the jaws is exceedingly rare, with a majority of patients dying within a year.

Review of Literature

John Horton et al in 1973 state that numbness of the chin, a rare neurological symptom was observed in 15 patients with malignancy. They suggest that metastases to the mandible may be implicated [5]. Piergiuseppe Colombo et al in 2005 reported a case of oral soft tissue metastasis from gastric cancer. They state that it may resemble a benign lesion and that oral soft tissue and hard palate metastases should be included in the differential diagnosis of ulcerative oral cavity lesions as they may be the first sign of an undiscovered malignancy [6].

Lipa Bodner, Netta Sion-Vardy, David B Geffen & Michael Nash in 2006 reported 8 cases with metastases to the jaws. They found that the mandible was most commonly involved and that paresthesia of lower lip and chin is an ominous sign for patients with jaw bone metastases [7]. Daniel Reyes Court, Susana Encina & Irene Levy in 2007 reported a case of mandibular metastases from prostatic adenocarcinoma. They stated that the most common sign is paresthesia of the area innervated by the mandibular alveolar dental nerve [8].

Tamiolakis D et al in 2007 in their retrospective study of four cases found a majority of metastases in the mandible. They reported oral symptoms similar to odontogenic infections or benign neoplasms causing delayed diagnosis and treatment. They advocated a high degree of clinical suspicion to ensure early multidisciplinary care [9]. Antonio Azoubel Antunes and Antonio Pessoa Antunes in 2008, in their retrospective study over a period of 20 years stated that metastatic tumors, while rare, may occur at any age and either in the maxilla or mandible. They concluded that the most common sites from which distance metastases in the jaws are found happen to be the thyroid and prostate and that adenocarcinoma is the most common histological type causing such metastases [10].

Erhan Aslan, Kayhan Kuzeyli, Ertugrul Cakir & Abdulkadir Reis in 2008 reported of a uterine leiomyosarcoma with temporalis muscle metastasis. They report that distant metastases are usually associated with a poor prognosis [11]. Ana Claudia Amorim Gomes et al in 2009 reported a case of metastatic carcinoma involving the condyle and mandible and also involving other bones of the body. The authors state that the exact location of the primary tumor is often difficult, even impossible to identify [12].

Rohit B Moharil, Shubhangi Khandekar and Alka Dive in 2010 reported a case of metastatic lesion to the oral cavity and brain with primary tumor which was diagnosed as undifferentiated epithelial malignancy of lung. They state that metastases to the oral region have vague symptoms, mimic dental infections, generally show poorly differentiated histopathologic picture and have poor prognosis [13]. Beena VT, Swagatika Panda, Heera R and Rajeev R in 2011 reported a rare case of multiple secondary tumors in the attached gingiva. They state that these metastases resemble benign lesions and may often be misdiagnosed [14].

Evmenios Poulas, Ioannis Melakopoulos and Konstantinos Tosios in 2011 reported a case of metastatic carcinoma of the breast in a 55 year old woman. The authors state that a high degree of suspicion should be maintained while evaluating patients with a history of cancer. They state that paresthesia of the lower lip and chin are ominous signs of metastatic disease [15]. Fu-gui Zhang et al in 2011 reported of a case with mandibular metastasis from the lung. They state that breast, lung, kidney, prostate and thyroid are the most common sites from which jaw bone metastases are noticed [16].

Muttagi SS et al in 2011 conducted a study over a period of five years and found that jaw bone metastases are rare and may often be the first site of metastasis. They also state that these metastases are usually associated with a poor prognosis [17]. Kyu Seob Lee et al in 2012 reported a rare case of metastasis to the oral mucosa with no bone involvement, which is more common, that originated from transitional cell carcinoma of the urinary bladder and rapidly progressed [18].

DISCUSSION

Malignant bone neoplasms cause morphological, functional and esthetic alterations due to their progression & local and regional involvement [10]. Metastatic tumors are more common in the jaws compared to oral soft tissues and are more often seen between the fifth and seventh decade [12]. The presence of red marrow in the mandible makes it more prone to metastases compared to the maxilla [9]. A common site for

development of metastasis in the molar area of the mandible is explained by the presence of hematopoietic areas in the mandible [8]. The soft tissues commonly involved are the gingival, tongue, lips and buccal mucosa⁶. Soft tissue metastases of the oral cavity resemble common dental infections and may mimic lesions such as granulomas, epulis and odontogenic infections [19]. The lungs, kidney and prostate are the most common primary sites for metastases to the jaws in men whereas in women the common primary sites are the breast, genital organs and kidneys [12]. The lungs are the most common primary sites for metastases to the oral soft tissues, whereas the breasts are commonly involved in oral soft tissue metastases in women [18]. The histologic origin of these tumors may be from odontogenic tissue, skeletogenic connective tissue or from non-odontogenic and non-skeletogenic tissue [10]. Homeostatic factors promoting tumor growth influence the potential of a metastatic tumor cell [16]. A prominent symptom of metastatic disease of the jaws is the presence of a rapid swelling [17, 20], lower lip and chin paresthesia, which has been described as mental nerve neuropathy or numb chin syndrome [15]. Radiographic features of bone metastasis shows bone destruction with areas of bone formation within or adjacent to the lesion and it may resemble osteomyelitis [21]. The criteria for diagnosing a malignant jaw tumor as a metastatic tumor are [13]:

- Verification by histology.
- The metastatic tumor should not be from a site common to primary oral tumors.
- Exclusion of any chance of direct spread from primary oral tumor.
- Analysis by genetic means-cytogenetic similarities between primary tumor and metastatic lesion.

The prognosis of these tumors is generally poor due to aggressive pathophysiology of primary tumor and also advanced stage of the disease when metastases occur [10]. The paucity of reported cases of metastases to the jaws may be explained by [22]:

- Lack of symptoms.
- Skeletal surveys excluding maxilla and mandible.
- Failing to examine jaws during autopsy.

Metastatic lesions of the jaws are important in that they may be the only or the first sign of malignancies elsewhere [9].

CONCLUSION

Metastatic tumors to the oral region are difficult to diagnose because they happen to be rare and should be considered in the differential diagnosis of inflammatory and reactive lesions common to the oral region. The diagnosis of metastatic lesions of the jaws is made more difficult due to the rarity of the lesions and benign clinical picture mandating thorough clinical and histopathological investigation.

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