

Metastatic Carcinomas of Oral Cavity : A Review

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ABSTRACT

Metastasis is the spread of disease from one organ or part of it to another non-adjacent organ or part. When the cancer cells at the originating site become clinically detectable, it is called a primary tumour. Metastasis of systemic primary tumours to oral cavity is uncommon. Such metastatic carcinomas involve the jaw bones and the oral soft tissues. Metastatic carcinomas in oral region can be the first clinical manifestation of an undiagnosed primary systemic tumour. The symptoms of metastatic carcinoma depend on the location of the tumour. This article discusses the age and sex distribution, signs and symptoms, common metastasizing tumours, pathogenesis, investigations and management of metastatic carcinomas in the oral region.

Key words: Cancer cells, Carcinoma, Metastasis, Metastatic tumours.

INTRODUCTION

The most deadly aspect of a cancer is its ability to spread, or metastasize. Metastasis is usually referred to as spread of a disease from one site to another. Carcinoma occurs after a single cell in a tissue is progressively genetically damaged to produce a cancer stem cell possessing a malignant phenotype. These cancer stem cells are able to undergo uncontrolled abnormal mitosis, which serves to increase the total number of cancer cells at that location. When the area of cancer cells at the originating site become clinically detectable, it is called primary tumour. Some cancer cells also acquire the ability to penetrate and infiltrate surrounding normal tissues in the local area, forming a new tumour. This process of formation of a newly formed tumour in the adjacent site is called metastasis. Tumour cells may also spread to near the primary tumour. For metastasize to occur, a cancer cell must break away from its tumour, invade

either the circulatory or lymph system, which then carry it to a new location and establish itself in a new site. Most tumours and other neoplasms can metastasize, although in varying degrees.¹

Metastasis as known, occurs by four routes namely, a) Spread into body cavities b) Lymphatic spread c) Hematogenous spread d) Transplantation of tumour cells by surgical instruments during operation or use of needles during diagnostic procedures. Hematogenous spread is the most feared consequence of a cancer when it metastasizes. It is the favoured pathway for sarcomas and carcinomas as well. Malignant cells loses cohesiveness and gets detached from primary tumour and attach to and degrade proteins that make up the surrounding extracellular matrix (ECM), which separates the tumour from adjoining tissue. By degrading these proteins, cancer cells are able to breach the ECM and escape. When tumour cells metastasize, the new tumour is called

secondary or metastatic tumour, and its cells are like as those in the original tumour. Malignancies involving the bones are metastatic tumours more commonly than primary tumours. The bones most frequently with metastatic diseases are the vertebrae, ribs, pelvis and skull². In contrast to it, the occurrence of metastasis from distant primary malignancies to the jaws is considered a rare disease. These metastatic tumours are usually carcinomas rather than sarcomas, which is consistent with malignancies of epithelial origin accounting for more than 80% of all primary tumours, regardless of tumour site³. Jaws are not common site of metastatic bone disease with metastases to the jaws composing less than 1% of all metastatic bone lesions⁴. Metastatic tumours to oral region are uncommon and it occurs in oral soft tissues and jaw bones. However, they tend to involve the jaw bone more than the oral soft part⁵. More often in 24% of patients the metastatic tumours in the oral cavity can be the first indication of the hidden distant primary tumour.

Age and sex distribution

Metastatic tumour in oral region occurs mostly in patients of age 40-70 years. A study showed an equivalent sex distribution for metastatic jaw disease, though women exhibited more metastases than men at 31 to 41 years of age and men exhibited a significantly greater incidence of metastases than women 71 to 80 years of age⁶. This is most likely is a reflection of the fact that primary breast carcinoma occurs at an early age in women, whereas prostate and lung carcinomas occurs later in life in men⁷.

Site

Metastatic tumours to the oral region are uncommon and accounts approximately 1-3% of all malignant oral tumour^{8,9}. Metastatic tumours to oral cavity may involve jaw bones or oral soft tissues. Mandibular lesions are more common accounting about 83.5% and mostly involve the posterior part of the mandible⁹. Mandibular predilection was more prominent in females than in males⁶. In dentulous patients, 80% of metastatic tumours to oral soft tissues occur in attached gingiva whereas in edentulous patients, they are equally distributed between the tongue and alveolar mucosa⁸. Metastatic tumours to jaws may extend to

overlying soft tissues, appearing to be dental and periodontal infection. Alternatively, metastasis may occur directly in soft tissues, usually gingiva².

Pathogenesis

The red bone marrow are said to be preferred sites for metastatic tumour. The scanty vascular channels in the fatty marrow do not permit ready dissemination and growth of tumour emboli⁹. The posterior mandible is found to be detected with remnants of hematopoietic active marrow and hence may be common site for metastatic lesions⁸. The rich capillary network of chronically inflamed gingiva has been suggested as a mechanism that entraps malignant cells. The proliferating capillaries have a fragmented basement membrane through which tumour cells can more easily penetrate. These could be the reasons for occurrence of metastatic tumours commonly in the gingiva.

Metastases of tumours in lower part of body are usually filtered in lungs. The lung metastasis is bypassed when tumour cells take up the Batson's plexus. The Batson's plexus is a valveless vertebral plexus and this vascular system bypasses lungs and venacava. The metastatic head and neck tumours in absence of lung metastasis reveal the spread of tumor cells through Batson's plexus.

Oral Presentation

Metastatic tumors show variable presentation. Tongue and gingiva are common sites of metastatic tumours. Gingival metastatic tumours in their early stages resemble hyperplastic reactive lesions. They also show polypoid exophytic growth. In the tongue it could be a submucosal mass or may present as an ulcer. In the edentulous patients, metastatic lesions are spread between the tongue and alveolar mucosa.

Signs and Symptoms

In a study, out of 114 cases of metastatic jaw tumours the most common symptoms were pain, paresthesia, swelling, bleeding and temporomandibular joint problems. The most common jaw symptom was pain⁶. According to another study on these tumours, pain and pathological fractures are shown to be indicators of poor prognosis¹⁰. The clinical manifestations of the metastatic lesions in bone include bony swelling

with tenderness, pain, ulcer, hemorrhage, paresthesia, and pathological fracture.

Common metastasizing tumours

The most common primary tumours metastasizing to oral region are breast, lungs, male reproductive system and colorectal region⁶. In male subjects metastasis to jaws occurred frequently from the lungs than from prostate and in female subjects occurs from breast cancer⁶ whereas both men and women had equivalent number of metastatic lesions from colorectal region. In a review, the breast and lung were most common primary sites in women and men respectively¹¹. Prostate cancers are usually uncommon metastasizing to the oral cavity. FDG-PET scanning plays important role in diagnosing locally advanced prostate cancers¹². According to Nishimura and colleagues, the uterus was the most common primary tumour location with the most common type of cancer being choriocarcinoma, which has high occurrence rate in the Japanese population¹³. The common sources of metastatic tumours to oral region are breast, lung and kidney. Breast is the common primary site for metastatic tumours to the jaw bones where as lung is the most common source for metastasis to the oral soft tissues⁹.

In a retrospective study of metastatic tumours of jaw in Greek population from 1989 to 2005 showed two cases originating from thyroid gland, one from oesophagus and one from liver. Among these four cases three were in mandible and one in maxilla.¹⁴

Radiographic features

Radiographically, metastatic lesions are most often found with ill-defined border and usually are osteolytic (radiolucent), but they may be osteoblastic (radiopaque) or mixed radiopaque and radiolucent lesions. The radiographic appearance of lesions has been attributed to a disruption of balance between osteoclastic and osteoblastic activity that occurs during normal bone turnover¹⁵. Tumour type may affect the radiographic appearance of the lesion, prostatic carcinoma metastases are classically osteoblastic while metastatic breast or renal carcinoma may be osteolytic, osteoblastic or mixed.

Histopathological features

The histologic appearance of metastatic jaw tumour often is poorly differentiated, making it challenging in determining the location of the primary lesion.² A thorough medical history can facilitate in diagnosing. On suspicion of a metastatic tumor referral for complete oncologic work up is required. Advanced imaging, scintigraphy, screening using panel of immunohistochemical stains and regional investigations based on the suspected source should be done to find out or confirm the origin and identify the other areas of secondary spread. The diagnosis of such lesion is based on pathology but it is still difficult because they often show varied indifferent histological findings than primary tumour.¹⁶

Tumour specific markers for determination of tissue of origin

Metastatic breast carcinomas typically are positive for cytokeratin 7, but negative for cytokeratin 20, thyroid transcription factor-1 (TTF1) and Prostate specific antigen (PSA).¹⁷ In contrast, metastatic colorectal carcinomas are typically CK20 positive, but CK7, TTF1 and PSA negative.^{18,19,20} A metastatic lesion that stains positively for CK7 and TTF1 likely would be from a lung carcinoma²⁰. Metastatic prostate carcinoma would be positive for PSA²¹ but negative for other three markers.

Prostate markers

Prostate-Specific Antigen (PSA), Prostatic Acid Phosphatase (PSAP), Prostate-Specific Membrane Antigen (PSMA), and P501S (prostein) (all cytoplasmic reactivity(1-12); NKX3.1(nuclear reactivity)

PSA and PSAP antibodies have been around a long time, and they are very useful for detecting prostate adenocarcinoma, although they may also be found in some other types of tumours. PSA is very specific for prostate carcinoma, although it will also stain a small number of breast carcinomas and some salivary gland tumours.

Breast markers: Gross Cystic Disease Fluid Protein-15 and Mammaglobin (cytoplasmic reactivity)

GCDFP-15 is a very useful marker for the identification of breast carcinomas, although it is

positive in only about 50-60% of primary breast carcinomas. It is important to note that the pattern of reactivity with this antibody is often very focal, and only a small percentage of tumor cells may be immunoreactive. Some sweat gland carcinomas, salivary gland tumors, and prostate carcinomas are positive, but it is only rarely positive in carcinomas of other sites. Mammaglobin is a more recently available antibody that is useful as a marker of breast origin.

TTF-1 (Thyroid Transcription Factor-1) (nuclear reactivity)

TTF-1 is a protein involved in the regulation of surfactant proteins, and it is well established as a useful antibody for metastatic carcinoma of unknown origin. TTF-1 is normally expressed in the brain (diencephalon), parathyroid, C-cells of the thyroid, anterior pituitary, thyroid, and nonciliated respiratory and alveolar epithelium. Overall, it is expressed in 75% of nonmucinous lung adenocarcinomas, 10% of mucinous lung adenocarcinomas, and 40% of large cell carcinomas of lung.

Napsin A (cytoplasmic reactivity)

Napsin A is similar to TTF-1 with respect to its sensitivity and specificity for lung carcinoma. Renal clear cell carcinomas, papillary renal cell carcinomas were also positive.

Estrogen Receptor (ER) and Progesterone Receptor (PR) (nuclear reactivity)

Estrogen receptor can be very useful in determining the origin of metastatic carcinoma. It is common knowledge that ER is positive in many breast carcinomas and also female genital tract tumours (both epithelial and stromal), but it can also be positive in a number of other tumours. Tumours that may express ER include thyroid tumours, salivary gland tumours, sweat gland carcinomas, genital angiomyofibroblastoma, and 80% of aggressive angiomyxomas.

p63 (nuclear reactivity)

In the past several years, p63 has found increasing utility in a number of areas of diagnostic pathology, including its use as a marker of myoepithelial cells in breast and elsewhere, and as a marker of prostatic basal cells that can be used as an alternative to high molecular weight cytokeratin. In addition, it serves as a useful marker of squamous cell carcinoma.²²

Management

The treatment and prognosis is primarily based on the site of origin and the degree of metastatic spread. When cancer has metastasized, it may be treated with chemotherapy, radiation therapy, biological therapy, hormone therapy, surgery or a combination of these. The choice of treatment generally depends on the type of primary cancer, the size and location of the metastasis, the patient's age and general health, and the types of treatments used previously. Oral metastases usually are evidence of a widespread disease and indicate a poor prognosis. If there is a evidence of widespread metastases, the jaw lesion should be managed conservatively. The goal of palliative treatment is primarily to reduce the patient's pain and preserve oral function.²³

CONCLUSION

Metastasis is one of the hallmarks of malignancy and most of the tumours and other neoplasms can metastasize in varying degrees. However, not all cancers have equivalent ability to metastasize. About two-thirds of the cases had an unknown silent primary malignancy at the time of presentation of the jaw lesion. Metastatic carcinomas of oral cavity may lead to diagnosis of a symptomless primary tumour. These lesions should be kept in mind while diagnosing oral malignancy. Patients may have innocuous dental symptoms, such as pain of pulpal or periodontal origin. Therefore all tissues excised from the oral cavity should be submitted for pathological evaluation for a better and faster treatment, thus improving the condition of the patient's health.

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