Metastatic tumours of oral cavity - A clinico pathological appraisal of six cases

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Abstract

Background: Tumors metastasizing to the oral and maxillofacial region are rare and contribute to about 1% of all malignancies. Oral metastases usually occur in advanced stages of cancers. Mandible is the most common site for metastasis. It is a great challenge for a clinician to diagnose a metastatic lesion due to lack of pathognomonic signs and symptoms. Dental surgeons play an important role in patients where oral metastasis is the first sign of undiscovered cancer in other parts of the body.

Aim: The aim of this study is to analyse the clinical, radiological and histopathological features of metastatic lesions to the oral & maxillofacial region.

Materials And Methods: A total of 6 different histopathologically diagnosed cases of metastasis to the oral cavity were included in this study. Clinical demographic profile, radiographic findings, histopathological findings, treatment and follow up data were recorded and analysed.

Results: All the cases included in the study were histopathologically diagnosed as metastatic tumors. The age of occurrence was in the range of 40 to 70 years and involved 3 males and 3 females. 4 cases had extra oral swelling as the clinical presentation. 4 cases involved the mandible. Radiolucent lesions involving the bone were seen in 87% of the cases.

Conclusion: Based on the cumulative clinical data from the 6 cases, identification of metastatic tumors were based on histopathological findings correlating with the clinical radiographic and other investigations. Early diagnosis of the metastatic tumors of unknown origin could improve the chance of survival of patients.

Keywords: oral cancer; malignancy; mandible; metastasis

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INTRODUCTION

A tumor is a mass of abnormal cells that may remain in situ or invade surrounding tissues is malignant. When tumor cells shed into blood or lymph, these circulating tumor cells are the reason for the distant spread of tumor from the primary site. (1)(2) Metastasis to the oral cavity is a rare phenomenon (1% of all malignancies) and bears a grave prognosis. Metastasis of tumor to oral cavity can be found both in jaw bones and soft tissues. (3)

Oral metastases were found to be the earliest indicator of metastatic dissemination in 25% of patients, and the first indication of an unreported cancer at a distant site in 23% of instances. The jaw bones, especially the mandible, is the common site for metastasis in the oral cavity (2:1), in oral soft tissues gingiva is the most commonly affected site. Patients present with pain, swelling and paresthesia in jaw bone metastasis whereas an exophytic growth like lesion is mostly presented in soft tissue metastasis. Primary tumor site is mostly lungs in males and in females most common sites are from the lungs and the breast.
Lung Adenocarcinoma is the most common metastatic histologic type to the mandible. Approximately 23-30% of newly diagnosed patients with solid tumors present with metastases. For solid tumors, 66.7% of cancer deaths were registered with metastases as a contributing cause (5) with an average of 14.4 months after manifestation of metastasis and 43.4 months after manifestation of primary tumor. (6)

Metastasis is defined by spread of tumour to sites that are physically discontinuous with the primary tumour, and unequivocally masks a tumor as malignant. (7) Metastasis is more found in the jaw bones than in the soft tissue of the oral cavity. (8) The most affected site of the lower jaw is the posterior region of mandible, ramus and condyle. (8)(9)

In this article, we analyse 6 cases of metastatic tumors to the oral cavity with clinical, radiographic and histopathological findings.

**Materials And Methods**

All the histopathologically diagnosed cases in the Department of Oral pathology from Jan 2018 to April 2021 were included in the study. The clinical data, radiographic, histopathological and laboratory findings were retrieved and analysed. The data were analysed based on age, gender, site of lesion, symptoms, history of primary tumor, treatment and follow up. The biopsy tissue samples sent for histopathological diagnosis were examined grossly and processed for routine paraffin sections. These tissue preparations were stained with Hematoxylin and Eosin (H&E) and immunohistochemistry whenever needed.

Based on these cumulative data, pathogenicity of the metastasis tumors of the oral cavity was analysed and a possible hypothesis was attempted.

**Results**

**Clinico-demographic Profile**

Total histologically diagnosed cases (n=2349) from Jan 2018 to April 2021 were included in the study of which only 6 cases were metastatic tumors to the oral cavity. The 4th and 7th decade was found to be the age of occurrence. 4 cases involving the posterior mandible region, one case involving the maxilla and one case involving the cheek region were found. 4 cases did not have a previous history of carcinoma and 2 cases had a history of carcinoma of breast and thyroid respectively.

**Radiographic Profile**

Out of 6 cases, 4 cases had Orthopantomogram data, one case was analysed using CBCT and one case had Craniofacial radiograph (AP view). 5 cases showed radiolucent lesions suggestive of osteolytic activity. 3 cases showed ill defined radiolucent lesions and 2 cases showed well defined radiolucent lesions.

**Histopathology Diagnosis**

6 cases were histopathologically diagnosed as metastatic tumors. 4 cases were diagnosed as Metastatic Carcinoma of Unknown Primary, 1 case was lung adenocarcinoma and 1 case was metastatic follicular thyroid carcinoma. The characteristic malignant tumor cells were visualised with H&E stains showing cellular and architectural dysplastic features predominantly epithelial cell pleomorphism and altered nuclear cytoplasmic ratio. All the 6 cases of metastatic tumor showed infiltrative malignant neoplastic cells in the connective tissue. The arrangement of tumour cells in the pattern of nests, follicles, ductal, glandular etc resembled the tumor of primary site. Numerous mitotic figures were evident in all the cases. Only one case showed areas of keratinisation and necrosis.

**Immunohistochemistry Profile**

To confirm the metastatic tumour 3 cases were analysed by immunohistochemistry using several markers like Pan CK, EMA, CK7, CK8, CK19 showed strong positivity in all the three cases suggestive of epithelial neoplasm. These markers also suggest tumors of epithelial origin. Ki67 showed mild positivity in the case analysed suggestive of low proliferation of the tumor cells.
Other investigations

To rule out the primary site of tumor PET-CT scan was done in 2 cases and 3 other cases were examined by PSA level, mammogram and TSH level individually. PET-CT revealed two cases having primary malignant mass in breast and lung respectively. PSA was found to be high which revealed primary malignant mass might be of prostate origin. Mammogram revealed malignant mass of right breast carcinoma and TSH levels revealed abnormality of thyroid gland.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Age/Gender</th>
<th>Site of lesion</th>
<th>Clinical Presentation</th>
<th>Radiographic Finding</th>
<th>Histopathologic feature</th>
<th>Histopathologic Diagnosis</th>
<th>Other investigations</th>
<th>Follow up</th>
<th>Primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70yrs/Male</td>
<td>Right side of mandible</td>
<td>Pain &amp; single solitary diffuse extra oral swelling for past 3 months</td>
<td>OPG - large ill defined radiolucent lesion i.r.t 43 to ramus region</td>
<td>Papillary and ductal arrangement of malignant vacuolated epithelial cells with central areas of keratinisation and necrosis</td>
<td>Intraosseous epithelial malignancy</td>
<td>High level Prostate Specific Antigen (PSA)</td>
<td>Patient expired 6 months post diagnosis</td>
<td>Unknown (Prostate?)</td>
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<tr>
<td>2</td>
<td>41yrs/Female</td>
<td>Right angle of mandible</td>
<td>Pain &amp; Single Fibrous intraoral swelling for past 5 months</td>
<td>OPG - well defined radiolucent lesion distal of 46 to anterior ramus of mandible</td>
<td>Connective tissue stroma with malignant epithelial cells showing pleomorphism and hyperchromatism.</td>
<td>Malignancy - secondary metastatic deposits?</td>
<td>Mammogram suggestive of right breast carcinoma</td>
<td>Patient is healthy after 1 year follow up</td>
<td>Breast cancer 3 years back under treatment for chemotherapy and radiotherapy</td>
</tr>
<tr>
<td>3</td>
<td>61yrs/Female</td>
<td>36 to RM region</td>
<td>Pain and extra oral swelling for past 6 months</td>
<td>CBCT - irregular ill defined osteolytic radiolucent lesion from periapica</td>
<td>Infiltrative malignant neoplasm in connective tissue stroma, cells arranged in glandular pattern and in nests, Neoplastic cells</td>
<td>Moderately differentiated metastatic adenocarcinoma</td>
<td>PET-CT scan - primary malignant mass of the left breast with the left axillary lymph node was found and</td>
<td>No follow up data</td>
<td>Unknown (Breast? Lungs? GIT?)</td>
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<tr>
<td>Case</td>
<td>Age</td>
<td>Gender</td>
<td>Region</td>
<td>Symptoms</td>
<td>Imaging</td>
<td>Pathology</td>
<td>Additional Information</td>
<td>Follow-up</td>
<td>Diagnosis</td>
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<td>4</td>
<td>49 years</td>
<td>Female</td>
<td>Right mandibular coronoid and condylar region</td>
<td>Pain and extra oral swelling for past 2 months</td>
<td>OPG- Unicystic well defined radiolucient lesion in the ramus of mandible</td>
<td>Pleomorphic tumor cells with clusters of neoplastic follicles filled with colloid and lined by cuboidal cells, suggestive of reminiscent thyroid follicles</td>
<td>Metastatic Follicular Thyroid Carcinoma?</td>
<td>TSH level is high</td>
<td>No follow up data</td>
</tr>
<tr>
<td>5</td>
<td>73 years</td>
<td>Male</td>
<td>Left cheek region for past 15 days</td>
<td>Extra oral ulceration of the cheek for past 2 months</td>
<td>Connective tissue stroma with highly Pleomorphic malignant cells arranged in the form of nests and syncitium separated by a thin fibrovascular septae.</td>
<td>Metastatic neoplasm of Epithelial Origin</td>
<td>PET-CT - left lung primary with nodal, pulmonary, skeletal and soft tissue involvement</td>
<td>Patient healthy after 1 month follow up</td>
<td>Unknown Primary Lung?</td>
</tr>
</tbody>
</table>
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| 6 | 71 years/ Male | Upper front tooth region | Pain and Fibrous exophytic swelling for past 2 years | OPG-large radiolucent lesion in the anterior maxillary region till premolar region | Malignant epithelial cells arranged in the form of islands and nests consisting of pleomorphic polygonal cells with scant neoplasm and large hyperchromatic round nuclei. Several areas of pseudocyst formation within tumor cells and loss of adhesion of tumor cells. | Carcinoma of Unknown origin | Pan CK, CK8, CK19- Positive, P63, S100 focal strong positive, | Patient healthy after 3 months follow up | Unknown Primary |

Discussion

Metastatic tumor of unknown primary is defined as the presence of metastases on cytopathologic and histopathologic examination but the primary tumor remains unidentified despite standard diagnostic procedures. (10) Clinical correlation with histopathologic and radiographic findings have been done to give a suggestive diagnosis of metastatic lesion with an unknown primary tumor. (11) Three main criteria have been suggested to diagnose a metastatic lesion are histopathologic verification, exclusion of possible local spread, unification of histological type of metastatic or primary tumour. (8)

In our study, all the patients came with a chief complaint of pain associated with swelling. 2 cases had a history of cancer treatment and 2 cases were identified as metastatic tumors of unknown origin and found out primary site using PET CT. Radiographically a large radiolucent lesion in the posterior region of mandible mostly involving the ramus region, lesion was unilocular and progressed anteroposteriorly in the body and ramus of mandible. Clinically visible extra oral swelling in all the 4 cases made the patient visit the dentist. Common histopathological features found were, numerous neoplastic cells were present, showed pleomorphism with high nuclear:cytoplasmic ratio, prominent nucleoli with hyperchromatism, few colloid filled spaces lined by follicular cells, occasional mitotic figures and mild inflammatory infiltrate. Correlating the chief complaint, history, clinical, histological, radiographic findings, blood investigations, PET CT, Immunohistochemistry, PSA estimation the diagnosis was made. A study conducted by M. A. Wolujewicz also confirmed the finding. (12) Biopsy was performed on the received bone specimen and histologically, malignant epithelial cells were observed (Fig2a,2b) and hence, intraosseous epithelial carcinoma as the histopathological diagnosis was provided. PSA estimation confirmed that the carcinoma of primary origin was that of prostate carcinoma. It is to be noted that almost 21% of the metastasizing tumors in oral cavities have prostate carcinoma as their primary origin. (13)

Carcinoma of unknown primary origin is a broad category of cancers characterised by the occurrence of metastatic disease in the absence of a primary tumor at the time of diagnosis. Cases make up between 2% to 5% of all cancer cases, according to reports. The degree of workup in Carcinoma of Uncertain Primary Origin remains a challenge, despite the availability of advanced imaging techniques and selective therapies in the treatment of cancer. It should be focused on the clinical appearance, anatomy, and the patient's ability to withstand therapy. Most of the cases in this case series were of unknown primary origin. Oral Pathologists have played an important role in suspecting this condition based on histopathology. Identification of these life threatening conditions in an earlier stage creates a great impact in the prognosis of the patient.

Metastasis could be of 2 types: regional metastasis and distant metastasis. Regional metastasis takes place when tumor cells from the primary site penetrate lymphatic channels forming micrometastasis. (14) Distant metastasis takes place by cascade mechanism. The process invasion-metastasis cascade involves sequential steps including invasion through extracellular matrix, intravasation into blood vessels, survival in circulation. Circulating tumor cells settle in microvasculature and extravasate
through the vessel wall into the stroma by MMPs, proteases and other enzymes. Followed by angiogenesis and growth of metastatic deposits. Infiltrated cells may progress directly as a metastatic lesion with or without intervening period of latency. Further cancer cells reactivate their proliferation, thereby generating clinically detectable neoplastic growth referred to as ‘metastatic colonization’. In metastasis, a small minority of thousands of cells released into circulation eventually lead to constituting an overt colony at a distant organ regulated by signalling pathways. Invasion and dissemination of cancer cells are by ‘epithelial-to-mesenchymal transition’. (15) Few theories about the mechanism of metastasis are (i) organ selection theory; (ii) adhesion theory; (iii) Organ distribution theory; (iv) pre- metastatic niche concept. Finally, the new theory explains the bidirectional relationship between primary and metastatic sites. According to this theory, surviving cancer cells from a secondary site have the ability to return to the primary site and accelerate tumor progression. (16)(17)

The histology assessment of metastasis is by pathological TNM staging; differences in stromal desmoplasia; degree of nodal architecture; differences in intercellular cohesion and tumor cell phenotype; degenerative changes includes necrosis leading to cavitation; cystic change and dystrophic calcification, extracapsular spread is breach in nodal capsule; nodal reactions includes sinus histiocytosis, sarcoidosis granulomatous inflammation, hyalinization and sinusoid always vascular transformation. (18) In our study common findings were loss of intercellular cohesion, varied tumor cell phenotype, degenerative changes leading cavitation was evident in case 4(Fig10a,10b), nodal reactions were not assessed.

Metastatic tumors may occur in soft tissue or jaw bones in the oral cavity, occurring two times more frequently in jaw bones than soft tissues of the oral cavity. Hirshberg et al and his colleagues found that the most common primary site for metastasis to the jawbones is breast (21.8%), whereas to soft tissue was lung (26.7%). Mandible is the most common site for metastasis to jaw bones (81%), where molar area being the most affected site followed by premolar. In soft tissue of the oral cavity, the most common affected site is the attached gingiva (54.8%) followed by tongue (27.4%). (19) Most of the published data was metastasis to jaw bones rather than soft tissue. Even though soft tissue lesions are easily recognised, metastasis to jaw bones are more commonly reported. Likewise in our study, the posterior region of mandible jaw bone (body and ramus) was the site of metastatic involvement.

Bodner et al reported 8 metastatic tumor cases out of which 5 in posterior mandible and 3 in anterior region associated with paresthesia of lower lip. (20) In our study we reported 6 metastatic tumour cases out of which 4 in posterior mandible, 1 in anterior maxilla and cheek. Irani et al in her review of 453 cases reported male-to-female ratio was 1.2:1, mean age was 53.4. In our study there was no gender predilection with male-to-female ratio 1:1, mean age of 60.8 years. Primary site of the tumor was lung in men and breast in women. Breast cancer was the common primary tumor in our study for women. Adenocarcinoma was the most frequent histological diagnosis. Oral metastasis as the first sign was 27.6%. Mandible was the most common metastasis site in the oral cavity. (21)

Metastasis to the jaws often have symptoms mimicking dental infections. In our study, pain and pain associated with swelling was the common symptom shown. D’silva et al (3) in his study of 114 cases of metastasis to jaw bones reported pain associated with swelling being the most common symptom. Two-third of primary malignancy were undetected until the oral metastasis was diagnosed. In our study all the cases had pain with swelling as a common symptom, paresthesia was not found.

Suresh et al suggested multiple histological features tested to predict metastasis includes nuclear pleomorphism, mitotic index, lymphoma-vascular invasion, perineural invasion and grade of tumor .Immunohistochemical markers like p53, Ki67, cyclinD1, epidermal growth factor receptor, CD31, cyclooxygenase 2, mucin 1, laminin 5γ2, E-cadherin and β-catenin(22). Sowmya et al suggested usage of EMT biomarkers like E-cadherin, β-catenin, MMP2, MMP9 for the prediction of metastasis in oral squamous cell carcinoma. (23) In our study case 3 showed CK8 diffuse Positivity suggestive for malignant cells.

The promoting factors of metastasis may be due to some degree of inflammation. In chronically inflamed gingiva, the capillary network constantly proliferates and develops fragmented basement membranes, thus attracting the metastatic cells(24). On the other hand tooth extraction may promote a micro-environment rich with local growth factors which favours growth of metastatic cells(19). The tongue is also a highly vascular organ and is in agreement with the role of both inflammation and angiogenesis in cancer metastasis. (25,26)

Recent advances in knowledge related to cancer biology, synthesis of cancer hallmarks, and new genomic technologies are applied in the growing field of personalised medicine. (27) Genomic stability is regulated through the cell cycle. Aberrations in genome structure and sequence leads to apoptosis or senescence. When genetic mutations may cause instability in nucleotide, microsatellite, chromosomal leads to instability in epigenomic instability like DNA methylation, Histone modification, nucleosome remodelling. (28)

Limitations of this study were follow-up of patients to elicit a primary tumor was not done, OPG radiographs may not elicit micrometastasis to the bone, Blood investigations were not reported. Future scope of research pathognomonic histopathologic features suggestive only for metastatic lesions, biomarkers and genomic studies in the field of cancer metastasis.
Conclusion

Based on the cumulative clinical data from the following 6 cases metastatic tumors were made out based on histopathological findings correlating with the clinical radiographic and other investigations. Early diagnosis of the metastatic tumors of unknown origin could improve the chance of survival of patients. The detection of oral metastatic lesions is a challenge to the oral pathologist when the patient is unaware of primary malignancy. To overcome this challenge application of newer genomic studies and adequate research to explore knowledge on cancer biology of metastasis is required.

Conflict of interest

None

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Fig1: Panoramic radiograph revealed large radiolucency in relation to the right body of the mandible region extending anteriorly distal of 43.

Fig2a,2b: connective tissue revealed stroma showing malignant epithelial cells arranged in the form of few islands.

Fig3a: Panoramic radiograph revealed radiolucent lesion in relation to angle of mandible extending anteriorly from distal to 46 and posteriorly to retromolar trigone.

Fig3b: Panoramic radiograph when review after 6 months

Fig4a,4b: connective tissue revealed stroma with cells showing pleomorphism and hyperchromatism.
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Fig5: Panoramic radiograph revealed radiolucent lesion distal to 36 extending till the posterior border of ramus and involving the coronoid process.

Fig6: CBCT revealed lesions involving almost the entire ramus on the left side and and the body of mandible distal to 36 sparing the condylar process and posterior border of ramus.

Fig7a,7b: Connective tissue revealed infiltration malignant neoplasm in connective tissue stroma of cells were pleomorphic with high nuclear:cytoplasmic ratio and prominent nucleoli.

Fig8: Immunohistochemical studies on CK 8 marker revealed diffuse positivity (>90%) for the malignant cells.

Fig9: Panoramic radiograph revealed large radiolucent lesion of the right mandibular ramus involving the condylar and coronoid process.

Fig10a,10b: Histopathology section shows connective tissue revealed numerous neoplastic cells with eosinophilic cytoplasm and dark nuclei along with clusters of neoplastic follicles filled with colloids and lined by a single layer of cuboidal cells.

Fig11a,11b,11c: PET-CT revealed left lung lesion, mediastinal nodes, deposits in buccal mucosa, skeletal deposits.
Fig 12 - Histopathology section shows connective tissue stroma with highly pleomorphic malignant epithelial cells arranged in the form of small nests and syncytium separated by fibrovascular septae. Numerous mitotic figures were evident.

Fig 13a, 13b, 13c - Panoramic radiograph and AP view revealed large radiolucent lesion of the anterior maxillary region.

Fig 14 - Histopathology section shows dense connective tissue stroma with malignant epithelial cells arranged in the form of large islands, nests, strands and cords consisting of pleomorphic round nuclei.

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