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Case Report

Oral cavity: a horbor for metastasis

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ABSTRACT

The early recognition and appropriate diagnosis of lesions or growths which do not appear to have probable aetiology is of utmost importance. In such cases metastatic lesion or secondary tumours should be considered in differential diagnosis. Metastasis from distinct organs, outside the head and neck region, accounts for about 1% of all malignancies of the oral cavity. A comprehensive approach to history-taking, clinical examination, and diagnostic evaluation is necessary when suspecting metastatic disease in the oral cavity. The most common primary sites are lung carcinoma in males and breast carcinoma in females, followed by renal cell carcinoma. It presents with clear cells and exhibit a tendency for hematogenous distant metastasis to various sites including the oral mucosal tissue. Renal cell carcinoma metastasis to the oral cavity is relatively rare, but it highlights the significance of thorough examination and consideration of metastatic disease in patients presenting with oral lesions, particularly those with a history of cancer. Here, we present a case of metastasis of renal cell carcinoma to oral cavity of a 65-year-old Male patient, which represented the first sign of disease.

Keywords: Oral cavity, Renal cell carcinoma, Metastasis, Clear cell variant, Pyogenic granuloma

INTRODUCTION

The early recognition and appropriate diagnosis of lesions or growths which do not appear to have probable aetiology is of utmost importance. In such cases metastatic lesion or secondary tumour should be considered in differential diagnosis. Among cancers originating from distant organs to the head and neck, metastatic breast carcinomas are the most common to spread to the oral cavity, followed by lung and kidney cancers, collectively representing approximately 1% of oral malignancies.[1]

Metastatic lesions most frequently occur in the body of the mandible within the oral and maxillofacial region, particularly in the premolar and molar areas, due to their abundant blood supply and dense bone marrow.[2] Renal cell carcinoma (RCC) is a lethal urologic cancer which originates in the lining of the proximal convoluted tubule representing almost 3% of adult malignancies. It often metastasizes to the lungs, regional lymph nodes, bones, liver, adrenal glands, contralateral kidney, and brain. The nose and paranasal sinuses are commonly affected, followed by the oral cavity. In the oral cavity, the tongue is a frequent site of RCC metastasis, while isolated cases in the floor of the mouth are rare.[3] A literature review of the past 10 years (2007–2017) revealed only 25 cases of metastatic RCC to oral soft tissues, with 12 of these cases representing initial manifestations of a primary occult tumour.

Metastatic neoplasms tend to mimic inflammatory lesions of the periodontal tissues in natural teeth, as well as similar issues in edentulous individuals wearing dental prostheses.4 Here we describe a case involving a 65-year-old male patient diagnosed with renal cell carcinoma, where metastasis occurred in an uncommon location—the mandibular anterior gingiva. Remarkably, this metastasis

served as the initial discovery of an unidentified primary cancer, underscoring its unusual clinical presentation.

CASE REPORT

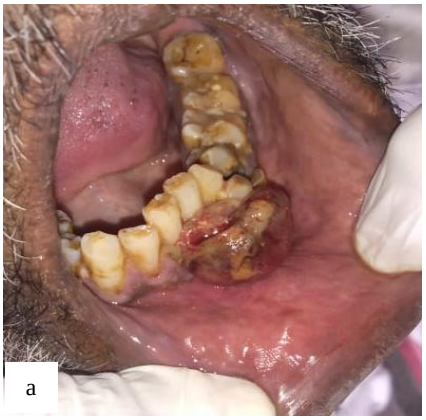
A 65-year-old male patient visited the OPD section of the Oral Medicine Department in PMNM Dental College with a chief complaint of swelling in the lower front tooth region since, 3 months. The patient revealed that the swelling was sudden in onset, initially smaller in size, and gradually increased to its present size of a coin.

During intraoral examination, a solitary localized exophytic growth, measuring approximately 1x1 cm in size and roughly oval was observed on the attached gingiva in relation to 41, 31 and 32. The overlying mucosa appeared erythematous with ulcerations, while the surrounding mucosa appeared normal (Figure 1a-b). The lesion extended medio-laterally from the mesial aspect of 41 to the mesial aspect of 33 and super-inferiorly from the attached gingiva, covering the crown structure of teeth 31 and 32. On palpation, the swelling was soft in consistency, non-tender with a pedunculated base (Figure 2). Based on the appearance of the lesion, a provisional diagnosis of pyogenic granuloma was considered, with differential diagnoses including irritational fibroma and peripheral giant cell granuloma. Then patient was advised for complete blood picture which revealed no relevant findings and periapical radiograph taken in relation to teeth 31, 32, and 41 showed horizontal bone loss present on both the mesial and distal aspects of 31 and 41 (Figure 3).

An excisional biopsy was performed (Figure 4). The excised specimen was taken to the oral pathology department for histological examination (Figure 5). The haematoxylin and Eosin-stained sections were studied and showed the presence of sheets, nests, and solid areas of cells. These cells were characterized by polygonal and round shapes with prominent vesicular nuclei and nucleoli in a clear cytoplasm background. The stroma exhibited prominent vascularity, and mild pleomorphism was also noted. The overall impression suggests an epithelial malignancy, specifically carcinoma of unknown origin (Figure 6).

An extensive array of immunohistochemical markers was subsequently employed to further classify the cells of origin. The cells were negative for CK20, CK7, p40, and CK5. The tumour cells showed strong positivity for Pan Cytokeratin, pax-8, and CD10 (Figures 7a-c).

The overall impression suggested clear cell carcinoma, consistent with metastatic clear cell carcinoma from the Kidney. The patient was subsequently referred to a general radiologist for CT scan pelvis and abdomen imaging which revelled large ill-defined infiltrating heterogenous enhancing lesion involving upper pole of left kidney and few well defined heterogenous enhancing lesion in lobes of liver (Figures 8).



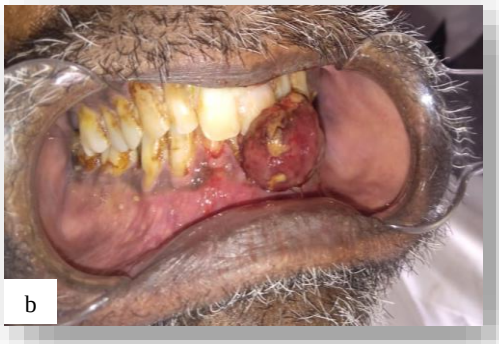


Figure 1: a) Clinical image showing exophytic growth seen on attached gingiva i.r.t 31 32. B) Clinical image in occlusal view showing.

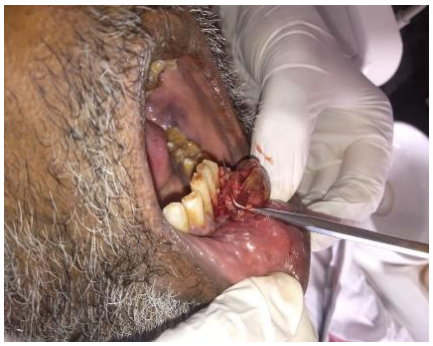


Figure 2: Clinical image showing pedunculated base.

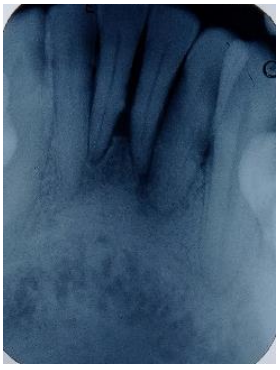


Figure 3: IOPA showing no signs of odontogenic infections.

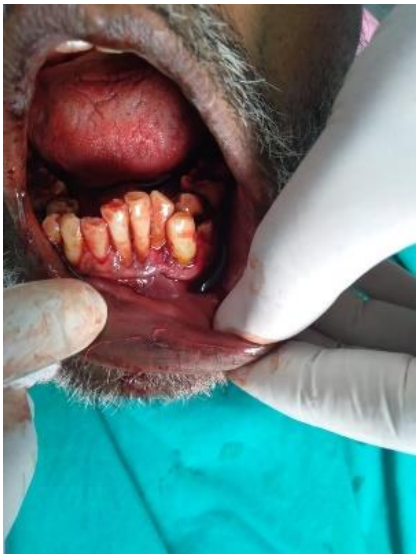


Figure 4: Post operative haemostat achieved.

Figure 5: Excised specimen.

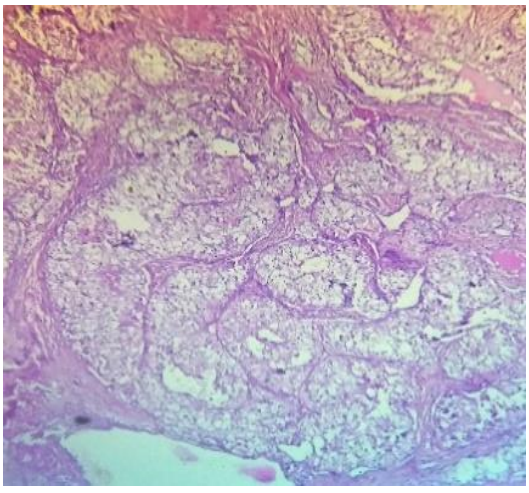


Figure 6: The haematoxylin and eosin-stained section showing the presence of sheets, nests, and solid areas of lesion cells.

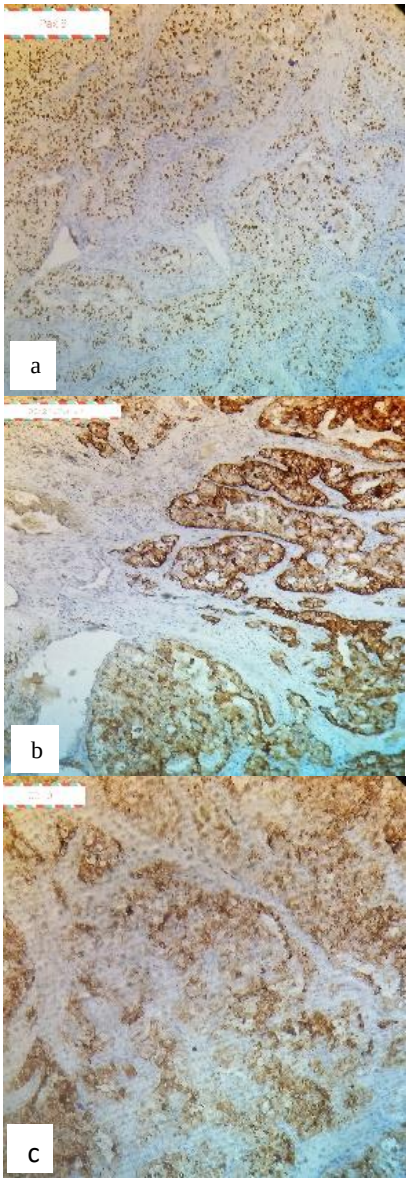


Figure 7: a) Pan cytokeratin, b) Pax-8, c) CD10.

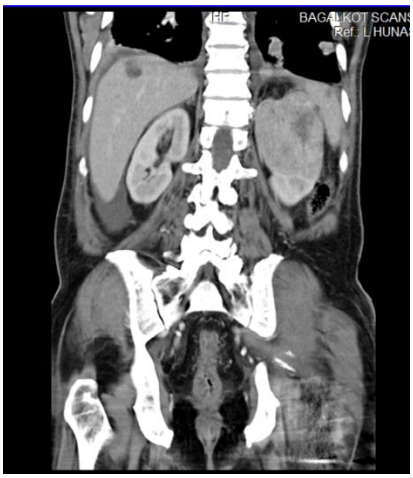


Figure 8: Heterogenous non enhancing lesion seen on upper pole of left kidney.

DISCUSSION

Metastasis to the oral cavity from malignant tumours is uncommon, occurring in approximately 1% of oral malignancies. Ironically in nearly a quarter of these instances, oral metastases are the initial manifestation of an unidentified primary tumour elsewhere in the body, the most common sites being the tongue and mandible.[5]

In renal cell carcinoma (RCC), metastasis develops in 30%-40% of patients. The most prevalent sites for metastases listed in frequency include the lungs (76%), regional lymph nodes (66%), bones (42%), and liver (41%). Extracranial metastases to the head and neck area are observed in around 15% of RCC cases.6 Identifying metastatic RCC in the oral cavity poses a challenge due to the necessity of accurately identifying these lesions and determining their primary source. Typically presenting as exophytic mass, these oral lesions may or may not manifest symptoms, necessitating a comprehensive differential diagnosis. Therefore, performing a biopsy, whether incisional or excisional, is crucial for confirming the diagnosis and guiding appropriate treatment.[7,8]

Metastasis is a complex biological process characterized by several sequential steps. Initially, tumour cells detach from the primary tumour, infiltrate nearby tissues, and then enter either blood vessels or lymphatic vessels. Once in circulation, Batson's paraspinal venous plexus, a valveless network linking the prevertebral, vertebral, and epidural systems, facilitates the spread of tumour emboli.9 This venous pathway offers minimal resistance, particularly during activities that increase intra-abdominal or intrathoracic pressure. Consequently, the vertebral venous plexus allows metastasis to occur in the head and neck region without involving the lungs, bypassing the pulmonary venous system.[10] RCC's association with multiple arteriovenous shunts may also contribute to retrograde propulsion of tumour emboli, enhancing metastatic dissemination.[11]Once they navigate through the bloodstream get settle in the microvasculature of any target organ, these tumour cells then cross the vessel walls, invade the parenchyma of the target organ, and establish proliferation. To grow beyond 2–3mm in size, micro metastases depend on angiogenesis to ensure sufficient oxygen and nutrient supply.[12]

Numerous factors contribute to the development of RCC, including smoking, tobacco use, alcohol consumption, obesity, high blood pressure, cardiovascular conditions, liver and kidney diseases, urinary stones, diabetes, pharmaceutical use, and malnutrition.[13,14] Studies indicate that cigarette smoke contains carcinogens and nicotine, are metabolized through the kidney's filtering process, trigger inflammation and DNA damage, thereby promoting carcinogenesis.[15] Individuals who smoke have a higher risk of RCC compared to non-smokers globally, in 2018, there were 403,000 new cases of RCC and 175,000 deaths attributed to this malignancy.

In India, the incidence rate is approximately 2 per 100,000 population among males and about 1 per 100,000 population among females. RCC has become increasingly common in developed countries in recent decades. Research conducted by Prajapati et al, identified that United States as having the highest number of cases, followed by Japan, the United Kingdom, Turkey, India, Spain, Poland, and Europe. Typically affecting individuals in their fifth to sixth decades of life, RCC exhibits a male predominance with a ratio of 1.5:1 globally, and 2.5:1 in their study.[16]

Clinically metastatic lesions resemble gingival lesions pose a diagnostic challenge due to the presence of several benign conditions that will complicate differential diagnoses such as Pyogenic Granuloma, Peripheral Giant Cell Granuloma, Ossifying Fibroma and Fibrous Hyperplasia are common examples that often lead to delays in diagnosis.17 Clinical signs such as rapid enlargement or invasion of underlying bone can aid in distinguishing these lesions from inflammatory origin to malignancy. Pyogenic granuloma, is a frequently occurring gingival lesion characterized by soft, bright red swellings with focal ulceration, sometimes giving a grey/yellow appearance.[18] In our case clinical appearance of growth were same as pyogenic granuloma.

The lesion's clinical presenting with tendency to bleed easily after palpation, and absence of ulcero-proferalative lesion necessitates consideration of malignant lesions like metastasis, as well as systemic causes of gingival vascular expansion such as leukemia and granulomatosis with polyangiitis.[19] Peripheral odontogenic tumors commonly involving the gingiva include Peripheral Odontogenic Fibroma and Peripheral giant cell granuloma also considered as differential diagnosis. These tumors exhibit slow growth, and typically present as gingival swellings with intact overlying mucosa, which are crucial factors for differentiating them from malignancies.[20]

Histologically clear cell renal cell carcinomas (CCRCCs) typically display solid or lobular architecture, characterized by clusters of polyhedral cells. These cells exhibit prominent cytoplasmic clearing, attributed to glycogen and lipid accumulation, giving the cytoplasm a clear or pale appearance. The boundaries between these cells are often unclear. The nuclei of CCRCC cells are generally rounded or oval, occasionally with noticeable nucleoli. Intra-tumoral haemorrhage is a common feature, presenting as either small aggregates of red blood cells within the tumour or larger haemorrhagic areas that displace nearby carcinoma cells.[21]

In our current case histologically showing presence of sheet's, nests, and solid areas of lesional cells characterized by polygonal and round cells with prominent vesicular nuclei and nucleoli in clear cytoplasm. Background stroma shows prominent vascularity and mild pleomorphism. Based on histological features, the diagnosis was stated as 'Epithelial

malignancy - carcinoma of unidentified origin', leading to the decision to perform Immunohistochemistry for further clarification to know the origin of tumour.

For diagnosis CCRCC the following markers are used Pancytokeratin (panCK) (AE1/AE3) Paired Box 8 (PAX-8) and Cluster of Differentiation (CD) 10 were positive. cytokeratin (CK), P40 , CK 7, CK 20, Mucicarmine were negative.[22] Pancytokeratin (panCK) (AE1/AE3) and Epithelial Membrane Antigen (EMA) are specific markers for epithelial cells and are commonly employed to differentiate tumors based on their epithelial line. The Renal Cell Carcinoma Marker (RCC-Ma) targets an antigen present in normal renal proximal tubules and is particularly useful in identifying primary clear cell renal cell carcinoma (RCC). Paired Box 8 (PAX-8) is expressed in normal renal tissue and various renal tumor types. Clear cell RCC typically displays diminished PAX-8 expression compared to normal renal tissue and other histological variants of renal tumors; nevertheless, the absence of PAX-8 expression does not prevent a renal origin for the tumor.[23]

Abdominal CT is a key for staging RCC this includes evaluating the primary tumor and checking for metastases in nearby lymph nodes and abdominal organs. Imaging procedures are designed effectively by assessing both the extent of the primary tumor and potential metastases.[24] The recommended CT technique involves capturing images in two distinct phases Arterial Phase to capture hypervascular tumors and arterial structures. And Nephrographic/Portal Venous Phase are used to visualize venous structures and assess the tumor's enhancement. Clear cell carcinoma exhibits significant arterial enhancement because of its high level of intertumoral vascularity. Subsequently, metastases originating from clear cell carcinoma also display strong arterial enhancement and might not be detectable during the nephrographic phase.[25] In the case at hand, Showing Ill-defined heterogenous enhancing lesion involving upper and mid pole of left kidney which is suggestive of early enhancement in arterial phase with multiple prominent intra-lesional arteries and arteriovenous shunts.

CONLUSION

Oral cavity metastases from renal cell carcinoma (RCC) are rare but can be a critical diagnostic clue to an unidentified primary tumor to challenges in distinguishing these lesions from benign conditions and other malignancies, a thorough histopathological evaluation and immunohistochemical profiling are essential for accurate diagnosis. Early detection and appropriate imaging such as CT scans are crucial for effective management and treatment of RCC and its metastatic manifestations.

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