

Buccal Mucosal Metastasis of Renal Cell Carcinoma: A Case Report and Review of Literature

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Abstract:

Background: Intraoral metastasis of Renal Cell Carcinoma (RCCs) are unusual, especially when it comes to buccal mucosal metastases, which are extremely rare, accounting for less than 1% of metastatic RCC. The buccal mucosal metastatic lesion from RCC poses a challenge in diagnosis and treatment. Due to their scarcity, there doesn't exist any literature primarily concentrating on them.

Case Report: In this work, we describe the case of a 58-year-old man previously affected and operated for renal cell cancer, brought to our care for the appearance of a buccal mucosal ulcer. Pathological analysis revealed a metastasis compatible with clear-cell carcinoma. Its renal origin was confirmed by immunohistochemical technique. The patient was evaluated and managed after post multidisciplinary tumor board discussion with palliative radiotherapy for local disease.

Conclusion: There should be no hurry in starting treatment for a buccal mucosal lesion, and it should be histopathologically evaluated keeping in mind a differential of metastasis from the distant primary. Multidisciplinary tumor board discussion plays an important role in such rare scenarios.

Keywords: *Metastatic Renal Cell Carcinoma, Buccal Mucosal Metastasis, Radiotherapy, Intraoral metastasis, Rare metastatic*

Introduction:

Renal cell carcinoma (RCC) is the most common primary renal neoplasm, accounting for 80-85% of renal neoplasm. Globally, the incidence of renal cell carcinoma (RCC) varies widely from region to region, with the highest rates observed in the Czech Republic and North America [1]. An estimated 18% of patients with RCC have metastasis at diagnosis, and more than 50% will develop metastatic RCC after nephrectomy during follow-up [2]. The most common sites of metastases are lungs (45%), followed by bones (30%) and lymph nodes (22%), liver (20%), adrenal glands (9%), and brain (9%) [3]. The buccal mucosa is a rare site for RCC metastasis, accounting for less than 1% of all metastatic RCC [4]. Here we present an unusual case of RCC in a 58-year-old male who presented with buccal mucosal, brain, lung, and cutaneous metastasis. This diagnosis can be considered a tricky task in the case of unusual metastatic sites, especially with an undiagnosed primary. Always a diagnosis of the benign lesion should be kept in mind. Treatment of metastatic RCC is complex and should be decided based on a multidisciplinary team discussion. It can be treated with radical intent therapy also but as most of the RCC present with widespread metastasis, they are treated with tyrosine kinase inhibitors and palliative local therapy in the form of radiotherapy or surgery.

Case Presentation

A 58-year-old gentleman, known to have diabetes mellitus, hypertension and hypothyroidism, on medications, presented complaining of flank pain of 15 days in March 2020. There is no significant history or family history. He was started on symptomatic management and evaluated using ultrasonography (USG), which showed an enlarged right kidney. Further evaluation with positron emission tomography (PET)-computed tomography (CT) scan revealed a 14.9x10.3x9.9cm enhancing necrotic hypervascular mass arising from the upper pole of the right kidney, infiltrating the inferior margin of segment VI of the liver, and

abutting the right posteroinferior diaphragmatic fibers, suggesting a diagnosis of RCC. After pre-anesthetic evaluation, he underwent open right radical nephrectomy and adhesiolysis under general anesthesia on 30th April 2020. His histopathology report revealed 9x8x7cm clear cell RCC grade III with negative margins and negative lymphovascular invasion and staged as pT2aN0M0. The patient was then advised to have regular follow-ups.

The patient was asymptomatic and doing well, until January 2021, when he presented with loss of appetite, disorientation, drowsiness, and ulcer in the mouth as depicted in Figures 1 and 2. Biopsy from the ulcer revealed metastatic clear cell RCC. He was further evaluated with a PET-CT scan, which revealed tumor bed recurrence, fluorodeoxyglucose (FDG) avid lung nodules, and hilar nodes. Scan reported a right frontal and parietal lobe lesion of 3x2.5cm with significant edema and midline shift to the left by 0.5cm.



Figure 1: Ulcero-proliferative buccal mucosal lesion extending onto the lower lips and having haemorrhagic spots.

Given increasing symptoms of raised intracranial tension, he was immediately started on stereotactic radiotherapy of 5 Gray per fraction for 5 fractions, to the brain lesions on the TrueBeam STx machine. The patient tolerated the treatment well. Simultaneously he was started on anti-edema medication as well as on tyrosine

kinase inhibitor (TKI)-Sunitinib 50mg once a day.

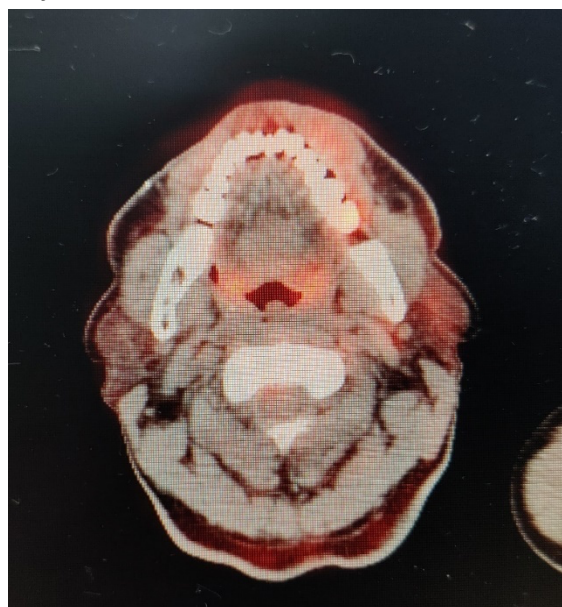


Figure 2: Axial section of PET scan demonstrating FDG uptake at the buccal mucosal lesion.

In April 2021, the swelling and ulcer over the left buccal mucosa increased, and he also developed swelling over the left parieto-occipital region of the scalp. The differentials considered at this point were metastatic lesions from RCC or second primary carcinoma. He was further evaluated with a biopsy which proved that the lesions were metastatic RCC and he was planned for palliative radiotherapy.

The patient underwent CT simulation with a thermoplastic head and neck cast, with the head rotated to the right side and a wax bolus on the lesions. Using 6 mega voltage (MV) photon energy, a dose of 4 Gray per fraction was delivered for 5 fractions to treat the buccal mucosal lesion, as depicted in Figure 3. The patient tolerated the radiation treatment well. He was started on Pazopanib 400mg twice per day, since he had developed sunitinib-induced thrombocytopenia in May 2021. The patient is on systemic therapy, presently asymptomatic and on regular follow-up.

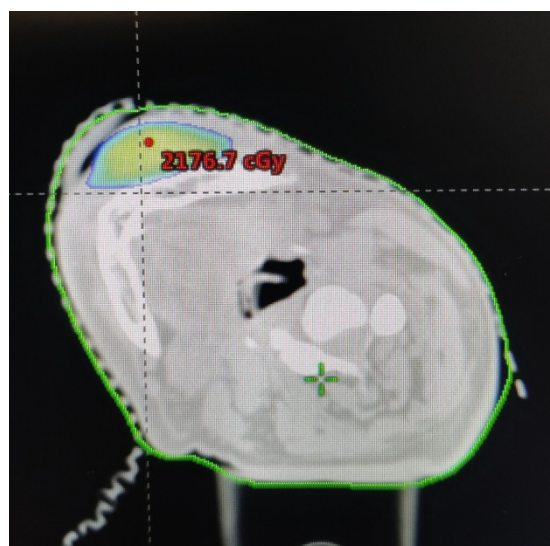


Figure 3: Planning CT scan done with the head tilted to opposite site, showing the dose distribution with hot spot in the centre of lesion.

Discussion

Worldwide, 403,000 new cases of RCC and 175,000 deaths due to this malignancy were recorded in 2018. This accounts for 2% of global cancer diagnoses and deaths [5]. It has more than doubled in incidence, and according to the 2020 statistics, it is the ninth most common neoplasm in the United States (US) [6]. According to Indian statistics, the incidence of RCC among males is about 2/100000 population and among females is about 1/100000 population [7].

Approximately 68% of RCCs demonstrate metastasis either at presentation or following radical surgery [2]. The most common sites of metastases are the lungs (45%), bones (30%), lymph nodes (22%), and liver (20%) [3]. According to the literature, RCC is the third most common primary tumor site metastasizing to the head and neck region, among which an intraoral metastasis is extremely rare [8]. Mandible and gingiva are the common intraoral sites of metastasis, and buccal mucosa accounts for less than 1% of oral metastasis, with only 6 cases reported in the past decade [4]. In addition, no pieces of literature are reviewing exclusively the buccal mucosal metastatic RCC. In this study, we have reviewed five pieces of literature involving buccal mucosal

metastasis of RCC.

Upon their analysis, the mean age of presentation was 60 years, and the male-to-female ratio was highly similar to the scenario observed in different parts of the world [7]. Ulcers over the buccal mucosa lasting one to two months, that bleed on manipulation, and not resolved on oral medication, were the most common presentation. All the patients in our literature had approached a dentist and then had been directed to an oncologist, post initial radiological or histological evaluation. According to this observation, the dentist plays an crucial role especially when it comes to time for diagnosis after presentation and should rule out metastatic lesions of the buccal mucosa, before planning for therapy or referral.

In around 80% of the cases, unlike in our case, distant organ metastases may present the first symptoms and pose a clinical challenge in diagnosis. In an intraoral manifestation like in our case, ulceration or swelling with no palpable lymph nodes may mimic a non-neoplastic proliferative process, hence an early detailed radiological and histological evaluation is of supreme importance.

Clinically, an important characteristic of mRCC reported in the literature and also present in our case is the intense vascularisation that can lead to the patient suffering from a large amount of blood loss [9,10]. This was also proven on histological evaluations with intense vascularisation, cells with pleomorphic and hyperchromatic nuclei, and may present cells with clear cytoplasm in clear cell variant of RCC [11]. Due to this clinicopathological characteristic of RCC, palliative local therapy plays an important role in hemostasis.

Clear cell histology formed 80% of our literature search, and it is the most common histology in RCC, comprising 75%–80% of cases. Non-clear cell RCC histologies comprise roughly 20%–25% of patients overall, and among them papillary RCC accounts for 10%–15% of cases. It is critical to acknowledge that the histology and the

underlying molecular biology of tumors may differ across sites of metastasis and each histological variant observed carries prognostic importance [8,11].

Immunohistochemistry also plays a pivotal role in accurate and faster diagnosis. The main markers used are PAX8, positive in approximately 90% of cases, CD10 positivity observed in 98%, and classic markers, AE1/AE2, positive in 88% of the cases [12].

The radiological aspect resembles other malignant metastatic neoplasms in the oral cavity with contrast-enhanced soft tissue lesions infiltrating into the surrounding normal tissues, on contrast-enhanced computer tomography (CT) scan. CT scan is the preferred modality of radiological evaluation in most head and neck mRCC. An alternate modality like MRI is used in certain sites, like in a lesion on the tongue [4,13].

According to the literature, the interval between primary diagnosis and development of metastasis ranges from half a year to three years [14]. In our case, it was about nine months. There are multiple theories regarding the biological mechanisms that drive RCC metastasis. According to certain authors, the tumor-derived microvesicles that appear to possess CD105-positive cells break off from the primary site and disperse tumors through hematogenous routes [15]. These microvesicles carry a cancer stem cell phenotype and microRNAs which stimulate angiogenesis. The immune milieu may also play a critical role in the evolution of metastasis [3]. Makos et al, stated that the metastatic spread to the head and neck region and intraoral sites occurs via pulmonary circulation and Batson's paravertebral venous plexus [16].

The treatment plan of mRCC should be decided by a multidisciplinary approach. The decision is directed based on the state of the primary disease, the number, and the site of metastasis, and also on the patient's performance status. According to reports, patients with diagnosed intraoral mRCC have widespread systemic metastasis in the lungs and liver. Furthermore, this study

identifies that if metastasis is identified in the oral cavity, then the possibility of widespread metastatic disease should be thoroughly investigated in an appropriate multidisciplinary setting [17].

Some prospective studies have shown that immunotherapy combined with cytoreductive nephrectomy prolongs the period without metastases to 17 months [18]. Since most of the patients present in advanced disease stages, surgery is not usually indicated. Radiotherapy and systemic therapies like Tyrosine Kinase Inhibitors (TKI) are primarily used for palliating symptoms. In addition to these, immune therapies can also be used.

In our literature review of similar cases, the longest survival time was 22 months; however, other authors report a smaller survival time, such as two months. Despite these critical advances, the reality is that the majority of patients with mRCC are diagnosed late and have very bad prognosis with their overall survival being less than a year [3,7].

Conclusion

Buccal mucosal metastasis of RCC is a rare presentation and is often diagnosed late. This differential diagnosis should be kept in mind, and treatment should always follow a clear histopathological diagnosis and multidisciplinary tumor board discussion.

References

1. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. *Eur Urol*. 2015;67(3):519-530. PMID: 25449206. <https://doi.org/10.1016/j.eururo.2014.10.002>
2. Brufau BP, Cerqueda CS, Villalba LB, Izquierdo RS, González BM, Molina CN. Metastatic renal cell carcinoma: radiologic findings and assessment of response to targeted antiangiogenic therapy by using multidetector CT. *Radiographics*. 2013;33(6):1691-1716. PMID: 24108558. <https://doi.org/10.1148/rg.336125110>
3. Gong J, Maia MC, Dizman N, Govindarajan A, Pal SK. Metastasis in renal cell carcinoma: Biology and implications for therapy. *Asian J Urol*. 2016;3(4):286-292. PMID: 29264197. <https://doi.org/10.1016/j.ajur.2016.08.006>
4. Hirshberg A, Shnaiderman-Shapiro A, Kaplan I, Berger R. Metastatic tumours to the oral cavity - pathogenesis and analysis of 673 cases. *Oral Oncol*. 2008;44(8):743-752. PMID: 18061527. <https://doi.org/10.1016/j.oraloncology.2007.09.012>
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [published correction appears in *CA Cancer J Clin*. 2020 Jul;70(4):313]. *CA Cancer J Clin*. 2018;68(6):394-424. PMID: 30207593. <https://doi.org/10.3322/caac.21492>
6. Padala SA, Barsouk A, Thandra KC, et al. Epidemiology of Renal Cell Carcinoma. *World J Oncol*. 2020;11(3):79-87. PMID: 32494314. <https://doi.org/10.14740/wjon1279>
7. Abraham G, Cherian T, Mahadevan P, Avinash T, George D, Manuel E. Detailed study of survival of patients with renal cell carcinoma in India. *Indian J Cancer* 2016; 53(4):572-4. <https://doi.org/10.4103/0019-509X.204758>
8. Jatti D, Puri G, Aravinda K, Dheer DS. An atypical metastasis of renal clear cell carcinoma to the upper lip: a case report. *J Oral Maxillofac Surg*. 2015;73(2):371.e1-371.e3716. PMID: 25579020. <https://doi.org/10.1016/j.joms.2014.09.006>
9. Altuntaş O, Petekkaya İ, Süslü N, Güllü İ. Renal cell carcinoma metastatic to the tongue: a case report and review of the literature. *J Oral Maxillofac Surg*. 2015;73(6):1227-1230. PMID: 25843819. <https://doi.org/10.1016/j.joms.2014.12.031>
10. Ganini C, Lasagna A, Ferraris E, et al. Lingual Metastasis from Renal Cell Carcinoma: A Case Report and Literature

Review. Rare Tumors. August 2012:130-133. PMID: 23087797.

<https://doi.org/10.4081/rt.2012.e41>

11. Lee C, Park JW, Suh JH, Nam KH, Moon KC. Histologic variations and immunohistochemical features of metastatic clear cell renal cell carcinoma. Korean J Pathol. 2013;47(5):426-432. PMID: 24255630.

<https://doi.org/10.4132/KoreanJPathol.2013.47.5.426>

12. Ma F, Dai L, Wang Z, Zhou L, Niu Y, Jiang N. Evaluating prognosis by CK7 differentiating renal cell carcinomas from oncocytomas can be used as a promising tool for optimizing diagnosis strategies [published correction appears in Oncotarget. 2018 Jun 26;9(49):29285]. Oncotarget. 2016;7(29):46528-46535. PMID: 27341023.

<https://doi.org/10.18632/oncotarget.10225>

13. Liu Y, Vargo RJ, Bilodeau EA. Analytic survey of 57 cases of oral metastases. J Oral Pathol Med. 2018;47(3):275-280. PMID: 29283437.

<https://doi.org/10.1111/jop.12672>

14. Thrasher JB, Paulson DF. Prognostic factors in renal cancer. UrolClin North Am. 1993;20(2):247-262. PMID: 8493748.

15. Grange C, Tapparo M, Collino F, et al. Microvesicles released from human renal cancer stem cells stimulate angiogenesis and formation of lung premetastatic niche. Cancer Res. 2011;71(15):5346-5356. PMID: 21670082.

<https://doi.org/10.1158/0008-5472.CAN-11-0241>

16. Makos CP, Psomaderis K. A literature review in renal carcinoma metastasis to the oral mucosa and a new report of an epulis-like metastasis. J Oral Maxillofac Surg. 2009;67(3):653-660. PMID: 19231796.

<https://doi.org/10.1016/j.joms.2008.10.006>

17. van der Waal RI, Buter J, van der Waal I. Oral metastases: report of 24 cases. Br J Oral Maxillofac Surg. 2003;41(1):3-6. PMID: 12576032.

[https://doi.org/10.1016/s0266-4356\(02\)00301-7](https://doi.org/10.1016/s0266-4356(02)00301-7)

18. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001;345(23):1655-1659. PMID: 11759643.

<https://doi.org/10.1056/NEJMoa003013>