

# Clear Cell Renal Cell Carcinoma Metastatic to the Mandible: a Unique Case Report and Literature Review

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*Renal cell carcinoma (RCC) is often diagnosed in advanced stages and a third of patients have distant metastasis at diagnosis. Metastasis may be the first evidence of clear cell RCC in many cases. RCC most often metastasises to the lung, liver, bone, brain and thyroid; however, metastatic disease to the oral cavity, especially the mandible, is rare. The purpose of this study is to report a case of clear cell RCC metastatic to the mandible and review the literature. The mandible lesion underwent radical excision in this case. Notably, no metastatic lesions were detected in the lungs and liver in this patient until 15 months after the mandibulectomy. The patient lived for around 2.5 years after the diagnosis of RCC.*

**Key words:** mandible, mandibular metastasis, renal cell carcinoma (RCC)

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Renal cell carcinoma (RCC) is a cause of significant morbidity and mortality that accounts for 2% to 3% of all adult cancers, with 77,410 new cases and 46,345 deaths in China in 2022<sup>1,2</sup>. A severe smoking habit has been associated with its development<sup>3</sup>. Clear cell RCC, which represents 85% to 90% of all RCC cases, is the predominant histological type<sup>1,4,5</sup>. Since RCC is resistant to both traditional chemotherapy and radiation therapy and a third of patients have distant metastatic disease at diagnosis<sup>6–8</sup>, the prognosis for RCC is usually unfavourable and the median overall survival time is approximately 12 months. Clear cell RCC accounts for 94% of cases of metastatic RCC<sup>1,2</sup>. The most common sites of metastasis are the lung (50% to 70%), liver (30% to 40%), bone (30% to 40%), brain (9% to 17%) and thyroid (25%)<sup>2</sup>; however, metastasis of RCC to the oral cavity is relatively rare, with a reported incidence of 15%<sup>9</sup>. The present case report describes a 48-year-old man who suffered meta-

static clear cell RCC to the left mandible and lived for 2.5 years after his diagnosis.

## Case presentation

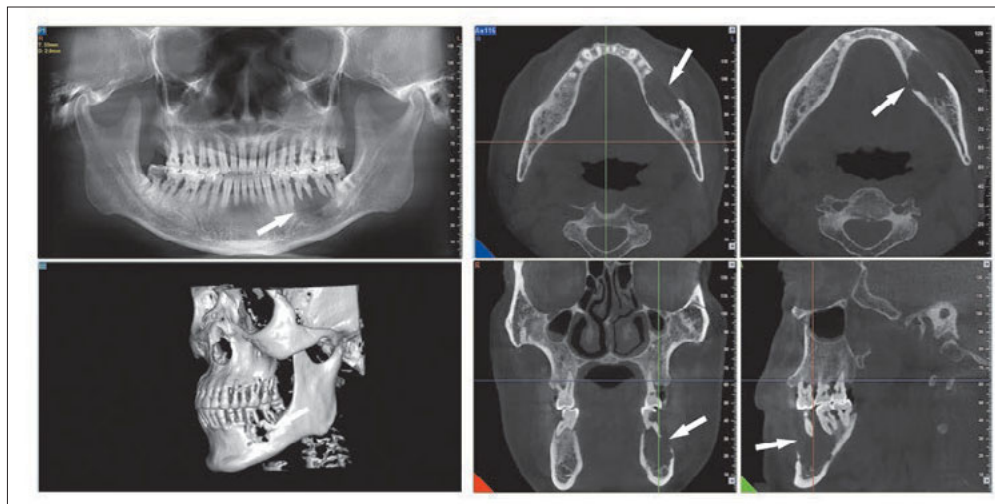
This study was approved by the review board of the Ethics Committee of Hospital of Stomatology, Wuhan University, Wuhan, China. The use of human tissues was in accordance with the National Institutes of Health guidelines, and written consent to publish this information was obtained from the study participants.

In August 2016, a 48-year-old man was admitted to the Department of Oral and Maxillofacial Surgery, School and Hospital of Stomatology, Wuhan University, with a chief complaint of swelling of the gingiva and mobility of molars in the left mandible. The gingival masses were noticed 4 years previously and he had experienced fluctuations in size for 4 years. One month previously, the gingival swelling and numbness of his left lower lip had become increasingly severe. He had a history of smoking 2.5 packs of cigarettes per day for 30 years, and alcohol consumption of 250 ml every day for 30 years. The patient denied experiencing any odontogenic symptoms before the appearance of the mandibular swelling. His medical history showed that he had had clear cell renal cell carcinoma (RCC) in the right kidney and had undergone a right nephrectomy to treat it in September 2015. He attended follow-up

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**Fig 1** CBCT images of mandible lesion. The arrow indicates the location of the lesion.

visits for nearly 1 year and no metastasis was detected in the lungs, liver or left kidney. The physical examination showed a mass measuring 2 cm × 1 cm × 1 cm on the gingiva on the buccal side in the mandibular left molar region with no trismus. The mass was soft to the touch, fluctuant and tender. The mandibular left first and second molars displayed significant mobility. No ulceration was observed on the mass, and no cervical lymph node was palpable.

On the CBCT examination, a radiolucent, ill-defined lesion with dimensions of around 3.1 cm × 1.7 cm × 2.3 cm with no clear margin was observed at the apex of the mandibular left second premolar to second molar (Fig 1). The bone cortex on the buccal side of these teeth had disappeared and the bone continuity of the lingual side was interrupted. The chest radiograph did not show any abnormalities. The laboratory examination revealed no abnormalities except for increased uric acid (UA, 579 μmol/L). Considering the aforementioned clinical features, the patient was presumptively diagnosed with a malignant tumour of the left mandible. A biopsy specimen was taken of the gingival mass to identify the pathological nature of the mandible lesion. To the present authors' surprise, inflammatory cell infiltration was observed in the gingival swelling (Fig 2a) and there were no carcinoma cells in the gingival lesion. Confronted with this contradiction, we realised that the result of the biopsy specimen taken of the gingival mass might not represent the pathological nature of the mandibular lesion. After considering the results of the CBCT examination (a radiolucent, ill-defined lesion) and symptoms, such as numbness of the left lower lip, a decision was made to take an excisional biopsy specimen. The mandibular lesion was excised surgically in its entirety via mandibulectomy.

The surgical steps were as follows:

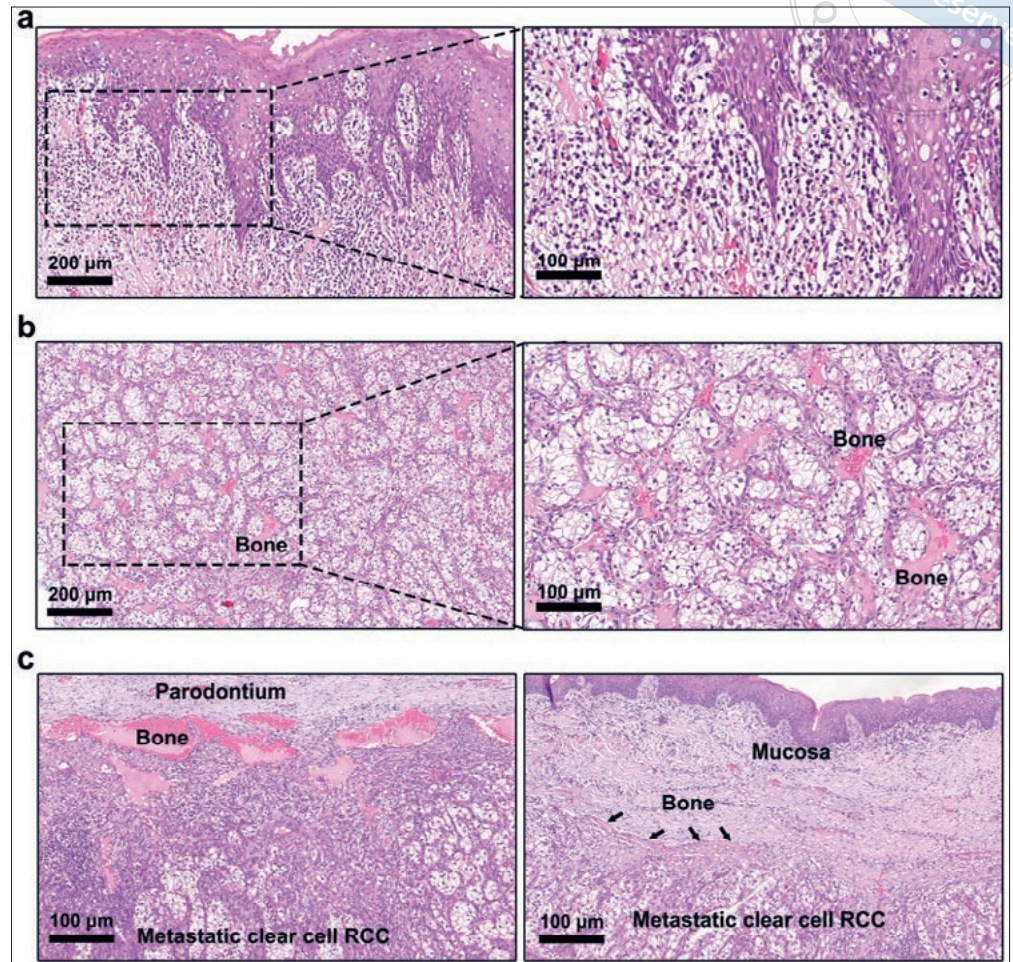
1. Extraction of the mandibular right central incisor;
2. Sectioning of the mandible near the extraction site;
3. Cutting of the associated muscles;
4. Opening of the temporomandibular joint capsule;
5. Complete removal of the patient's left mandible.

The patient was discharged 8 days after surgery for home care. Six months after the diagnosis of the mandible metastasis, he did not present any signs of recurrence.

Haematoxylin and eosin (H&E) staining showed that the lesions were composed of extensive areas of carcinoma cells forming small nests or clusters (Fig 2b). These cells have clear intracytoplasmic vacuoles and are arranged in nests that are invested by fibrous tissue, frequently small-calibre blood vessels and a small lake of erythrocytes. The nuclei of carcinoma cells are small, hyperchromatic and round. The histological characteristics of the left mandibular lesion met the diagnostic criteria for clear cell RCC<sup>10</sup>. Moreover, the lesion was located in the cancellous supporting bone and did not involve alveolar bone proper, compact supporting bone, periodontium or mucosa (Fig 2c).

Additional immunohistochemistry (IHC) staining revealed that the carcinoma cells were positive for vimentin, CD10, cytokeratin-19 (CK-19) and PCK but negative for CK-5/6, CK-7, CK-20, P63, smooth muscle actin (SMA) and calponin (Fig 3). The Ki-67 proliferation index was 30%. Considering these findings, this lesion was diagnosed as clear cell RCC metastasis to the left mandible. H&E staining was also used to evaluate the relationship between the gingival mass and metastatic carcinoma. As shown in Fig 4, inflammatory cell infiltration was observed in the gingival swelling. The inflammatory lesions and metastatic clear cell RCC





**Fig 2** Results of the biopsy specimens taken of the gingival mass and mandibular lesion. The pathological nature of the (a) gingival mass and (b) mandibular lesion was determined by H&E staining. (c) Mandibular lesion located in the cancellous supporting bone.

were separated by compact supporting bone, indicating that the gingival inflammation had no direct connection with metastatic carcinoma.

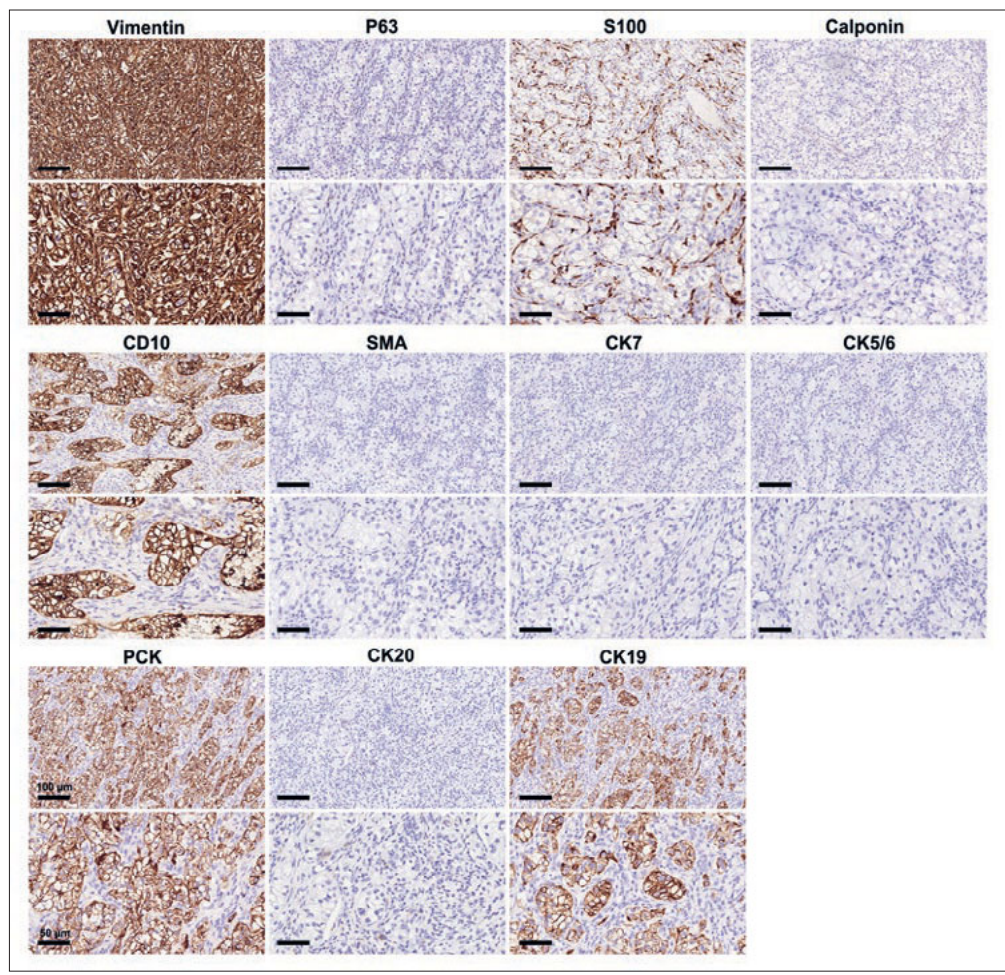
## Discussion

Metastatic cancer of the oral cavity is extremely rare<sup>11</sup>, estimated to account for only around 1% of all diagnosed oral malignancies<sup>12,13</sup>, and only 16% of these reported cases originate from the kidneys<sup>14</sup>. In many cases, metastasis is the first indication of clear cell RCC<sup>12</sup>. Approximately one-third of clear cell RCC patients have distant metastatic disease at diagnosis. The most common sites of metastasis are the lung, liver, bone, brain and thyroid. Metastatic disease of the oral cavity is rare, but in the present patient, no metastasis was detected in the lungs, and a live, metastatic lesion was only observed in the left mandible. A severe smoking habit has been associated with the development of RCC. The present patient had a history of consistent smoking,

having consumed 2.5 packs of cigarettes per day for 30 years. The present authors speculate that the patient's mandibular metastatic cancer may be associated with his long-term history of heavy smoking.

A review of the scientific literature published in English reported five cases of metastatic clear cell RCC in the mandible (Table 1). The present authors report one more case. In the six cases, patients' age ranged from 48 to 71 years (mean 56.3 years). Oral metastasis was more frequent in men (four cases) than women (two cases), with a male/female ratio of 2:1. Among these six cases, three patients were identified to have simultaneous metastasis in the ribs, femur and ilium, along with metastasis in the mandible<sup>15</sup>; however, in two patients, including the patient in the present study, no metastasis was found in any bones apart from the mandible. Carcinoma cells were found in the gingival lesion in only one patient, indicating that mandibular metastasis does not typically involve the gingiva. According to the existing literature, metastasis of RCC to the gingiva





**Fig 3** IHC staining images of the mandibular lesion.

is extremely rare, and the exact mechanism behind this phenomenon remains unclear. The phenomenon is that cancer cells are mainly located in the cancellous bone. First, tumour cells disseminate through the bloodstream and reach the trabecular bone. Once they reach the trabecular bone, they become trapped, which hinders their ability to reach the gingival tissue. Second, in contrast to the trabecular bone, the gingival mucosa is regularly exposed to external stimuli, leading to a more active mucosal immune system. This heightened immune activity is unfavourable for metastatic tumour growth in the gingival mucosa.

The diagnosis of metastatic RCC should ideally involve a comparison of the tissue acquired outside the site of primary disease to the primary histology. Histological evaluation should include common markers of RCC, including paired box gene 8 (PAX8) and carbonic anhydrase IX (CAIX). Clear cell RCC consists predominantly of clear cells, and these carcinomas can be difficult to distinguish from a wide variety of other clear cell tumours that may also involve the arches,

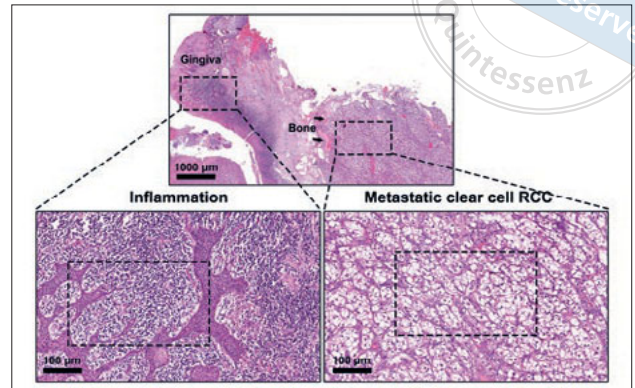
such as salivary gland (mucoepidermoid tumour, acinic cell tumour) and odontogenic tumours (calcifying epithelial odontogenic tumour, clear cell odontogenic carcinoma). IHC staining helps in this distinction. Clear cell odontogenic carcinoma immunohistochemically showed positive staining for CK-19 and epithelial membrane antigen (EMA), but negative for vimentin, SMA and S-100 protein. CK-19 has been proven to react with all kinds of odontogenic epithelial cells<sup>16</sup>. Both clear cell odontogenic carcinoma and clear cell RCC showed positive immunoreactivities in the cytoplasm for CK-19 and negative for SMA; however, most clear cell RCCs are positive for vimentin<sup>12</sup>. CK-7 staining became negative and there was a strong reaction for vimentin, which rules out salivary gland tumours<sup>17</sup>. Additionally, the previous medical history of clear cell RCC was very helpful for diagnosing a metastatic lesion to the mandible of renal origin.

Tissue biopsy specimens are extremely useful for disease diagnosis. Because the gingival mass was in the region of the mandibular lesion, it would have

been easy to assume that the gingival mass originated from the mandibular lesion and thus had the same pathological characteristics; however, the pathological characteristic of the gingival mass was chronic inflammatory cell infiltration. The biopsy specimen taken of the gingival mass does not represent the pathological characteristics of the mandibular lesion and may even lead to misdiagnosis of such lesions. The present case shows that the biopsy sites play a crucial role in the diagnosis of lesions. As a result, multiple biopsy sites are encouraged<sup>18</sup>.

The prognosis for patients with oral metastases of RCC is usually poor<sup>12</sup>. Most patients diagnosed with metastatic RCC to the oral cavity succumb to the disease within the first year, highlighting the fact that oral metastases often imply the presence of multiple metastatic sites<sup>19</sup>; however, no metastatic lesions were detected in the present patient's lungs or liver. To optimise the therapeutic effect and improve the survival rate, the mandibular lesion was excised radically in this case. After surgery, the patient was monitored diligently for 6 months, with three essential follow-up appointments scheduled. No complications or local oral recurrence were found. Regrettably, the patient chose not to attend any further examinations at the hospital. To ensure his well-being, the present authors maintained regular communication with him via phone to inquire about his condition and provide necessary support. The patient was still alive 1 year after diagnosis of the mandibular metastasis. Subsequently, metastasis was detected in the left leg and the patient died 15 months after mandibulectomy, having lived for around 2.5 years after the diagnosis of RCC.

According to the ASCO Guideline, all patients with metastatic RCC who require systemic therapy in the first-line setting should undergo risk stratification into risk grade: favourable (0), intermediate (1 to 2) and poor (3+) risk groups<sup>20</sup>. For first-line systemic treatment of metastatic RCC, patients with intermediate- or poor-risk disease should be offered combination treatment with two immune checkpoint inhibitors (ICIs) or an ICI in combination with a vascular endothelial growth factor receptor r (VEGFR) tyrosine kinase inhibitor (TKI). Patients with favourable-risk disease who require systemic therapy may be offered an ICI in combination with a VEGFR TKI. For optimal second- or later-line systemic treatment, nivolumab or cabozantinib should be offered to patients who experienced progression on a VEGFR TKI alone. Patients progressing on combination immunotherapy should be offered a VEGFR TKI, and those who progress after initial therapy combining VEGFR TKI with an ICI may be offered an alter-



**Fig 4** Pathological characteristics of the gingival mass.

nate VEGFR TKI as a single agent. Patients with bone metastases from metastatic RCC should be offered a bone resorption inhibitor when clinical concern for fracture or skeletal-related events is present. In the present case, the metastatic mandibular lesion was excised completely, which is in accordance with the ASCO guideline that recommends surgical resection for patients with low-volume metastatic RCC. There is no recommendation regarding optimal systemic treatment for metastatic RCC patients with bone metastasis. The present patient did not receive postoperative anti-tumour medication treatment.

## Conclusion

Although oral metastatic tumours only represent approximately 1% of oral tumours, oral oncologists should be aware of and fully understand the patient's medical history.

## Conflicts of interest

The authors declare no conflicts of interest related to this study.

## Author contribution

Drs Xiao Fei HUANG and Zi Li YU analysed the data, performed the reference search, and drafted and revised the manuscript. Both authors read and approved the final manuscript.

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**Table 1** Data on cases of clear cell RCC in the mandible.

Study	Histological type	Sex	Age, y	Location	Metastasis in other tissue
Pick et al <sup>15</sup>	RCCC	Male	71	Left mandible	Ribs/cervical lymph node
Jones et al <sup>14</sup>	CCRC	Female	62	Right mandible and gingiva	Femur/brain
Jones et al <sup>14</sup>	CCRC	Female	52	Right mandible	Ilium
Van der Waal et al <sup>13</sup>	RCCC	Male	48	Mandible	Not available
Ahmadnia et al <sup>8</sup>	RCCC	Male	57	Right mandible	No
Huang et al (present study)	RCCC	Male	48	Left mandible	No

CCRC, clear cell renal carcinoma; RCCC, renal clear cell carcinoma.

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