Metastatic clear cell variant of renal cell carcinoma of the mandible: Review and case report

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ABSTRACT
A case of metastatic renal cell carcinoma (RCC) to the mandible is reported. A 22-year-old man consulted us for hypoesthesia of the right lower lip. Panorama X-ray film showed a radiolucent lesion in the right mandibular body. A diagnosis of a metastatic tumor to the mandible from the right kidney was made after evaluation by computed tomography and bone scan with Tc99 methyl diphosphonate which also revealed multiple bone metastases. Histologically diagnosis was clear cell variant of RCC. Patient has been put on radiotherapy for symptomatic treatment and a molecularly targeted drug. The therapy effectively stopped the progressive growth of oral and other metastatic lesions. The quality of life is relatively well maintained with tolerable adverse effects. The patient is still on our follow-up with an improved quality of life.

Keywords: Clear cell variant of renal cell carcinoma, molecular targeted therapy, oral metastatic lesion

INTRODUCTION
Worldwide, renal cell carcinoma (RCC) is the 13th most common malignancy. Approximately, 270,000 cases of kidney cancer are diagnosed every year, and 116,000 patients die of their cancer.[1] However, metastatic tumors to the oral cavity are very uncommon and represent approximately 1% of oral neoplasms.[2] Renal carcinoma is the third most common infraclavicular neoplasm that metastasizes to the oral cavity, following that of lung and breast carcinoma.[3] RCC occurs predominantly in the sixth to eighth decade of life with a median age at diagnosis around 64 according to 2003–2007 National Cancer Institute’s Surveillance, Epidemiology, and End Results cancer statistics review. In addition, it is very rare to find in blacks and Asians. It is extremely rare rather unusual to find this tumor <40 years of age. This tumor at a younger age has certain peculiarities that it is usually symptomatic and has a chromophobe histiogy.[4,5] RCC that has metastasized at the time of initial diagnosis has an extremely poor prognosis, and more than 80% of patients die within 1 year.[6] Clear cell variant of RCC often shows local invasion and distant metastasis. Clear cell RCC (ccRCC) is the most common histologic variant, accounting for 75–88% of RCCs in contemporary surgical series.[7,8] The prognosis is worse than that of other types of tumor,[9,10] with a median survival time of 20 months for patients with zero risk factors, 10 months for intermediate risk, and 4 months for poor risk patients.[11] They have 5-year disease-specific survival rates of 50–69%, compared with 67–87% for papillary RCC and 78–87% for ccRCC.[12,13]

CASE REPORT
A 22-year-old man consulted our hospital on March 27, 2014, with a complaint of swelling of right lower face since 1½ month which was associated with hypoesthesia of the right lower lip.
for 2 months. His past history was unremarkable except for two fractures of his both forearms as a result of trauma some years back, treated by some local quack but they had healed, but now with an inability to supinate. Pertinent to mention also was the fact that he had recurrent urinary tract infection which responded to antibiotics prescribed by local medical practitioner. He also complained of mild pain in his ribs, shoulders, and back.

There was no history of fever, discharge, tooth decay, or rashes or eruptions. He had no adverse habits, bladder and bowel habits were normal, and sleep undisturbed.

His face was asymmetric with a bony hard swelling, roughly 3 cm x 4 cm with ill-defined borders, tender, nonmovable, nonfluctuant, noncompressible, and nonreducible in nature in the right body of the mandible. Overlying skin was freely movable; both cortices felt as expanded, [Figure 1a and b]. Submandibular lymph nodes in right side were palpable, tender, freely mobile, nonmatted but not increased in size. Hypoesthesia was observed in the right mental region. Associated with it was mobility of two molars 46, 47 with missing 48 but no toothache or decayed tooth.

Aspiration with an 18 gauge needle revealed blood venous but nonindicative of a vascular lesion. A fine-needle aspiration biopsy was ordered which revealed the following histology “high cellular smears comprised of discrete as well as clusters of osteoblasts with moderate to severe pleomorphism with prominent nucleoli and mitotic figures within osteoid matrix.” This raised the suspicion of a metastatic bone tumor. Hence, an incisional biopsy was planned to confirm.

In the meantime, an orthopantomogram, contrast-enhanced computed tomography (CECT) abdomen and a bone scan was ordered. Panorama X-ray film showed a diffuse radiolucent lesion of 4 cm x 5 cm in the right mandibular body. There was a loss of lamina dura around the roots of 46.47 with their circumferential resorption but not apical [Figures 2 and 3], and a 4 cm x 3 cm diffuse radiolucent lesion in the body of the mandible. On a total body scan with (Tc99 methyl diphosphonate), increased tracer uptake was seen in the right mandibular body, the upper thoracic T5 vertebrae, the right sternoclavicular joint, and the right 9th rib near angle. All these were leading to a metastatic bone disease.

After about 3 days of taking an incisional biopsy, the patient reported back with the right flank pain which turned the suspicion toward RCC. A ultrasound was ordered which was reported by the consultant radiologist as “a right renal complex cyst likely mitotic Bosniak type IV.”

Moreover, the CECT demonstrated a heterogeneous mass 4.5 cm x 3 cm at the upper pole of the right kidney with cystic changes [Figure 4a and b]. Multiple bone resorbing lesions in vertebrae, pelvis (acetabular and ischial region), right mandibular body, and left ramus and condylar region [Figure 5].

Hence, a diagnosis of RCC metastasizing to the mandible, sternoclavicular joint, rib, and vertebra and pelvis was established. It was confirmed by the histopathological examination (HPE) of the incisional biopsy which revealed a clear cell variant of the RCC [Figure 6].

These findings led to the clinical diagnosis of a metastatic tumor of the mandible from the right kidney, although characteristic clinical symptoms of renal carcinoma such as abdominal pain, hematuria, and abdominal mass were not observed. The patient was referred to the Cardiovascular Surgery, Urology, and Radiology and Medical Oncology Departments for further evaluation. The patient then underwent radiation therapy for the tumor of the mandible, as it was progressively increasing and showing a tendency to bleed, and also the tender cervical vertebral lesions as a symptomatic treatment.

Since the patient had multiple unresectable lesions all over the body, it was decided to put the patient on molecular targeted therapy. His symptoms are improving and are still on follow-up.

**DISCUSSION**

Hereditary RCC syndromes are estimated to be a reason for 3–5% of RCC cases. To date, ten such syndromes have been described, all inherited with an autosomal dominant trait.

Tobacco smoking and obesity are the most consistently established causal factors, with a dose-dependent effect and strength of the association. Moreover, male gender (Woldrich et al. 2008), hypertension (Navai and Wood 2012), and acquired renal cystic disease involve a marked risk (Maisonuneuve et al. 1999). These tumors are relatively rare, among RCC cases 3.5–7.3% have been shown to occur in those younger than 40 years.

The most common symptoms of metastatic disease are asthenia (30%), bone pain (26%), fever (17%), weight loss (15%), abdominal pain (15%), dyspnea (11%), neurological disturbances (10%), and cough (6%). However, 22% of patients with metastatic diseases are asymptomatic or atypical presentation. As was our patient. Furthermore, in a Chinese study, 26% of patients were asymptomatic, 56% had local, and 19% had paraneoplastic symptoms as stated by Ou et al.

Metastatic neoplasms to the oral cavity occur more often in patients over 60-year-old. In approximately 20% of cases, these tumors were found before the primary tumors, and most commonly developed in the molar region of the mandible. Good blood supply to the mandibular molar region is believed to contribute to hematogenous metastasis. Hypoesthesia of the lower lip with no evidence of cyst-like lesion is a crucial indication of a somewhat sinister when osteomyelitis has been ruled out. In the present case, primary or metastatic mandibular tumor was suspected from the progressive hyporesthesis of the lower lip. Nowadays, the diagnostic algorithm is to perform an abdominal ultrasound and then 2/3-phase helical computed tomography (CT) with 5 mm collimation to minimize partial volume artifacts. In our case also, using several radiological examinations such as CT, scintigraphy, and positron emission tomography, the clinical diagnosis of the renal tumor with multiple metastases was obtained.

Histologically, ccRCCs is a renal cortical tumor typically characterized by malignant epithelial cells with clear cytoplasm and a compact alveolar (nested) or acinar growth pattern interspersed with intricate, arborizing vasculature. A variable
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Figure 1: (a) Right mandibular body swelling. (b) Intraoral view of the lesion

Figure 2: Occlusal view showing moth-eaten cortex

Figure 3: Orthopantomogram showing the right body rarefaction

Figure 4: (a) Right kidney lesion. (b) Contrast-enhanced computed tomography showing the right kidney lesion

Figure 5: Vertebral body lesion

Figure 6: Histopathology of the mandibular lesion showing clear cells

The proportion of cells with granular eosinophilic cytoplasm may be present.

Clinically, ccRCCs present more often with high stage and grade and are more likely to develop distant metastases than papillary or chromophobe tumors. These non-clear cell histologies carry a favorable prognosis after nephrectomy for a localized tumor. The cystic variant of ccRCC seems to be an indolent tumor.\(^\text{[28,29]}\)

The prognosis of patients with metastatic neoplasms in the oral region is poor.\(^\text{[20,21]}\) Most patients die within 1 year since metastatic tumors in the oral region are often preceded or accompanied by multiple metastatic lesions at other sites and organs.\(^\text{[10]}\) Renal clear cell carcinoma, with metastasis at the initial diagnosis, shows an extremely poor prognosis with the median survival time of 6.3 months.\(^\text{[9-11]}\) The NCCN guideline\(^\text{[30]}\) also indicates radiation therapy for bone metastases in some instances for palliation of symptoms such as pain or cord compression.

M1 placed our patient directly in stage IV category according to the tumor, nodes, and metastases staging.\(^\text{[3]}\) Based on the most widely used Memorial Sloan Kettering Cancer Center model,\(^\text{[12]}\) our patient was classified as having good prognosis as his Karnofsky performance was >70, serum lactate dehydrogenase less than 1.5 times the upper limit of normal (ULN), hemoglobin level was within normal limits, corrected serum calcium level was less than ULN, and time from diagnosis to therapy less than 1 year. Therefore, the expected survival period according to the NCCN guidelines was thought to be about 30 months in this case.\(^\text{[30]}\)

In the present case also, same guidelines were followed, and radiation therapy was performed as surgical measures could not be done. This decreased the size of the lesions and also provided the patient with symptomatic relief. The patient was put on molecular targeted therapy and is still on our follow-up.
CONCLUSION

A case of metastatic renal clear cell carcinoma to the mandible is reported. The age of presentation of the patient as well as the presenting complaint was both unusual. The bottom line being swelling with hypoesthesia should never be underestimated, it can be fatal.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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