

Clival metastasis of renal clear cell carcinoma: Case report and literature review

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Abstract

The clivus is an atypical metastatic site for renal clear cell carcinoma (RCCC). Here we report a 54 year old man with acute cavernous sinus syndrome. Brain magnetic resonance imaging identified a clival-based lesion with associated bony erosion. The patient underwent endoscopic endonasal biopsy and partial resection of the clival mass. Because histologic examination of the resected specimen resulted in a diagnosis of RCCC, contrast-enhanced computed tomography scan of the abdomen was performed and showed an enhanced left renal mass. The patient subsequently underwent laparoscopic left radical nephrectomy and gamma knife was planned for the residual clival lesion. We also retrospectively reviewed available published reports on clival metastases, specifically those from RCCC, since 1990.

Key words: Clival metastases; Endoscopic skull base surgery; Renal clear cell carcinoma; Renal; Carcinoma

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Core tip: Clival metastasis is an extremely rare presentation of renal clear cell carcinoma. The symptom of sudden onset of cranial neuropathy, most commonly

involving the abducens nerve, and findings on radiologic examination are crucial for making an early diagnosis. Histopathological diagnosis and resection of the clival mass can be safely achieved through an endoscopic endonasal approach. Multidisciplinary management, including surgery, stereotactic radiotherapy and tumor-targeted agents, is often required to prolong survival and maximize the quality of life for patients with metastatic renal cell carcinoma.

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INTRODUCTION

Renal cell carcinoma (RCC) is the ninth most common cancer in men, and the fourteenth most common in women^[1]. Approximately 90% of kidney cancers are RCCs^[2,3]. The most common subtype is renal clear cell carcinoma (RCCC), comprising about 75%-80% of RCCs in surgical series^[4]. Almost one-third of patients with RCC present with metastatic disease. The usual metastatic sites are lungs (45.2%), bone (29.5%), lymph nodes (21.8%), liver (20.3%), adrenal gland (8.9%), and brain (8.1%)^[5]. Tumors originating primarily in the clivus region are very rare. Chordomas, which are the most frequent tumor affecting that region, represent only 0.15% of all intracranial tumors and 6% of all skull base tumors^[6,7]. Common differential diagnoses of clival neoplasms are meningioma, chordoma, lymphoma, pituitary adenoma, nasopharyngeal carcinoma, bone marrow reconversion, and metastatic lesions^[8]. Clival metastases from RCCC account for a small proportion of clival tumors. Few cases have been reported.

CASE REPORT

A 54-year-old man presented to the ophthalmology outpatient clinic of our institution with asthenia for one month and acute onset drooping of his right eyelid with diplopia for fourteen days. He had smoked ten cigarettes daily for 30 years. On admission, physical examination revealed palsies of right cranial nerves III, IV, VI, and V2 manifesting as right-sided ptosis, diplopia, and decreased sensation over the right cheek. Both pupils were normal in size and reacted to light.

Results of routine laboratory tests were normal apart from a high urinary red blood cell (RBC) of 14.80/hpf. A non-contrast brain magnetic resonance imaging (MRI) showed a mass with irregular margins in the clivus. The mass was invading the sphenoid and cavernous sinuses bilaterally and encasing both carotid arteries. It was isointense on T1-weighted images and slightly hyperintense on T2-weighted images (Figure 1). Brain

computed tomography (CT) scan showed obvious osteolysis of the cranial base involving the clivus and both petrous apices. There was marked enhancement of the clival lesion following intravenous contrast injection (Figure 2).

To obtain a tissue diagnosis and decompress the cavernous sinus, the patient underwent endoscopic endonasal transclival resection of the lesion. Intraoperatively, the tumor was noted to be firm and highly hemorrhagic. Massive bleeding necessitated interruption of the procedure and caused a marked drop in blood pressure. Hemostasis was achieved once the tumor had been partially resected and 400 mL of blood transfused. An early postoperative CT scan showed no evidence of major complications. Immediately after the procedure, the patient's right-sided ptosis and diplopia improved slightly. Pathological examination of the operative specimen resulted in a diagnosis of clear cell carcinoma (Figure 3A). Ki67 was expressed in 10%-20% of the neoplastic cells and immunohistochemical staining was positive for cytokeratin, vimentin, CK8/18, paired box gene 8 and cluster of differentiation 10. On the sixth postoperative day, the patient underwent a contrast-enhanced CT scan of the abdomen, which showed a slightly inhomogeneous, enhancing, roundish mass in the upper pole of the left kidney. No tumor thrombus in the left renal vein or retroperitoneal lymphadenopathy was detected. Contrast-enhanced thoracic CT scan showed no pulmonary metastases (Figure 4). Laparoscopic left radical nephrectomy was performed twelve days after the clival surgery. A 4 cm × 4 cm × 4.5 cm tumor and a 2 cm × 2.5 cm × 2.5 cm isolated tumor satellite focus were noted in the posterosuperior part of the left kidney. The patient did not develop any postoperative complications such as abdominal infection and was discharged ten days after the second surgery. Histopathologic examination of the resected kidney resulted in a diagnosis of RCCC consistent with that of the intracranial tumor (Figure 3). The patient underwent gamma knife for the residual clival lesion one month later. An MRI performed one month after this procedure demonstrated expected postoperative changes. At the four month follow-up, the patient was in good general condition, though his right cavernous sinus syndrome had not improved. Further follow-up is ongoing.

DISCUSSION

Most reports of metastases to the clivus have been in the form of case reports, case images, or small series^[9]. We performed an extensive review of available reports on clival metastases from RCCC and identified nine patients, including the present case (Table 1). The male/female ratio was 5:4 and mean age was 54 years (range 27-62 years). The clival metastasis was diagnosed first in seven of the nine patients. The main clinical manifestations were sixth nerve palsy, headache, and diplopia. Our results are similar to those reported by Dekker *et al.*^[10]. All reported primary RCCCs were

Table 1 Case reports of clival metastasis from renal clear cell carcinoma

Ref.	Age/sex	Symptoms	First diagnosis and interval	Position and size of Primary Tumor	Surgery for clival metastasis	Surgery for primary tumor	Additional treatment	Follow-up
Fumino <i>et al</i> ^[28]	58/M	Diplopia	Clival metastasis, NA	The left kidney, 6 cm × 4 cm	None	Left radical nephrectomy	Radiotherapy to the clivus	NA
Endo <i>et al</i> ^[29]	59/M	Occipital pain, dysarthria, CN XII palsy	Clival metastasis, NA	The right kidney, 9 cm	None	None	Radiotherapy for the clivus	DOD (6 mo)
Sepúlveda <i>et al</i> ^[30]	62/M	Sixth nerve palsy, dysarthria, right tongue deviation and right facial paralysis	Clival metastasis, NA	The right kidney, NA	Biopsy	None	Radiotherapy and palliative care	NA
Patel <i>et al</i> ^[31]	59/F	Headaches and acute onset cranial nerve neuropathies	Clival metastasis, NA	The left kidney, NA	Endoscopic endonasal near complete resection	None	Palliative radiation treatment	NA
Mendelson <i>et al</i> ^[32]	59/F	Headaches and dropping of left eye with double vision	Clival metastasis, NA	The left kidney, NA	Endoscopic decompression of clival lesion	None	Palliative radiotherapy for renal mass	NA
Mani <i>et al</i> ^[12]	55/M	Headache and diplopia photophobia of right eye	Clival metastasis, NA	The left kidney, 6.5 cm × 6.0 cm × 5.5 cm	None	Biopsy	External beam radiation therapy and supportive palliative care	DOD (6 mo)
Gil Salu <i>et al</i> ^[33]	56/F	Diplopia	Primary RCCC, 8 yr	The right kidney, NA	Endoscopic endonasal partial resection	Right nephrectomy	NA	NA
Santhosh <i>et al</i> ^[34]	27/F	Pain in right lower limb	Primary RCCC, NA	The right kidney, NA	None	Right radical nephrectomy	Immunotherapy	AWD (28 mo)
Zhang <i>et al</i>	54/M	Asthenia and drooping of his right eyelid with diplopia	Clival metastasis, 6 d	The left kidney, 4 cm × 4 cm × 4.5 cm	Endoscopic endonasal biopsy and partial resection	Laparoscopic left radical nephrectomy	Gamma knife for residual clival lesion	AWD (4 mo)

F: Female; M: Male; NA: Not available; AWD: Alive with disease; DOD: Dead of disease.

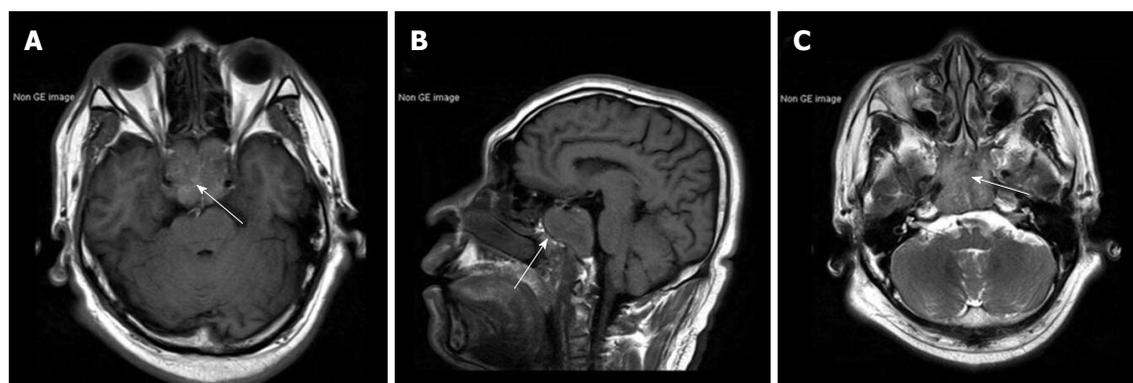


Figure 1 Brain magnetic resonance images. A: Axial T1-weighted magnetic resonance imaging (MRI) showing isointense mass (white arrow) with encasement of the bilateral carotid arteries; B: Sagittal T1-weighted MRI showing sphenoid sinuses involvement (white arrow); C: Axial T2-weighted MRI showing hyperintense central areas suggest cyst degeneration or central necrosis (white arrow).

unilateral.

The clivus, part of the skull base, is located between the foramen magnum and dorsum sellae and lies deep in the midline in intimate relationship with various

critical neurovascular structures^[9,11]. In particular, the sixth nerve is very prone to involvement by tumors growing from the clivus and petroclival regions because of its long serpentine course from the brainstem to the

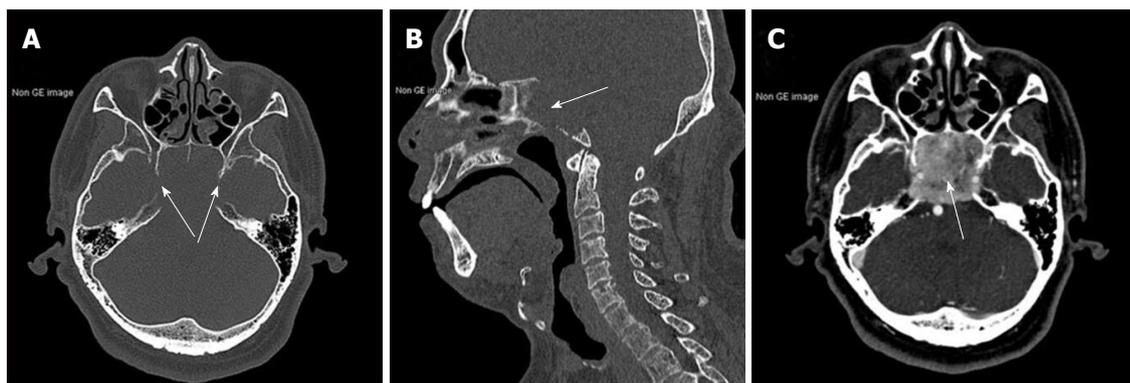


Figure 2 Brain computed tomography scans. A: Axial computed tomography (CT); B: Sagittal CT showing obvious osteolysis at the cranial base with clivus and bilateral petrous apices (white arrow); C: Axial CT angiogram showing obvious enhancement (white arrow) after intravenous contrast injection.

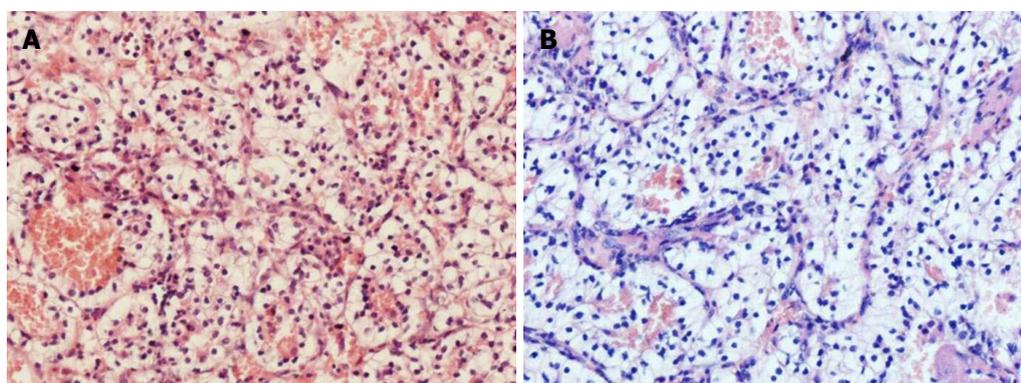


Figure 3 Histological findings. A: H and E stain of the clival lesion, 200 ×; B: H and E stain of the left renal mass, 200 × showing clear cells with alveolar growth and separated by reticular separation of thin wall vessels. The two lesions demonstrated similar histopathologic features.

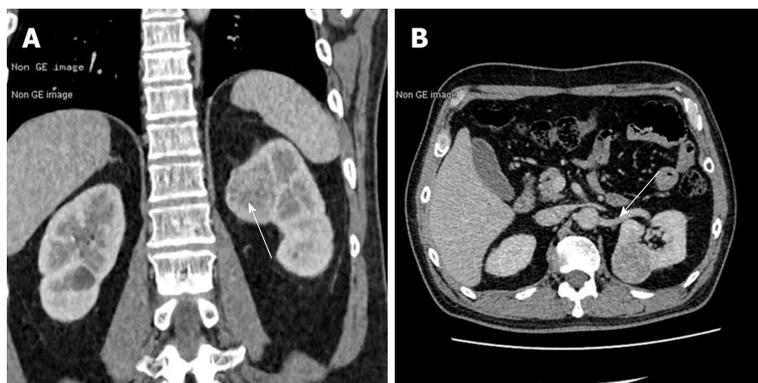


Figure 4 Contrast-enhanced computed tomography scans of abdomen. A: Coronal contrast-enhanced computed tomography (CT) showing slightly inhomogeneous enhancing round-like mass (white arrow) located at the upper pole of the left kidney; B: Axial contrast-enhanced CT showing no tumor thrombus in the left renal vein (white arrow) and retroperitoneal lymphadenopathy revealed.

superior orbital fissure^[12]. Abducens nerve palsy was the presenting manifestation in 46% of patients with chordoma and 47% of those with chondrosarcoma reported by Deconde *et al*^[13]. Above 40% of clival metastases present with isolated sixth nerve palsy according to the review conducted by Dekker *et al*^[10]. That our patient's tumor extended into the right cavernous sinus may explain the presence of multiple cranial nerve palsies. The possibility of metastatic RCCC should be

considered in patients with a clival lesion and cranial neuropathies. Patients with RCC usually present with the classical triad of macroscopic hematuria, abdominal mass, and flank pain. However, many such tumors are asymptomatic and detected incidentally on health check-ups or imaging examinations^[2].

Most reported diagnoses of clival metastases are based on imaging examinations including CT, MRI, positron emission tomography scan with CT (PET-CT) and

radionuclide bone scans using technetium or gallium^[14]. The superior sensitivity of MRI in detecting bone marrow diseases allows precise localization and evaluation of the signal characteristics of clival lesions^[8]. Because of its central location, the clivus is best seen on a midsagittal view on MRI. A normal clivus characteristically shows mild enhancement. Low-intensity clival lesions in the marrow tend to be isointense with normal marrow on contrast enhancement. Thus, unenhanced images are more sensitive for detecting clival lesions^[8,15]. The usual normal adult clival signal is iso- or hyperintense compared with the pons on T1-weighted images and approximately isointense with the pons on T2-weighted images. Replacement of fatty bone marrow by clival lesions may explain why most clival lesions appear hypointense on T1-weighted images and hyperintense on T2-weighted images^[8,12]. Integrated PET-CT has been shown to be an effective means of preoperative staging and follow-up surveillance of patients with skull base tumors (overall sensitivity of 77% and specificity of 81%)^[14]. However, clival metastases do not appear to have any distinctive radiological features. Radiologic examinations alone have limited ability to distinguish metastases from primary lesions such as chordomas and chondrosarcomas^[16].

An endoscopic endonasal approach is reported as a promising option for managing clival lesions with minimal morbidity^[17]. With the use of a rigid endoscope and angled telescopes, an endoscopic endonasal approach provides a significantly wider and better-illuminated surgical field than traditional open surgeries^[18]. In the articles we reviewed, an endoscopic endonasal approach was used in four patients to obtain a biopsy or achieve partial resection. Endoscopic skull base surgeries aided by surgical navigation systems based on preoperative imaging, such as CT and MRI, allow the surgeon to recognize critical structures and maximize the precision of the resection^[18]. The application of intraoperative navigated angiosonography techniques for skull base surgery may be helpful in approaching the tumor and avoiding vascular damage^[19]. However, endoscopic endonasal approaches have some limitations, including limited working space, reduced maneuverability, and the need for special instrumentation. It is important to carefully select the most appropriate approach for each patient on the basis of patient- and tumor-related factors as well as the experience of the surgeon.

RCC can be associated with a favorable outcome when diagnosed at an early stage^[20]. Unfortunately, 30% of these patients have metastatic disease at diagnosis or after treatment of local disease^[20]. The largest published retrospective study comprised 286 patients with brain metastases from RCC and their median survival was 9.63 mo^[21]. Disease-specific prognostic factors include Karnofsky performance status and the number of brain metastases. A study by Vickers *et al*^[22] revealed that histologic diagnoses of RCC are more common in patients with brain metastases than in those with metastases to other sites (96%

of these patients had clear cell histology). The median survival of patients with brain metastases from RCC is reportedly 14.4 mo, whereas that of patients with RCC without brain metastases is 19.0 mo^[22].

Although multiple advances have been made in systemic therapy for RCC, management of metastatic RCC (mRCC) is still challenging^[4]. Surgical treatment of our patient, namely partial removal of the metastatic lesion, nephrectomy, and gamma knife treatment were performed successively because he had a solitary metastasis and his physical status was good. The role of radiotherapy in the treatment of RCC remains unclear and it is not recommended^[23]. However, several case series have reported that stereotactic radiotherapy is a valuable means of reducing local symptoms from tumor bulk and stabilizing the growth of metastatic lesions in both cranial and extracranial sites^[2,24]. Approximately 70% of RCCs are associated with loss of function of the von Hippel-Lindau gene (VHL). VHL can result in high concentrations of hypoxia inducible factor (HIF) and vascular endothelial growth factor (VEGF), which facilitates tumor-associated angiogenesis^[25]. Tumor-targeted therapies for RCC can combat tumor angiogenesis and inhibit tumor cell proliferation. Extended clinical trials of sunitinib and sorafenib have shown that these targeted drugs improve the efficacy of treatment of brain metastasis from RCC^[26,27]. A combination of surgery, stereotactic radiotherapy, and non-targeted and/or targeted agents is often required for management of mRCC. Clinicians should always focus on the goals of treatment and tailor an individual treatment plan to ensure the best possible outcomes.

ARTICLE HIGHLIGHTS

Case characteristics

A 54-year-old man with a history of smoking presented with asthenia and acute right cavernous sinus syndrome.

Clinical diagnosis

Palsies of right cranial nerves III, IV, VI, and V2, likely caused by intracranial lesions.

Differential diagnosis

Differential diagnoses included clival chondroma, clival chondrosarcoma, intraosseous lymphoma, and meningioma.

Laboratory diagnosis

Results of routine laboratory tests were normal, apart from a high urinary red blood cell of 14.80/hpf.

Imaging diagnosis

Non-contrast brain magnetic resonance imaging demonstrated a mass lesion in the clivus with irregular margins that had invaded the sphenoid and cavernous sinus bilaterally. Brain computed tomography (CT) scan showed obvious osteolysis of the cranial base involving the clivus and both petrous apices. Contrast-enhanced CT scan of the abdomen showed a slightly inhomogeneous, enhancing, roundish mass in the upper pole of the left kidney.

Pathological diagnosis

Histopathological examination of the operative specimens revealed clear cells

in an alveolar pattern, being separated by a reticular meshwork of thin walled vessels.

Treatment

Endoscopic endonasal partial resection of the clival metastasis. Laparoscopic left radical nephrectomy of the primary renal clear cell carcinoma (RCCC). Gamma knife for the residual clival lesion.

Related reports

Few reports of clival metastasis from RCCC have been published. These tumors tend to be very aggressive, as evidenced by presentation at an advanced stage of the disease. Multidisciplinary management is necessary.

Term explanation

The Karnofsky Performance Scale is a means of classifying patients' functional impairment. Scores can be used to compare effectiveness of different therapies and assess the prognosis of individual patients. The lower the Karnofsky score, the worse the prognosis.

Experiences and lessons

Clival metastasis from RCCC should be considered in the differential diagnosis of bony lesions of the clivus in patients with cranial neuropathy of sudden onset. Early diagnosis, clinical experience, and multidisciplinary management are crucial for effective treatment of such lesions.

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