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CASE REPORT

Confronting Orbital Metastasis of Renal Cell Carcinoma – Retrospective Case Series

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ABSTRAK

Kami melaporkan 3 kes karsinoma sel renal metastatic (RCC) dengan gejala okular dan orbital sebagai tanda pertama. Dua kes yang pertama melibatkan pesakit warga emas dengan gejala serupa iaitu protrusi mata unilateral tanpa sakit, kemerosotan tahap penglihatan dan pembengkakkan kulit kepala temporal. Pemeriksaan menunjukkan proptosis, jisim keras pada kulit kepala temporal dan kemerosotan fungsi saraf optik. Pengimejan otak dan orbit menunjukkan tumor sayap sphenoid ekstraksial dengan infiltrasi ke otot temporalis. Pembedahan pemotongan tumor dilakukan pada salah seorang pesakit dengan pemeriksaan histopatologi yang menunjukkan RCC varian sel jernih. Tomografi berkomputer toraks, abdomen dan pelvis (CT TAP) kemudiannya menunjukkan RCC dengan metastasis. Kes ketiga adalah RCC yang menyamar sebagai mata buta yang menyakitkan pada seorang lelaki berusia 65 tahun yang pada awalnya dirawat sebagai glaukoma mutlak dan menjalani prosedur eviscerasi. Semasa pembedahan, jisim fibrotik yang melekat pada permukaan dalaman cangkerang sklera kemudiannya disahkan oleh pemeriksaan histopatologi sebagai RCC metastatik. Ketiga-tiga pesakit tersebut tidak menunjukkan tanda dan gejala sistemik RCC. Ciri-ciri yang dikongsi dalam kes-kes ini, faktor risiko yang berpotensi, perkembangan klinikal, intervensi terapeutik, hasil dan cabaran yang dihadapi dalam mendiagnos penyakit yang jarang berlaku ini juga dibincangkan dalam artikel ini.

Kata kunci: *Gejala okular; karsinoma sel renal; metastasis orbital*

ABSTRACT

We reported three rare cases of metastatic renal cell carcinoma (RCC) with ocular and orbital symptoms as the first presentation. The first two cases depicted both elderly patients with a similar presentation of unilateral painless eye protrusion, blurring of vision and temporal scalp swelling. Examination revealed non-axial proptosis, temporal scalp firm pulsating mass and optic nerve dysfunction. Brain and orbit imaging revealed an extra-axial sphenoid wing tumour with infiltration to the temporalis muscle. Tumour excision was performed in one of the patients

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with histopathological examination showing RCC of clear cell variant. Subsequent computed tomography of thorax, abdomen and pelvis (CT TAP) revealed RCC with metastasis. The third case was RCC masquerading as a painful blind eye in a 65-year-old gentleman who was initially treated as absolute glaucoma and subjected to evisceration. Intraoperatively an adherent fibrotic mass on the inner surface of the scleral shell was later confirmed by histopathological exam as metastatic RCC. None of the patients has systemic signs and symptoms of RCC. Shared characteristics among these cases, potential risk factors, clinical progression, therapeutic interventions, outcomes, and challenges encountered in accurately diagnosing this uncommon disease were also discussed in this article.

Keywords: Ocular symptom; orbital metastasis; renal cell carcinoma

INTRODUCTION

Renal cell carcinoma (RCC) is a relatively infrequent malignancy with exceedingly rare occurrence of orbital metastasis. The diagnosis often experiences delays, particularly in instances where patients exhibit no overt systemic complaints. This case series study aims to elucidate the presentation of RCC in three distinct cases, where orbital and ocular metastases constituted the initial manifestations. We also delved into the shared characteristics among these cases, potential risk factors, clinical progression, therapeutic interventions, outcomes and challenges encountered in accurately diagnosing this uncommon disease.

CASE REPORT

Case 1

Our first patient is a 69-year-old Chinese man who complained of right eye redness, progressive painless protrusion, generalised blurring of vision and right temporal scalp swelling for the past 4 months. He had been a chronic smoker of 50 pack-years. He was initially diagnosed as right eye conjunctivitis by the general practitioner, given antibiotic eye drops but failed to respond. He denied haematuria, flank pain or any constitutional symptoms.

Examination revealed right eye inferotemporal dystopia with non-axial proptosis. Scalp examination revealed a right temporal firm pulsating mass measuring 8 x8 cm with no obvious skin changes (Figure 1). Right eye visual acuity was reduced to 6/24 with a positive grade 3 relative afferent pupillary defect (RAPD). Optic nerve function was also impaired as evidenced by reduced red saturation and light brightness. Extraocular movement of the right eye was limited at all gazes. Conjunctiva was mildly injected. Intraocular pressure (IOP) was raised to 29 mmHg. Cornea was clear with a quiet anterior chamber. Fundus was unremarkable with no optic disc swelling, choroidal folds or torturous vessels. Systemic examination did not reveal any obvious abnormality such as palpable lymph nodes or organomegally.

Magnetic resonance imaging (MRI) brain and orbit revealed an extra-axial right sphenoid wing tumour measuring 5.0 x 5.2 x 5.6 cm with bone destruction and infiltration to the right temporalis muscle and right optic nerve (Figure 2a). A combined craniotomy and tumour excision was performed alongside with our neurosurgical colleagues.

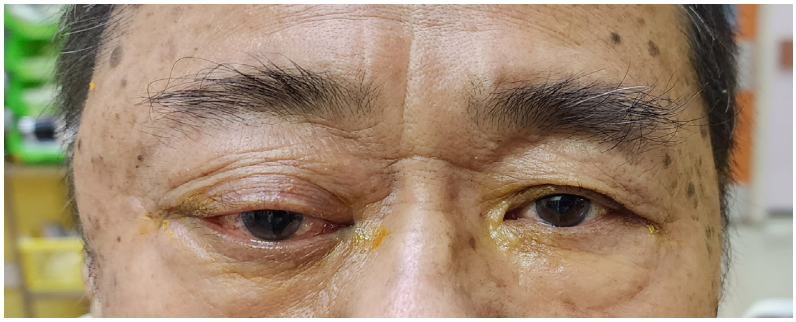

FIGURE 1: Photo of case 1 showed right eye redness, proptosis and temporal scalp swelling

Histopathological examination came back as round, pleomorphic neoplastic cell with clear cytoplasm which was suggestive of RCC with a clear cell variant. Subsequent computed tomography of thorax, abdomen and pelvis (CT TAP) showed a right kidney mass with multiple lung nodules (Figure 2b). Patient was referred to oncology department and was prescribed with tablet pazopanib 400 mg once per day for tumour progression control. After the orbital tumour resection, his best corrected vision improved to 6/12 with nearly full range of extraocular muscle movement. Additionally, optic nerve function showed improvement, as evidenced by a reduction in RAPD to grade 1 and normal results on the Farnsworth D-15 test. At the time of writing, patient was coping well with the treatment.

Case 2

Our second case is a 73-year-old Chinese lady who presented with progressive left eye painless protrusion, generalised blurring of vision and diplopia for 2 months. She had no systemic complaint. She was a smoker of 8 packs/year. Examination showed left eye visual acuity of 6/60, non-axial proptosis,

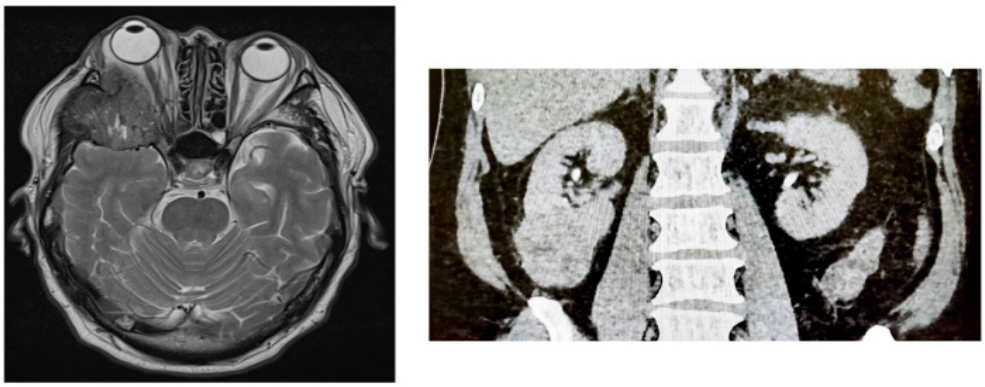

FIGURE 2: (a) MRI T1 weighted image of case 1 revealed an extra-axial mass arising from the right sphenoid wing with adjacent bone erosion, extending into the right retroorbital region; (b) CT TAP of case 1 showed a heterogeneous lobulated hypodense mass at the lower pole of the right kidney

limited extraocular muscle movement, and impaired optic nerve function evidenced by grade 2 RAPD and abnormal Farnsworth D-15 test. A firm, multilobulated and pulsatile mass over the left superotemporal orbit extending to the supraorbital region was noted. Fundus examination showed a pale optic disc with a 0.7 cup disc ratio over the left eye. Systemic examination was unremarkable. CT orbit showed a mass arising from the left greater wing of sphenoid bone with lytic destruction and infiltration to the left lateral rectus, left superior oblique, and lacrimal gland (Figure 3a). Surveillance CT TAP revealed a left renal mass with para-aortic lymph nodes, lungs and bone metastasis (Figure 3b). A provisional diagnosis of RCC with metastasis was made. However, patient refused surgical intervention and opted for palliative care. Patient eventually succumbed to the disease 7 months after the diagnosis.

Case 3

Our third case is a 65-year-old Chinese gentleman with underlying ischaemic heart disease and hypertension who presented with right eye blindness and progressive pain for the past 2 years. He was also a smoker of 30 pack-years. He had right eye poor vision since the age of 15 years for unknown reason. He was diagnosed with absolute glaucoma and treated with transcleral cyclophotocoagulation (TSCPC) once in another eye centre but subsequently was referred for second opinion due to intractable eye pain. On examination right eye vision was no light perception with positive RAPD. IOP was 90 mmHg. Cornea was opaque with generalised conjunctival injection and scleral thinning. B-scan ultrasound did not show any intraocular mass. A diagnosis of painful blind eye secondary to absolute glaucoma was made, and evisceration was performed. Intraoperatively, an unusual finding of adherent fibrotic mass on the inner surface of the scleral shell raised the suspicion of malignancy, which was later confirmed by histopathological examination as RCC with clear cell type. Blood investigations such as renal profile and tumour marker were within normal range. CT orbit revealed a well-defined heterogeneously enhancing right

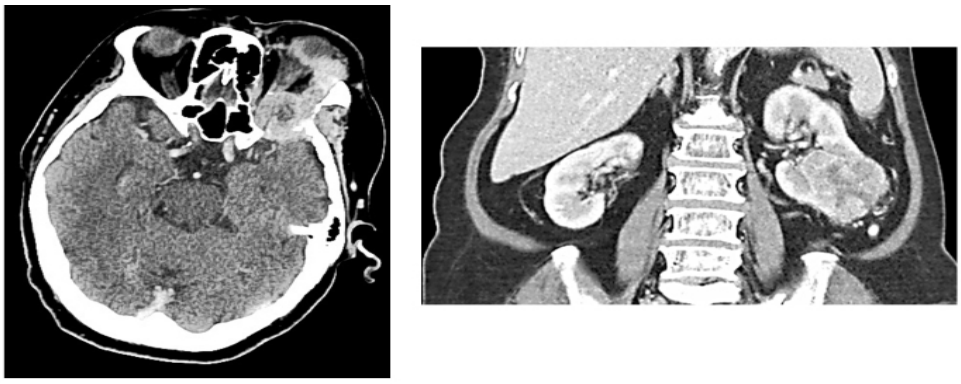

FIGURE 3: (a) CT orbit showed a large intraconal lobulated mass arising from the left greater wing of sphenoid with bony destruction and lateral rectus infiltration. b) CT abdomen showed RCC at lower pole of the left kidney. These features were strikingly similar to our case 1 patient except for the laterality

intraconal lesion arising from the distal part of the affected optic nerve, with rest of the right optic nerve appearing bulky and enhancing (Figure 4). However, we were unable to detect the primary tumour or other distant metastasis during the surveillance CT TAP scan. Patient was treated with right eye exenteration and orbital radiotherapy. He eventually succumbed to local recurrence and brain metastasis 2 years later.

DISCUSSION

The ocular and orbital metastases stemming from RCC represent a rare subset, constituting less than 2% of metastatic occurrences in the eye (Kurli & Finger 2005). The classical symptoms of haematuria, abdominal pain and flank mass only occur in less than 10% of the patients with RCC (Luciani et al. 2000). Nowadays more than 50% of RCC cases are detected incidentally (Hsieh et al. 2017; Lázaro et al. 2020), reflecting the heightened utilisation of abdominal imaging modalities capable of discerning small, localised tumours measuring less than 4 cm in size (Sun et al. 2011).

Orbital metastases can be the initial presentation of previously undiagnosed cancer in up to 25% of patients with orbital metastatic lesions (Ahmad & Esmaeli 2007). The prevalence of orbital metastasis from RCC is notably low, ranging from 3.9% to 5%, with breast and prostate cancers rank as the most common sources (Palmisciano et al. 2021; Shields et al. 2001). The most frequently involved site by metastatic RCC is the orbit (36.8%), followed by choroid (29.4%) (Shome et al. 2007). The three cases share distinctive commonalities, including an age of 65 and above, Chinese ethnicity, a history of chronic smoking, and ocular symptoms as the initial presentation. Intriguingly, there were no overt systemic signs or symptoms indicative of RCC, representing a diagnostic challenge. Differentials for our first two patients include lacrimal tumour, orbital lymphoma and cavernous haemangioma. As for our third patient, malignancy was not suspected initially as the patient presented with typical signs and symptoms suggestive of absolute glaucoma.

Smoking is one of the notable risk factors identified in this case series. The association between smoking and RCC is robust, with a heightened relative risk of 1.54 for men and

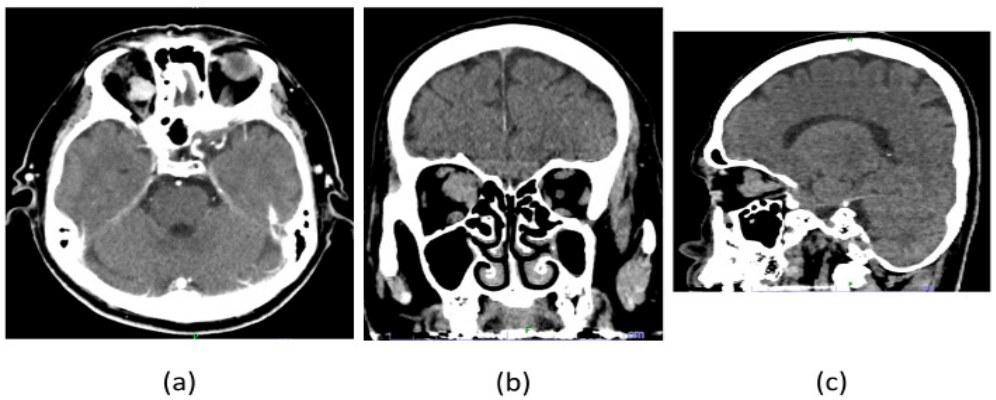

FIGURE 4: CT brain and orbit of case 3 showed axial (a), coronal (b), and sagittal (c) cut of post eviscerated eye with a well define heterogenous intraconal lesion arising from distal part of the right optic nerve, abutting right medial and superior rectus muscles. No evidence of bone erosion was seen

1.22 for women (Hunt et al. 2005). Dose-dependent increment in risk associated with the number of cigarettes smoked per day is also observed. Crucially, smoking cessation emerges as a protective measure - individuals with 11-20 years of cessation exhibit a more favourable risk profile compared to those who quit smoking within the preceding 11 years (Theis et al. 2008). This finding underscores the importance of inquiring about the patient's smoking history and advocating for smoking cessation. Importantly, heavier smoking is linked to an increased risk of advanced RCC, and durable smoking cessation has been associated with a reduction in the likelihood of advanced disease (Tsivian et al. 2011).

Proptosis was found in two of our patients, aligning with one of the most prevalent presentations of orbital metastasis, with a reported range from 26 to 78.4% (Wladis et al. 2021). The tumour infiltrated the right temporalis muscle in our first patient and the left lacrimal gland in the second patient, resulting in the development of a palpable mass over the superotemporal orbit. Pulsating mass at the superotemporal region with dystopia provides critical clues regarding the vascular nature of the lesion. Pulsating orbital mass has been reported in the literature, owing to the feeding vessels from ophthalmic and maxillary arteries (Howard et al. 1978). Bleeding during tumour resection in our first patient was profuse, approximately 2 litres of blood loss, reflecting the vascular nature of the tumour. Pulsation may also result from the transmission of cerebrospinal fluid pulsation through a destructed orbital bone, adding complexity to the diagnostic considerations (Korn et al. 2021). These factors should be conscientiously factored into the surgical planning for tumour resection.

The diagnostic utility of a CT scan is pivotal in the differentiation of lesions. Well-encapsulated, discrete and focal intraconal masses are unlikely to be metastases while masses which involve the extraocular muscles and bone are more likely to be metastases (Allen 2018). This discrimination is paramount in guiding clinical decision-making. Eldesouky & Elbakary (2015) found that variable degree of osteolytic lesion were reported in CT orbital scan in 73.3% of their patients with orbital metastatic mass. This finding is congruent with the CT results observed in our first and second patients. Of significance, the sphenoid bone is the second most common site of orbital metastasis after extraocular muscles due to the relatively high volume of low-flow blood in this area (Korn et al. 2021). Therefore, clinicians should be particularly attentive to the presence of osteolytic lesions originating from the sphenoid bone, as this should prompt a heightened suspicion of metastatic cancer.

Orbital tumours can present a diagnostic challenge, mimicking symptoms characteristic of both primary and secondary glaucoma (Yang et al. 2015). Mechanisms of tumour causing high IOP include tumour invasion-related outflow obstruction, trabecular meshwork seeding, neovascularisation, angle closure due to compressive and inflammation (Radcliffe & Finger 2009). Notably, the identification of solid fibrotic tissue adhering to the sclera during evisceration raised suspicion of potential malignancy involving choroidal tissue with scleral invasion. The decision to perform evisceration in cases of unsuspected ocular malignancies warrants careful consideration, as it has been associated with a poor outcome attributed to orbital recurrence and metastasis (Lemaître et al. 2017). It is imperative to exercise diligence in investigating any abnormal findings during routine eye procedures. Based on our case, we strongly recommend sending the excised tissue for histopathological examination.

This precautionary measure is essential in preventing the oversight in the diagnosis of ocular malignancies, ultimately contributing to timely interventions.

Currently, the surgical approach for RCC metastases remains a subject of ongoing exploration, especially given the relatively rare incidence (Kang & Wojno 2019). However, orbital metastasectomy may be appropriate to improve the patient's symptoms of pain, diplopia, disfiguring proptosis and visual function (Ahmad & Esmaeli 2007). For systemic treatment, RCC has exhibited notable resistance to traditional chemo and radiotherapy (Kurli & Finger 2005). However, radiotherapy can still play a role in palliating symptoms of bone and brain metastases (Choueiri & Motzer 2017). Immunotherapy such as tyrosine kinase inhibitor, immune checkpoint inhibitors and anti-vascular endothelial growth factor (VEGF) antibody has emerged as first-line treatment for metastatic RCC (Lázaro et al. 2020). These modalities function by inhibiting angiogenesis and vascular proliferation of RCC through inhibiting VEGF receptor, thereby impeding the progression of RCC (Rassy et al. 2020). Despite the anticancer treatment, patient prognosis is still poor in the presence of orbital metastasis, with the 5 years survival rate of merely 8% (Choueiri & Motzer 2017). Nevertheless, a cohort study by Schwab et al. (2018) demonstrated a high response rate of patient treated with tyrosine kinase inhibitor with a significant improvement in survival rate. This highlights the importance of a multidisciplinary approach to address the complexities associated with orbital metastases.

CONCLUSION

Diagnosing RCC with orbital metastasis poses a formidable challenge when systemic signs and symptoms are absent. The ocular presentation alone can mimic common eye conditions such as conjunctivitis and glaucoma as demonstrated in our case series. A meticulous clinical assessment, coupled with precise imaging studies and histological examination, may assist in unravelling the correct diagnosis. While treatment is mainly palliative, orbital metastasectomy can be a viable option which holds the potential to restore vision and improve the patient's quality of life.

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