Case Report

RENAL CELL CARCINOMA CHOROIDAL METASTASIS WITHOUT THE PRIMARY TUMOUR: A CASE REPORT AND REVIEW

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ABSTRACT

A 65-year-old Chinese man sought treatment for right painful blind eye of 2 years duration which progressively worsened over time. His vision had been poor since the age of 15 years old. He was unsure of the cause. He was initially treated as a case of painful blind eye secondary to glaucoma and evisceration was performed. The vitreous cavity was found to be filled with hard fibrotic tissue. Histopathological examination revealed metastatic renal cell carcinoma, clear cell variant. Further investigation was performed and he underwent exenteration in view of right optic nerve involvement. All tumour markers were negative. Computed Tomography (CT) thorax, abdomen and pelvis did not reveal any primary tumour. There were no signs and symptoms to suggest renal pathology.

INTRODUCTION

Renal cell carcinoma (RCC) is a rare malignancy characterized by a variety of clinical features. It represents approximately 3% of all adult malignancies and ranks 13th in frequency of all carcinomas [1,2]. Renal cell carcinoma has been documented to metastasize to every organ in the body although metastasis to the eye and orbit is uncommon. Metastases may present decades after the removal of the primary disease. However, it is uncommon for patients who present with ocular metastasis before primary RCC is identified. We report a rare and unique case of metastatic renal cell carcinoma presenting as a choroidal mass despite no evidence of primary tumour.

CASE REPORT

A 65-year-old, Chinese gentleman, with underlying hypertension, dyslipidemia and ischemic heart disease presented with a right-sided painful blind eye for 2 years which became progressively more intense. He had a history of right poor vision since the age of 15 but was unsure of the cause. The pain was associated with redness and tearing of the affected eye. He experienced headache, but no nausea or vomiting. There was no aggravation factor and occasionally relieved by analgesia. On the first visit to the ophthalmologist, he was told to have high intraocular pressure and planned for laser transscleral cyclophotocoagulation and counselled for evisceration. He was referred to us for a second opinion. On examination, he has no perception of light in his right eye, while the left best corrected visual acuity(BCVA) was 6/12 due to very early cataract. The affected eye was phthisical with the presence of generalized conjunctiva injection and uveal tissue visualised underneath thinned sclera at 11 o'clock. Seidel test was negative. Intraocular pressure (IOP) was 90 mmHg. Due to cornea opacity, the posterior segment was unable to be examined. We proceed with B-scan ultrasonography examination of the right eye which revealed the loss of globe contour with no obvious mass detected (Figure 1). A diagnosis of painful blind eye secondary to absolute glaucoma was made hence evisceration was performed. Intraoperatively, we noticed that there was multiple strongly adhered hard fibrotic mass on the inner surface of the scleral shell. Histopathological examination showed hyaline stroma infiltrated by atypical cells arranged in nest and papillary-like pattern, hyperchromatic nuclei, with a surrounding area of osseous metaplasia, haemorrhage and tissues necrosis which suspicious of metastatic renal cell carcinoma (Figure 2).

A systemic workup was done and tumour marker showed negative for α-Fetoprotein (AFP), prostate-specific antigen (PSA), carcinogenic embryogenic antigen (CEA), CA 125 and CA 19-9. CT scan of the brain, orbit, thorax, abdomen and pelvis was

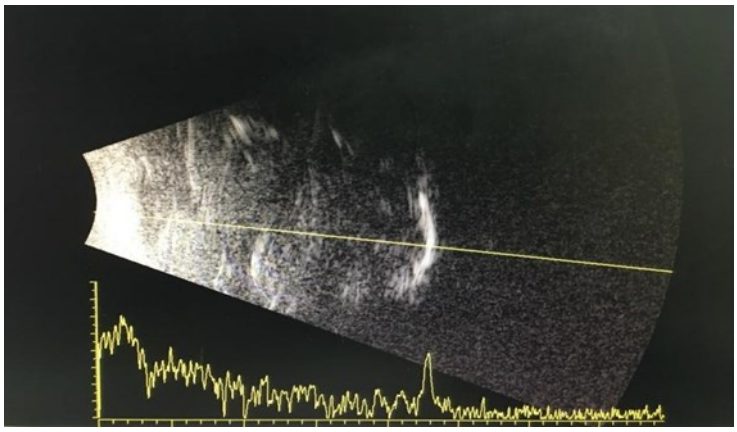

Figure 1: B-scan showing loss of globe contour with no obvious mass able to be detected.

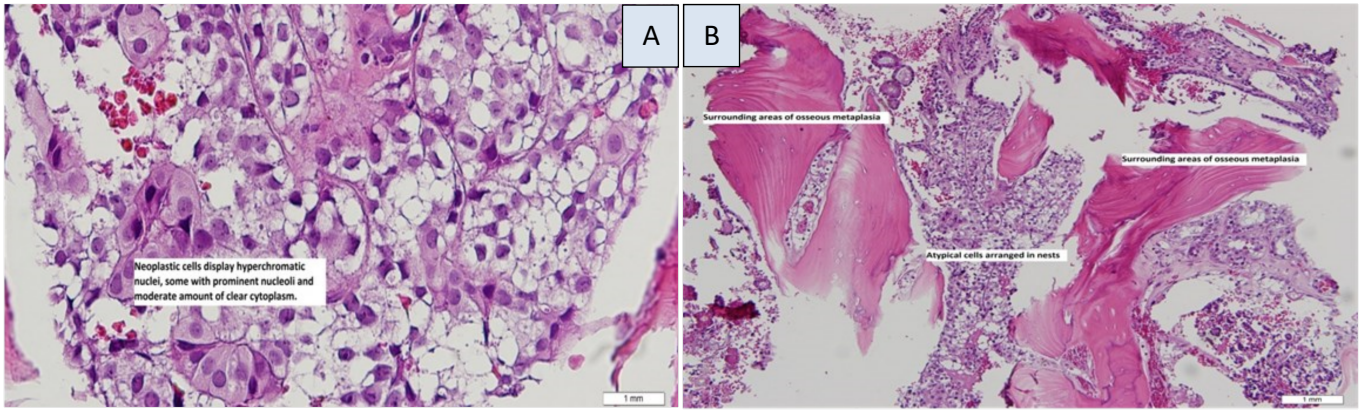

Figure 2A: Neoplastic cells display hyperchromatic nuclei, some with prominent nucleoli and moderate amount of clear cytoplasm.
Figure 2B: Hyaline stroma infiltrated by atypical cells arranged in nest and papillary-like pattern with surrounding area of osseous metaplasia.

performed to search for the primary tumour. A well-defined heterogeneously enhancing right intraconal lesion was seen, which arose from the distal part of the affected optic nerve, with the lesion abutting the right superior rectus muscle. The rest of the right optic nerve appeared bulky and enhancing (Figure 3). Otherwise, it did not extend intracranially. The lungs, abdomen and both kidneys showed normal enhancement with no focal lesion seen. Interestingly, there was no CT evidence of primary renal tumour.

Subsequently, we proceeded with exenteration of his right orbit. Biopsy from optic nerve was taken. Microscopically, it showed infiltration of malignant cells arranged in papillary architecture with a fibrovascular core consistent with papillary adenocarcinoma (Figure 4). Immunohistochemically, the malignant cells are positive for renal cell carcinoma and PAX8, which suggest kidney in origin (Figure 5). He was then referred to the oncology department and started with radiotherapy.

DISCUSSION

Renal cell carcinoma (RCC) is previously known as hypernephroma to describe adenocarcinoma or clear cell carcinoma of the kidney. It represents approximately 3% of all adult malignancies and ranks 13th in frequency of all carcinomas [1,2]. It usually occurs in male between the ages of 30 and 60 years. Metastases commonly occur, with about 40% of patients presenting with metastatic disease [1,2]. The occurrence of distant metastasis appears in approximately one-third of cases after nephrectomy. However, metastasis can also appear as the first presenting sign of RCC. The most common sites of metastatic spread are lung (76%), regional lymph nodes (66%), bone (42%), and liver (41%) [1]. Among all eye neoplasms, only a minority is due to renal cell carcinoma. In a pathology survey, only 7 out of 196 cases of ocular metastatic carcinoma originated from renal cell carcinomas [3]. Ocular structures involved include iris (9%), ciliary bodies (2%) and choroid (88%) although eyelid, orbital, extraocular muscles,

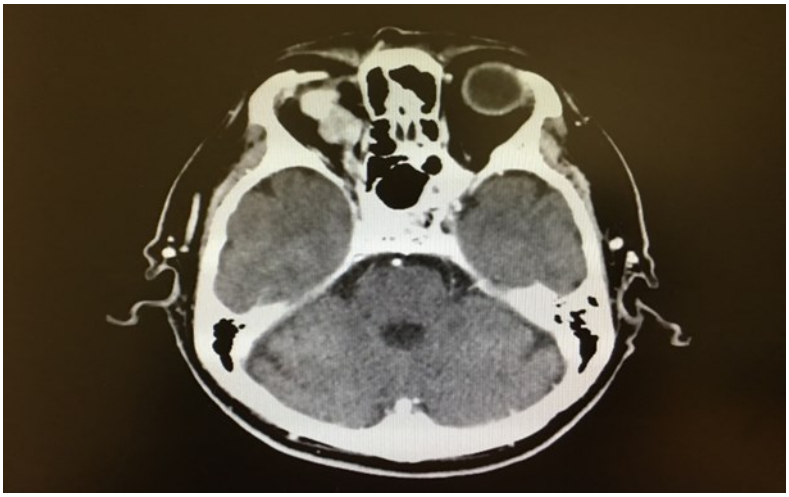

Figure 3: Arrow showing a well-defined heterogenously enhancing right intraconal lesion, which appeared to arise from distal part of the right optic nerve. The rest of the right optic nerve appeared bulky.

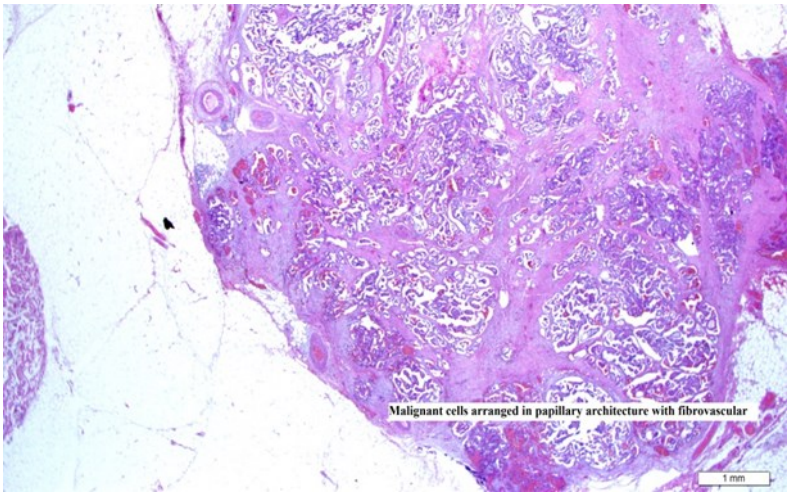

Figure 4: Infiltration of malignant cells arranged in papillary architecture with fibrovascular core, consistent with papillary carcinoma

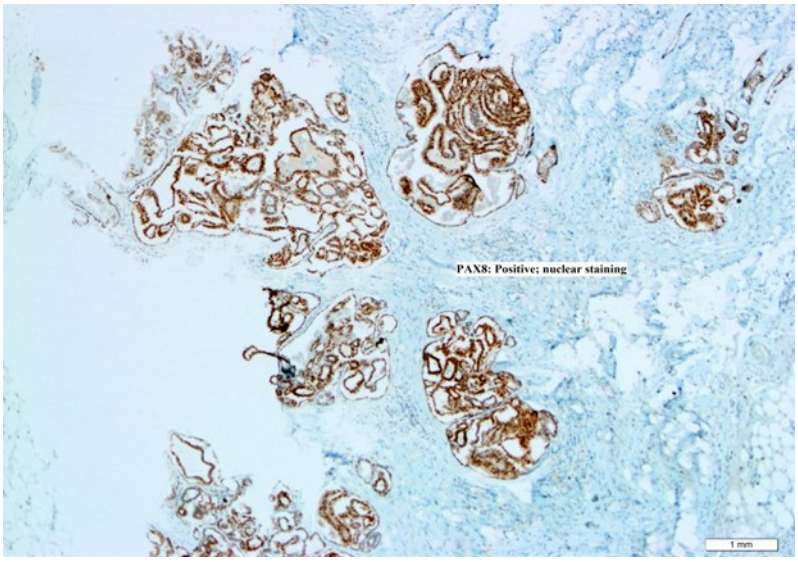

Figure 5: Nuclear staining positive for PAX 8 in immunohistochemistry test

lacrimal gland, conjunctiva, sclera, retina and optic nerve involvement have also been reported [4,5].

Choroid is the most common site for ocular metastasis due to its high vascularity. Metastasis to the ciliary body and iris is rare but has been described as a fleshy mass with prominent vascularisation [4]. Choroidal metastases generally appear as a unifocal, solitary, yellow or reddish-orange-coloured mass in fundus examination. However, it is difficult to distinguish it from non-pigmented choroidal melanoma and other types of metastases. This reddish coloured tumour can also be seen in cases of choroidal haemangioma and other metastases [6]. A study of uveal metastasis in 520 eyes by Shield et al revealed that tumour appeared as a solitary mass (71%) with the mean basal width of 9 mm and mean thickness of 3 mm. Other associated findings include subretinal fluid (73%) and retinal pigment epithelial alterations (57%), vitreous opacities, retinal infiltrates and haemorrhages [7]. There is also finding of vitreous haemorrhage as an initial sign of RCC. Haimovici et al. (1997) described a case of a 77-year-old man with known renal cell carcinoma who presented with hemorrhagic retinal detachment from choroidal metastasis [6].

Reported cases of ocular metastasis from renal cell carcinoma are summarized in Table 1. The clinical features of choroidal metastases are variable and till now no sufficient data to distinguish them from other types of metastatic carcinoma. Choroidal metastases commonly present with complaints of painless loss of vision, loss of peripheral visual field, myodesopsia or pain due to neovascular glaucoma [8]. In our case, the patient presented with right painful blind eye with high intraocular pressure. Given the history of many years of unknown cause for poor vision since childhood with no known systemic illness, a diagnosis of secondary glaucoma was made, hence laser transscleral cyclophotocoagulation (TSCPC) was performed once by the first attending ophthalmologist. He was then referred to our centre for intolerable eye pain despite TSCPC and maximum topical anti glaucoma medication.

Metastasis from renal cell carcinoma frequently cause diagnostic confusion as it may not present with the clinical triad of haematuria, pain, and abdominal swelling. Other signs and symptoms include weight loss, night sweats and malaise. The most common eye symptoms are blurred vision, flashes of lights and floaters. Orbital proptosis, ptosis, lid swelling, diplopia, or cranial nerve palsies are commonly associated with orbital metastasis. Patients may complain of pain due to secondary inflammation and glaucoma. However, these symptoms occur in only less than 10% of cases [8]. Almost half of the cases with ocular metastases had ocular signs and symptoms that preceded the diagnosis [3,9], similar to our case. Interestingly, another feature of RCC is the tendency for long latency periods between the primary diagnosis and metastatic presentation which can manifest from months to years, with the most extended case reported up to 25 years after the nephrectomy [10]. In contrast, all these signs and symptoms were absent in our case, except for recent unilateral painful blind eye which accounts for only 10% of RCC cases as reported by Kurli et al. [8].

A retrospective review conducted by Shields et al. (1997) revealed that among 520 patients with uveal metastasis, only 2% of them were found to have primary renal cell carcinoma [9]. Shield also revealed that 34% of patients had no previous history of cancer and at the end of the study, the primary site remains unknown in approximately half of these patients (17%) despite extensive investigations [9]. Many of them have a high risk of mortality and eventually die by a disseminated metastatic disease with the primary site still undiscovered as demonstrated in our case. Majority of RCC cases were detected through systemic evaluation and multi-modality imaging of ultrasonography, CT scan and magnetic resonance imaging. However, in our case, CT scan of thorax, abdomen and pelvis revealed no evidence of primary tumour.

In our patient, we postulated the lesion was from uveal tissue, judging from visualized uveal tissue seen underneath the thinned sclera. Its origin was unsure as we were unable to view the fundus as the cornea was very opaque. The origin of the lesion cannot be ascertained from B-scan ultrasonography due to loss of globe contour with no apparent mass can be detected. B-scan has substantial clinical variability with findings usually mimick choroidal melanoma mass, with low internal reflectivity and acoustically hollow lesion [2,11]. In case of choroidal involvement in RCC, there is homogenous lesion with presence of a dome-shaped lesion and collar button configuration seen in B-scan [2]. Our patient had no known history of renal cell carcinoma, and no suspicion for metastases when performing B-scan. The only information that alerted us was the presence of hard fibrotic mass intra-operatively, which strongly adhered to the inner scleral shell which probably arises from the choroid.

Accurate diagnosis is possible through clinical findings in only 11 (16.4%) out of 68 cases of ophthalmic metastasis of RCC in the literature, whereas histopathology examination (HPE) is crucial in aiding diagnosis in the rest [12]. This emphasises the role of histopathology and immunohistochemistry in the diagnosis of metastatic renal cell carcinoma as per our case. It was only confirmed after second biopsy from the optic nerve, which revealed positive nuclear staining for PAX 8 in immunohistochemistry test (Figure 5).

The management of renal cell carcinoma involves treatments of the primary tumour with one or a combination of surgery, chemotherapy, radiotherapy, or immunotherapy. If nephrectomy for primary tumour has already performed, the intraocular and orbital metastasis is generally treated with radiotherapy [12]. Realistically, ophthalmologic treatment, in our case, was exenteration for his intractable pain since he also had optic nerve involvement. Our patient was also referred to the oncology team for radiotherapy.

Table 1: Review of the reported cases of ocular metastasis from renal cell carcinoma

Authors	Case	Age	Sex	Chief complaint	Duration	RCC	Location of ocular mets	Ophthalmic examination	Imaging	Biopsy
Wyzinski P et al (1981)	1	60	M	Right painless blurred vision	1month	Nil	Bilateral iris	2.8mm fleshy mass at both iris collarette	-	Iris mass: Clear cell carcinoma
Kindermann WR et al (1981)	2	66	M	Expanding mass Left upper lid	10 days	Nephrectomy & radiotherapy 15 months earlier	Left upper eyelid	Ovoid mass 12x 8x 4mm pointed towards lid margin	-	Eyelid mass: Metastasis from RCC
	3	58	M	Left eye photopsia, floaters, nasal field defect	5 weeks	Nephrectomy for urinating blood 9 years earlier	Left posterior segment	Choroidal mass 12mm diameter and 5mm elevation	USG : dome shaped mass lesion 8mm, acoustic hollowness with choroidal excavation	Enucleated eye: Malignant cells suggestive of RCC
	4	58	M	Vertical diplopia	-	Nephrectomy 15 years earlier	Right eye inferior orbital rim	Mahogany-coloured mass 15 x 15 x 10mm, posterior to orbital septum, not adherent to periosteum	USG : Discrete mass that was separate from globe CT orbit : well delineated mass suggestive orbital hemangioma	Malignant tumour cells suggestive of RCC
Haimovici R et al (1997)	5	54	M	Left eye foreign body sensation	2 months	Right Nephrectomy 18 years earlier for chronic flank pain	Left posterior segment	Reddish-white, dome-shaped mass 9mm x 8mm diameter superotemporal, serous retinal detachment (RD)	A-scan : choroidal mass 3.9mm with medium-to-high reflectivity	Autopsy done for sudden death : RCC found in left choroid, right lung, peripancreatic lymph nodes, left kidney, right cerebellum
	6	62	M	Left eye pain, decreased vision, floaters	6 weeks	Nil	Left iris and posterior segment	Left eye posterior synechiae with iris neovascularization. Fundus: vitreous opacity, large scattered creamy choroidal infiltrates, intraretinal hemorrhages and perivascular sheathing	FFA : obliterated retinal capillaries, blocked fluorescence at deeper choroid, staining in more superficial lesion	No eye biopsy Renal biopsy: RCC

Table 1: Review of the reported cases of ocular metastasis from renal cell carcinoma (continued).

Authors	Case	Age	Sex	Chief complaint	Duration	RCC	Location of ocular mets	Ophthalmic examination	Imaging	Biopsy
	7	48	M	Right eye metamorphopsia	1 week	Nil	Right posterior segment	Pigmented mass at inferior border of optic disc with serous RD	USG : mass 14 x12mm across base, 6.4mm height	No eye biopsy Renal mass biopsy: RCC
	8	66	F	Left eye photopsia and blurred vision	1 week	Left nephrectomy 9 years earlier	Left posterior segment	Whitish bilobed choroidal mass 17 x 12mm superior arcade, RPE mottling periphery and serous RD	USG: mass with 3mm elevation, low internal reflectivity FFA : early and intense hyperfluorescence with pooling in subretinal space	No eye biopsy
	9	77	M	Right eye decreased vision	3 months	Nephrectomy 6 years earlier	Right posterior segment	Reddish-orange, amelonotic, lobulated mass inferotemporal with hemorrhagic RD	A-scan: low-to-moderate reflectivity tumour with 13mm elevation	Enucleated globe : Metastatic RCC
Pompeu ACL et al (2005)	10	59	M	Diplopia and mass right eye	3 months	Haematuria 1 year with flank pain	Right conjuntiva	Conjunctiva lesion causing proptosis	CT scan: retroocular mass inferior to optic nerve	Inferior rectus: Metastatic adenocarcinoma, renal origin
	11	72	M	Right eye lesion	-	Nil	Right inferior tarsal conjunctiva	6mm ulcerated lesion at tarsal conjunctiva	-	Conjunctiva: Clear cell carcinoma
Debraj et al (2007)	12	67	M	Left eye gradual painless blurred vision	3 months	Nephrectomy 14 months earlier	Left iris and posterior segment	Dilated feeder vessels. Left orange-red mass 2.8 x 1.5mm at nasal part of iris extending to ciliary body (CB) posteriorly with shallow exudative RD	B-scan : high reflectivity of nasal aspect CB, shallow RD	Iris mass: Large polygonal clear epithelial cells suggestive of RCC
	13	58	M	Left eye painful proptosis with blurred vision	6 months	Nil	Left orbit	8mm proptosis with hard, palpable mas superior aspect of orbit, chemosis and corneal exposure	CT scan: Diffuse irregular soft tissue mass involving superior, temporal and inferior parts of orbit	Orbital mass: Metastatic adenocarcinoma

Table 1: Review of the reported cases of ocular metastasis from renal cell carcinoma (continued).

Authors	Case	Age	Sex	Chief complaint	Duration	RCC	Location of ocular mets	Ophthalmic examination	Imaging	Biopsy
	14	23	F	Right gradual painless blurred vision and proptosis	3 months	Nephrectomy 7 months earlier	Right orbit	4mm non tender orbital mass with axial proptosis	CT scan: Soft tissue mass entire right orbit, both intraconal and extraconal with intracranial extension	-
Zachary C et al (2014)	15	79	M	Left eye floaters and photopsia	3 weeks	Nephrectomy 8 years earlier	Left posterior segment	Left eye dense vitreous haemorrhage (VH)	USG : intraocular cavitated mass 17mm in basal diameter x 11mm thick MRI orbit: oval-shaped enhancing solid mass	Fine needle aspiration biopsy: Malignant cells suggestive metastatic RCC
Komanski CB et al (2017)	16	73	M	Left eye redness and progressive blurring of vision	2 months	Nephrectomy 4 years earlier	Left posterior segment	Pigmented ciliochoroidal mass nasally, subsequently progress to exudative RD after plaque radiotherapy	B-scan: 15 x 12 x 7mm solid homogenous mass A-scan: medium internal reflectivity	Enucleation: Metastatic clear-cell RCC
Bellerive C et al (2017)	17	73	M	Right blurred vision	2months	History of RCC 25 years earlier, Nephrectomy	Right Posterior segment	Amelanotic choroidal lesion (19.9mm x 17.1mm in diameter, 9.5mm height), mild VH, exudative RD	USG: Dome-shaped lesion with collar button	Enucleated globe: Metastatic clear-cell renal origin

In short, diagnosing RCC metastasis can be extremely confusing. Patients with intraocular metastasis may remain undiagnosed unless they become symptomatic. A detailed history taking such as previous nephrectomy and specific or non-specific renal signs will be beneficial to aid in the diagnosis. All patients must be carefully examined and investigated, particularly when they present with a suspected ocular metastasis with no history of malignancy.

The main highlight of this case was till this date, we are still unable to identify and detect the location of primary tumour. Renal assessment by the nephrology team could not rule out the possibility of renal being primary tumour. There was absence of urinary symptoms and other signs to suggest a concurrent renal pathology. All relevant tumour markers were negative and CT thorax, abdomen and pelvis showed no evidence of any primary tumour. A study by Ferry *et al*. (1974) revealed that the interval from ocular therapy to the detection of a primary tumour in the Figure 3: Arrow showing a well-defined heterogenously enhancing right intraconal lesion, which appeared to arise from distal part of the right optic nerve. The rest of the right optic nerve appeared bulky. Kidney can be up to one year [3]. Therefore, even with no apparent source of primary tumour at time of assessment, a patient must be closely observed and followed up in the urology department to enable early detection should the tumour arise later.

CONCLUSION

This is a case of a rare disorder, made more confounding by its uncommon presentation. It appeared as a pathology in the eye and had no apparent signs and symptoms to suggest that the primary disease was in the kidney. Unfortunately, the uncommon presentation and the lack of renal symptoms had lulled the patient into complacency. By highlighting this case, we hope to bring awareness to this condition and improve its current dismal prognosis through early diagnosis.

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