SURVEY OF OPHTHALMOLOGY VOLUME 52 • NUMBER 2 • MARCH–APRIL 2007

ELSEVIER

CLINICAL PATHOLOGIC REVIEWS

MILTON BONIUK AND STEFAN SEREGARD, EDITORS

Metastasis to the Eye and Orbit from Renal Cell Carcinoma—A Report of Three Cases and Review of Literature

Debraj Shome, MD, FRCS,[1] Santosh G. Honavar, MD, FACS,[1] Pankaj Gupta, MD,[1] Geeta K. Vemuganti, MD,[2] and P. Vijay Anand Reddy, MD[1]

[1]Ocular Oncology Service; and [2]Ophthalmic Pathology Service, LV Prasad Eye Institute, Hyderabad, India

Abstract. We report three cases of renal cell carcinoma metastatic to the eye and orbit and review the relevant literature. The case reports of a 67-year-old man, a 58-year-old man, and a 23-year-old woman with metastatic renal cell carcinoma are described. The iris mass occurred in a 67-year-old man, a known case of renal cell carcinoma. Whereas the orbital metastasis in the 58-year-old man was the initial presenting sign in a hitherto undiagnosed patient, the orbital metastasis in the 23-year-old female patient was detected following nephrectomy for renal cell carcinoma. Renal cell carcinoma metastasizing to the eye and orbit are very rare, with only 68 cases reported previously. In patients presenting with atypical orbital or ocular masses, the possibility of renal cell carcinoma metastasis should be considered, especially if there is a history of previous renal disorder. Incisional biopsy with histopathological evaluation may be an important means to diagnose this condition and facilitate appropriate therapy. (**Surv Ophthalmol 52**:213–223, 2007. © 2007 Elsevier Inc. All rights reserved.)

Key words. eye • iris • metastasis • orbit • renal cell carcinoma

Renal cell carcinoma (RCC), a tumor originating from the renal cortex, accounts for 2% of all systemic malignancies but constitutes over 80% of all malignant renal tumors.[22] RCC has been reported to occur nearly twice as often in men as in women and predominantly occurs in individuals in their seventh and eighth decades of life. Although most of the cases of RCC are sporadic, there is a known association with von Hippel-Lindau (vHL) disease, a familial cancer predisposition syndrome. Around 40% of patients with vHL disease develop RCC in their lifetime.[26]

About 30% of patients have overt metastasis at the time of initial diagnosis of RCC with the most common sites of involvement being lung parenchyma, bones, liver, and brain.[30] Unusual sites of metastases are characteristic of RCC, however, and virtually any organ site can be involved including the thyroid, pancreas, skeletal muscle, and skin or underlying soft tissues.[30]

Intraocular and orbital metastasis of RCC are rare, with Ferry and Font's series of 227 cases of metastatic tumors to the eye demonstrating only seven cases (3%) of metastasis from a RCC primary.[8] Herein we present three case reports of RCC metastasis, one to the iris and two to the orbit, and review all available English language literature with reports of ocular and orbital metastasis of RCC.

© 2007 by Elsevier Inc.
All rights reserved.

0039-6257/07/$–see front matter
doi:10.1016/j.survophthal.2006.12.004

Case Reports

CASE 1

A 67-year-old man presented with gradual painless reduction in vision in the left eye for 3 months. He had been noted to have high intraocular pressure and was on treatment with oral acetazolamide and topical timolol maleate 0.5% eye drops. The patient had undergone right nephrectomy 14 months ago for RCC. He had metastasis to paraaortic lymph nodes but had not received any form of adjuvant therapy.

The best corrected visual acuity was 20/25 in the right eye and it was unremarkable. The affected left eye had a visual acuity of 20/50. The intraocular pressure by applanation tonometry was 41 mm Hg in the left eye. There was an elevated orange-red mass measuring 2.8 × 1.5 mm present in the nasal aspect of the iris of the left eye, associated with dilated episcleral feeder vessels (Fig. 1A). Gonioscopy demonstrated the iris mass extending to the nasal aspect of the left anterior chamber angle. Fundus examination showed the mass extending posteriorly to involve the ciliary body from 7:30 to 9:30 and overhanging the peripheral retina with shallow exudative retinal detachment. High-frequency immersion B-scan ultrasonography confirmed the involvement of the nasal aspect of the ciliary body with high surface reflectivity and medium regular internal reflectivity with an overlying shallow exudative peripheral retinal detachment.

Fine needle aspiration cytology (FNAC) from the iris mass by the translimbal approach demonstrated clumps of large polygonal clear epithelial cells with abundant foamy cytoplasm, vesicular nucleus, and small nucleoli suggestive of a renal cell carcinoma metastasis (Fig. 1B).

The patient underwent technetium-99m bone scan, a chest computed tomography scan, and ultrasonography and computed tomography scan of the abdomen. The computed tomography scan of the chest revealed multiple hilar and parenchymal lesions suggestive of lung metastasis. The bone scan showed intense technetium uptake in the lower cervical vertebral region suggestive of metastasis (Fig. 1C). The left eye received 3,000 cGy anterior portal external beam radiotherapy. The patient also received palliative alfa-interferon systemic immunotherapy, 3 million units, intravenous injection, alternate days, for three months.

The patient was reviewed 6 weeks following completion of radiotherapy. The iris mass had completely resolved with scarring. The visual acuity was stable and the intraocular pressure was controlled. The patient was alive with systemic

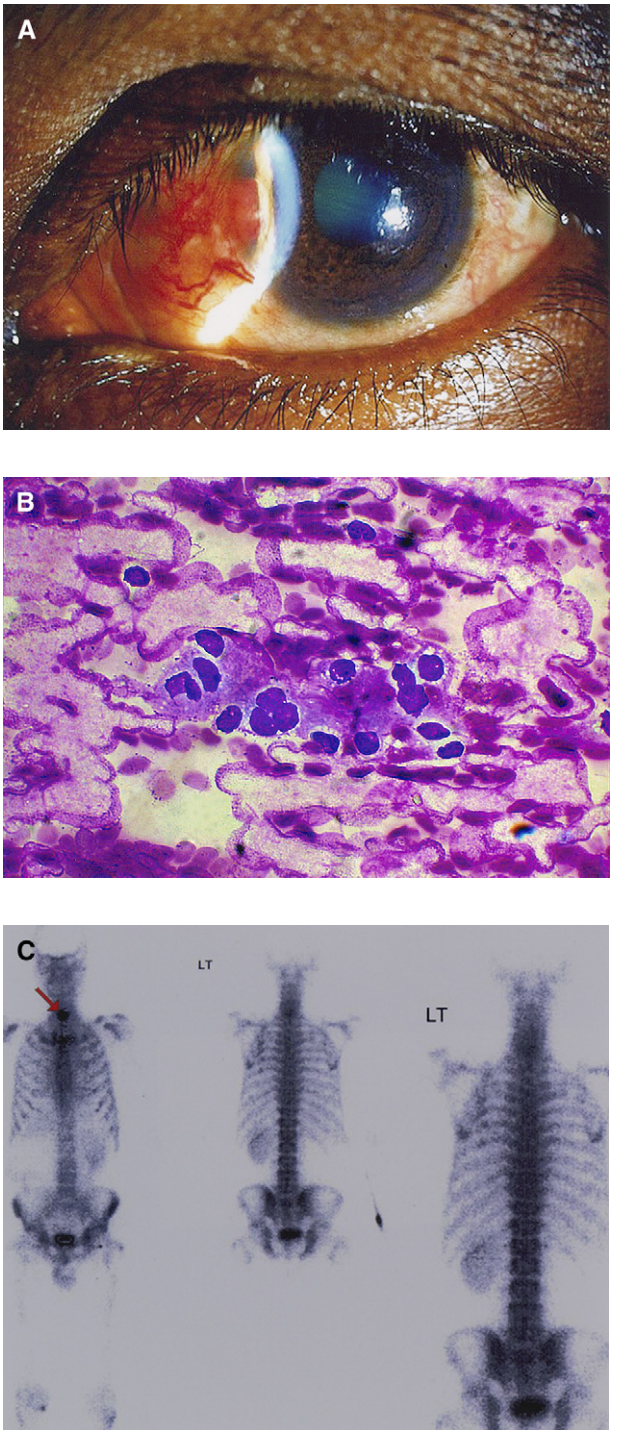

Fig. 1. 67-year-old man with iris metastasis from RCC. *A:* Clinical photograph showing an elevated orange-red mass present on the nasal aspect of the iris of the left eye. *B:* Photomicrograph of fine needle aspiration cytology sample demonstrating a few clumps of large polygonal clear epithelial cells with abundant foamy cytoplasm, vesicular nucleus and small nucleoli. (hematoxylin and eosin ×100). *C:* Technetium 99m bone scan showing the presence of increased uptake in the cervical vertebral region (arrow).

metastasis at the last follow-up 6 months after the iris metastasis was detected.

CASE 2

A 58-year-old systemically healthy man was referred with a progressively worsening painful proptosis and decrease in vision in the left eye for six months. On examination, the best-corrected visual acuity was 20/20 in the right eye. It was unremarkable. The affected left eye had light perception. There was an 8-mm proptosis of the left eye (Fig. 2A) with a hard palpable mass in the superior aspect of the orbit. Extraocular movements were grossly restricted in all directions of gaze in the left eye. There was conjunctival chemosis, and corneal exposure with diffuse cellular infiltration. No further view of the anterior segment or posterior segment structures was possible.

Computed tomography scan showed a diffuse irregular soft tissue mass involving the superior, temporal, and the inferior portions of the left orbit (Fig. 2B). Incisional biopsy of the mass was performed by an anterior orbitotomy approach. Histopathological evaluation showed a highly cellular lesion. The cells were predominantly arranged in glands, follicles, and in small clusters and infiltrating tissue planes and vascular structures. A single layer of cuboidal cells with abundant cytoplasm, vesicular nuclei, and prominent nucleoli lined the glandular structures. On periodic-acid Schiff (PAS) staining, a PAS-positive mucinous secretory material was seen within the gland-like structures. These features were suggestive of a metastatic adenocarcinoma (Figs. 2C–2E). Computed tomography scan of the abdomen revealed an enhancing mass with low central attenuation in the upper pole of the right kidney and another eccentric moderately enhancing soft tissue mass in the middle of the right kidney, highly suggestive of a renal cell carcinoma (Fig. 2F). The patient was advised palliative radiotherapy to the right kidney and the left orbit. However, he elected not to pursue any form of treatment.

CASE 3

A 23-year-old woman presented with a 3-month history of gradual, painless reduction in vision and proptosis of the right eye. She had undergone right nephrectomy for RCC 7 months prior to developing visual symptoms. Past medical records showed that there had been involvement of the paraaortic regional lymph nodes.

There was no light perception in the right eye. It showed 4-mm axial proptosis with a diffuse, firm, non-tender orbital mass. The ocular motility was restricted in all directions of gaze. The intraocular pressure by applanation tonometry was 29 mm Hg. Gonioscopy demonstrated angles open to the scleral spur. The right eye demonstrated a relative afferent pupillary defect. Fundus examination showed temporal optic nerve head pallor in the right eye. The left eye was unremarkable.

A computed tomography scan showed an irregular soft tissue mass involving the entire right orbit. The mass involved the intraconal as well as the extraconal space and contiguously extended intracranially and to the ethmoidal sinus as well. Systemic evaluation did not reveal features of vHL disease. The patient refused any further intervention to prove the clinical diagnosis. She was referred to the oncologist with a clinical suspicion of orbital and intracranial metastasis of RCC for possible palliative therapy. The patient was subsequently lost to follow-up.

Discussion

Metastasis from a systemic malignancy is one of the most common malignant intraocular tumors in an adult.[33] Among intraocular metastasis, the choroid has been found to be involved in 88%, the iris in 9%, and the ciliary body in 2%.[31] In cases of choroidal metastasis, breast and lung metastasis together accounted for more than two thirds of the primary tumor sites.[31] The breast is the most common site of primary cancer in women, followed by the lungs. In men, the lungs are the most common sites of primary malignancy.[31] The kidney was the site of the primary in only 2% patients, in this series.[31] Shields et al, in their experience of 520 eyes with choroidal metastasis, noted that 34% of patients gave no previous history of cancer.[31] In approximately half of these (17%), the primary site remained undiagnosed in spite of extensive systemic investigations.

Metastasis is a rare cause of a mass in the orbit, comprising 3–7% of the cases.[4] It is more likely to be found in elderly individuals, the mean age of the patients in different series being around 60 years, with patients most commonly presenting with proptosis or diplopia.[4,9,10] Other possible signs and symptoms at presentation include pain, diminished vision, ptosis, and enophthalmos.[4,10] It is not uncommon to have orbital metastasis with an occult primary, as seen in almost one third of the cases.[4,10] The most common sources for orbital metastases are carcinoma breast in women and carcinoma lung and prostate in men.[4,10] Other common primary sites are the gastrointestinal tract, kidney, and thyroid.[4,10] Orbital metastases from renal cell carcinoma, however, are rarely reported.

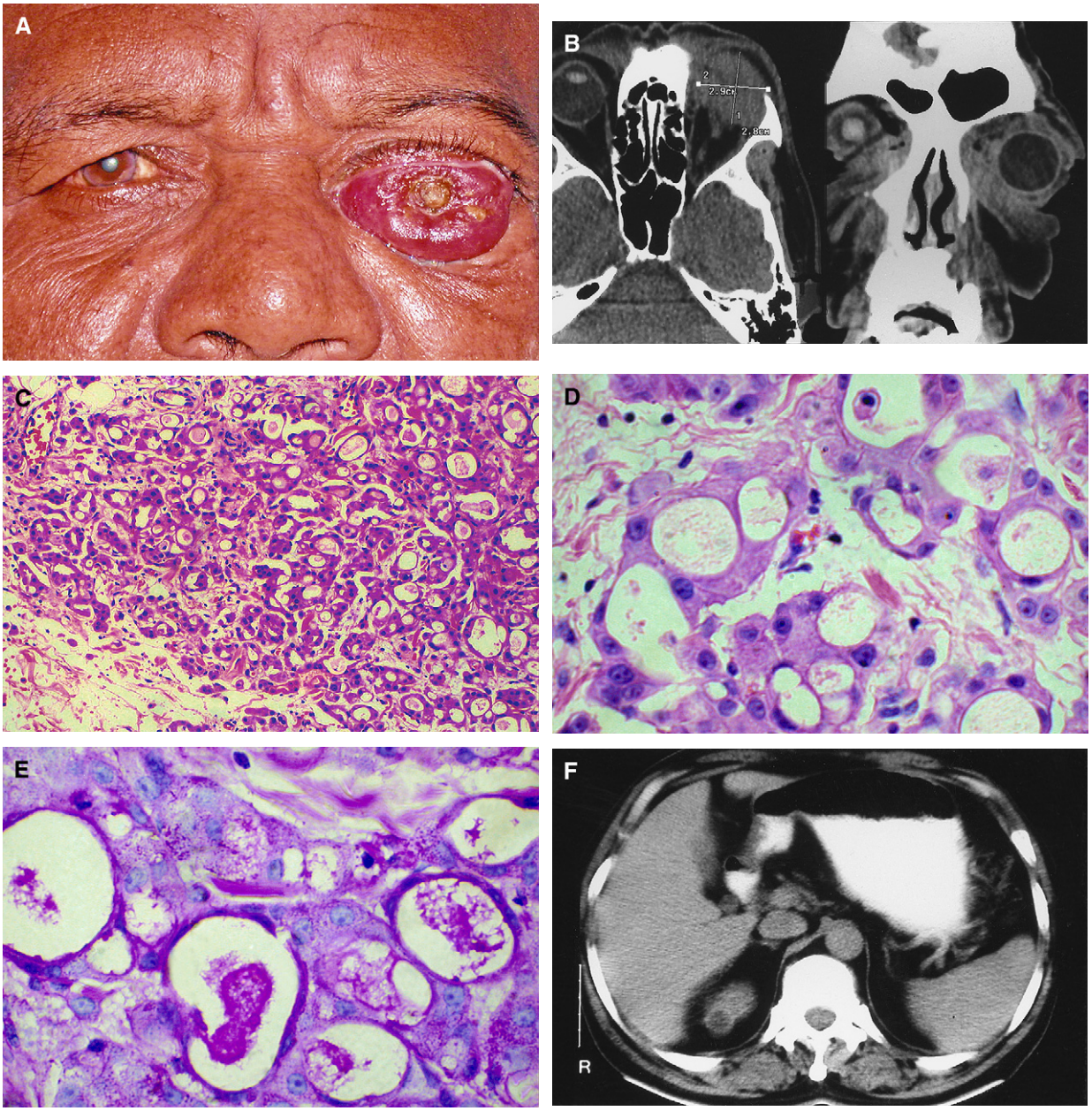

Fig. 2. A 58-year-old man with orbital metastasis from an occult RCC. *A:* Clinical photograph showing severe left eye proptosis with conjunctival chemosis, corneal exposure and diffuse infiltration. *B:* Coronal and axial computed tomography scan showing diffuse irregular soft tissue mass involving the superior, temporal and the inferior portions of the left orbit. *C:* Photomicrograph showing a highly cellular lesion with cells predominantly arranged in glands, follicles, and in small clusters, as well as infiltrating tissue planes and vascular structures (hematoxylin and eosin ×125). *D:* Photomicrograph showing a highly cellular lesion with cells predominantly arranged in glands, follicles, and in small clusters with a single layer of cuboidal cells with abundant cytoplasm, vesicular nuclei, and prominent nucleoli lining the glandular structures. (Periodic-acid Schiff ×500). *E:* Photomicrograph showing presence of PAS-positive material present within the cellular structures (Periodic-acid Schiff ×500). *F:* Computed tomography scan of the abdomen showing an enhancing mass with low central attenuation in the upper pole of the right kidney.

A total of 68 cases of RCC metastatic to the eye and orbit have been described in the English literature (Table 1). Information available in published articles is varied and limited and the data presented in this review are derived from the available data. The age of the patients described ranged from 38 to 77 years with a mean age of 59.86 ± 10.08 years. One of our patients was a 23-year-old female. This is probably the youngest patient reported with an ocular or orbital RCC metastasis. This patient did not manifest any systemic feature of vHL disease. There was a strong sex predisposition

TABLE 1

Metastasis to the eye and orbit from renal cell carcinoma: Summarized data

	Age	Sex (M:F)	Laterality	Previous History of RCC	Time to Detection of Metastasis after the Detection of Primary RCC	Duration of Ocular Symptoms
Summary of cases reported in the literature (n = 68)	38–77 years (Mean 59.9 ± 10.08 years)	63:5	Unilateral 64 Bilateral 4	30	5–216 months (96.5 ± 83.1 months)	3 days–6 months (Mean 19.9 ± 60.3 months)
Our series (n = 3)	23–67 years (Mean 49.3 ± 23.25 years)	2:1	Unilateral 3 Bilateral 0	2	7–14 months (10.5 ± 4.9 months)	3–6 months (Mean 4 ± 1.7 months)
All cases (n = 71)	23–77 years (Mean 57.3 ± 11.2 years)	65:6	Unilateral 67 Bilateral 4	32	5–216 months (93.2 ± 81.2 months)	3 days–6 months (Mean 18.9 ± 58.9 months)

noted in the literature with 63 (92.65%) males and 5 (7.35%) females.[12,25,31,40] RCC metastasis are predominantly unilateral with only four bilateral cases reported.[11,31,37,45]

The duration of presenting ocular symptoms range from 3 days to 6 months (mean 19.85 ± 60.28 months). Past history of renal disease was available in 33 cases (48.5%). Of these, 30 cases were known cases of RCC, 2 had past history of renal infections, and 1 had history of intermittent hematuria. The time duration between onset of renal disease in 33 patients with past history of the same, and ocular or orbital metastasis ranged from 5 months to 18 years (mean 96.45 ± 83.08 months). In the 35 (51.5%) patients with no past history of renal disease, investigations such as computed tomography scan, intravenous pyelography, and retrograde pyelography helped in making the diagnosis of RCC.

The orbit (25 cases, 36.8%) was the most frequently involved site by metastatic RCC, followed closely by choroid (20 cases, 29.4%). The other involved structures reported are iris (7 cases, 10.3%),[11,18,19,28,31,42,45] ciliary body (4 cases, 5.9%),[7,19,24,31] lacrimal gland (2 cases, 2.9%),[5,34] conjunctiva (1 case, 1.5%),[42] eyelid (1 case, 1.5%),[21] eyebrow (1 case, 1.5%),[41] and extraocular muscles (1 case, 1.5%).[37] In another six cases of intraocular metastatic RCC (8.8%), the authors have not provided the exact details of structural involvement. Overall, of 62 cases where there was documentation of the structural involvement, 31 (50%) were intraocular and 31 (50%) were extraocular (Table 2).

The clinical features of choroidal metastases in RCC have been well described (Table 3).[31] They are usually dome-shaped and yellow in color.[31] Some RCC metastases may appear reddish-orange in color and this might be on account of the high vascularity and tendancy for hemorrhage in these tumors. Such bleeding is extremely rare in choroidal metastasis from other sites that have a homogenous yellow color.[11,34] Choroidal metastasis from RCC needs to be clinically differentiated from choroidal hemangioma, posterior scleritis, amelanotic uveal melanoma, or metastases from sites such as from thyroid cancer and from carcinoids.[13] Shields et al, in a review of 520 eyes with uveal metastases, found that RCC metastases tended to be thicker than other uveal metastases with the mean thickness being approximately 4 mm and almost double the thickness of breast cancer metastases.[31]

TABLE 2

Metastasis to the eye and orbit from renal cell carcinoma: Site of metastasis

Location of Metastasis	Summary of Cases Reported in the Literature (n = 68)	Our Series (n = 3)	All Cases (n = 71)
Intraocular	31	1	32
Choroid	20	0	20
Iris	7	1	8
Ciliary body	4	0	4
Extraocular	31	2	33
Orbit	25	2	27
Lacrimal gland	2	0	2
Extraocular Muscles	1	0	1
Eyelid	1	0	1
Eyebrow	1	0	1
Conjunctiva	1	0	1
Not specified	6	0	6

TABLE 3

Summary of all cases with RCC metastasis

Author (year)	Age/Sex	Location of Metastasis	History of RCC	Time to Metastasis (months)	Other Synchronous Metastasis	Therapy		Systemic Outcome
						Systemic	Ocular	
Hudson (1934)[18]	55/M	Right Iris	Yes	24	Brain	NA	NA	Deceased
Kalt (1939)[20]	NA/M	Orbit	No			Left nephrectomy	Mass excision	NA
Houghton (1956)[16]	NA/M	Right Orbit	No		No	Right nephrectomy	Mass excision	NA
Van Amam (1957)[41]	59/M	Right Orbit	Yes	48	Ethmoid sinuses sphenoid sinus, anterior cranial fossa, left kidney, adrenal gland, liver, skull	Right nephrectomy, RT through right orbital & left nasal ports 7000 rads	Partial excision of orbital mass	Deceased
	72/M	Right Eyebrow	Yes	84	Lung vertebrae	Left nephrectomy	Mass excision	NA
Amdur[1] (1959)	53/M	Left Orbit	No		Lung	Left nephrectomy	Mass excision	Alive
Woody (1966)[44]	64/M	Right Orbit	Yes		Lung	Right nephrectomy	RT 3200 rads, CT with 5 FU, Eye eviscerated	Alive
Emanuel (1974)[6]	50/M	Right Choroid	Yes		NA	NA	Enucleation	NA
Ferry (1974)[8]	All male patients	Intraocular –7 cases Orbit – 2 cases	No – 8 cases Yes – 1 case		NA	Nephrectomy – all cases	NA	NA
Ferry (1975)[7]	69/M NA–case2	Ciliary body mass	No – both cases		Nil	Nil	Nil	Deceased
Laszczyk (1975)[24]	56/M	Right Ciliary Body	No		NA	NA	Enucleation	NA
Font (1976)[9]	2 male patients	Orbit	NA		NA	NA	NA	NA
Howard (1978)[17]	47/M	Right Orbit	No		Nil	Left nephrectomy + immunotherapy	EBRT 3500 rads	
Stephens (1979)[38]	Age NA/M	Choroid	Yes		NA	NA	NA	Deceased
Kindermann (1981)[21]	66/M	Left Upper Eyelid	Yes	15	Nil	Previous nephrectomy, CT	RT-4800 rads	Deceased
	58/M	Right Orbit	Yes	180	Nil	Previous nephrectomy	Excision biopsy	NA
	58/M	Left Choroid	No	108	NA			Alive

Wyzinski (1981)[45]	60/M	Bilateral Iris	No		Cerebrum	Nephrectomy	Iris mass excision	Deceased
Denby (1986)[5]	65/M	Right Lacrimal Gland	No		Ribs	Right renal embolizaiton	Mass excision	Alive
Slamovits (1998)[37]	63/M	Bilateral Extraocular Muscles	No		Skull, Ribs	Nil, patient refused therapy	Nil	Deceased
Halbach (1990)[14]	75/M	Right Choroid	Yes	196	Nil	Nephrectomy	Enucleation	NA
Portnoy (1991)[28]	65/M	Left Iris	No		Nil	NA	Iris mass excision	NA
Tijl (1992)[40]	60/F	Right Orbit	Yes	5	NA	NA	Surgery and RT in both cases	NA
	72/F	Left Orbit	No		NA	NA		NA
Parnes (1993)[27]	53/M	Right Orbit	No		Chest, skull, spine, ribs, pelvic bones	Palliative RT	Palliative RT	Deceased
Woline (1993)[43]	66/M	Right Orbit	No		Intracranial extension	Nephrectomy	RT	Alive
Bersani (1994)[3]	50/M	Left Orbit	Yes	180	Right lung, brain, mouth, back	Right lung lobectomy, brain & mouth RT, back Lumpectomy	Excision biopsy	Alive
Holt (1994)[15]	56/M	Left Orbit	No – both cases		Lungs, mediastinum	Right Nephrectomy	RT, medroxyprogesterone therapy	Alive
	60/M	Left Orbit			Left lung		RT, IV interferon & IL-2	
Langmann (1994)[23]	56/M	Left Choroid	Yes	6	Widespread, no details	Nephrectomy	Nil	Deceased
Günalp (1995)[10]	NA	Orbit	NA		NA	NA	NA	NA
Shields (1995)[35]	NA	Iris	No		NA	NA	NA	
Haimovici (1997)[11]	54/M	Left Choroid	Yes	16	Right cerebellum, right lung, peribronchial lymph nodes, peripancreatic lymph nodes, choroid plexus, left kidney	Nephrectomy	RT 70 Gy in 5 fractions	Deceased
	62/M	Bilateral Choroid	No		Nil	Nil		Alive

(*Continued*)

TABLE 3
Continued

Author (year)	Age/Sex	Location of Metastasis	History of RCC	Time to Metastasis (months)	Other Synchronous Metastasis	Therapy		Systemic Outcome
						Systemic	Ocular	
	48/M	Right Choroid	No		Brain	Systemic CT & palliative brain RT	RT 30 Gy to both orbits	Deceased
	66/F	Left Choroid	Yes	108	Brain and lungs	Nephrectomy, Brain Irradiation	NA	Deceased
	77/M	Right Choroid	Yes	72	Nil	Nephrectomy	RT 28 Gy in 2 fractions	NA
Mezer (1997)[25]	70/F	Right Orbit	Yes	84	NA	Nephrectomy	Orbital mass excision	Alive
Shields (1997)[31]	Total 10 eyes of 9 cases Mean age-65 yrs, Sex M:F = 8:1	Iris– 1 Ciliary body – 1 Choroid – 8	Yes – 9 cases		NA	NA	NA	NA
Ware (1999)[42]	70/M	Left iris Left Bulbar Conjunctiva	No		Nil	Left nephrectomy	Iridocyclectomy Excisional biopsy with cryotherapy	NA
Ikeda (2000)[19]	55 M	Right Iris & Ciliary Body	Yes	24	Lymph nodes, lung, liver, brain, bones	Cerebral mass excision	Systemic interferon alfa	Deceased
Shields (2001)[36]	40–59/M	Orbit	Yes		NA	NA	NA	NA
	40–59/M	Orbit	Yes					
	16–59/M	Orbit	Yes					
	60–79/M	Orbit	Yes					
	60–79/M	Orbit	Yes					
Shields (2001)[34]	59/M	Palpebral Lobe of Lacrimal Gland & Right Choroid	Yes	48	Right Kidney, parotid gland, local lymph nodes, widespread bones	Systemic RT & CT	Mass excision	Alive
Hammad (2003)[12]	48/F	Left Choroid	No		Lung, brain	Left radical nephrectomy	None, spontaneous regression postnephrectomy	Deceased

Srinivasan (2003)[39]	38/M	Right Choroid	No		Lungs, lymph nodes, bones	Palliative RT	Palliative RT	Deceased
Zdinak (2004)[46]	39/M	Left Orbit	No		Lymph nodes, lungs, liver, bones	Palliative therapy with IL2	Orbital mass debulking	Deceased
Current study	67/M	Left Iris	Yes	14	Lungs	Systemic interferon	RT	Alive
	58/M	Left Orbit	No		Nil	Lost to follow-up		NA
	23/F	Left Orbit	Yes	7	Intracranial extension, paranasal sinuses	Lost to follow-up		Alive

RT = radiotherapy; CT = chemotherapy; IL = interleukin; NA = details of case not available. All details were unavailable in some patients. Data table is based on the availability of data in the original articles.

Iris and ciliary body metastases of RCC are relatively rare and are often not clinically diagnosed unless there is history or clinical evidence of systemic malignancy.[8,31] Iris and ciliary body involvement is mostly unilateral and unifocal but rare cases of simultaneous bilateral iris involvement have been noted.[35,45] Iris metastases usually present with ocular pain and discomfort but could often be asymptomatic.[2,45] These lesions initially present as a gelatinous gray-white or yellow nodule that may extend into the angle. Larger lesions often appear pink due to abundant vascularization, which is a feature seen with all RCC metastases.[17,45]

Most orbital metastasis of RCC involve the orbital fat, muscle, or bone.[34] Orbital metastasis may be from an occult primary tumor.[5,10] Conversely, metastasis may be long delayed, occurring decades after the initial diagnosis of primary RCC.[41] Orbital metastasis from RCC generally manifests as a diffuse orbital mass. It may rarely present as a localized orbital mass with pseudo-capsule formation.[3] Sometimes, the extreme vascularity of orbital metastasis can lead to pulsating exophthalmos.[17] RCC metastasis to the lacrimal gland is very rare with only two such cases documented in the literature.[5,34] A detailed clinicopathologic review of lacrimal gland lesions by Shields et al did not have any lacrimal gland metastasis from RCC.[32] Other extraocular sites involved are conjunctiva and eyelid.[21,29,42] Clinically, it may be difficult to suspect a RCC metastasis to the orbit and adnexa without prior contributing history. Biopsy is often required to establish the diagnosis.

Other concurrent systemic metastases were seen in 18 patients (26.8%) at the time of diagnosis of intraocular or orbital metastasis. Lung (13, 72.2%) followed by brain (9, 50%), bones (8, 44.4%), liver (1, 5.5%) and ethmoid sinus (1, 5.5%) were the sites involved.

Diagnosis of RCC metastasis can be suggested by prior medical history, ocular evaluation, orbital imaging studies, and systemic evaluation and confirmed with a biopsy and histopathology. Of 68 cases of ocular and orbital metastasis of RCC reported in the literature, accurate clinical diagnosis was possible in only 11 cases (16.4%),[3,7,11,12,19,23,34,39] whereas histopathology was necessary for diagnosis in the rest. This emphasizes the importance of biopsy in a suspected case and histopathology in the diagnosis of metastatic renal cell carcinoma.

The management involves treatment of the primary tumor with one or a combination of surgery, chemotherapy, radiotherapy, or immunotherapy. If the primary tumor has already been adequately managed, the intraocular and orbital metastasis is generally treated with radiotherapy. Although local

control of the tumor may be possible, the systemic prognosis is poor.[34]

Of all, 31 patients (46.2%) underwent nephrectomy for systemic disease, 7 (10.3%) patients underwent radiotherapy and/or chemotherapy, and 1 patient (1.5%) was subjected to embolization. Local therapy for intraocular and orbital metastasis was in the form of orbital mass excision in 14 (20.6%) cases, enucleation in 5 (7.4%),[8,18,21,24,42] evisceration in 1 (1.5%),[44] iridectomy in 2 (2.9%), and external beam radiotherapy in 13 (19.1%). The visual outcome was favorable in 12 cases (17.6%). Of these, 10 cases had orbital or eyelid involvement and 2 had uveal involvement.[45,11] Visual acuity deteriorated in 3 cases and the rest of the cases do not have the data regarding visual outcome. The details of the systemic status were available in 39 cases—13 (33.3%) patients were alive and 26 (66.6%) were deceased at the final follow-up.

We have included three patients of our own in this comprehensive review. Our patients were a 67-year-old man, a 58-year-old man, and a 23-year-old woman with metastatic renal cell carcinoma. The iris mass in the 67-year-old man occurred in a known case of RCC and responded to local radiation and immunotherapy. The orbital metastasis in the 58-year-old man was the initial presenting sign in a hitherto undiagnosed patient with RCC; he refused further treatment. The orbital metastasis in the 23-year-old woman was detected post-nephrectomy for RCC. To the best of our knowledge, she is the youngest patient with RCC orbital metastasis. This patient was investigated for vHL disease and no abnormalities were detected.

In summary, metastatic RCC can masquerade as a benign or a malignant structural lesion and can be clinically confounding. This, associated with the tendency for long latent periods between the primary diagnosis and metastatic presentation (sometimes in decades), leads to further difficulties in the diagnosis.[21] Ocular metastases may be the presenting symptom a significant number of patients.[8] Biopsy helps in confirming the diagnosis of RCC and plan appropriate therapy.[31]

Method of Literature Search

Articles in the English language literature were searched with the combination of key words *renal cell carcinoma, renal cell carcinoma with ocular metastasis, renal cell carcinoma with orbital metastasis, renal cell carcinoma with uveal metastasis, orbital metastasis, and eye and metastasis* on MEDLINE up to July 1, 2005. Individual case reports, case series of metastatic renal cell carcinoma, as well as other reviews detailing lists of primary tumors contributing to orbital and ocular metastasis were reviewed. Cross-references from these articles not highlighted in the Medline search were also obtained and reviewed. The first article on renal cell carcinoma metastasis was published in 1934, hence this article includes a review of at least 71 years of relevant literature.

References

1. Amdur J, Leopold I: Metastatic hypernephroma to the orbit: Report of a case with review of the literature. Am J Ophthalmol 48:386–8, 1959
2. Barbee JY, Edwards WC, Macdonald R Jr: Metastatic iris tumor. Surv Ophthalmol 16:160–4, 1971
3. Bersani TA, Costello JJ, Mango CA, Streeten BW: Benign approach to a malignant orbital tumor: Metastatic renal cell carcinoma. Ophthal Plast Reconstr Surg 10:42–4, 1994
4. Char DH, Miller T, Kroll S: Orbital metastases: diagnosis and course. Br J Ophthalmol 81:386–90, 1997
5. Denby P, Harvey L, English MG: Solitary metastasis from an occult renal cell carcinoma presenting as a primary lacrimal gland tumor. Orbit 5:21–4, 1986
6. Emanuel M, Guerra W: Renal cell carcinoma metastasis to choroid of eye 20 years after nephrectomy for calculus disease. J Maine Med Assoc 65:273–5, 1974
7. Ferry AP, Font RL: Carcinoma metastatic to the eye and orbit II. A clinicopathological study of 26 patients with carcinoma metastatic to the anterior segment of the eye. Arch Ophthalmol 93:472–82, 1975
8. Ferry AP, Font RL: Carcinoma metastatic to the eye and orbit. I. A clinicopathologic study of 227 cases. Arch Ophthalmol 92:276–86, 1974
9. Font RL, Ferry AP: Carcinoma metastatic to the eye and orbit III. A clinicopathologic study of 28 cases metastatic to the orbit. Cancer 38:1326–35, 1976
10. Günalp I, Gündüz K: Metastatic orbital tumors. Jpn J Ophthalmol 39:65–70, 1995
11. Haimovici R, Gragoudas ES, Gregor Z, et al: Choroidal metastases from renal cell carcinoma. Ophthalmology 104: 1152–8, 1997
12. Hammad AM, Paris GR, van Heuven WA, et al: Spontaneous regression of choroidal metastasis from renal cell carcinoma. Am J Ophthalmol 135:911–3, 2003
13. Harbour JW, De Potter P, Shields CL, et al: Uveal metastasis from carcinoid tumor. Clinical observations in nine cases. Ophthalmology 101:1084–90, 1994
14. Holbach LM, Chévez P, Snyder WB, et al: Unsuspected renal cell carcinoma metastatic to the choroid nine years after nephrectomy. Am J Ophthalmol 110:441–3, 1990
15. Holt BA, Holmes SA, Kirby RS: Renal cell carcinoma presenting with orbital metastases. Br J Urol 75:246–7, 1995
16. Houghton JD: Solitary metastasis of renal carcinoma. Am J Ophthalmol 41:548–9, 1956
17. Howard GM, Jakobiec FA, Trokel SL, et al: Pulsating metastatic tumor of the orbit. Am J Ophthalmol 85:767–71, 1978
18. Hudson AC, Lister W: Metastatic hypernephroma of the iris. Proc R Soc Med 27:1613–5, 1934
19. Ikeda T, Sato K, Tokuyama T: Interferon alfa therapy against metastatic iris tumor of renal cell carcinoma. Arch Ophthalmol 118:846–7, 2000
20. Kalt M, Tille H: Metastatic orbital tumor, secondary to a renal epithelioma with late manifestation. Arch Ophthalmol 22:933–4, 1939
21. Kindermann WR, Shields JA, Eiferman RA, et al: Metastatic renal cell carcinoma to the eye and adnexae: a report of three cases and review of the literature. Ophthalmology 88: 1347–50, 1981

22. Kosary CL, McLaughlin JK: Kidney and renal pelvis, in Miller BA, Ries LAG, Hankey BF, et al (eds): SEER Cancer Statistics Review, 1973–1990. Bethesda, MD, National Cancer Institute (NIH publication no. 93-2789), 1993. pp. XI.1–XI.22
23. Langmann G, Mullner K, et al: Spontaneous regression of a choroidal metastasis from renal carcinoma. Br J Ophthalmol 78:883, 1994
24. Laszczyk WA: Metastatic tumour of the ciliary body—hypernephroma. Ophthalmologica 170:543–7, 1975
25. Mezer E, Gdal-On M, Miller B: Orbital metastasis of renal cell carcinoma masquerading as Amaurosis fugax. Eur J Ophthalmol 7:301–4, 1997
26. Motzer RJ, Bander NH, Nanus DM: Renal-cell carcinoma. N Engl J Med 335:865–75, 1996
27. Parnes RE, Goldberg SH, Sassani JW: Renal cell carcinoma metastatic to the orbit: a clinicopathologic report. Ann Ophthalmol 25:100–2, 1993
28. Portnoy SL, Arffa RC, Johnson BL, et al: Metastatic renal cell carcinoma of the iris manifesting as an intrastromal iris cyst. Am J Ophthalmol 111:113–4, 1991
29. Riley FC: Metastatic tumors of the eyelids. Am J Ophthalmol 69:259–64, 1970
30. Ritchie AW, Chisholm GD: The natural history of renal carcinoma. Semin Oncol 10:390–400, 1983
31. Shields CL, Shields JA, Gross NE, et al: Survey of 520 eyes with uveal metastases. Ophthalmology 104:1265–76, 1997
32. Shields CL, Shields JA, Eagle RC, et al: Clinicopathologic review of 142 cases of lacrimal gland lesions. Ophthalmology 96:431–5, 1989
33. Shields JA, Shields CL: Metastatic tumors to the uvea, retina, and optic disc, in Shields JA, Shields CL (eds): Atlas of Intraocular Tumors. Philadelphia, Lippincott Williams & Wilkins, 1999, pp. 151–67
34. Shields JA, Shields CL, Eagle RC, et al: Metastatic renal cell carcinoma to the palpebral lobe of the lacrimal gland. Ophthal Plast Reconstr Surg 17:191–4, 2001
35. Shields JA, Shields CL, Kiratli H, et al: Metastatic tumors to the iris in 40 patients. Am J Ophthalmol 119:422–30, 1995
36. Shields JA, Shields CL, Brotman HK, et al: Cancer metastatic to the orbit: the 2000 Robert M. Curts Lecture. Ophthal Plast Reconstr Surg 17:346–54, 2001
37. Slamovits TL, Burde RM: Bumpy muscles. Surv Ophthalmol 33:189–99, 1988
38. Stephens RF, Shields JA: Diagnosis and management of cancer metastatic to the uvea: a study of 70 cases. Ophthalmology 86:1336–49, 1979
39. Srinivasan S, Gray DG: Images in clinical medicine. Choroidal metastasis from renal-cell carcinoma. N Engl J Med 349:e22, 2003
40. Tijl J, Koornneef L, Eijpe A, et al: Metastatic tumors to the orbit—management and prognosis. Graefes Arch Clin Exp Ophthalmol 230:527–30, 1992
41. Van Arnam CE, Fine M: Orbital metastasis of renal carcinoma. Arch Ophthalmol 57:694–701, 1957
42. Ware GT, Haik BG, Morris WR: Renal cell carcinoma with involvement of iris and conjunctiva. Am J Ophthalmol 127: 460–1, 1999
43. Wolin MJ: Metastatic renal cell carcinoma manifesting as an orbital mass. Am J Ophthalmol 115:542–3, 1993
44. Woody JH, Geeraets WJ: Orbital metastasis of renal cell carcinoma. Eye Ear Nose Throat Mon 45:90–3, 1966
45. Wyzinski P, Rootman J, Wood W: Simultaneous bilateral iris metastases from renal cell carcinoma. Am J Ophthalmol 92: 206–9, 1981
46. Zdinak LA, Nik NA, Hidayat AA, et al: Renal medullary carcinoma metastatic to the orbit: a clinicopathologic report. Ophthal Plast Reconstr Surg 20:322–5, 2004

Support for this study was provided by the Hyderabad Eye Research Foundation, Hyderabad, India. The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article. The authors thank Ms Sabera Banu, Librarian, LV Prasad Eye Institute, for help with the literature retrieval.

Reprint address: Santosh G. Honavar, MD, FACS, Ocular Oncology Service, LV Prasad Eye Institute, LV Prasad Marg, Banjara Hills, Hyderabad 500034 India.