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Orbital Metastasis From Urothelial Carcinoma: A Comprehensive Literature Review

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Abstract

Purpose: To review the clinical features of orbital and choroidal metastases from urothelial carcinomas of the urinary tract among cases reported in the literature, and to describe a case of orbital metastasis from bladder cancer presenting as apparent internuclear ophthalmoplegia.

Methods: Case reports of orbital and choroidal metastases from urothelial carcinomas published in the literature from 1965 to 2018 were reviewed. Data collected included patient demographics, cancer stage and primary site, time to onset of ocular symptoms, length of presenting ocular symptoms, types of primary ocular symptoms, diagnostic imaging, histology, systemic and ocular treatments, and survival time.

Results: Twenty-eight cases of urothelial carcinoma with metastasis to the orbit or choroid were reviewed. Men were significantly more likely to suffer from this condition than women (p = 0.011). The average age of presentation with orbital symptoms was 63 years, with an average time of 19 months between primary cancer diagnosis and onset of orbital symptoms. Twenty-two patients had metastasis to the orbit and 6 to the choroid. In 4 cases, ocular deficits secondary to orbital and/or choroidal metastases were the initial presenting symptoms in patients with previously undiagnosed urothelial carcinoma. The most commonly noted primary ocular symptoms and signs consisted of decreased visual acuity, decreased ocular motility, proptosis, and diplopia. Average survival from onset of ocular symptoms was 4.67 months.

Conclusions: Urothelial carcinoma may metastasize to the orbit or choroid; furthermore, its presentation may mimic internuclear ophthalmoplegia. It is recommended that any patient with visual symptoms and known urothelial cancer should undergo expedited workup for metastatic disease.

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Orbital metastases may occur in 2% to 3% of patients with cancer.[1] Although this condition is rare, in 19% to 25% of cases patients may have no history of systemic cancer when presenting with ophthalmic symptoms.[1,2] The most common primary tumors to metastasize to the orbit are breast, prostate, and lung.[1] Prognosis is poor in this population given metastatic disease to other organs.

To date, there have been ~30 reported cases of urothelial carcinomas of the urinary tract with orbital or choroidal metastases.[3–27] Here, the authors present the first case of urothelial carcinoma of the urinary bladder to present with acute symptoms consistent with internuclear ophthalmoplegia (INO) and presumed stroke. Previously, there was 1 reported case of colorectal carcinoma metastatic to the orbit presenting as apparent INO.[28] The authors further provide a systematic review of published cases and analysis of the literature on urothelial carcinomas with orbital or choroidal metastasis.

CASE REPORT

Collection and evaluation of protected patient health information was compliant with the Health Insurance Portability and Accountability Act. A 65-year-old Caucasian male with a medical history of hepatitis B, 10 pack-year smoking history, and stage intravenous urothelial carcinoma of the bladder status-post radical cystectomy with pelvic and pulmonary recurrence, initially presented with fever and feculent drainage from the urethra secondary to urorectal fistula. The patient was hospitalized, started on intravenous antibiotics, and underwent transverse loop colostomy for persistent urethral drainage.

On postoperative day 2, a stroke code was called for acute onset left ophthalmoplegia, vision loss, and vomiting. The patient reported acute worsening of diplopia and “dimming vision in the left eye, starting in the center” that had started 2 to 3 weeks prior. Initial physical examination was significant for impaired adduction of the left eye on rightward gaze, horizontal nystagmus of the right eye, and preserved convergence. Examination also showed mild left exophthalmos, diplopia on rightward gaze, and tenderness to palpation in the left peri-orbital region. CT of the head showed no acute hemorrhage. On ophthalmology consultation, the patient denied eye pain, redness, tearing, flashes, floaters, and curtains. The patient endorsed chin numbness but denied numbness or paresthesias in the V2/V3 distribution. Visual acuity was OD 20/25, OS 20/200. Left afferent pupillary defect and mild proptosis were present. Ophthalmologic examination was significant for extra-ocular movements of OS −4 in adduction, −3.5 to −4 in supraduction, −2.5 in infraduction, and −1 in abduction. Extraocular movements were full OD. Left inferocentral and central scotomas were present with grossly intact periphery, and visual fields were full on the right. Sensation was decreased in CN V1 distribution, but all other cranial nerves were intact. Anterior segment examination was within normal limits. On dilated fundus examination, cup-to-disc ratio OS was 0.1 with 360° of optic nerve head edema and flame heme nasally. The cup-to-disc ratio OD was 0.2 and disc margins were sharp. The macula and blood vessels were within normal limits bilaterally. On examination of the retinal periphery, 1 flame hemorrhage was present in the periphery OS.

MRI brain and orbits with and without contrast demonstrated a 1.6 × 2.6 × 1.8 cm T2 hypointense and T1 hyper-intense infraorbital mass OS encasing the inferior rectus and abutting the medial rectus, elevating the optic nerve and extending posteriorly to the orbital apex. The patient subsequently underwent decompression of the orbital floor and excision of a large portion of the mass from the medial orbit. Pathologic finding was consistent with metastatic urothelial carcinoma by morphology and + p40 and GATA3 staining. The patient ultimately decided to pursue hospice care and died 3 weeks after the initial presentation of ocular symptoms.

METHODS

The authors reviewed case reports of orbital and choroidal metastases from urothelial carcinomas published in the literature from 1965 to 2018. Data collected included patient demographics, cancer stage and primary site, time to onset of ocular symptoms, length of presenting ocular symptoms, types of primary ocular symptoms, diagnostic imaging, histology, systemic and ocular treatments, and survival. This report adhered to the ethical principles outlined in the Declaration of Helsinki as amended in 2013. This research was compliant with the Health Insurance Portability and Accountability Act. Written consent for publication was obtained from the patient's next of kin and is on file with the authors. Statistical analysis was performed using R to complete a binomial test (2 tailed).

RESULTS

In addition to the case described above, 28 cases of urothelial carcinoma with metastasis to the orbit or choroid were reviewed from the published literature (Table). There were 23 men and 5 women (ratio 4.6/1; $p = 0.011$). The average age at first presentation of orbital symptoms was 63 years (range 43–88, median 62). The average time between diagnosis of primary urothelial carcinoma and the onset of orbital symptoms was 19 months (range 0–132, median 8).

There were 25 cases of urothelial carcinoma originating in the urinary bladder, 1 case in the renal pelvis, and 1 in the ureter. Twenty-two patients had metastases to the orbit, 6 to the choroid(s), and 1 nonspecific intraocular metastasis. There were 23 unilateral lesions (13 right, 10 left) and 5 bilateral (3 orbital and 2 choroidal). Metastases to other locations within the body were noted in 13 (49%) cases. Lung metastases were present in 7 (24%) of cases.

In 4 cases, ocular deficits secondary to orbital and/or choroidal metastases were the initial presenting symptoms in patients with previously undiagnosed urothelial carcinoma (14%). The average time the patient experienced ocular symptoms before diagnosis of metastasis was 28 days (range 0–112, median 18). Three patients received alternate presumed diagnoses prior to definitive diagnosis of metastatic disease, including stroke (presented case), infection, and central retinal vein occlusion.

The most commonly noted primary ocular symptoms and signs consisted of decreased visual acuity (22, 76%), decreased ocular motility (19, 66%), proptosis (17, 59%), diplopia (15, 52%), chemosis (8, 26%), pain (7, 24%), relative afferent pupillary defect (5, 17%), palpable mass (5, 17%), ptosis (4, 14%), change in intraocular pressure (2, 7%), photopsia (2, 7%),

and reduced color vision (1, 3%). Twenty-two patients experienced visual loss, the visual acuities of whom were as follows: no light perception (4, 18%), hand motion (1, 4.5%), count fingers (2, 9%), and 20/200 (1, 4.5%). Of the 19 patients with decreased ocular motility, 10 had limitation of movement in all directions, 2 had CN VI palsy, 1 had CN intravenous nerve palsy, and 1 had INO (case described).

Abnormal findings were apparent on CT for 16 cases (55%), dilated fundus examination for 14 cases (48%), MRI for 5 cases (17%), ultrasound for 2 cases (7%), anterior segment examination for 2 cases (7%), optical coherence tomography for 1 case (3%), fluorescein angiography for 1 case (3%), and skull films for 1 case (3%). Ocular-directed treatment included decompression surgery for 2 cases and orbital radiotherapy for 6 cases, one of which was followed by enucleation. Systemic therapy typically included a combination of chemotherapy agents and local radiotherapy. Average survival from the time of ocular symptoms was 4.67 months (range 13–1460 days). Kaplan–Meier survival curve is found in the Figure.

Two cases noted that the orbital lesion described was the singular site of metastasis. Three patients had a known smoking history, and 1 had a history of lead exposure.

DISCUSSION

The American Cancer Society estimates that in 2018 there will be 81,190 new cases of urothelial cancer of the urinary bladder and 17,240 related deaths in the United States.[29] The most common sites of metastasis from urothelial carcinoma of the bladder include the lymph nodes, bones, lungs, liver, and peritoneum.[30] In general, the presence of orbital metastasis indicates hematogenous spread of a primary cancer and is accompanied by poor prognosis.[2]

This is the first reported case of urothelial carcinoma of the bladder metastatic to the orbit presenting as apparent INO with subsequent stroke workup. Symptoms consistent with INO included paralysis of adduction in the left eye for conjugate eye movements, horizontal nystagmus in the right eye, and preservation of convergence. True INO is caused by a brainstem lesion involving the medial longitudinal fasciculus in the pons.[31] In a case series investigating the etiology of INO in 410 inpatients over a 33-year period, 38% were due to infarction, 34% were due to multiple sclerosis, and 28% were due to “unusual causes” including tumors, trauma, and infection affecting the medial longitudinal fasciculus.[32] One prior report documented apparent INO from orbital metastasis originating from a rectal adenocarcinoma, presenting with left adduction deficit.[28]

In this case, the patient’s symptoms included acute unilateral vision loss, ocular motility defects, and vomiting. The differential for these symptoms included a stroke in the setting of malignancy, pupil sparing ischemic third nerve palsy, lymphoma, and metastatic disease. Other possible etiologies of orbital masses include vascular lesions (cavernous hemangiomas, lymphangiomas), benign tumors (schwannomas, dermoid cysts), and malignancies (lymphoma, metastasis, rhabdomyosarcoma).[33,34] One study of 2480 patients evaluated for an orbital mass found that orbital metastases accounted for 3.5% of all lesions and 11% of malignant lesions.[34]

Analysis from the literature review shows that orbital and choroidal metastases from urothelial carcinoma affect men significantly more frequently than women (ratio 4.6/1; $p = 0.011$). This is consistent with the incidence of primary urothelial carcinoma, which favors males. In Norway, the reported ratio of males to females with urothelial carcinoma was 3.2 in 2016, and the American Cancer Society estimates that the incidence of new cases will affect 3.3 males per female in 2018.[29,35]

Prognosis for patients with orbital metastases is poor. The average survival for patients with metastatic orbital tumors has been reported to be 15 months.[1,36] Previous reviews of patients with orbital metastasis from urothelial carcinoma of the bladder found the average survival to be 3 months.[11] The analysis of patients with orbital and choroidal metastases from urothelial carcinoma showed an average survival of 4.67 months.

In this review, decreased visual acuity, impaired ocular motility, proptosis, and diplopia were the most common symptoms of orbital metastasis. While orbital masses of various etiologies may produce these symptoms, it is important to consider metastatic disease in patients with known primary urothelial carcinoma. Furthermore, ocular symptoms preceded the diagnosis of primary bladder cancer in 4 cases; therefore, metastasis should be considered in the differential diagnosis for an orbital mass.

CONCLUSIONS

The findings in this literature review suggest that urologists, neurologists, hospitalists, and ophthalmologists should be aware that not only can urothelial carcinoma metastasize to the orbit or choroid but its presentation may mimic INO. Any patient with visual symptoms and known urothelial cancer should receive prompt workup for metastatic disease.

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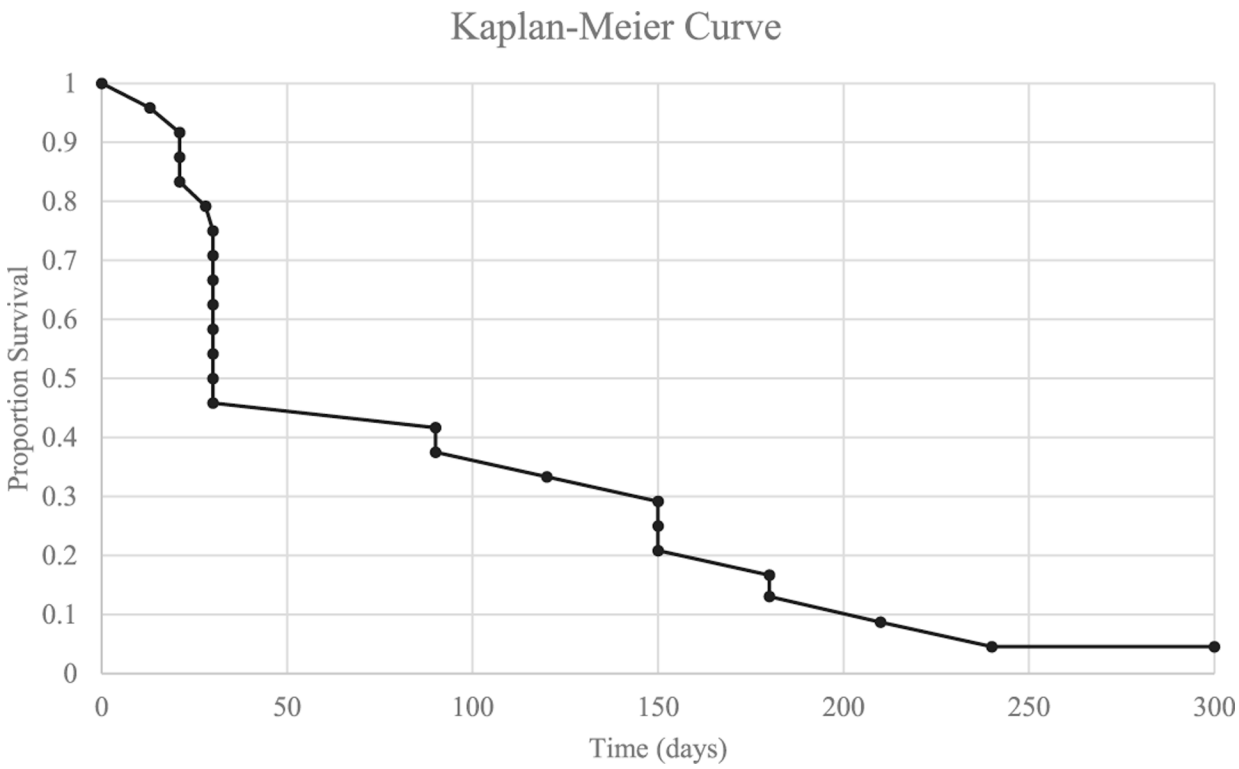

Kaplan-Meier curve showing proportion survival versus time (days). Five patients were excluded because no length of survival was reported. Of the excluded patients, 1 was described as alive at the time of publication while the status of the other 4 is unknown.

Reported cases of orbital and choroidal metastases from urothelial carcinoma

Authors	Year	Age	Sex	Origin	TCC first	Site	Time from TCC to met	Laterality	Ocular symptoms	Abnormal findings	Ocular therapy	Systemic therapy	Survival
Sklar et al.	2018	64	M	**B**	Y	Orbit	6 months	OS	D, M, Pain, Prop	**MRI**	Decompression, surgical debulking	Comfort	3 weeks
Gene et al.	2017	67	**M**	**B**	N	Orbit	0 day	OD	M, V	MRI	NS	Chemotherapy + RT	Unknown
Magrath et al.	2015	57	F	**B**	Y	Orbit	-	OD	M, Prop, V	CT	NS	NS	3 weeks
Mitsui et al.	2014	48	M	**B**	Y	Choroid	17 months	OD	V	OCT, US, MRI	NS	Chemotherapy	5 months
SooHoo et al.	2012	53	F	**B**	Y	Orbit	-	OD	Pt	CT	NS	NS	3 months
Wiltshire et al.	2009	88	M	**B**	Y	Choroid	-	OU	V	DFE, ultrasonography	RT bl	RT	4+ years
Wettach and Steele	2008	66	**M**	**B**	N	Orbit	-	OD	D, M, Pain, Prop, Pup, V	CT	NS	NS	1 month
Zwicker et al.	2008	50	M	**B**	Y	Orbit	-	OS	Ch, D, M, Prop	MRI, AS, DFE	RT	NS	6 months
Lin et al.	2007	60	**M**	**B**	Y	Orbit	8 months	OD	Ch, D, M, Prop, V	CT, DFE	NS	Chemotherapy	6+ months
Shikishima et al.	2006	74	**M**	**B**	Y	Orbit	3 years	OD	Ch, D, IOP, M, Pain, Palp, Prop, V	CT, DFE	NS	Chemotherapy + RT	7 months
Souza Filho et al.	2005	53	M	**B**	Y	Orbit	3 weeks	OS	Ch, D, M, Prop, V	MRI	NS	NS	1 month
Chua et al.	2004	78	F	**B**	Y	Orbit	4 years	OD	Ch, D, M, Palp, Prop, Pt, V, Pain	CT	NS	NS	Unknown
Amemiya et al.	2003	55	M	**B**	Y	Orbit	5 months	**OU**	D, M, Pain, Prop	MRI	NS	NS	1 month
Amemiya et al.	2003	73	M	**B**	Y	Orbit	6 months	OD	M, V	MRI	NS	NS	1 month
Fynn-Thompson et al.	2003	68	M	**B**	Y	Orbit	11 years	OS	M, Prop, Pup, V	CT, DFE	NS	NS	1 month
Nabi et al.	2002	43	F	**B**	Y	Orbit	6 months	OS	Ch, Prop, V	CT, DFE	NS	Chemotherapy	1 month
Nabi et al.	2002	79	**M**	**B**	Y	Intraocular	8 months	OD	D, Ph, V	CT, DFE	NS	Chemotherapy	3 weeks
Scott and Williams	1995	75	M	**B**	Y	Orbit	3 years	OD	Ch, D, IOP, M, Pain, Prop, Pup, V	CT	NS	Steroids + abx	13 days

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Authors	Year	Age	Sex	Origin	TCC first	Site	Time from TCC to met	Laterality	Ocular symptoms	Abnormal findings	Ocular therapy	Systemic therapy	Survival
Hugkulstone et al.	1994	45	M	**B**	N	Orbit	0 days	**OU**	Ch, D, M, Palp	CT, DFE	NS	Chemotherapy + RT	5 months
Angulo et al.	1991	61	M	**B**	Y	Orbit	11 months	OD	D, Prop	CT	NS	NS	4 weeks
Felip et al.	1991	58	**M**	**B**	Y	Orbit	3 weeks	**NS**	M, Pt, T, V	CT	NS	NS	3 months
Felip et al.	1991	62	M	**B**	Y	Orbit	3 years	OS	D, M, Pain, Prop, V	CT, DFE	NS	Declined	Unknown
Prats **et** al.	1989	58	M	**B**	Y	Orbit	3 weeks	OS	M, Prop, Pt, T, V	CT	Decompression	NS	4 months
Pe'er and Zimmerman	1984	69	**M**	**U**	Y	Choroid, ON	2.5 years	OS	IOP, Pain, V	AS, DFE	RT, enucleation	NS	Unknown
Atta	1983	50	F	RP	Y	Choroid	2 years	OS	Ph	DFE, US, FA	NS	Chemotherapy + RT	5 months
Krauss et al.	1982	64	F	**B**	Y	Orbit	15 months	OD	C, D, M, Prop, Pt, Pup, T, V	CT	RT	NS	1 month
Cieplinski et al.	1982	57	M	**B**	Y	Choroid	6 months	**OU**	V	DFE	RT bl	Chemotherapy	Unknown
Gordon and Munro	1974	65	M	**B**	Y	Choroid	2 years	**OU**	V	DFE	RT bl	NS	1 month
Smiley	1965	75	**M**	**B**	N	Orbit	0 day	OS	D, M, Palp, Prop, Pup, V	DFE, skull films	NS	NS	8+ months

AS, anterior segment; B, bladder; bl, bilateral; C, reduced color vision; Ch, Chemosis; D, diplopia; DFE, dilated fundus examination; FA, fluorescein angiography; IOP, change in intraocular pressure; M, motility defect; NS, not stated; OCT, optical coherence tomography; ON, optic nerve; Palp, palpable mass; Ph, photopsia; Prop, proptosis; Pt, ptosis; Pup, pupillary defect; RT, radiotherapy; RP, renal pelvis; T, trigeminal hypoesthesia; TCC, transitional cell carcinoma; U, ureter; US, ultrasound; V, decreased visual acuity.