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Original Article

Malignant tumors infiltrating the optic pathway

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Abstract

Purpose: The purpose of the study was to describe the 15-year experience of three tertiary medical centers with malignant infiltration of the optic nerves in children and adults.

Methods: The databases of three medical centers were searched for all patients with malignant optic nerve infiltration diagnosed clinically, radiologically, and pathologically in 2003–2017. Data were derived from the medical records, biopsy reports, and revision of the imaging scans.

Results: Patients included three children (two male and one female) and five adults (four male and one female) aged 8–77 years. Presenting symptoms were progressive monocular vision loss (n = 4), acute monocular vision loss (n = 1), bitemporal hemianopia (n = 1), homonymous hemianopia (n = 1), and vomiting (n = 1). All children had a previous diagnosis of brain tumor in another part of the brain (ependymoma, n = 1) or primitive neuroectodermal tumor (PNET, n = 2), and one adult had meningeal carcinomatosis arising from carcinoma of bladder. Neuroimaging identified a right sinus tumor in one patient, diagnosed pathologically as rhabdomyosarcoma. The remaining patients were diagnosed pathologically with malignant ganglioma, glioblastoma, PNET, and transitional cell cancer. Seven patients died within 1 year, and one was lost to follow-up.

Conclusion: This study highlights the high index of suspicion necessary for diagnosis of malignant optic nerve involvement in patients with unsolved vision loss, the role of repeated magnetic resonance imaging and the wide variety of causative tumors.

Introduction

Almost all intrinsic tumors of the optic pathway occurring in children originate in the optic pathway itself and are low-grade.[1] Some intrinsic tumors of the optic nerve are malignant, tend to occur in adults and may be primary or secondary due to local spread or metastasis.[2,3] The clinical presentation is non-specific and may initially mimic benign inflammatory processes.[4,5] Although initial imaging is often negative,[4,6] repeated diffusion-weighted magnetic resonance imaging (MRI) has been found to be useful.[6] Biopsy samples are rarely taken so long as there is potential for visual recovery. When performed, the main pathologic findings are anaplastic astrocytoma and glioblastoma multiforme (GBM).[7]

The aim of this study was to describe the recent 15-year experience of three tertiary university-affiliated medical centers with malignant tumors involving the optic nerve.

Methods

A retrospective cohort design was used. The clinical databases of three tertiary medical centers were searched for all patients

with malignant optic nerve infiltration of tumor diagnosed clinically, radiologically, and pathologically between the years 2003 and 2017. Data on demographic parameters, age at initial presentation, presenting symptoms and signs, and follow-up findings were collected from the medical files. All imaging scans were reviewed to identify the presence, location, and progression of the tumor during follow-up. Pathological data from diagnostic or postmortem biopsy studies were recorded as well. The study was approved by the local institutional ethics review boards.

Results

Eight patients met the study criteria. Their clinical data are shown in Table 1. Three (two males and one female) were children, aged 8, 14, and 16 years, and five (four males, and one female) were adults, aged 32–77 years. Tumor location was optic nerve (six), chiasm (one), and tract (one). All the children and one of the adults had a previous diagnosis of a malignant condition and in the children, this was in the central nervous system. We present the detailed work-up, treatment, pathologic findings, and outcome for two patients: one adult with primary and one adult with secondary tumor and brief summaries of the relevant clinical and neuroimaging findings for the remaining patients [Table 1].

Case 4

A 77-year-old man presented in 2004 with vision loss in the right eye associated with severe frontal headache diagnosed as trigeminal neuralgia by a neurologist. Medical history was significant for hypertension, ischemic heart disease, and a basal cell carcinoma on the left forehead which had been removed 4 years previously. Two years before presentation, he had undergone cystectomy for invasive transitional cell carcinoma (TCC) and chemotherapy with cisplatinum and gemcitabine. Visual acuity was 20/100 and afferent pupillary defect was noted with normal optic disc appearance. Workup at the time of right visual loss included complete blood count, erythrocyte sedimentation rate, and imaging. Findings were normal or negative. MRI of the brain and orbits was interpreted as showing only ischemic white matter age-related changes with normal optic nerves. Computed tomography scans of the chest and abdomen were negative. On suspicion of giant cell arteritis, the patient was referred for temporal artery biopsy and treatment with intravenous methylprednisolone pending the results. The patient reported pain relief after starting steroids and return of the pain when the steroids were discontinued following negative biopsy results.

Two months later, on ophthalmological evaluation, visual acuity was finger counting in the right eye and 20/25 in the left eye. Scores on the Ishihara color plate test were 0 in the right eye and 14/14 in the left. Trigeminal and facial functions were intact. Evaluation of ocular movements showed mild limitation of elevation. The right pupil was barely reactive to light, with +4 afferent pupillary defect. Dilated fundus examination revealed mild pallor and nasal swelling of the optic disc on the right, with no cells in the vitreous, and a normal optic disc on the left. Slit-lamp biomicroscopy demonstrated bilateral 3+ nuclear sclerosis cataracts. Humphrey visual field (VF) test (24-2) revealed a dense temporal superior defect in the right eye and mild superior constriction in the left eye. The rest of the general and neurological examination was unremarkable.

Careful review of the initial MRI performed at one of the other centers showed enlargement and enhancement of the right optic nerve, and the patient was sent for repeated brain and orbit MRI. The T1 post-contrast fat-suppression views demonstrated enhancement of the right optic nerve sheath [Figure 1] but no abnormalities in any other cranial nerves sixth, seventh and

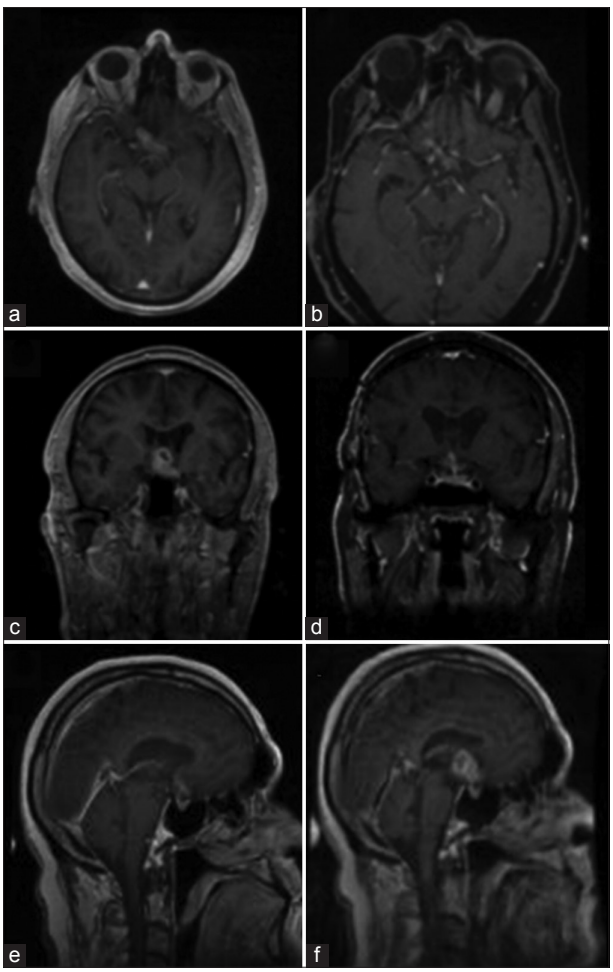

Figure 1: (Case 4) Magnetic resonance imaging axial T1 post-contrast, with no fat saturation (a) and with fat saturation (b) showing enhancement of the right prechiasmatic optic nerve with extension to the chiasm also in the left side. (c and d) Coronal T1 fat saturation post contrast showing progression of the findings with enhancing lesion extending from the chiasm to the floor of the 3rd ventricle (2 months later). (e and f) Sagittal section showing progression at the same time point

Table 1: Data on demographics, imaging, pathology, treatment, and outcome of eight patients with malignant optic nerve infiltration

Pt.	Age (year)/ sex	Presentation	First imaging	VF defect	Time to diagnostic imaging	Clinical deterioration	Pathology	Treatment	Outcome (time of follow-up since diagnosis)
1	16/F	Vomiting, no visual symptoms or signs	Enlarged chiasm	Normal eye exam and VFs	Early after vomiting; patient had known multiple previous recurrences of pinealoblastoma	None	Metastatic PNET	Chemotherapy and radiotherapy	Died Short follow-up since chiasmal involvement (10 years since diagnosis of primary tumor) Died 4 months after the 4th relapse
2	8/M	Homonymous hemianopia	Optic tract infiltration	Homonymous hemianopia		Stable homonymous hemianopia with preserved vision	Known metastatic ependymoma		Died (4 years since visual function involvement, 5 years from initial diagnosis)
3	14/M	Progressive monocular visual loss 2.5 years RE 20/200 further in 3 months to 1/18 LE after 8 months from 20/25- to 1/18 to NLP	Initially normal, past post-operative changes post-temporal PNET resection, later thinning of RE optic nerve, followed by thickening of LE optic nerve	Reduced vision, N/A	4 months	At 2.5 years, progressive monocular VL followed by fellow eye involvement and CRAO with clinical deterioration to complete binocular visual loss	Metastatic PNET	Radiation (post-chemotherapy and radiation at initial diagnosis)	Died (2 yrs since visual deterioration, 5yrs since initial diagnosis)
4	77/M [Figure 1]	Decreased vision in RE to finger counting, deteriorating to NLP	Enhancement of RE optic nerve	N/A RE, normal LE VF	1 month (delayed diagnosis of optic nerve enlargement and enhancement)	Progressive visual loss in the right eye	Known BCC Metastatic TCC	Steroids	Died (4 months since visual deterioration of RE)
5	69/M	Monocular progressive visual loss RE	Enhancement of RE optic nerve ring enhancement of the optic chiasm	No data	6 months	No data	Anaplastic astrocytoma	Steroid for optic neuritis	Lost to follow-up
6	64/M [Figure 2]	Bitemporal hemianopia	Normal MRI X2	Bitemporal hemianopia	3 months, third MRI	Progressive binocular visual loss	Malignant GG	Radiosurgery and chemo-therapy	Died (36 months)

(*Contd...*)

Table 1: (*Continued*)

Pt.	Age (year)/ sex	Presentation	First imaging	VF defect	Time to diagnostic imaging	Clinical deterioration	Pathology	Treatment	Outcome (time of follow-up since diagnosis)
7	57/F	Acute monocular visual loss	Tumor infiltrating sinus and adjacent Optic nerve (no compression), susp infiltrating optic nerve	NLP RE, normal VF LE	Immediately	Acute monocular visual loss	Rhabdomyo-sarcoma	Chemotherapy	Died (12 months)
8	62/M	Progressive monocular visual loss LE 4 months followed by VF defect in the RE	CT and CT angio initially normal, followed by MRI showing thickening of the chiasm and both optic nerves, and later involvement of the left optic tract and radiation	NLP LE, visual deterioration RE	Within 2 weeks, but 4.5 months from onset	Progressive binocular visual loss	Glioblastoma multiforme	Radiation and chemotherapy	Died (12 months from diagnosis)

BCC: Basal cell carcinoma, CRAO: Central retinal artery occlusion, GBM: Glioblastoma multiforme (grade IV), GG: Ganglioglioma, RE: Right eye, LE: Left eye, NLP: No light perception, PNET: Primitive neuroectodermal tumor, RAPD: Relative afferent papillary defect, RMS: Rhabdomyosarcoma, TCC: Transitional cell carcinoma, VFs: Visual fields, VL: Visual loss

eighth. There was diffuse brain atrophy and periventricular white matter changes which were interpreted as normal for age.

Findings on comprehensive laboratory panel (erythrocyte sedimentation rate, C-reactive protein, complete blood count, antinuclear antibody, p-antineutrophil cytoplasmic antibody, c-antineutrophil cytoplasmic antibody, angiotensin converting enzyme, serum protein electrophoresis test, fluorescent treponemal antibody test, prostate specific antigen, and carcinoembryonic antigen) and tuberculosis test were within normal limits or negative. Lumbar puncture revealed a normal opening pressure (19 cm of water) with elevated levels of protein (119 mg/dL), normal glucose levels (55 mg/dL), and 24 white cells. Gram stain and acid fast stain revealed no organisms. Cryptococcal antigen was negative. Cerebrospinal fluid (CSF) cultures for fungus and mycobacterium were negative. Polymerase chain reaction for herpes simplex virus was negative. CSF cytology demonstrated lymphocytes and ependymal cells. A second lumbar puncture showed elevated protein (104 mg/dL) and 23 white cells identified as mature lymphocytes. Lymphoma could not be ruled out; carcinomatous cells were not found on cytological examination of the CSF. The patient refused optic sheath biopsy. He was treated with IV methylprednisolone for 3 days followed by tapering of oral prednisone. No change in vision was noted, but he reported less pain. Within 1 month, the patient experienced gait disturbance, general weakness, and hearing loss and was re-admitted for evaluation. Visual acuity was found to be no light perception in the right eye and 20/30 in the left. Disc pallor and swelling were noted on the right, and pallor in the left. Repeated MRI evaluation demonstrated enhancement of the optic nerves, more noticeable on the right, and enhancement of the cranial nerves. Repeated chest and abdominal computed tomography revealed no abnormalities. Cellularity was normal on bone marrow biopsy. Lumbar puncture revealed elevated opening pressure of 33 cm water, elevated protein level of 254 mg/dL, and 2 cells (cytology inconclusive). A fourth lumbar puncture performed at the oncologist's request again revealed an elevated opening pressure (25 cm of water), extremely elevated protein level of 533 mg/dL, and no cells. There was no change on repeated chest and abdominal computerized tomography or repeated bone marrow biopsy. Optic nerve sheath biopsy was performed to obtain a tissue diagnosis. The pathology and immunohistochemistry findings were consistent with meningeal carcinomatosis arising from transitional cell carcinoma. The patient's condition continued to deteriorate, and he died 2 months after presentation at our medical center.

Case 6

A 64-year-old man presented with blurred vision and rapidly progressive bitemporal VF defects. His third MRI [Figure 2] showed enhancing lesions within the prechiasmatic optic nerves, chiasm, and right hypothalamus. Biopsy study showed malignant ganglioglioma. The patient's condition improved significantly after radiosurgery and chemotherapy. He died within 3 years from presentation.

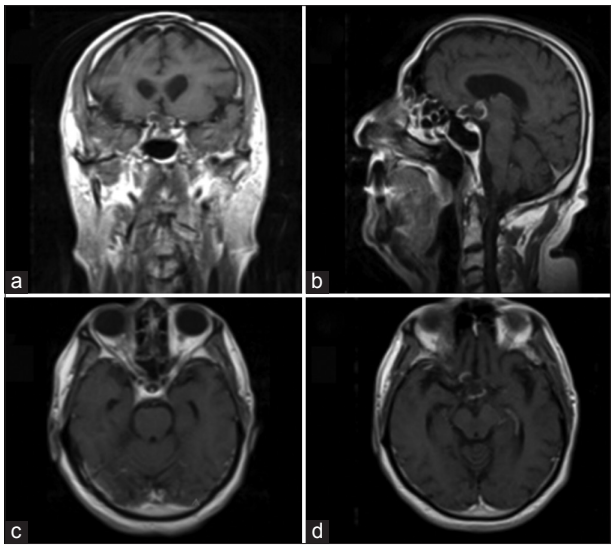

Figure 2: (Case 6) Magnetic resonance imaging in coronal (a), sagittal (b), and axial (c and d) T1 fat saturated post-contrast planes, showing progression with enhancement of retrobulbar and prechiasmatic optic nerves bilaterally more on the right

Discussion

We describe eight patients with malignant tumor involvement of the optic pathway. All but one presented with painless impairment in vision. All the pediatric cases but only one of the adult cases had prior history of malignant disease or remarkable findings on initial imaging. Seven died within a year of diagnosis of optic nerve involvement, and one was lost to follow-up.

Malignancy to the optic tract presents with rather non-specific symptoms of gradual vision loss.[1-4,8-10] It is therefore not surprising that other diagnoses such as optic neuritis or ischemic neuropathy are initially suspected. Although rare, malignancy should be considered in the differential diagnosis in patients with this complaint.

Only one of our patients presented with acute irreversible monocular vision loss (patient 7). On ophthalmologic examination just 1 week before, no abnormalities were noted in vision or in retinal and optic nerve appearance. Imaging showed a tumor infiltrating the sinus and adjacent structures and possibly the optic nerve. Our search of the literature yielded only one other case of optic nerve tumor presenting with acute monocular vision loss.[11] The tumor in that report was identified as an optic glioma affecting the pulvinar region of the optic tract, and the patient died 3 weeks after diagnosis and 11 weeks after onset of symptoms.

Intrinsic tumors of the optic nerve in children tend to be primary low grade gliomas, whereas all three children in our series with "malignant" optic nerve tumors had secondary involvement and none were gliomas. In adults, low-grade gliomas are much less common and intrinsic tumors of the optic nerve tend to be malignant and may be primary such as malignant glial tumors or secondary from metastatic or local spread. On pathologic study, all three children had metastases from a previously diagnosed primitive neuroectodermal tumors (PNET) or ependymoma. Accurate diagnosis is vital in these cases, as with new treatment modalities PNET carry better prognosis than in the past.[12,13] Although optic pathway gliomas are common in children, they are primary intrinsic tumors of the optic pathway and not metastases, usually low-grade gliomas with unpredictable clinical behavior and almost never show malignant transformation.[3,4] By contrast, in adults, they are highly malignant and rapidly fatal.[4,6,7,11,14,15] In our series, three of the five adult patients had a malignant optic glioma (anaplastic astrocytoma and two malignant ganglioglioma). There was also one of rhabdomyosarcoma of the sinus involving the optic nerve. One patient had TCC metastasis from the bladder. Although the literature contains some cases of ocular[16,17] and orbital[9] infiltration of ependymoma, PNET, and TCC, direct infiltration of these tumors into the optic nerve is rare.[15,18] One case with lymphoma was excluded due to lack of data. However, lymphoma may involve the optic tract, but it is easily detected on imaging.[15,19] This study highlights that recurrent tumors can directly infiltrate the optic nerve.

MRI has replaced high-resolution computed tomography as the gold standard for visualization of the optic tract.[6,20] The findings are usually non-specific, such as enhancement of the optic nerve on T1-weighted imaging with contrast or enlargement of the optic canal,[6] both of which may also be characteristic of optic neuritis, lymphoma, and leukemia.[5,21] In our series, imaging findings ranged from no abnormalities to optic nerve enhancement to gross infiltration of tumor. Repeatedly negative inflammatory work up in the setting of progressive visual deterioration should prompt biopsy despite the risks involved in biopsy of the optic nerve since there is often no other way of diagnosing malignancy. In addition, if the patient has known central nervous system malignancy, then metastatic involvement of the visual pathway should be strongly considered and repeating inflammatory work-up has very low yield and may only delay accurate diagnosis.

In summary, this study emphasizes the high index of suspicion needed for the diagnosis of malignant involvement of the optic nerve in patients who present with progressive vision loss, the need for repeated MRI to improve diagnosis and treatment, the wide variety of causative tumors, and the risk of optic nerve infiltration when tumors are incompletely eradicated. In addition, pediatric oncologists should be aware that malignant optic nerve involvement is not limited to the adult population.

Conclusion

This study emphasizes the high index of suspicion needed for the diagnosis of malignant involvement of the optic nerve in patients who present with progressive vision loss, the need for repeated MRI to improve diagnosis and treatment, the wide variety of causative tumors, and the risk of optic nerve infiltration when tumors are incompletely eradicated. Additionally, pediatric

oncologists should be aware that malignant optic nerve involvement is not limited to the adult population.

Declarations

The study was accordance with the ethical standards of the Rabin Medical Center Institutional Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Availability of Data and Materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Competing Interests

The authors have no conflicts of interest to disclose.

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Authors' Contributions

All authors participated in all areas of study design and manuscript approval.

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