Primary Gliosarcoma of the Optic Nerve: A Unique Adult Optic Pathway Glioma

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Abstract: A 90-year-old woman presented with 1-year history of right-sided progressive proptosis, neovascular glaucoma, blindness, and worsening ocular pain. No funduscopic examination was possible because of a corneal opacity. Head CT scan without contrast demonstrated a heterogeneous 4.1 cm (anterior–posterior) by 1.7 cm (transverse) cylindrical mass arising in the right optic nerve and extending from the retrobulbar globe to the optic canal. She underwent palliative enucleation with subtotal resection of the orbital optic nerve and tumor. Pathological examination showed effacement of the optic nerve by an infiltrative high-grade glial neoplasm with biphasic sarcomeric differentiation. Invasion into the uvea and retina was present. The neoplasm was negative for melan-A, HMB45, tyrosinase, synaptophysin, smooth muscle actin, and epithelial membrane antigen. The glioma had strongly intense, but patchy immunopositivity for glial fibrillary acidic protein. Multiple foci of neoplastic cells had pericellular reticulin staining. The overall features were diagnostic of a gliosarcoma (World Health Organization grade IV) of the optic nerve. Postoperative MRI demonstrated postsurgical changes and residual gliosarcoma with extension into the optic chiasm. The patient died 2 and a half months after her enucleation surgery at her nursing home. Autopsy was unavailable due to the caregiver wishes, making a definitive cause of death unknown. Gliosarcoma is a rare variant of glioblastoma, and this is the first documented case presenting as a primary neoplasm of the optic nerve.

Optic pathway gliomas are uncommon central nervous system neoplasms represented by variable histopathological classifications ranging from the most common pilocytic astrocytoma to rarer high-grade infiltrating astrocytomas. Clinical behavior depends in large part on the histopathological classification, which is represented as a World Health Organization grade assignment ranging from I to IV. Optic pathway gliomas are more common in the pediatric population, are usually low grade, and can be associated with neurofibromatosis type 1. In this report, the authors present a case of a sporadic high-grade optic pathway glioma classified histologically as a gliosarcoma, World Health Organization grade IV, which is a rare form of glioblastoma. Gliosarcoma generally involves the cerebral cortex. This is the first report in the literature of a primary gliosarcoma presenting in the optic nerve. All patient images and information presented in this case report are deidentified in accordance to the guidelines set forth by the Health Insurance Portability and Accountability Act.

CASE REPORT

A 90-year-old woman with history of long standing dementia presented with 1-year progression of right-sided proptosis (Fig. 1A) and had been noted to have blindness, ocular pain, central retinal vein occlusion, and neovascular glaucoma by the referring outside provider. Her worsening proptosis and pain prompted the referral. Complete physical examination was limited secondary to her advanced dementia. There was retraction of the right upper eyelid, 8 mm of proptosis, hypoglobus of the eye, and elevated intraocular pressure of 41 mm Hg. The corneal surface exhibited significant epitheliopathy. Examination under general anesthesia, at the time of enucleation, verified these findings. Funduscopic evaluation could not be performed due to her dementia and the dense corneal haze that precluded an adequate view.

Head CT scan without contrast demonstrated a heterogeneous 4.1 cm (anterior–posterior) by 1.7 cm (transverse) cylindrical mass arising in the right optic nerve and extending from the retrobulbar globe to the optic canal (Fig. 1B, C). Neuroimaging features were suspicious for an aggressive optic nerve glioma. Given her age, dementia, risk of corneal infection, and overall poor prognosis, she underwent palliative enucleation with gross subtotal resection of the orbital optic nerve and tumor for pain relief. Intraoperative and gross pathological examination of the enucleation specimen demonstrated a firm, elongated tan-white mass effacing, and expanding the optic nerve (Fig. 1D, E). On cut surface, grossly, the mass barely extended into the uveal layer of the globe (Fig. 1E).

Microscopic examination of the neoplasm confirmed significant effacement and expansion of the optic nerve, with approximately 4 mm of invasion into the retina with retinal detachment and ganglion cell loss (Fig. 2A). Hematoxylin and eosin-stained sections showed an overall biphasic architecture of the neoplasm, with 1 phase appearing more glial to epithelioid and the other component favoring a mesenchymal appearance (Fig. 2A, B). Necrosis and microvascular proliferation were observed (Fig. 2C, D). Focal heterologous osteoid formation within the neoplasm was present (Fig. 2E). The neoplastic nuclei were variably pleomorphic and mitotic activity was brisk (Fig. 2F). Immunohistochemistry demonstrated strongly intense positive staining for S-100 and vimentin diffusely throughout the neoplasm, while glial fibrillary acidic protein immunostaining was primarily limited to the glial portion of the neoplasm (Fig. 2G). The neoplasm was largely immunonegative for markers of melanoma (melan-A, HMB45, tyrosinase), neuroendocrine neoplasm (synaptophysin), sarcoma (alpha smooth muscle actin), and carcinoma (epithelial membrane antigen). Histochemically, the mesenchymal, or sarcomatous, component of the neoplasm was reticulin rich with pericellular staining in some areas (Fig. 2H). Ultrastructural examination demonstrated abundant intermediate filaments but no definite myofibers, sarcomeric differentiation, melanosomes, or premelanosomes (Fig. 2I). The overall histomorphologic, histochemical, immunohistochemical, and ultrastructural features were diagnostic for a gliosarcoma, World Health Organization grade IV.

The non-neoplastic portion of the globe was characterized by histopathologic changes confirmatory for the clinical history of neovascular glaucoma, including peripheral anterior synechiae and iris neovascularization. The patient was seen in follow-up 2 weeks after enucleation and was noted to be pain free both by her accompanying

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FIG. 1. Clinical, imaging, and gross pathologic features. A, The patient presented with right-sided proptosis. B, C, Preoperative head CT showed a cylindrical heterogeneous mass involving the optic nerve. D, External surface of the globe shows an attached significantly expanded optic nerve. E, Cut surface of the enucleation specimen demonstrates a solid tumor with some invasion into the uvea. F, Postoperative MRI highlights residual tumor with involvement of the optic chiasm.

FIG. 2. Histopathological features of optic nerve gliosarcoma. A, H&E-staining showed a biphasic neoplasm with glial and sarcomatous components, which effaced the optic nerve and extended into the retina (20x original magnification). B, Cytologically, there were pleomorphic cells, some with multi-nucleation, in both the glial and sarcomatous components (200x original magnification). High-grade features included (C) necrosis (100x original magnification) and (D) microvascular proliferation (400x original magnification). E, Intradural heterologous osteoid formation was found focally (100x original magnification). F, The neoplasm was highly mitotically active with several mitotic figures present in a single high-powered field (400x original magnification). G, The glial portion of the neoplasm was immunopositive for GFAP (400x original magnification). H, The sarcomatous areas were reticulin-rich with peri-cellular staining (400x original magnification). I, Electron microscopy showed abundant intermediate filaments.
Characteristics of low-grade optic nerve gliomas, high-grade optic nerve glioma, and gliosarcoma of the optic nerve

<table>
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<tr>
<th>WHO grade</th>
<th>Histologic features</th>
<th>Special stains</th>
<th>Age of onset</th>
<th>Gender</th>
<th>Associated diagnoses</th>
<th>Associated genetics</th>
<th>Ophthalmic findings</th>
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<th>Report of Primary Gliosarcoma of the Optic Nerve (Current Case)</th>
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<td>I–II</td>
<td>Pilocytic astrocytoma (piloid morphotype, Rosenthal fibers, eosinophilic granular bodies); diffuse astrocytoma (infiltrating growth pattern)</td>
<td>Diffuse GFAP and Olig2 positivity; low Ki-67 proliferative index</td>
<td>Childhood</td>
<td>Equal when sporadic</td>
<td>NF1: 15–25%</td>
<td>NF1 and BRAF mutations for pilocytic astrocytomas; IDH1/2, TP53, ATRX mutations for diffuse astrocytomas</td>
<td>Proptosis, swollen optic disc</td>
<td>Often close observation. Resection for concern of intracranial spread. Vision threatening: possible radiation and chemotherapy</td>
<td>Good</td>
<td>Death within 1–2 years</td>
</tr>
<tr>
<td>III–IV</td>
<td>Infiltrating astrocytoma with increased mitotic activity; glioblastoma has microvascular proliferation and/or necrosis; rarely intravitreal seeding by neoplasm</td>
<td>Diffuse GFAP and Olig2 positivity; high Ki-67 proliferative index</td>
<td>Adulthood</td>
<td>Equal</td>
<td>Sporadic</td>
<td>EGFR amplification, polysony chromosome 7, chromosome 10q loss</td>
<td>Proposis. Swollen optic disc, CRVO, CRAO, NVG</td>
<td>Radiation + chemotherapy</td>
<td></td>
<td>Death within 2 years</td>
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<tr>
<td>IV</td>
<td>Gliosarcoma variant of glioblastoma (biphasic high-grade astrocytoma and high-grade sarcoma); highly mitotically active; positive retinal invasion</td>
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<td></td>
<td></td>
<td></td>
<td>Not performed; probable CDKN2A deletion, TP53 mutation, and TERT promoter mutations</td>
<td></td>
<td>Enucleation. Gliomas: often radiation + chemotherapy</td>
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CRAO, central retinal artery occlusion; CRVO, central retinal vein occlusion; EGFR, epidermal growth factor receptor; GFAP, glial fibrillary acidic protein; NF1, neurofibromatosis type 1; NVG, neurovascular glioma; WHO, World Health Organization.

providers from her facility and by clinical examination. Postoperative MRI performed during the same visit demonstrated postural changes and residual gliosarcoma with extension into the optic chiasm (Fig. 1F). The patient’s dementia-related cortical atrophy made a precise comparison difficult but the lesion had signal intensity on both T1 and T2 similar to grey matter. One month later in a telephone conversation, her caregivers reported that the patient remained comfortable. The patient died at 2 and a half months after her enucleation surgery at her nursing home, under Do Not Resuscitate protocol. Autopsy was unavailable due to the caregiver wishes, making a definitive cause of death unknown.

**DISCUSSION**

Primary gliosarcoma is an uncommon variant of glioblastoma, accounts for approximately 2% to 3% of all cases of glioblastoma with some overlapping histological and clinical features.1,4,8,9 Optic nerve and chiasm glioblastomas (i.e., “malignant gliomas”) are rare entities that comprise only a small subset of optic pathway gliomas, and are usually found in adults.5,7 Although it is believed that resection of high-grade optic nerve gliomas does not provide local control or offer a survival benefit, it can be used for palliative control of ocular pain.8 Optic pathway glioblastoma has a rapidly progressive course with a low reported average survival, ranging from 6 to 14 months, which is similar to that of glioblastoma in other locations.5,9 There are conflicting reports regarding whether or not there is a survival difference when comparing gliosarcoma to classic glioblastoma regardless of anatomical location.10–14 In a retrospective study using data from the Surveillance, Epidemiology, and End Results database, a multivariate Cox proportional hazards model reported a slightly worse prognosis for gliosarcoma when compared with classic glioblastoma (hazard ratio = 1.17, 95% confidence interval = 1.05–1.31).12 However, in a randomized prospective clinical trial, there was no difference in survival or prognosis when comparing gliosarcoma to classic glioblastoma.16 In addition, the current 2016 World Health Organization classification of central nervous system tumors does not recognize a significant prognostic difference between gliosarcoma and classic glioblastoma.1 This current case is in keeping with the expected survival of patients with optic nerve and chiasm glioblastoma.5,11,15

Clinically, significant differences exist in presentation between low-grade optic nerve gliomas and high-grade optic nerve glioblastoma (HGONG) and gliosarcoma (Table). Low-grade optic nerve gliomas typically present in childhood and may be associated with neurofibromatosis type 1. They are relatively slow growing with vision loss resulting from infiltrative and compressive optic neuropathy, clinically manifested as optic nerve swelling. While management is controversial, observation is frequently recommended with serial ophthalmic examination to confirm clinical stability. Should tumor progression and visual decline occur, treatment with surgery, chemotherapy or radiation therapy may be considered. Surgical resection almost always results in complete blindness of the affected eye and therefore is largely reserved for palliation in nonseeing eyes and/or to prevent involvement of the contralateral side. Radiation therapy, while effective at delaying progression, is associated with severe neurologic side effects, particularly in young children. Chemotherapy, usually consisting of vincristine and carboplatin, is also useful in delaying progression and can be used as a stop-gap measure to delay radiation therapy in younger children. Survival of low-grade optic nerve glioma patients has been reported to be 96% at 5 years and 85% at a median follow up of 17 years in published case series.8,16
In contrast, HGONG typically occurs in older individuals, and is sporadic with no known association with neurofibromatosis type 1. Rapid intracranial growth and death within 1 to 2 years, despite aggressive treatment with radiation and chemotherapy, is characteristic. Patients may or may not have initial proptosis and rapid evolution of disc swelling to frank central retinal vein occlusion is often seen. Unsurprisingly, our patient with primary gliosarcoma of the optic nerve followed the clinical course usually associated with HGON and gliosarcomas found in other locations. In addition to developing neovascular glaucoma secondary to central retinal vein occlusion and significantly, rapidly evolving proptosis, imaging revealed progression with extension to the optic chiasm soon after presentation. Conservative management allowed the patient to be free of pain, with death approximately 1.5 years after onset of symptoms, which was 2.5 months after her enucleation.

Of the 67 cases of HGONG reported in the literature, only 1 case found clinical subretinal involvement and 1 other described intravitreal seeding. Neither case had histologic confirmation of the clinical findings. Our case for the first time histopathologically demonstrates that aggressive HGONG and the gliosarcoma variant can rarely infiltrate anteriorly from the optic nerve into the eye, as well as the more commonly known posterior extension intracranially.

Cytogenetic abnormalities and genetic mutations found in gliosarcoma have similarities to those of primary glioblastoma. Cytogenetic copy number alterations include chromosome 10q loss and polyomavirus chromosome 7, although unlike glioblastoma the latter is not usually associated with epidermal growth factor receptor amplification. Gene level mutations within gliosarcoma include $CDKN2A$ deletion, $TP53$ mutation, and $TERT$ promoter mutations. Gliosarcoma generally lacks mutations in the genes associated with lower-grade diffuse gliomas, including $IDH1/2$ and $ATRX$. In addition to these genetic changes, gliosarcoma rarely (11.5%) shows the epigenetic change of $MGMT$ promoter methylation. So, while there is some overlap of histological and molecular characteristics when comparing gliosarcoma to glioblastoma, gliosarcoma generally lacks genetic markers associated with favorable prognosis and predictive treatment response in some glioblastoma. These differences have led some propose that gliosarcoma may require more specific therapy, rather than the current generalized therapy given for glioblastoma. In the current case, genetic profiling was not performed, as ancillary diagnostic support was not needed, and these genetic mutations currently hold no prognostic significance.

In the majority of cases, gliosarcoma arises in a supratentorial location involving the cerebral hemispheres (with a predilection for the temporal lobe) and involves dura to its superficial location. Extremely rare cases of gliosarcoma are reported outside of the cerebral cortices, and include anatomical sites, such as intraventricular, cerebellar, spinal cord, and brainstem regions. To our knowledge, this is the first report of a primary gliosarcoma arising in the optic nerve and includes involvement by the optic chiasm. Unique features not previously described histologically with HGONG includes tumor invasion into the uvea and retina. This case expands the spectrum of prechiasmatic and chiasmatic optic pathway gliomas to include gliosarcoma.

REFERENCES