Malignant transformation of an optic pathway glioma without prior radiation therapy

Case report

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Optic pathway gliomas (OPGs) arise from the optic nerves, optic chiasm, and/or hypothalamus and most commonly occur in childhood. Although these tumors can be quite challenging to manage, they are typically low-grade astrocytomas histologically, most commonly pilocytic astrocytomas. The few previously reported cases of malignant degeneration of an OPG occurred after external beam radiation therapy. The authors report the first case in the English literature of an OPG that transformed from a low-grade astrocytoma, with features most consistent with a pilocytic astrocytoma, to a malignant glioma without any exposure to radiation therapy.

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Key Words • pilocytic astrocytoma • malignant transformation • optic pathway glioma • glioblastoma multiforme • radiation therapy

Optic pathway gliomas are typically low-grade astrocytomas that arise from the optic nerves, optic chiasm, and/or hypothalamus. Optic pathway gliomas constitute 1–5% of pediatric intracranial tumors, with roughly 75% occurring within the first decade of life.1,2,16 In previous publications the majority of OPGs are classified as pilocytic astrocytomas (WHO Grade I), and the remainder are classified as fibrillary astrocytomas (WHO Grade II).8,14 Unlike pilocytic astrocytomas in the cerebellum and cerebral hemispheres, which can often be resected completely with excellent long-term outcomes, OPGs are typically not completely resectable and can be associated with considerable morbidity.1,16

Optic pathway gliomas confined to 1 or both optic nerves that are not enlarging are typically observed using serial imaging studies. Larger tumors involving the optic chiasm and hypothalamus often require surgery, both to distinguish them pathologically from other suprasellar neoplasms and to relieve mass effect.9,10 Gross-total resection is typically not performed due to potentially severe endocrine and visual morbidity. Depending on the age of the patient and the clinical and radiographic findings, chemotherapy, radiation therapy, or observation may be considered postoperatively.9 In general, patients with OPGs who have NF1 tend to have tumors with a more benign course than those without NF1, so particular effort is made to avoid radiation therapy in this population. Moreover, patients with NF1 and suprasellar lesions typical of OPGs do not necessarily need a biopsy specimen to prove the diagnosis, and surgery is offered only to relieve mass effect.

Whereas radiographic progression of subtotally resected OPGs is common, malignant transformation of pilocytic astrocytomas of the optic apparatus and hypothalamus has only been previously reported after treatment with radiation therapy.7 In this paper we present the first case in the English literature of malignant transformation of a subtotally resected OPG that transformed from a low-grade astrocytoma, with features most consistent with a pilocytic astrocytoma, into a malignant glioma (anaplastic vs GBM) without any exposure to radiation therapy.

Abbreviations used in this paper: GBM = glioblastoma multiforme; NF1 = neurofibromatosis Type 1; OPG = optic pathway glioma.

This article contains some figures that are displayed in color online but in black and white in the print edition.
Case Report

History and Presentation. This 5-year-old boy presented in 2005 with profound visual loss bilaterally. His physical examination was remarkable for blindness in the left eye and 20/400 vision in the right eye, but he was otherwise neurologically intact. No endocrinopathy was noted. There was no family history of NF1, and the patient did not have any cutaneous stigmata such as café-au-lait spots or axillary freckling. Genetic testing for NF1 was not performed. Magnetic resonance imaging of the brain revealed a large suprasellar mass that enhanced heterogeneously with Gd (Fig. 1A).

First Operation and Postoperative Course. The boy underwent a left frontotemporal craniotomy, at which time the mass was found to blend indistinguishably into the optic chiasm and hypothalamus. A limited subtotal resection was performed after frozen section revealed a low-grade astrocytoma, and the final pathology was determined to be a pilocytic astrocytoma (Fig. 1B and C). The tumor was noted to contain scattered granular bodies, occasional eosinophilic droplets, and rare Rosenthal fibers, with glial fibrillary acidic protein positivity and a low MIB-1 labeling index (estimated as < 2%). Subsequent review by pathologists at 2 outside institutions (see Acknowledgments) agreed with the diagnosis of low-grade astrocytoma with features most consistent with pilocytic astrocytoma. It was noted that the lesion was more compact and cellular than the classic pilocytic astrocytoma but there were no malignant features noted. The MIB-1 labeling index, as noted above, stained positively and was very low (estimated as < 2%). Upon subsequent review of the lesion at the second institution, no cells stained positively with MIB-1, which may have been a false negative.

Postoperatively, the patient was placed on vincristine and carboplatin with the goal of delaying tumor progression and avoiding radiation therapy. Over the course of the next 2 years, the patient was clinically stable and experienced no visual deterioration. Multiple MR images demonstrated no definitive increase in tumor size, but imaging changes suggesting central necrosis of the tumor were noted.

Second Operation and Postoperative Course. Two years and 1 month after the initial surgery, the patient presented with deteriorating vision and lethargy. Repeat MR imaging showed a dramatic increase in the size of the tumor with significant frontal lobe edema (Fig. 2A). The patient was taken back to the operating room for tumor resection via an interhemispheric transcallosal approach. A generous but subtotal tumor resection was performed in an attempt to debulk the tumor prior to radiation therapy without causing an endocrinopathy (Fig. 2B). Histologically, the tumor now demonstrated features consistent with a malignant glioma, including conspicuous mitotic activity, necrosis, and an MIB-1 labeling index estimated as 20% overall but with areas approaching 50% (Fig. 2C and D). There were no areas of the tumor that demonstrated any features of a pilocytic astrocytoma or in any way resembled the pathological findings of the original specimen. The tumor was now a highly cellular epithelioid neoplasm.
consisting largely of gemistocytic astrocytes with focal areas of necrosis and mitoses. One outside neuropathology expert classified the recurrent tumor as a GBM, and the second neuropathology expert classified the recurrent tumor as an anaplastic glioma.

The patient was treated postoperatively with external beam radiation therapy and temozolomide. Four months later, he presented with severe headaches and was found to have hydrocephalus on imaging studies. He underwent ventriculoperitoneal shunt placement and endoscopic fenestration of the septum pellucidum. Unfortunately, over the next few weeks he continued to deteriorate neurologically despite decompressed ventricles. At the request of his family, a “do not resuscitate” order was initiated, and the patient died.

**Discussion**

Malignant glioma of the optic chiasm and hypothalamus is a rare clinical entity and usually only involves these structures secondarily. Only a few case reports have been published in which a GBM clearly developed primarily within the optic chiasm prior to involving adjacent structures. Malignant gliomas involving the optic nerves and/or chiasm typically have a clinical presentation that is quite distinct from the more common benign OPGs of the pediatric population, and at the present time only a single case of a primary GBM developing within the optic chiasm has been reported in a child.

Although uncommon, malignant transformation of pilocytic astrocytomas in various anatomical locations of the brain has been presented in a number of prior reports. To date, however, the few such patients reported all have received radiation therapy prior to the malignant transformation. In the case currently reported, the patient had a biopsy-proven low-grade astrocytoma with features most consistent with a pilocytic astrocytoma and received only relatively mild chemotherapy (vincristine and carboplatin) postoperatively, but a clear malignant transformation was noted at reoperation more than 2 years after the initial diagnosis.

In a recent article, Parsa and Givrad refute the notion that malignant transformation of pilocytic astrocytomas can occur spontaneously. The authors studied all...
previous publications describing malignant transformation of pilocytic astrocytomas and found 52 such cases. Thirty of these cases occurred after radiation therapy, either at the same exact site as the primary tumor or separately but within the radiation fields. These were designated as radiation-induced malignant change, which is an established cause of malignant transformation of benign tissues, presumably due to resultant DNA mutations. The remaining 22 cases, in the view of the authors, all had insufficient histopathological classification either of the initial diagnosis of pilocytic astrocytoma or of the malignant transformation.13

The patient we currently report is the first case in the English literature of an OPG that transformed from a low-grade astrocytoma, with features most consistent with a pilocytic astrocytoma, to a malignant glioma without any exposure to radiation therapy. Moreover, this case refutes the notion advanced by Parsa and Givrad13 that malignant transformation of pilocytic astrocytomas does not occur and that these lesions should be classified as hamartomas rather than as true neoplasms. The histological findings from both the initial and subsequent surgical specimens in our patient unequivocally indicate that spontaneous malignant degeneration of a low-grade astrocytoma has occurred and is consistent with his rapid clinical progression to death after recurrence of the tumor.

Conclusions

To the best of our knowledge, this is the first case of spontaneous transformation of a low-grade optic pathway astrocytoma into a malignant glioma. The clinical progression and pathological changes reported in this case directly repudiate previous contentions that pilocytic astrocytomas cannot undergo malignant transformation in the absence of radiation therapy.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References


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