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Pilocytic astrocytoma of the optic nerve with intracystic hemorrhage in an adult: illustrative case

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BACKGROUND Optic pathway gliomas are uncommon, accounting for 3–5% of childhood brain tumors, and are mostly classified as pilocytic astrocytomas (PAs). PAs of the optic nerve are particularly rare in adults.

OBSERVATIONS The authors presented the case of PA of the left optic nerve in a 49-year-old woman along with detailed pathological and molecular analyses and sequential magnetic resonance imaging. The tumor had progressed during 5 years of follow-up along with cyst formation and intracystic hemorrhage; it had a thick capsule and contained xanthochromic fluid. The boundary between tumor and optic nerve was unclear. B-type Raf kinase (*BRAF*) V600E point mutations or translocations, IDH1-R132H mutations, loss of alpha-thalassemia/mental retardation X-linked, and 1p/19q codeletion were negative.

LESSONS *BRAF* alterations in pediatric PAs of the optic nerve are less frequent than those observed in PAs in other lesions; the same molecular pattern was observed in the adult case, without changes in *BRAF*. Surgical management should be indicated only in cases with severely impaired vision or disfigurement because there is no clear border between the tumor and optic nerve. Further discussion is needed to optimize the treatment for adult optic pathway gliomas, including radiotherapy, chemotherapy, and molecular-targeted therapies, in addition to surgical intervention.

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KEYWORDS pilocytic astrocytoma; orbital tumor; optic glioma; optic nerve glioma; hemorrhage; adult

Pilocytic astrocytomas (PAs) are circumscribed central nervous system (CNS) brain tumors mostly observed in children and adolescents, and 11–30% of cases are associated with neurofibromatosis type 1 (NF1).[1] These tumors often occur in the posterior fossa (40%), followed by supratentorial lesions (35%) and the optic pathway (11%).[2] They are categorized as World Health Organization grade I, and the 10-year survival rate is extremely high (>95%).[2] The uncommon optic pathway gliomas (OPGs) account for 3–5% of childhood brain tumors and are especially rare in adults.[1] Herein, we present the first case of PA of the optic nerve in an adult with detailed pathological and molecular analyses.

Illustrative Case

A 49-year-old woman presented to an ophthalmologist because of low vision. Clinical examination showed that her relative afferent pupillary defect was positive, and swelling of the optic disc was found in the left eye. Computed tomography revealed an isodense mass lesion in the left orbit, so she was referred to the ophthalmology department of our hospital. The tumor was located in the intraocular space and showed heterogeneous enhancement on magnetic resonance imaging (MRI) (Fig. 1). Follow-up in an outpatient ward confirmed that her left eye vision had gradually worsened; MRI showed tumor progression and enlarged cyst formation with intracystic hemorrhage (Fig. 2). The patient was referred to our department approximately 3 years later and

ABBREVIATIONS BRAF = B-type Raf kinase; CNS = central nervous system; MRI = magnetic resonance imaging; NF1 = neurofibromatosis type 1; ONG = optic nerve glioma; OPG = optic pathway glioma; PA = pilocytic astrocytoma.

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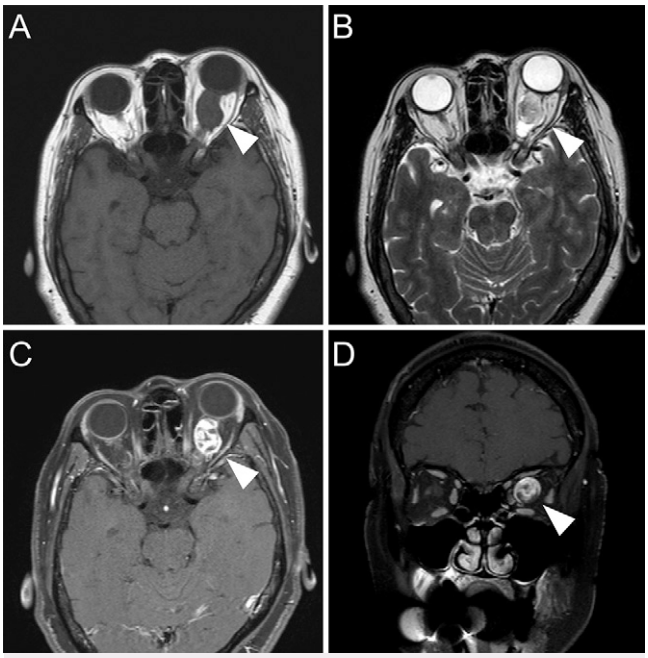

FIG. 1. Axial T1- (**A**) and T2-weighted (**B**) MRI show a well-defined mass lesion in the left orbit (*arrowheads*). The tumor was heterogeneously enhanced in contrast-enhanced T1-weighted MRI with fat saturation (**C and D,** *arrowheads*).

was recommended for resection or stereotactic radiosurgery; she chose to continue with follow-up observation. Approximately 2 years later, the vision in her left eye had progressed to complete blindness with disfiguring exophthalmos. Thus, tumor removal was scheduled for cosmetic reasons and to prevent tumor progression in both optic pathways. Six months later, tumor removal was performed through a semicoronal skin incision after lumber drain placement, followed by frontotemporal craniotomy. Although the orbital roof was drilled, orbital bar was left untouched. The tumor was removed through the space between the superior oblique muscle and the levator and superior rectus muscles, as described for the medial orbitofrontal approach.[3] The tumor had a hard capsule (Fig. 3A), and xanthochromic fluid was evacuated from the cyst (Fig. 3B). The border between the tumor and optic nerve could be hardly identified around the posterior globe (Fig. 3C) and the optic canal (Fig. 3D). Therefore, we declined preservation of the optic nerve because it did not override maximum tumor resection in this case of complete blindness. It was also difficult to find the tumor border around the optic canal. However, the thickness and color appeared to be similar to the optic nerve. In addition, frozen section for intraoperative diagnosis showed no evidence of malignancy. We then did not inspect inside the optic canal and decided to truncate the tumor as far posteriorly as possible in the orbit. Histopathological examination of the resected tumor revealed hyalinized juxtaposed vessels (Fig. 4A) and proliferation of bipolar spindle cells with round-to-oval nuclei and eosinophilic granular bodies (Fig. 4B). Rosenthal fibers (Fig. 4C), microcystic changes, and hemosiderin deposition were also observed. Neural structures were not identified in the resected specimen, suggesting that the optic nerve was completely replaced by the tumor and the tumor cells remained in the stump of the residual optic nerve. Immunohistochemical analysis was positive for glial fibrillary acidic protein (Fig. 4D), S100 protein, and SOX10. The Ki-67 labeling index was approximately 1% (data not shown). Furthermore, we examined genetic alterations in the tumor by immunohistochemistry or fluorescence in situ hybridization. Analyses for B-type Raf kinase (*BRAF*) V600E point mutations (Fig. 4E) or rearrangement (Fig. 4F), isocitrate dehydrogenase 1-R132H mutations, loss of alpha-thalassemia/mental retardation

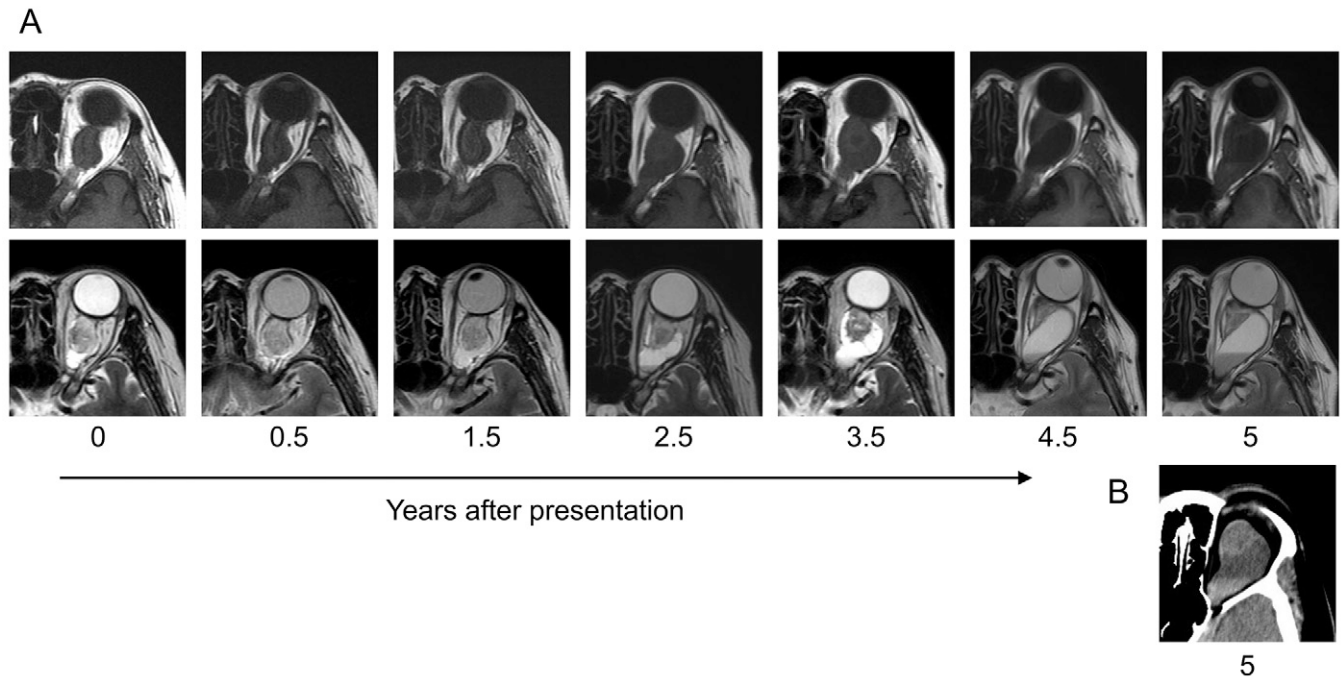

FIG. 2. A: Time series of axial T1- and T2-weighted MRI of the left orbit showing slow progression of the tumor with cyst formation. **B:** Left orbit CT showing intracystic hemorrhage.

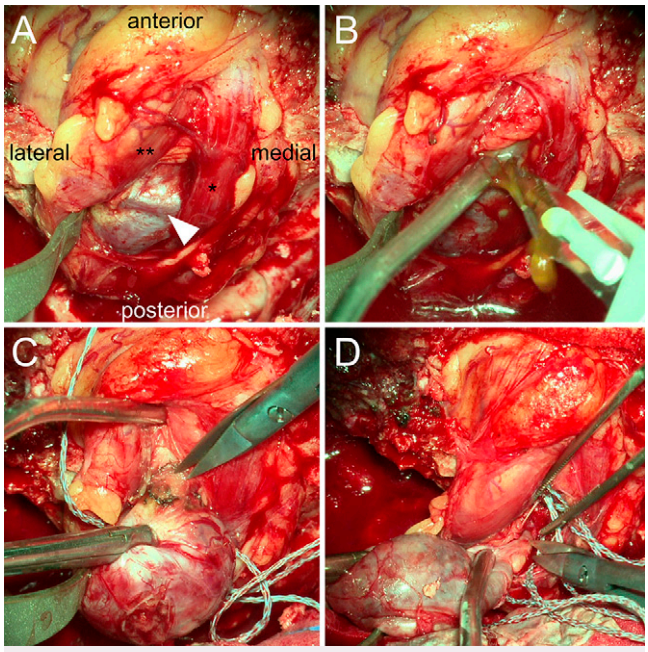

FIG. 3. Intraoperative photographs. (**A**) A well-defined tumor capsule was observed between the superior oblique muscle (*) and the superior rectus muscle (**). (**B**) The cyst contained xanthochromic fluid. The border between the tumor and optic nerve could be hardly determined around the posterior globe (**C**) and the optic canal (**D**).

syndrome X-linked, and 1p/19q codeletion (data not shown) were negative. Based on these pathological findings and molecular analyses, the patient was diagnosed with PA of the optic nerve. NF1-associated features, such as café-au-lait spots or skin neurofibromas, were not observed. Although complete resection of the cystic mass lesion in the left orbit was confirmed by MRI (Fig. 5), the patient experienced intracerebral hemorrhage in the left frontal lobe due to venous infarction,

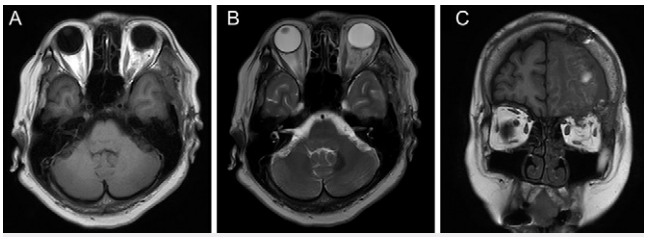

FIG. 5. Postoperative axial T1- (**A**) and T2-weighted (**B**) and coronal T1-weighted (**C**) MRI showing removal of the tumor.

possibly associated with brain retraction (Fig. 5C). The patient was discharged at request with minor neurological deficits (incomplete oculomotor nerve palsy) after 35 days.

Discussion

Observations

PAs are circumscribed CNS brain tumors that occur mostly in children and adolescents. OPGs comprise 0.6–3.5% of all orbital tumors and are mostly low-grade tumors that develop along the precortical visual pathway, including the optic nerve, chiasm, tracts, and radiations and the hypothalamus.[4,5] OPGs in adults are rare, reported to be clinically aggressive, and often pathologically malignant.[6–8] Mishra et al. reported that low-grade tumors accounted for only 22% of adult patients with OPG (≥50 years), whereas 96% of patients 5 to 9 years of age had low-grade gliomas.[9]

MRI features of PAs in the optic nerve are hypointensity on T1-weighted images, hyperintensity on T2-weighted images, and homogeneous gadolinium enhancement.[10] While cyst formation in pediatric OPGs is not uncommon,[11] intracystic or intratumoral hemorrhage is rare. Baarsen et al. reviewed 34 cases of OPG hemorrhage, most of which involved children and adolescents; in 4 cases (12%), the gliomas were located in the orbit, and adult patients (>40 years)

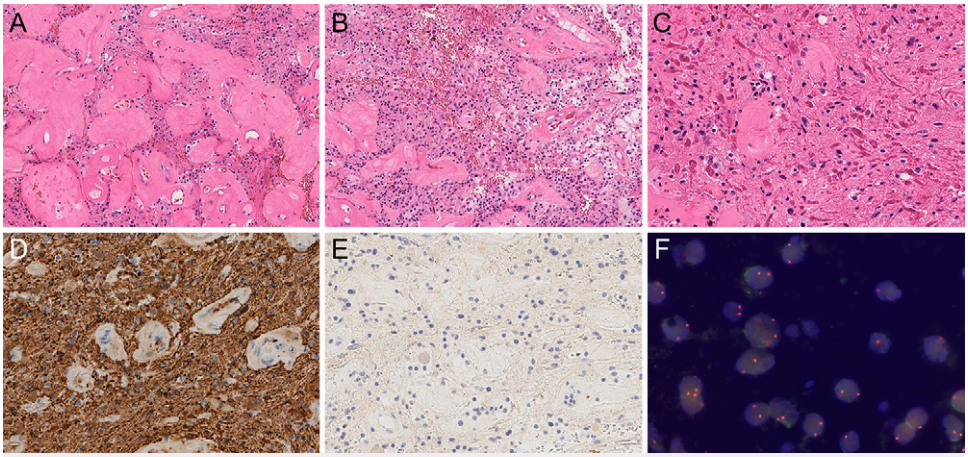

FIG. 4. Histopathological findings of the PA of the optic nerve. Hematoxylin and eosin staining showed abundant hyalinized juxtaposed vessels (**A**; original magnification ×100) and proliferation of piloid cells with eosinophilic granular bodies (**B**; original magnification ×100) and Rosenthal fibers (**C**; original magnification ×200). Glial fibrillary acidic protein was highly expressed (**D**; original magnification ×200), and no BRAF V600E mutation was detected in immunohistochemical analysis (**E**; original magnification ×200). No *BRAF* break-apart signal was detected by fluorescence in situ hybridization analysis (**F**).

accounted for only 6% (2/34 cases).[12] Intracystic hemorrhage in adult optic nerve gliomas (ONGs) has not been reported.

Histologically, PAs typically exhibit biphasic patterns composed of compact fibrillated areas and microcystic areas. Hyalinized vessels are commonly observed, especially in patients in the third decade of life or older, and Rosenthal fibers and eosinophilic granular bodies are also characteristic features of PA. Alterations in the *BRAF* gene are most common in sporadic PAs; it is an important regulator of the mitogen-activated protein kinase pathway, and its mutation is a well-established oncogenic driver in many different cancers.[13] The most frequent alteration in pediatric PAs, particularly in tumors of the posterior fossa, is a tandem duplication at 7q34, resulting in a fusion of *BRAF* with *KIAA1549*, followed by *BRAF* V600E point mutation.[14,15] These two gene alterations are associated with good prognosis and worse outcome, respectively.[16–18] Interestingly, changes within *BRAF* in PAs of the optic nerve are significantly less frequent (*BRAF* fusion: 23%; *BRAF* V600E: 8%) than in PAs in other CNS lesions;[19] in adults, *BRAF* mutations occur in 9.2% of PAs.[20] Trisolini et al. reported that adult PAs of the optic pathway did not exhibit *BRAF* mutations (0/9 cases).[21] In our case, *BRAF* transposition or point mutations were not identified, and these data are consistent with the characteristics of PAs of the optic nerve and adult PAs.

ONGs comprise approximately 25% of all OPGs.[5] Their management has been discussed but remains controversial.[11,22] In particular, there is no consensus on the standard therapy for adult ONGs due to their rarity. The timing for treatment initiation is mostly based on tumor progression, radiological evidence, or worsening symptoms in pediatric OPGs. Platinum-based chemotherapies have been chosen as a first-line treatment, and molecular-targeted therapies such as MEK inhibitors or bevacizumab have recently been reported as promising options for salvage treatment.[5] Although these options may be applied to adult OPGs, their efficacy is unknown. Although surgery may be the first-line treatment for PAs in other lesions, preserving visual function in the optic pathway is challenging. In most cases, surgical intervention is indicated in patients with severely impaired vision or disfigurement.[23] In our case, it was difficult to identify the border between the optic nerve and tumor using imaging and intraoperative findings: the optic nerve was completely replaced by the tumor. Thus, it was impossible to preserve the optic nerve. Although we cut the optic nerve in front of the optic canal based on its appearance and the result of frozen section for intraoperative diagnosis, residual tumor in the stump of the optic nerve was suspected based on histopathological findings. Therefore, careful follow-up is required. In addition, opening the optic canal needs to be considered in cases indicating possibility of tumor extension into the optic canal to avoid tumor progression to the chiasma.

Despite lumber drain placement, intracerebral hemorrhage possibly associated with brain retraction occurred. Generally, removal of the orbital bar is not necessary to access the anterior superior lateral orbit.[24] However, it makes it easier to access the orbit with less retraction of the brain that is needed to be considered, particularly in young and middle-aged patients.

Lessons

We presented the case of a 49-year-old woman who was diagnosed with PA of the left optic nerve with intracystic hemorrhage. This is the first report of an adult PA of the optic nerve with detailed pathological and molecular analyses in addition to serial MRI. *BRAF* mutations, which are representative genetic alterations of PAs, were not observed in our case; these data are consistent with those of previous reports.[19–21] Surgical management is indicated only in cases with severely impaired vision or disfigurement because there is no clear border between tumor and optic nerve. Nevertheless, attention should be paid to the fact that OPGs in adults are more clinically aggressive and rarely undergo malignant transformation. It is essential to accumulate cases of adult PAs in the optic nerve to investigate the optimal treatment with chemotherapy, molecular therapies, radiotherapy, and surgical intervention.

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Disclosures

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

Author Contributions

Conception and design: Kuramitsu, Suzaki, Ando, Tamari, Terao. Acquisition of data: Kuramitsu, Murakami, Tamari, Ito, Kimata, Terao. Analysis and interpretation of data: Murakami, Kajita. Drafting the article: Kuramitsu, Suzaki, Kajita. Critically revising the article: Kuramitsu, Suzaki, Murakami, Asai. Reviewed submitted version of manuscript: Kuramitsu, Suzaki, Takahashi, Murakami, Asai, Eguchi, Kajita. Approved the final version of the manuscript on behalf of all authors: Kuramitsu. Administrative/technical/material support: Suzaki. Study supervision: Suzaki, Takahashi.

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