

Pilocytic Astrocytoma With Histological Malignant Features Without Previous Radiation Therapy

—Case Report—

Ichiyo SHIBAHARA,¹ Tomohiro KAWAGUCHI,¹ Masayuki KANAMORI,¹
Shingo YONEZAWA,¹ Hiroki TAKAZAWA,¹ Kenichiro ASANO,² Hiroki OHKUMA,²
Mitsuomi KAIMORI,³ Tatsuya SASAKI,¹ and Michiharu NISHIJIMA¹

Departments of ¹Neurosurgery and ³Pathology, Aomori Prefectural Central Hospital, Aomori;
²Department of Neurosurgery, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori

Abstract

Pilocytic astrocytoma sometimes transforms to a malignant type, and previous radiation therapy is considered to be a key factor. We report a case of pilocytic astrocytoma with histological malignant features without previous radiation therapy. A 21-year-old man presented a sudden onset of severe headache. Neuroimaging had detected a cystic mass in the posterior fossa at the age of one year without therapeutic intervention. On admission, computed tomography depicted a brain tumor in the posterior fossa with cystic components, intratumoral hemorrhage, and upward herniation. Urgent surgery was performed, and histological examination revealed some features of pilocytic astrocytoma but also broad necrosis, high cellularity, and MIB-1 labeling index of more than 20%. The histological diagnosis was pilocytic astrocytoma with malignant features. This tumor had continued a benign clinical course for 20 years, but had eventually transformed to a malignant type. Therefore, pilocytic astrocytoma may undergo spontaneous malignant transformation during its natural clinical course.

Key words: pilocytic astrocytoma, malignant transformation, radiation therapy, pathology

Introduction

Pilocytic astrocytoma, classified as a grade I astrocytic tumor by the World Health Organization, is one of the most common brain tumors in children and arises in the cerebellum in 67% of patients. Pilocytic astrocytoma appears as a well circumscribed lesion often with cystic components on neuroimaging.⁸⁾ Surgical resection should be considered as the initial treatment, and the administration of chemotherapy or radiation therapy remains controversial for residual or recurrent tumors.^{3,11,14,15)} The survival rate after macroscopic total resection is 95.8% at 10 years and 82% at 20 years,^{2,5)} indicating that this tumor generally has a benign clinical course. However, pilocytic astrocytoma has been known to transform to a malignant type.^{1,4,7,9,10,17)} Previous radiation therapy is known to be a key factor for such malignant change,^{10,17)} but whether radiation therapy is the only cause of such transformations is disputed.^{4,5,7,15,20)}

Here, we report a case involving a juvenile cerebellar tumor, possibly a pilocytic astrocytoma, that transformed to a malignant tumor during 20 years of follow up without treatment, indicating that pilocytic astrocytoma may transform to a malignant type during its natural clinical

course.

Case Report

A 21-year-old man with no familial history of neurofibromatosis was admitted to our hospital due to sudden onset of severe headache. His clinical history revealed diagnosis of a brain tumor 20 years previously at the age of one year (Fig. 1), and follow up for 6 years until the age of 7 years (Fig. 2). Since no clinical or radiographical signs of tumor progression were detected, his family refused surgery, and he was not followed up as an outpatient from the age of 7 years.

On admission, he was alert but had severe headache and neck stiffness. Computed tomography depicted a cystic tumor occupying the posterior fossa, intratumoral hemorrhage, calcification, and acute obstructive hydrocephalus, with slight enhancement of the tumor capsule with contrast medium (Fig. 3). This emergent case with signs of upward herniation was admitted at midnight, so we could not evaluate the tumor by magnetic resonance (MR) imaging. Urgent surgery was performed using a suboccipital approach. During surgery, intratumoral hemorrhage and calcification were observed. The tumor strongly adhered to the medulla oblongata, so only partial removal and release of the fourth ventricle were achieved. Postopera-

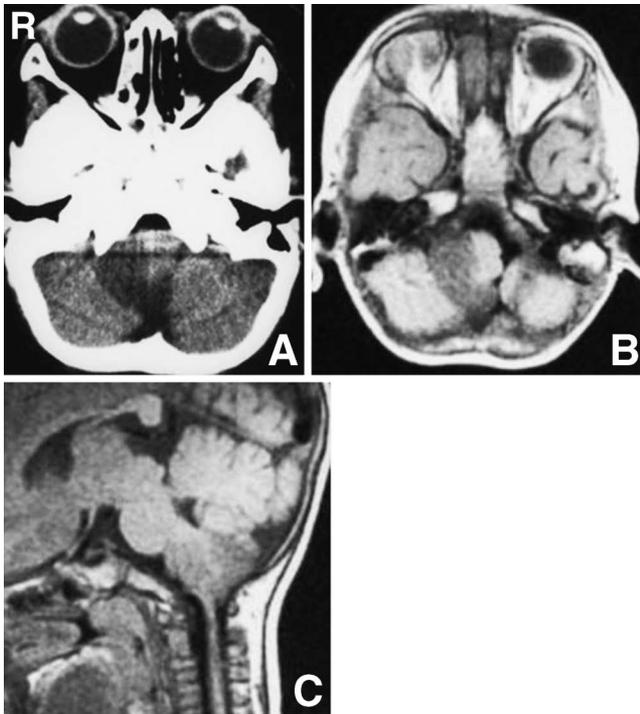


Fig. 1 Neuroimaging findings at age one year. A: Axial computed tomography scan showing a tumor mass with a cystic component at the posterior fossa as low density. B: Axial T₁-weighted magnetic resonance image showing the tumor as low intensity. C: Sagittal T₁-weighted magnetic resonance image showing a cystic component at the posterior fossa.

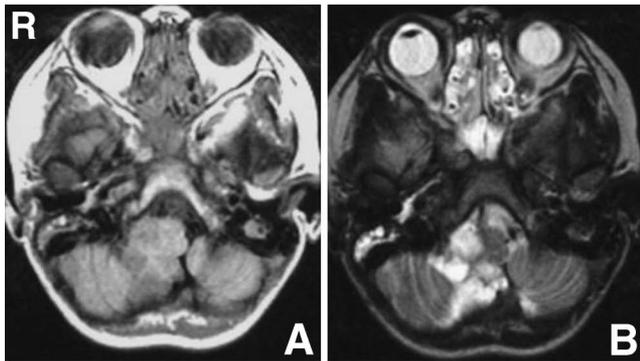


Fig. 2 Neuroimaging findings at age 7 years. Axial T₁-weighted (A) and T₂-weighted (B) magnetic resonance images showing a cystic tumor with no apparent tumor progression.

tive therapy consisted of 50 Gy irradiation with 75 mg/m² temozolomide. Final MR imaging did not show tumor regrowth (Fig. 4), and he was discharged without deficits.

Histological examination of the tumor specimen demonstrated biphasic pattern, eosinophilic granular bodies, and Rosenthal fibers (Fig. 5A-C). Moreover, small atypical cells were found in a high cellularity area with broad necrosis (Fig. 5D). Immunohistochemical staining demonstrated positive staining for glial fibrillary acidic protein

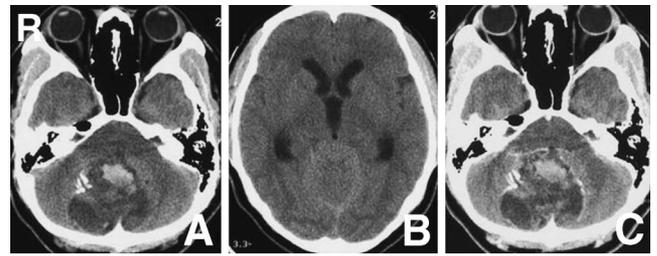


Fig. 3 Neuroimaging findings at age 21 years. A, B: Axial computed tomography scans on admission showing a tumor at the posterior fossa with a maximum diameter of 55 mm with intratumoral hemorrhage, calcification, and cystic components (A), acute obstructive hydrocephalus, and upward herniation (B). C: Axial computed tomography scan with contrast medium showing slight enhancement of the tumor capsule.

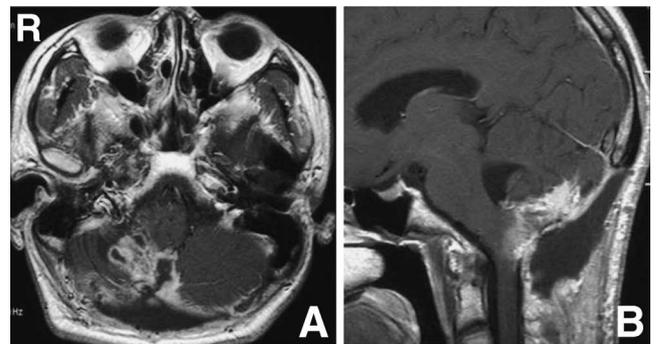


Fig. 4 Axial (A) and sagittal (B) T₁-weighted magnetic resonance images with gadolinium after surgery and radiation therapy showing an enhanced residual tumor at the posterior fossa and attached to the medulla oblongata.

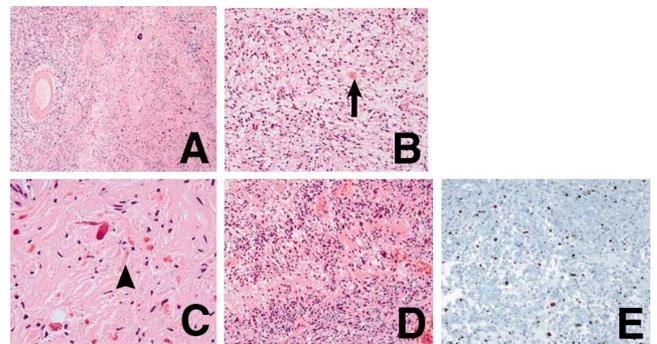


Fig. 5 A-D: Photomicrographs of surgical specimens demonstrating some features of pilocytic astrocytoma including biphasic pattern (A), eosinophilic granular bodies (B, arrow), and Rosenthal fibers (C, arrowhead), with a high density of small atypical cells with broad necrosis (D). Hematoxylin and eosin stain, original magnification A: $\times 200$, B-D: $\times 400$. E: Immunohistochemical analysis by Ki-67 staining demonstrated a high MIB-1 labeling index (more than 20%). Original magnification $\times 400$.

and a high MIB-1 labeling index (more than 20%) (Fig. 5E). Intratumoral hemorrhage was confirmed by findings of hemosiderin phagocytosis by macrophages. The histological diagnosis was pilocytic astrocytoma with malignant features.

Discussion

In this case, no histological evidence was available to prove that the tumor was pilocytic astrocytoma at the age of one or 7 years. Therefore, differential diagnoses of low-grade astrocytic tumors such as diffuse astrocytoma should also be considered. However, the circumstantial findings strongly suggest that the original tumor was pilocytic astrocytoma. Firstly, the initial radiographic findings demonstrated a pediatric brain tumor at the posterior fossa with cystic components. Secondly, the long symptom-free clinical course of this case (20 years) indicated a benign slow-growing tumor. Finally, the histological findings obtained during surgery at the age of 21 years showed typical features of pilocytic astrocytoma such as biphasic pattern, eosinophilic granular bodies, and Rosenthal fibers. Based on the radiographic findings, the clinical course, and the pathological features, the initial tumor was highly likely to be pilocytic astrocytoma. Twenty years later, the tumor specimen obtained during surgery had high cellularity with small atypical cells, broad necrosis, and an MIB-1 labeling index of over 20%. Based on these findings, we consider that this case was a pilocytic astrocytoma with malignant transformation rather than a de novo high-grade glioma. Since no interventions including surgery and chemoradiation therapy which can influence anaplastic changes were performed,¹⁰ this case, which progressed to higher grade glioma during its natural clinical course, represents spontaneous malignant transformation of pilocytic astrocytoma.

The underlying mechanism of malignant transformation of pilocytic astrocytoma is still unknown. Review of 52 previously published cases of pilocytic astrocytoma with malignant transformation found that all cases underwent radiation therapy prior to the malignant changes.¹⁰ Therefore, radiation therapy has been considered as a key factor for malignant changes. Recently, 34 of 2200 cases of pilocytic astrocytoma were found with anaplastic features, but clinical, therapeutic, and follow-up data were frequently absent.¹² In particular, only 4 cases had received previous radiation therapy, so this is not the only cause of pilocytic astrocytoma transformation. The present case provides some of these missing details. Pilocytic astrocytoma with anaplastic features without necrosis has a similar prognosis to St. Anne-Mayo grade 2 astrocytoma, whereas this tumor with necrosis has a similar prognosis to grade 3 but a better prognosis than grade 4 tumor.¹² Pilocytic astrocytoma occasionally shows increased cellularity, necrosis, nuclear abnormalities, and intratumoral hemorrhage, which also occur in glioblastomas, but these findings are not signs of malignancy or poor prognosis.^{8,13,16,18} However, since the present case of pilocytic astrocytoma with malignant transformation harbored broad necrosis, such patients may have a poor prog-

nosis.¹²

Recently, analysis of the genetic background of gliomas has given valuable information about the diagnosis. Tandem duplication at 7q34, a fusion between *KIAA1549* and the oncogene *BRAF*, was observed in 66% of cases of pilocytic astrocytoma.⁶ In contrast, somatic mutation at codon 132 of the isocitrate dehydrogenase 1 gene (*IDH1*) was rarely found in pilocytic astrocytoma and primary glioblastoma, whereas this mutation is observed in up to 90% of grade II to IV gliomas, such as diffuse astrocytoma, anaplastic astrocytoma, and secondary glioblastoma.¹⁹ These genetic changes may be useful diagnostic tools for the diagnosis of pilocytic astrocytoma rather than relying only on histology.

The present case of pilocytic astrocytoma developed malignant features in the absence of any previous therapeutic intervention. Malignant transformation of pilocytic astrocytoma is still controversial, and the underlying mechanism needs to be clarified. The present case suggests that pilocytic astrocytoma may spontaneously transform during its natural clinical course.

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Address reprint requests to: Ichiyo Shibahara, MD, Department of Neurosurgery, Aomori Prefectural Central Hospital, 2-1-1 Higashi-tsukurimichi, Aomori 030-8553, Japan.
e-mail: ichiyooo@hotmail.com