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Pilocytic Astrocytoma Presenting with Spontaneous Cerebellar Hemorrhage: A Case Report

Sae YAMANAKA,[1,2] Hiroshi TOKIMURA,[1] Nayuta HIGA,[2] Hirofumi IWAMOTO,[2] Yosuke NISHIMUTA,[1] Kazunobu SUEYOSHI,[3] Hajime YONEZAWA,[2] Kenichiro TAJITSU,[5] Toshiaki AKAHANE,[4,6] Akihide TANIMOTO,[4,6] and Ryosuke HANAYA[2]

[1]*Department of Neurosurgery, Kagoshima City Hospital, Kagoshima, Kagoshima, Japan*
[2]*Department of Neurosurgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Kagoshima, Japan*
[3]*Department of Pathology, Kagoshima City Hospital, Kagoshima, Kagoshima, Japan*
[4]*Department of Pathology, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Kagoshima, Japan*
[5]*Department of Neurosurgery, Sendai Medical Association Hospital, Kagoshima, Kagoshima, Japan*
[6]*Center for Human Genome and Gene Analysis, Kagoshima University Hospital, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Kagoshima, Japan*

Abstract

Hemorrhagic pilocytic astrocytomas (PAs) are rare, accounting for 1.1%-8.0% of all PA cases. They are reported to occur more frequently in older populations, with a male predominance. In this study, we report a case of a 14-year-old boy who presented with a headache, vertigo, and diplopia. As per his brain computed tomography scan, a small hematoma was observed in the left inferior cerebellar peduncle. Follow-up magnetic resonance imaging (MRI) revealed repeated minor bleeding from the lesion and mild expansion, with no neurological deficits. Four years later, the patient developed nausea, vomiting, and left abducens palsy. MRI revealed a mulberry-shaped mass surrounded by a hypointense rim, suggesting a cavernous angioma. The lesion was surgically resected via midline occipital craniotomy with the opening of the cerebellomedullary fissure. Histopathological examination of the lesion revealed PA. Next-generation sequencing analyses revealed that PAs harbored mutations in the *ARID1A*, *ATM*, and *POLE* genes but not in the *BRAF* gene. To the best of our knowledge, there are yet no reported studies on these mutations in PAs to date. Thus, PA should be considered in the differential diagnosis of cerebellar hemorrhage, especially in young adults and children.

Keywords: pilocytic astrocytoma, cerebellar hemorrhage, cavernous angioma, inferior cerebellar peduncle

Introduction

Pilocytic astrocytoma (PA) is a glioma that commonly affects younger patients, and predominantly occurs in the cerebellum (35%), visual tract (25%), brainstem, and fourth ventricle (10%).[1)] It is a well-circumscribed, well-differentiated, slow-growing tumor, corresponding to World Health Organization (WHO) grade I and is included in the group of "other astrocytic tumors" in the revised 4th edition of the current 2016 WHO Classification of Tumors of the Central Nervous System.[2)] Therefore, this tumor usually presents with slowly evolving focal deficits or signs of increased intracranial pressure, but hemorrhagic onset is considered rare. Herein, we encountered a case of hemorrhagic PA, which had a chronic clinical course and was suspected to be a cavernous angioma (CA) on radiological images. Furthermore, this PA case required a differential diagnosis of CA with repeated bleeding, including a literature review regarding its clinical, radiological, surgical, and histopathological features. Additionally, this is the first

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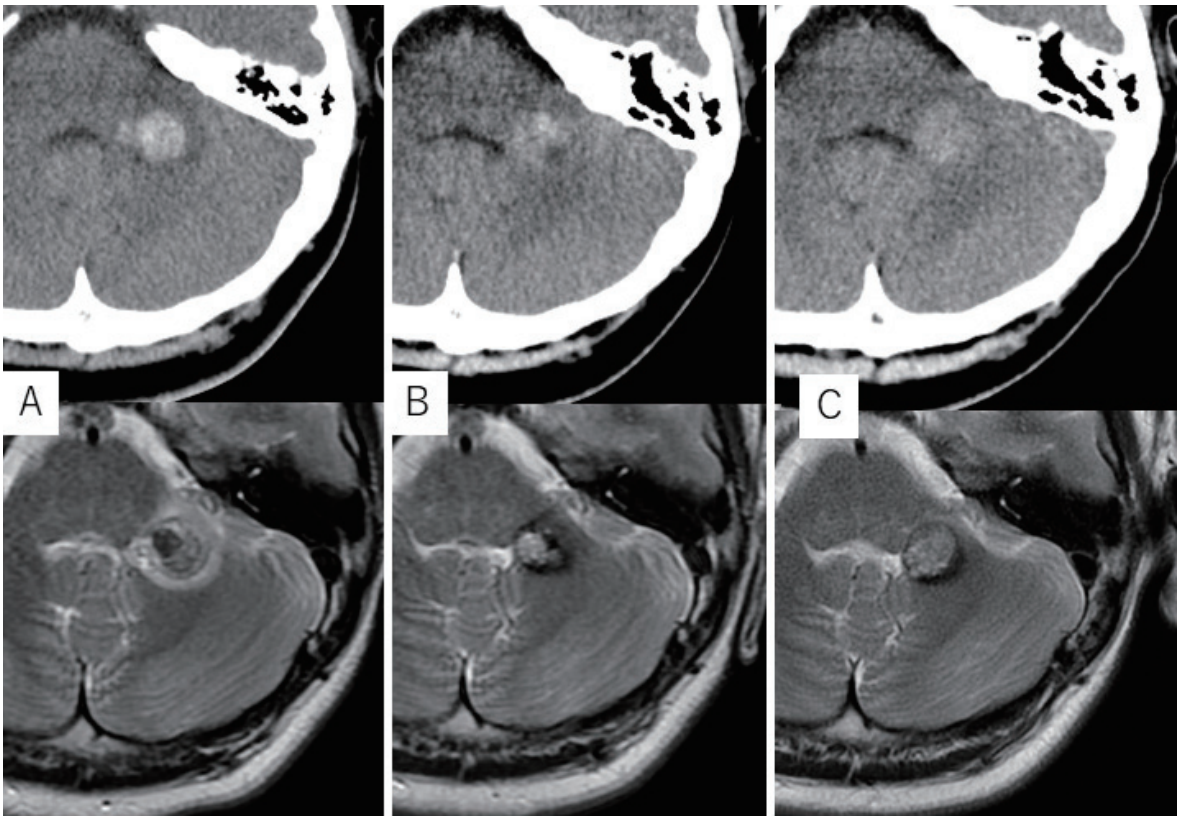

Fig. 1 Computed tomography (CT) at onset shows a high-density round mass lesion with perifocal edema in the left cerebellar peduncle, the core of which was hypointense on magnetic resonance imaging (MRI) (A).
Follow-up CT and MRI, 1 year after onset (B) and 2 years after onset (C), showing enlargement of the lesion and surrounding hypointense rim on MRI.

case in which hemorrhagic PA gene analysis was performed.

Case Report

A 14-year-old boy presented with a history of headache, vertigo, and diplopia after a head injury while playing basketball. As per his computed tomography (CT) scan, a small hematoma was noted in the left inferior cerebellar peduncle (Fig. 1). After conservative therapy, the patient was diagnosed with a cerebellar cavernous hemangioma as per his magnetic resonance imaging (MRI) findings. Although follow-up MRI revealed repeated minor bleeding from the lesion and mild expansion (Fig. 1), no deterioration of subjective symptoms and no neurological abnormalities were found. Four years after the onset, nausea and vomiting were noted, and diplopia persisted in the left gaze. CT and MRI on admission showed an increase in the hematoma and a mulberry-shaped mass surrounded by a hypointense rim, suggesting CA in the inferior cerebellar peduncle (Fig. 2). Clinical examination revealed no neurological deficits other than the left abducens nerve palsy. The patient's medical history was deemed uneventful. Thus, the differential diagnosis was CA of the left cerebellar peduncle, considering these preoperative investigations. Surgical resection was planned based on the symptoms of headache and abducens nerve palsy.

The patient was placed in the prone position, and a suboccipital craniotomy was performed under general anesthesia. After elevating the left cerebellar tonsil and opening the left cerebellomedullary fissure, the middle cerebellar peduncle turned dark (Fig. 3A). After incising the peduncle and evacuating the underlying hematoma, a berry-like tumor surface appeared (Fig. 3B). The tumor was thereafter completely resected by carefully dissecting the brain tissue (Fig. 3C).

Histopathological examination of the lesion revealed glial fibrillary acidic protein (GFAP)-positive bipolar cells and Rosenthal fibers, hemorrhage and hemosiderosis in the tumor tissue, and hyalinization of the vessels, suggesting a PA diagnosis (Fig. 4). We have also analyzed the patient's tumor sample using a glioma-tailored DNA-based panel and an RNA-based fusion panel for next-generation sequencing (NGS). NGS analyses revealed that the PAs harbored mutations in the *ARID1A*, *ATM*, and *POLE* genes.

Other than mild ataxia of the left upper extremity, the patient had no postoperative neurological deficits, and MRI performed on the 6th postoperative day revealed com-

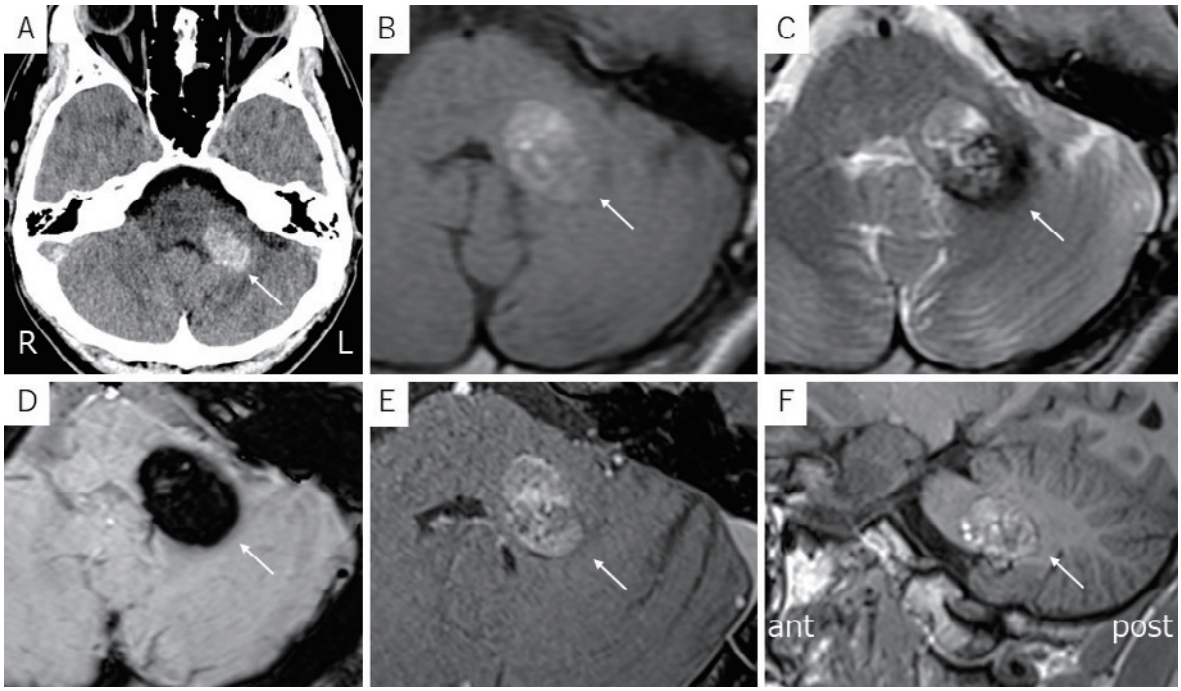

Fig. 2 A: Computed tomography (CT) on admission showing a high-density mass lesion in the inferior cerebellar peduncle (arrow).
Five series of axial magnetic resonance imaging (MRI) images: B (T1-weighted image = WI), C (T2WI), D (susceptibility WI = SWI), E (gadolinium-enhanced T1WI = Gd-T1WI), and F (sagittal image of Gd-T1WI). T1WI and T2WI show a heterogeneous hyperintense oval mass lesion in the left cerebellar peduncle (arrow), which appears as a hypointense mass on SWI. Axial and sagittal Gd-T1WI show a mulberry-shaped lesion.

plete removal of the tumor.

Discussion

PA with hemorrhage onset is considered to be rare, with reported incidence ranges between 1.1% and 8.0% of all PAs.[3,4] Hemorrhagic PAs are more commonly found in the older age population compared to the overall distribution of PAs, which typically show a male predominance. However, there is no specific predilection for tumor location.[5] Most hemorrhagic PA cases have been reported in adults with only a few isolated reports in children.[6,7] Hemorrhagic PAs are seen in the supratentorial location in adults and the cerebellum in children.[7-9] Recently, the previously reported 27 pediatric cases of hemorrhagic PA were compared with 26 adult cases, and the following characteristics were described: (1) The incidence of hemorrhagic PA in adults and children is about the same (1.1 to 1), which is different from non-hemorrhagic PA, which is common in children. (2) The site of the lesion is predominantly supratentorial in adults and the cerebellum in pediatric cases. (3) The male-to-female ratio is 1.1:1 in pediatric cases and 1.8:1 in adult cases, with males being more common in adult cases than that in pediatric cases. (4) With regard to the outcome, all three previously reported patients with morbidity had tumors located in the suprasellar location. (5) A death rate of 8% was reported in two adult cases as compared to the 18.5% in five pediatric cases.[10] The present case was a 14-year-old boy, and lesion was observed in his cerebellum, a finding consistent with that of previous studies stating that cerebellum is a common lesion site among children.

Koeller et al. described the enhancing PA patterns as follows: (a) a mass with an enhancing cyst wall and an intensely enhancing mural nodule, (b) a mass with a non-enhancing cyst and an intensely enhancing mural nodule, (c) a predominantly solid mass with minimal to no cystic component, and (d) a necrotic mass with a central non-enhancing zone. Hence, two-thirds of all the cases demonstrated the classic imaging manifestation of a cyst-like mass with an enhancing mural nodule.[11] The present case belongs to group (d), which accounted for only 17% of all PAs; repeated bleeding made it challenging to diagnose. Contrastingly, the radiological feature of cerebellar cavernous malformation was large in size exhibiting spherical, cystic, and often "pseudotumoral" morphology, and the presence of developmental venous anomalies supported this diagnosis.[12] Hence, the diagnosis of this present case as CA was considered unavoidable.

Histopathologically, closely packed, sclerotic, and largely hyalinized vessels can sometimes resemble vascular malformations, that is, CA. Neoplastic tissue may be scant and

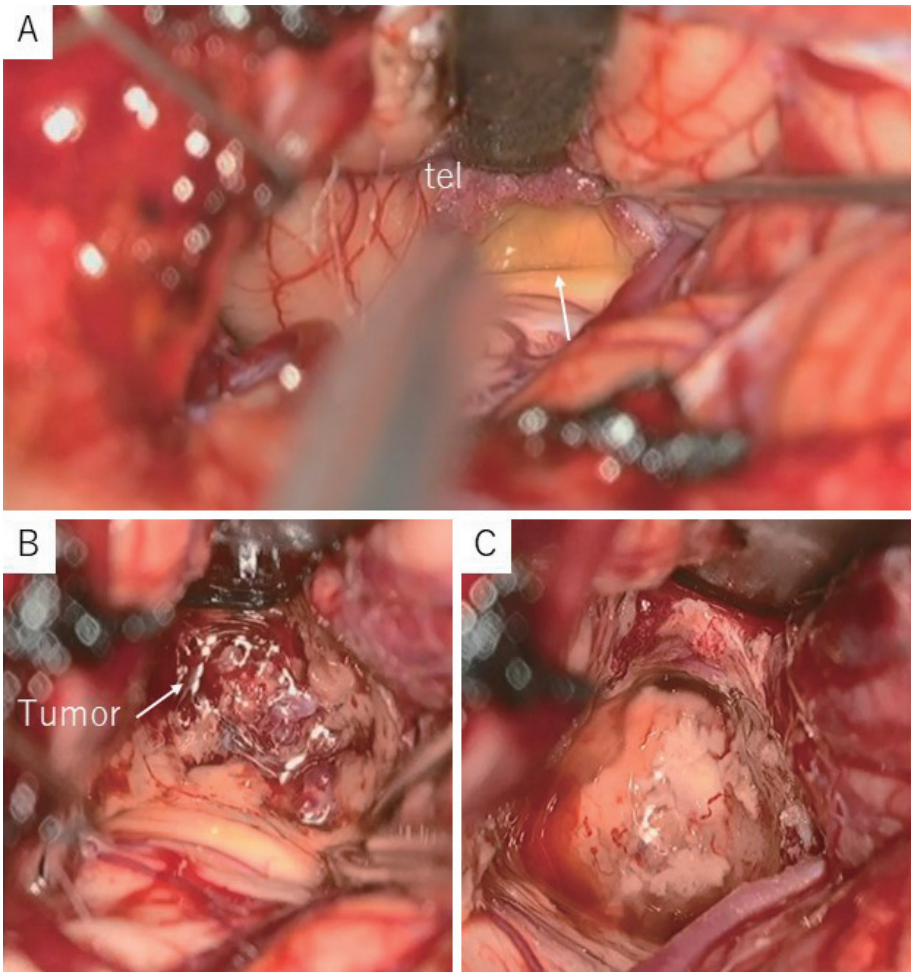

Fig. 3 Intraoperative photographs showing the middle cerebellar peduncle darkening after the opening of the cerebellomedullary fissure (A, arrow). After the incision of the cerebellar peduncle and removal of the hematoma, a berry-like tumor surface appeared (B). The tumor was then completely removed (C).

dispersed between conglomerates of thickened, hyalinized blood vessels, which mimic reactive piloid gliosis around a lesion of vascular pathology, rather than true neoplastic proliferation. In such cases, a misleading diagnosis of CA may be established.[2)]

Previously, an association between *FGFR1* mutation and hemorrhage in pediatric and young adult low-grade glioma, including PA, was determined; however, the mechanism by which *FGFR1* mutation results in hemorrhage is yet to be elucidated.[13)] Genetic alterations within the *MAPK* signaling pathway are considered a hallmark of PA. In particular, *KIAA1549-BRAF* fusion was the most frequent at 73%, followed by *BRAF* mutation, *FGFR1* mutation, *NTRK* fusion, and *NF1* mutation at 6%, 6%, 3%, and 3%, respectively.[14)] Our glioma-tailored DNA-based panel[15)] and RNA-based fusion panel included *BRAF*, *FGFR1*, *NTRK*, and *NF1*, whereas NGS analyses revealed no alterations in these genes. However, our patient harbored mutations in the *ARID1A*, *ATM*, and *POLE* genes. *ARID1A* acts as a tumor suppressor, is frequently observed in grade 3 oligodendroglioma with *IDH*-mutant and 1p/19q-codeleted, and is associated with poor progression-free survival (PFS).[16)] *ATM* is known to play a central role in the repair of DNA double-strand breaks and is often found mutated in glioblastoma.[16,17)] In addition, *POLE* mutations are observed in high-grade gliomas, associated with younger age, and linked to better PFS.[18)] To the best of our knowledge, no studies of *ARID1A*, *ATM*, and *POLE* mutations in PAs have been reported to date.

The clinical course and imaging findings of this present case revealed the appearance of CA, and the histopathological diagnosis after resection revealed that it was PA. Given that hemorrhagic PA is prevalent in the posterior cranial fossa, it should be considered a differential diagnosis for cerebellar hemorrhage, especially in young adults and children.

Abbreviations

PA, pilocytic astrocytomas; CA, cavernous angioma; NGS,

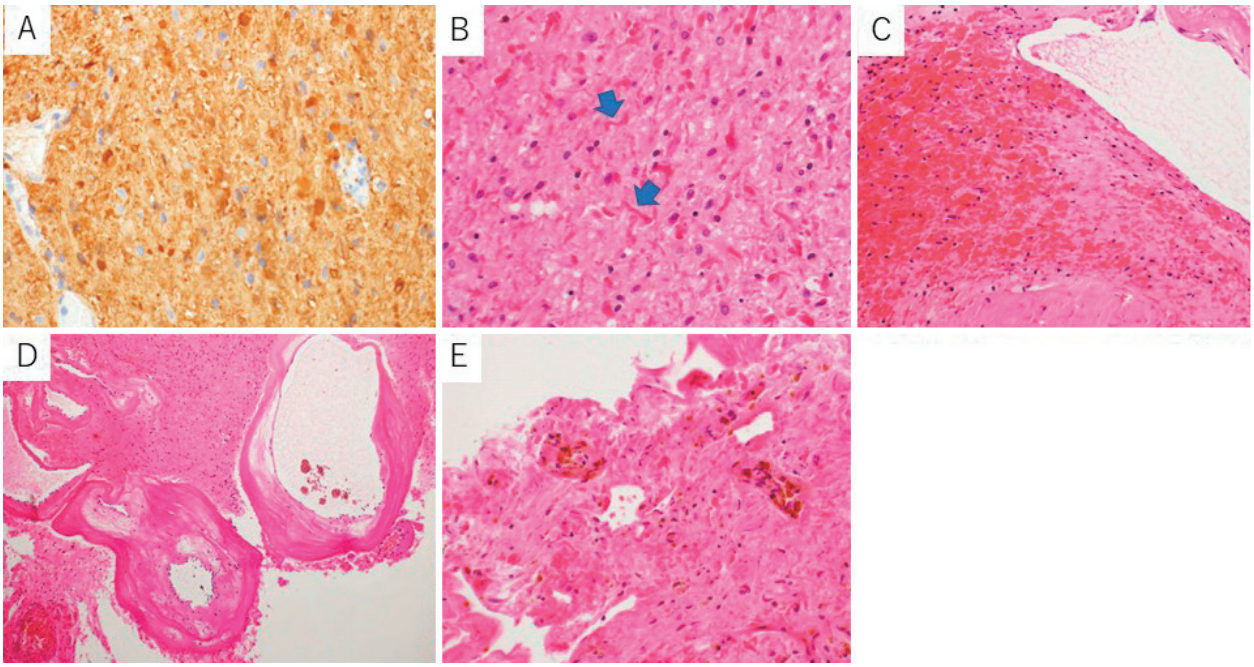

Fig. 4 Glial fibrillary acidic protein GFAP (A) and hematoxylin and eosin (B-E) staining of the lesion showing GFAP-positive bipolar cells and Rosenthal fibers (B) (blue arrow), hemorrhage in the tumor tissue (C), hyalinization of the vessels, and hemosiderosis (E).

next-generation sequencing

Informed Consent

Consent was obtained from all the participants.

Conflicts of Interest Disclosure

All authors report no conflicts of interest.

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Corresponding author: Hiroshi Tokimura, M.D., Ph.D.
Department of Neurosurgery, Kagoshima City Hospital, 37-1 Uearatacho, Kagoshima, Kagoshima 890-8760, Japan.
e-mail: hiroshitok@nag.bbiq.jp