



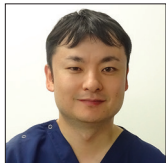
## Case Report

# Rare vermian pilocytic astrocytoma with recurrent spontaneous hemorrhage in the elderly: A case report and review of literature

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## ABSTRACT

**Background:** Pilocytic astrocytoma (PA) is a benign glial tumor predominately seen in pediatrics and early adolescence with associated overall good outcomes. Very few cases of elderly PA have been reported in the literature, and they are known to display unique anatomic, histologic, and genetic peculiarities distinct from pediatric disease. We report a rare case of vermian PA in an octogenarian with recurrent spontaneous intratumoral hemorrhage as a presenting symptom. Furthermore, a review of the literature on the peculiarities of PA in the elderly will be discussed.

**Case Description:** An 81-year-old woman presented with features suggestive of repeated posterior fossa hemorrhages characterized by headaches, diplopia, and alteration in sensorium occurring about 5 months apart. Brain neuroimaging showed a cerebellar vermian tumor with features suggestive of repeated intratumoral bleeding. She had an initial ventriculoperitoneal shunting for acute hydrocephalus and subsequently had a suboccipital craniotomy and subtotal tumor excision due to morbid adherence to the brainstem. The histologic diagnosis was PA with Ki-67 <1% and negative for isocitrate dehydrogenase-1. There was a slow but progressive clinical improvement, and she has remained symptom-free for 4 years on follow-up.

**Conclusion:** PA in the elderly is a rare disease with distinct histologic and genetic peculiarities. This case review showed one of the oldest cases of cerebellar vermian PA presenting with recurrent spontaneous intratumoral hemorrhage, an extremely rare occurrence in benign glioma. Although complete surgical excision is recommended, partial resection is advocated for morbidly adherent tumors. Overall prognosis is worse in elderly PA.

**Keywords:** Elder, Intratumoral hemorrhage, Pilocytic astrocytoma, Vermian tumor

## INTRODUCTION

Pilocytic astrocytoma (PA) is the most common primary central nervous system (CNS) glial neoplasm in childhood and early adolescence.<sup>[4,6,9]</sup> They are well-differentiated and circumscribed astrocytic tumors with an overall good prognosis. PAs are uncommon in adults and rarely

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reported in the elderly.<sup>[9,23]</sup> Studies have suggested that elderly PA exhibits distinct histologic and genetic alterations from pediatric disease and displays a higher incidence of anaplasia and malignant transformation.<sup>[1,7,17,22]</sup>

Clinical presentation depends on anatomic location and the associated mass effect. Although spontaneous intratumoral hemorrhages occur in malignant gliomas and metastatic brain tumors, they are unusual in PA and rarely reported in the elderly. Mechanisms of apoplectiform tumor bleeding have been attributed to abnormal neovascularization within the tumor and adjacent brain invasion.<sup>[12,16,25]</sup> Surgical excision is the standard of care with resultant excellent outcomes in pediatric disease; nevertheless, reports have shown higher recurrence risk and poorer outcomes in elderly PA.<sup>[6,9,23]</sup>

We present a rare case of vermian PA in an octogenarian who presented with recurrent hemorrhage and hydrocephalus. Furthermore, a review of the literature on the peculiarities of PA in the elderly will be discussed.

## CASE PRESENTATION

An 81-year-old elderly woman presented with cognitive decline characterized by memory impairment and behavioral changes, which progressively worsened with time. She subsequently developed sudden onset headache and rapid deterioration of her clinical condition, necessitating presentation to the hospital. There was no history suggestive of neurofibromatosis type-1. She has no comorbidities but had treatment for colon cancer about 7 years ago without evidence of recurrence.

Examination findings showed a confused lady with a Glasgow Coma Scale score of E4V4M6. The speech was fluent, and the Mini-Mental State Examination was 13/30 (suggestive of moderate to severe dementia). Her Karnofsky performance score was 60%. She has no meningeal signs, and cranial nerve examinations were essentially normal. Long tracts were normal, and no abnormal reflexes were elicited. However, she has an unstable gait and truncal ataxia. Finger nose testing was normal, and dysdiadochokinesia was absent.

Her cranial computed tomography scan showed a solid vermian hyperdense mass with intratumoral hemorrhage [Figure 1a]. Magnetic resonance imaging (MRI) confirmed the mass with associated effacement of the fourth ventricle and surrounding cerebellar signal changes suggestive of subacute hemorrhage and hydrocephalus [Figure 1b-e]. MRI showed no evidence of other hemorrhagic lesions such as microbleeds suggesting cerebral amyloid angiopathy. She had emergency ventriculoperitoneal shunting done and subsequently had marked clinical improvement and was independent and ambulant on discharge. The family was

counseled for surgical excision of the lesion but declined further care.

Five months later, she developed acute worsening symptoms with an associated alteration in consciousness, diplopia, florid cerebellar symptoms, and gait instability. Repeat neuroimaging showed rebleeding of the vermian lesion with features suggestive of posterior fossa hypertension [Figure 1f]. The families were counseled for surgical intervention; the indication was recurrent bleeding and mass effect of the cerebellar lesion. She had a midline suboccipital craniotomy and subtotal excision through the transcerebellomedullary fissure (Telovelar) approach. The mass was grayish, with features suggestive of an old clot within the lesion. Subtotal resection of the tumor was achieved, and a portion of the tumor morbidly adherent to the right portion of the floor of the fourth ventricle adjacent to the cerebellar peduncle was left behind [Figure 2a-c]. After surgery, she had slow but progressive improvement and was subsequently discharged for rehabilitation services. There was no evidence of recurrence after 4 years of follow-up.

Histology showed densely packed atypical glial lineage cells, with Rosenthal fibers (RFs) and eosinophilic granular bodies (EGBs) scattered in the background. Only a few mitotic figures were seen. The features were consistent with PA [Figure 3a]. There were no obvious vascular-rich components and angioma in the pathological examination. Immunohistochemistry shows strong staining for glial fibrillary acid protein (GFAP) [Figure 3b]. P53 was negative, Ki-67 was <1%, and isocitrate dehydrogenase-1 (IDH-1) was negative.

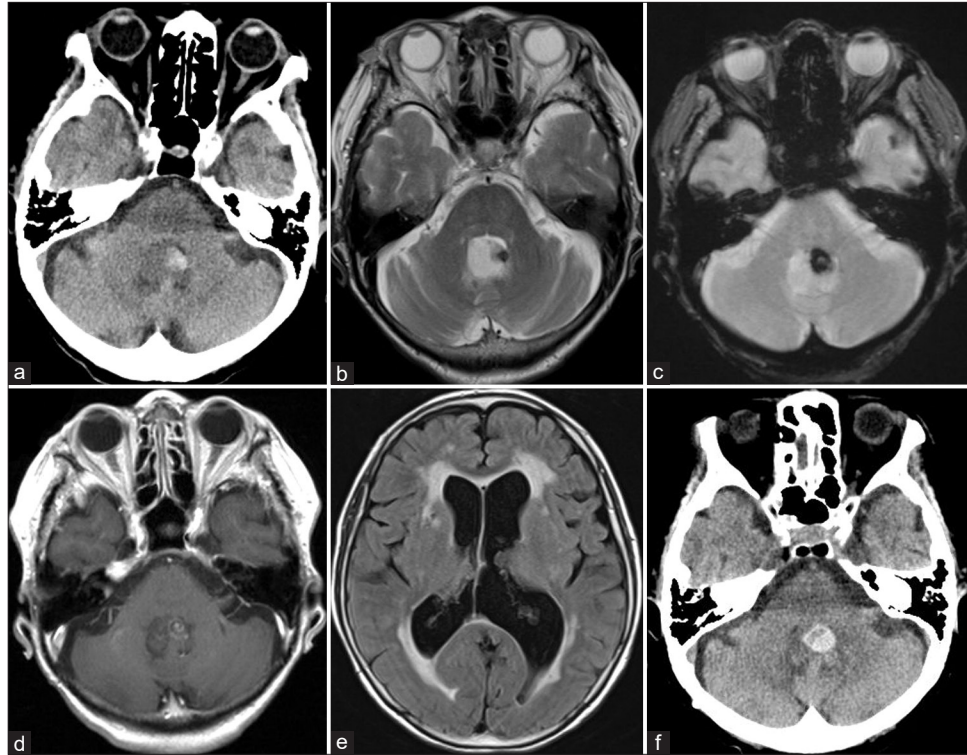
## DISCUSSION

PA was first described by Harvey Cushing in 1931 as a distinct tumor type found in the cerebellum with a better prognosis when compared to supratentorial glioma.<sup>[5]</sup> The recent World Health Organization grading classifies them as CNS grade 1 tumors. They usually arise sporadically; however, syndromic types have been described and are associated with neurofibromatosis type 1.<sup>[4,6,13]</sup>

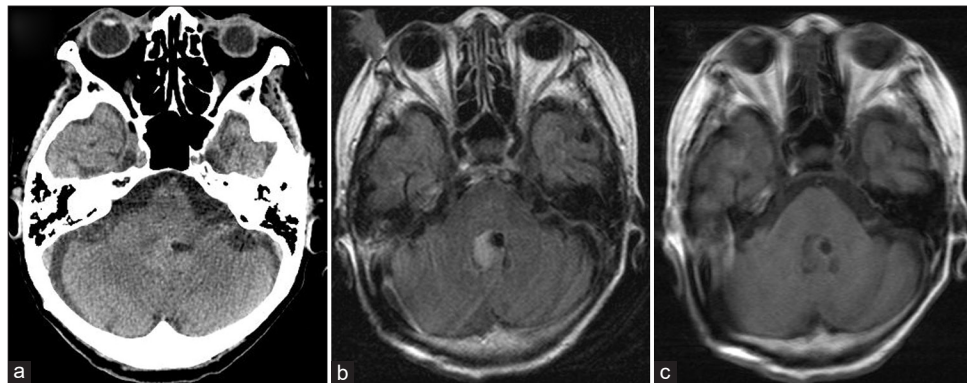
Although pediatric PA has an excellent prognosis, the disease in the elderly may have different biological behavior and comparatively worse outcomes.<sup>[9,18,23]</sup> Here, we reported one of the oldest cases of cerebellar vermian PA presenting with recurrent intratumoral hemorrhages and a literature review of the peculiarities of PA in the elderly.

### Epidemiology of PA in the elderly

PA is essentially a pediatric disease constituting about 30–40% of childhood brain tumors with predominant



**Figure 1:** (a-c) Initial computed tomography (CT) scan and T2- and T2-star-weighted images showing a vermian mass lesion with associated intratumoral hemorrhage. (d) Enhanced T1-weighted image showing minimal enhancement of the tumor. (e) Fluid-attenuated inversion recovery image showing hydrocephalus. (f) CT scan 5 months later showing a repeat spontaneous intratumoral hemorrhage.



**Figure 2:** (a-c) Postoperative computed tomography scan and fluid-attenuated inversion recovery image and T1-weighted image showing subtotal tumor excision.

posterior fossa localization.<sup>[13,24]</sup> It displays a bimodal peak at 0–4 and 11–15 years, and the incidence progressively declines with age. A 35-year review of the national cancer registry in the United States (SEER program) involving 3,066 PA found the incidence in patients above 60 years as 1.9%.<sup>[9]</sup> Similarly, Theeler *et al.*, in the largest single institutional analysis of PA, found only 3 out of the 127 patients presenting above 60 years and noted a very high recurrence rate.<sup>[23]</sup>

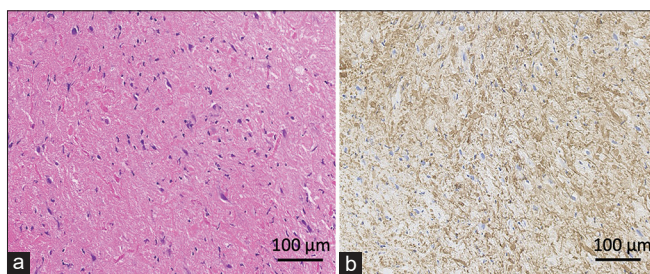
Unlike pediatric PA, most elderly cases involve the supratentorial compartment and display slight female preponderance.<sup>[6,23]</sup> The poor comparative prognosis in the elderly was demonstrated again in the SEER program report, where 60 months survival was 96.5% between 5 and 19 years compared to 52.9% in patients 60 years and above.<sup>[9]</sup> Presentation in the ninth decade is very rare, and only three have been reported in the literature, and none presented with spontaneous intratumoral hemorrhage, as seen in this index case [Table 1].



**Table 1:** Literature review of pilocytic astrocytoma in the elderly (60 years and above).

First author (Year)	Age/Sex	Location	Intratumoral hemorrhage	Imaging features	Resection	Recurrence
Behling (2015) <sup>[11]</sup>	72/F	Cerebellum hemisphere	-	Cyst+Solid	GTR	-
Burkhardt (2007) <sup>[3]</sup>	85/M	Midbrain/pons	-	Solid	-	-
Isobe (2017) <sup>[8]</sup>	70/F	Frontal	-	Cyst+Solid	GTR	-
Kitamura (2010) <sup>[10]</sup>	68/M	Temporal	-	Cyst+Solid	-	-
	71/F	Temporal	-	Solid	-	-
Lyons (2007) <sup>[12]</sup>	75/M	Temporal	+ (Warfarin)	Cyst+Solid	STR	-
Medress (2015) <sup>[14]</sup>	86/F	Cerebellar hemisphere	-	-	GTR	-
Narang (2019) <sup>[15]</sup>	60/F	Temporal	+	-	GTR	Yes
Sekula (2008) <sup>[20]</sup>	65/M	Suprasella	+	Solid	STR	-
Sun (2018) <sup>[21]</sup>	62/M	Cerebellar hemisphere	+	Cyst+solid	GTR	-
Tanaka (2020) <sup>[22]</sup>	83/F	Cerebellum hemisphere	-	Solid	STR	Malignant transformation
Yoshida (2011) <sup>[26]</sup>	76/M	Frontal	-	Cyst+Solid	GTR	-
Yoshiki (2020) <sup>[27]</sup>	66M	Cerebellum hemisphere	- (Siderosis)	Cyst+Solid	GTR	Yes
Present case	81/F	Vermis	+ (recurrent)	Solid	STR	No

+: Positive, -: Negative, GTR: Gross total resection, STR: Subtotal resection



**Figure 3:** (a) Histology showing spindle and stellate-shaped cells with Rosenthal fibers and eosinophilic granular bodies scattered in the background. (b) Glial fibrillary acidic protein showing diffusely positive for the tumor cells.

### Histopathology of PA

PA has biphasic histologic architecture characterized by loose microcystic areas containing astroglial cells and EGB with hyaline droplets and more solid components displaying increased cellularity and focal accumulation of RF.<sup>[4,13,18]</sup> Although RF and EGB are often seen in PA, they are not prerequisites for diagnosis and can also be demonstrated in ganglioglioma, craniopharyngioma, pleomorphic xanthoastrocytoma, and hemangioblastoma.<sup>[13]</sup>

Furthermore, features of cellular degeneration have also been described, including increased cellularity and mitosis, nuclear atypia, psammomatous calcification, necrosis, and endovascular proliferation.<sup>[4,13]</sup> This hybrid histologic nature of PA may be challenging to the histopathologist and can be confused with high-grade glioma, especially in elderly PA, where anaplastic features are more prevalent. Theeler *et al.* noted a 22% discordant diagnosis of adult PA in their institution, with most erroneously labeled Grade II–IV astrocytoma.<sup>[23]</sup> However, the presence of degeneration,

especially necrosis and endothelial proliferation, is usually innocuous in PA and does not confer a higher grading or worse prognosis.<sup>[12,13]</sup>

Immunohistochemistry is pivotal to typing these tumors correctly. They show typical astroglial lineage features, including strong positivity for GFAP and stain for S-100 protein and OLIG2. Ki-67 proliferative index is usually low except in cases of malignant transformation. Although this index case did not have the typical bipolar features, they had numerous RF and EGB in the compact background with positive stains for GFAP. In addition, KI-67 was low, and P53 gene and IDH-1 mutations were absent.<sup>[4,13,18]</sup>

Specific characteristic mutations seen in other gliomas are absent in PA; only two isolated case reports of IDH-1 mutation have been reported in PA, and all were in elderly patients.<sup>[1,14]</sup> Moreover, genetic alterations, including ATRX loss, cyclin-dependent kinase inhibitor 2ACDKN<sub>2</sub>A/B homozygous deletion, H3-K27M, and P53 mutation seen in anaplastic glioma, are absent in PA, and their presence may indicate malignant transformation.<sup>[6,22]</sup>

### Molecular peculiarities of PA

Pediatric astrocytoma was described as a one-pathway disease because more than 90% involve dysregulation of the mitogen-activated protein kinase (MAPK) pathway essential for cell proliferation and neurogenesis.<sup>[4,6,13,23]</sup> Constitutive activation of the MAPK pathway has been associated with BRAF fusion in 70–90%, BRAFV600E mutation in 10%, and NF1 gene alteration in 15% of pediatric PA.<sup>[6]</sup>

The BRAF fusion involves duplication of chromosome 7q34 encompassing the BRAF gene resulting in the fusion of the

N-terminal of KIAA1549 protein to the regulatory region of BRAF and attendant unregulated constitutive activity of the MAPK pathway.<sup>[4,6,18]</sup> Point mutation of BRAFV600E protein produces similar unregulated MAPK activation and has also been implicated in melanoma and thyroid cancers. Importantly, these mutations typically seen in childhood PA are uncommon in adults. Hasselblatt *et al.*, in a study examining 105 PA, found BRAF fusion (KIAA1549BRAF fusion) to be present in 79% of PA in the first decade of life and only 7% in adults over 40.<sup>[7]</sup> Similarly, another study observed fewer BRAF alterations in adult PA and noted a higher frequency of fibroblast growth factor receptor-related alteration which are upstream regulators of the MAPK pathway.<sup>[17]</sup>

Indeed, since elderly PA are extremely rare, and no large-scale characterization of the genetic abnormalities has been reported, it is assumed that they harbor similar mutations to adult PA. In addition, other rare genetic abnormalities have also been observed in elderly PA, including IDH R132H mutation, ATRX alteration, and CDKN2A loss.<sup>[1,6,22]</sup> It must be emphasized that molecular characterization plays only a supportive role in histology and immunohistochemistry findings in the diagnosis of PA.

### Clinical presentation and diagnosis

Clinical features of PA are related to the anatomic location and associated mass effect. Cerebellar lesions usually present with gait disturbances, coordination disorders, and hydrocephalus. Although reports of intratumoral bleeding are seen in glioblastoma and metastatic diseases, its occurrence in benign intracranial tumors is rare.<sup>[16,20,21]</sup> White *et al.* reported the incidence of spontaneous intracranial hemorrhage from PA to be 8% in a series of 138 patients; however, none occurred in the posterior fossa.<sup>[25]</sup> Indeed, this is the second and oldest case of spontaneous cerebellar intratumoral bleeding occurring in elderly PA [Table 1].

The etiology of bleeding in intracranial tumors is unclear. Neovascularization and endothelial proliferation within the tumor may be contributory, with the nascent vessels lacking elastic fibers and extracellular matrix support.<sup>[16,21,25]</sup> It is known that tumor cells elaborate high levels of vascular endothelial growth factors and hypoxia-inducible factor 1 $\alpha$ , resulting in abundant vasculogenesis and neovascularization.<sup>[15,16]</sup> In addition, invasion of surrounding brain parenchyma and adjacent vessels or sudden necrosis within the tumor are possible etiology. The elderly may be more prone to tumor-related bleeding due to a higher incidence of hypertension, use of anticoagulants, and amyloid angiopathy.

Brain MRI is the diagnostic imaging tool of choice, and PA may be solid, cystic, or a combination of both. The most

common neuroimaging finding in PA is a cystic lesion with an enhancing mural nodule, also seen in hemangioblastoma, cystic metastasis, ganglioglioma, and pleomorphic xanthoastrocytoma.<sup>[4,11,13,18]</sup> Histological confirmation is essential for diagnosis.

### Management options

Surgical excision is the primary treatment strategy for PA and results in excellent outcomes with 5-year progression-free survival of more than 95% in pediatrics.<sup>[6,9,13]</sup> Predictive factors for tumor recurrence are the extent of resection, tumor location, biological behavior, and age at diagnosis. Radical resection is advocated as an essential factor to prevent recurrence; however, an infiltrative lesion with morbid adherence to critical neurovascular structures should be left behind.<sup>[9,19]</sup> In this index case, the tumor was adherent to the floor of the fourth ventricle, and only subtotal resection was achieved.

Some authors opined that excision of the mural nodule suffices as it contains the neoplastic glioma cells, and the cyst wall should be left *in situ*.<sup>[2,18]</sup> Others believe in total excision of the mural nodule and the associated cyst wall, especially those cysts that demonstrate contrast enhancement.<sup>[2]</sup> Management strategy for PA in the elderly must put into cognizance the presence of comorbidities, fitness for surgery, and expected life expectancy keeping in mind the higher risk of recurrence and poorer outcome.

Adjuvant radiotherapy is advocated for disease recurrence, especially in poor surgical candidates; nevertheless, repeat surgery should be considered in all cases.<sup>[4,24]</sup> Chemotherapy is rarely used in the management of PA because of the associated toxic effects and poor clinical response. Since MAPK pathway dysregulation is central in the pathogenesis of PA, various targeted therapy against the pathway components has been tried. Early-generation BRAF inhibitor dabrafenib has proven effective in refractory or relapsed PA in pediatrics with good results; however, its role in adult and elderly PA is still uncertain.<sup>[6]</sup>

Care is multidisciplinary, involving the neurosurgeon, physician, radiologist, histopathologist, and rehabilitation expert. Counseling on recurrence risk and management options is essential before treatment and the need for long-term follow-up.

### CONCLUSION

PA is a common neoplastic glial tumor in pediatric and early adolescence but is rarely reported in the elderly population. Specific anatomic, histologic, and genetic peculiarities make elderly PA unique and distinct from pediatric disease and confer higher recurrence risk and

poorer outcomes. This case review showed one of the oldest cases of cerebellar vermian PA presenting with recurrent spontaneous intratumoral hemorrhage, an unusual occurrence in benign glioma. Although complete surgical excision is recommended, partial excision is advocated for morbidly adherent tumors.

### Ethical approval

Institutional Review Board approval is not required.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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