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Case Report

High-grade astrocytoma with piloid features: A case report and review of literature

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ABSTRACT

Background: High-grade astrocytoma with piloid features (HGAP) is a rare, newly recognized brain tumor, typically seen in middle aged to elderly patients, often associated with neurofibromatosis type 1.

Case Description: We report the first documented case of HGAP in Pakistan in a 57-year-old woman with tremors, vertigo, and cerebellar signs. Magnetic resonance imaging showed a cerebellar lesion, and after resection, initial pathology suggested a pilocytic astrocytoma. Molecular testing confirmed HGAP with a CDKN2A/B deletion. Despite treatment, including a second surgery, the disease progressed.

Conclusion: This case highlights the diagnostic challenges of HGAP and underscores the importance of advanced molecular testing for accurate diagnosis. Given the poor prognosis and limited treatment options, further research is needed to understand this rare tumor entity better and improve patient outcomes.

Keywords: Brain tumors, High-grade astrocytoma with piloid features, High-grade astrocytoma, Neurofibromatosis type 1, Piloid features, South Asia

INTRODUCTION

High-grade astrocytoma with piloid features (HGAP) is a rare, aggressive tumor that was newly classified in the 5th edition of the World Health Organization (WHO) central nervous system (CNS) tumor guidelines in 2021 and is defined by a characteristic DNA-methylation profile, with cases arising *de novo* or from preexisting pilocytic astrocytoma.[5] HGAPs commonly occur in middle aged to elderly individuals, with a predilection for the cerebellum and midline structures like the thalamus in neurofibromatosis type 1 (NF1) patients.[6,8] They can also involve the spinal cord with exophytic components and show leptomeningeal dissemination.[10] Histologically, these tumors exhibit high mitotic activity, Rosenthal fibers, eosinophilic granular bodies, and elongated glial cell processes.[2] Radiographically, HGAPs are heterogeneous, often appearing as peripherally enhancing lesions with low T1 and high T2/fluid-attenuated inversion recovery signals without diffusion restriction.[9] Common genetic alterations associated with HGAP include Neurofibromin 1 (NF1), B-Raf proto-oncogene, serine/threonine kinase (BRAF), Fibroblast growth factor receptor 1 (FGFR1), Cyclin-dependent kinase inhibitor 2A/2B (CDKN2A/B), and Alpha-thalassemia/mental retardation syndrome X-linked (ATRX) mutations.[7] Treatment typically involves maximal safe resection followed by chemoradiotherapy,

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although NF1-associated cases may benefit from mammalian targets of rapamycin and mitogen-activated protein kinase (MAPK) inhibitors.[3] Prognosis remains poor, with a 5-year survival rate of around 50%.[9]

Given the rarity of HGAP and its recent recognition in medical literature, there is limited information available on its epidemiology. To our knowledge, this case represents the first documented instance of HGAP from Pakistan.

CASE DESCRIPTION

A 57-year-old woman presented with a 5-month history of tremors, vertigo, and dizziness in September 2023. Her neurological examination revealed cerebellar signs, including right dysdiadochokinesia and right finger-nose ataxia. Both motor and systemic examinations were normal. Magnetic resonance imaging (MRI) of the brain [Figure 1] revealed a right cerebellar paravermal lesion.

The patient subsequently underwent a suboccipital craniotomy with maximum safe resection of the lesion in November 2023. The excised mass was sent for histological examination [Figure 2], showing tumor cells with bipolar cytoplasmic processes with round-to-oval nuclei loosely arranged in a prominent fibrillary matrix with myxoid change. Interspersed minigemistocytes, perivascular pseudorosettes, occasional eosinophilic granular bodies, and foci of microvascular proliferation were noted. The immunohistochemical analysis [Figure 3] of the tumor revealed that Isocitrate Dehydrogenase 1 (IDH1) (R132H) was negative (nonmutant), ATRX showed retained nuclear expression, H3K27M was negative (nonmutant), BRAF V600E was negative (nonmutant), p53 showed wild-type expression (nonmutant), and Ki67 showed areas with a raised proliferative index of approximately 15%.

Based on morphology and immunohistochemical profile, the initial diagnosis was pilocytic astrocytoma. However, the tumor was notably cellular and displayed high proliferation throughout. While pilocytic astrocytoma (CNS WHO grade 1) remained a possibility, a differential diagnosis of HGAP (CNS WHO grade 3) was also plausible. This recently defined tumor entity can only be accurately identified using methylation array analysis, characterized by alterations in the MAPK pathway. Hence, the case was subsequently sent for a methylation array analysis and expert opinion to University College London Hospitals.

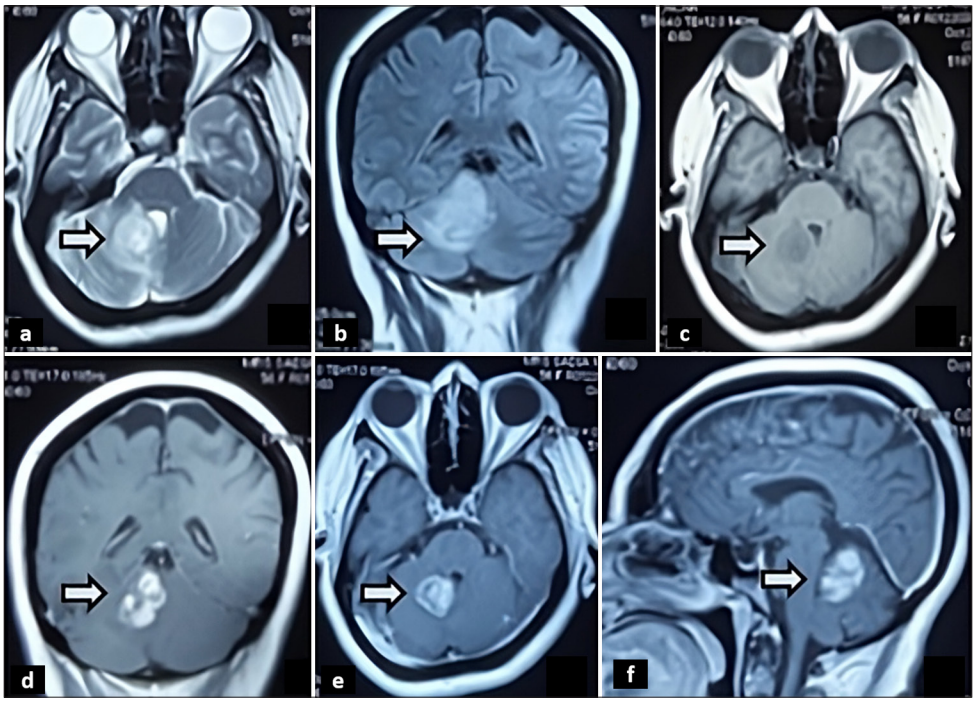

Figure 1: Magnetic resonance imaging findings in a 57-year-old woman with a posterior fossa lesion. (a). Axial T2-weighted image shows a partly defined lesion in the right paravermian location (arrow) with surrounding edema and mass effect over the fourth ventricle. (b). Coronal fluid-attenuated inversion recovery image demonstrates the same lesion (arrow)with similar features. (c). Axial T1-weighted image shows a hypointense lesion (arrow) with a subtle hyperintense rim. (d). Coronal T1 postcontrast image reveals intense nodular enhancement of the lesion (arrow) after gadolinium injection (arrow). (e). Axial T1 postcontrast image also shows intense nodular enhancement of the lesion (arrow). (f). Sagittal T1 postcontrast image further illustrates the intense nodular enhancement of the lesion (arrow) after gadolinium injection.

The DKFZ (Heidelberg) brain tumor classifier identified the tumor as HGAP, with a calibrated methylation score of 0.97. The MGMT promoter status prediction, determined through the O-6-methylguanine-DNA methyltransferase (MGMT)-STP27 logistic regression model, was unmethylated with a high calibrated score, identifying the tumor as HGAP. The chromosome copy number profile derived from the Illumina array data revealed multiple alterations, including a characteristic deletion of CDKN2A/B [Figure 4]. While a definitive CNS WHO grade assignment for this tumor entity is not established, it was provisionally considered that this entity exhibited biological behavior corresponding approximately to CNS WHO grade 3.

The patient did not receive adjuvant treatment such as radiation or chemotherapy due to the lack of resources. Later, the patient returned with complaints of seizures. An MRI revealed disease progression [Figure 5], leading to a decision to perform a redo surgery.

A posterior cranial fossa craniotomy was performed in August 2024. A follow-up MRI [Figure 6] after the second surgery revealed gross total resection with postsurgical changes.

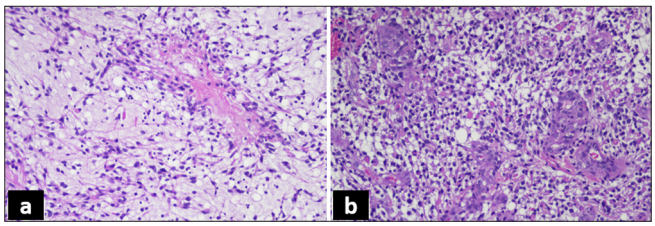

Figure 2: High-grade astrocytoma with piloid features. Hematoxylin and eosin (H&E) image (a) shows tumor cells with bipolar cytoplasmic processes with round to elongated hyperchromatic nuclei, focally centered around vessels with prominent myxoid background and occasional Rosenthal fibers. H&E image (b) shows a tumor exhibiting high cellularity with a prominent gemistocytic population and foci of microvascular proliferation. Magnification: × 40.

In November 2024, the patient showed clinical deterioration due to tumor progression.

DISCUSSION

HGAP is a rare and recently recognized entity within the spectrum of CNS tumors. First introduced in the 2021 WHO Classification of Tumors of the CNS, HGAP represents a distinct glioma subtype that combines the aggressive behavior typical of high-grade gliomas with histological features reminiscent of pilocytic astrocytoma.[2] This case report adds to the limited body of literature on HGAP, particularly highlighting its clinical presentation, diagnostic challenges, and treatment outcomes in a Pakistani patient, which, to our knowledge, is the first of its kind reported in this region.

Past literature on HGAP, though limited, provides valuable insights into its clinical and molecular attributes. Studies such as those by Soni *et al.*, Cimino *et al.*, and Bender *et al.* have contributed to our understanding of HGAP.[1,4,9] Soni *et al.* reviewed eight cases with a mean age of 45.5 years, identifying common tumor locations, including the posterior fossa (n = 4), diencephalon/thalamus (n = 2), and spinal cord (n = 2). Imaging features primarily included T1 hypointensity and T2 hyperintensity, with patterns such as peripheral irregular enhancement accompanied by central necrosis (n = 3) or mixed heterogeneous enhancement (n = 2). Molecular alterations involved IDH1 wild-type status, ATRX mutations, CDKN2A/B deletions, and NF1 mutations in NF1-associated cases. Treatment strategies primarily included surgical resection followed by adjuvant chemoradiation, resulting in six patients surviving and two succumbing to the disease.[9] Cimino *et al.* analyzed a broader cohort of 144 patients, out of which 83 had HGAP. This study highlighted key molecular characteristics, including CDKN2A/B homozygous deletions, ATRX

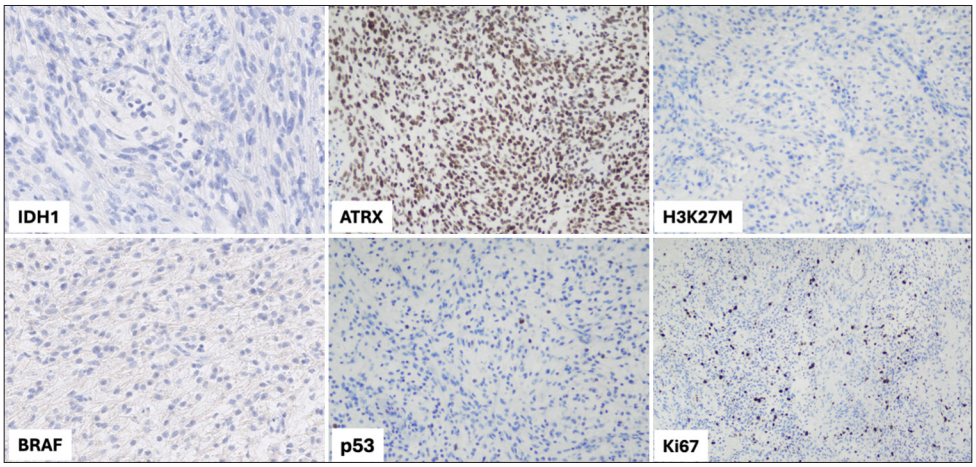

Figure 3: Immunohistochemical profile of high-grade astrocytoma with piloid features. IDH1: Isocitrate Dehydrogenase 1, ATRX: Alpha-Thalassemia/Mental Retardation Syndrome X-Linked, H3K27M: Histone H3 Lysine 27 Mutant, BRAF: B-Raf Proto-Oncogene, Serine/Threonine Kinase, P53: Tumor Protein p53, KI67: Antigen Ki-67.

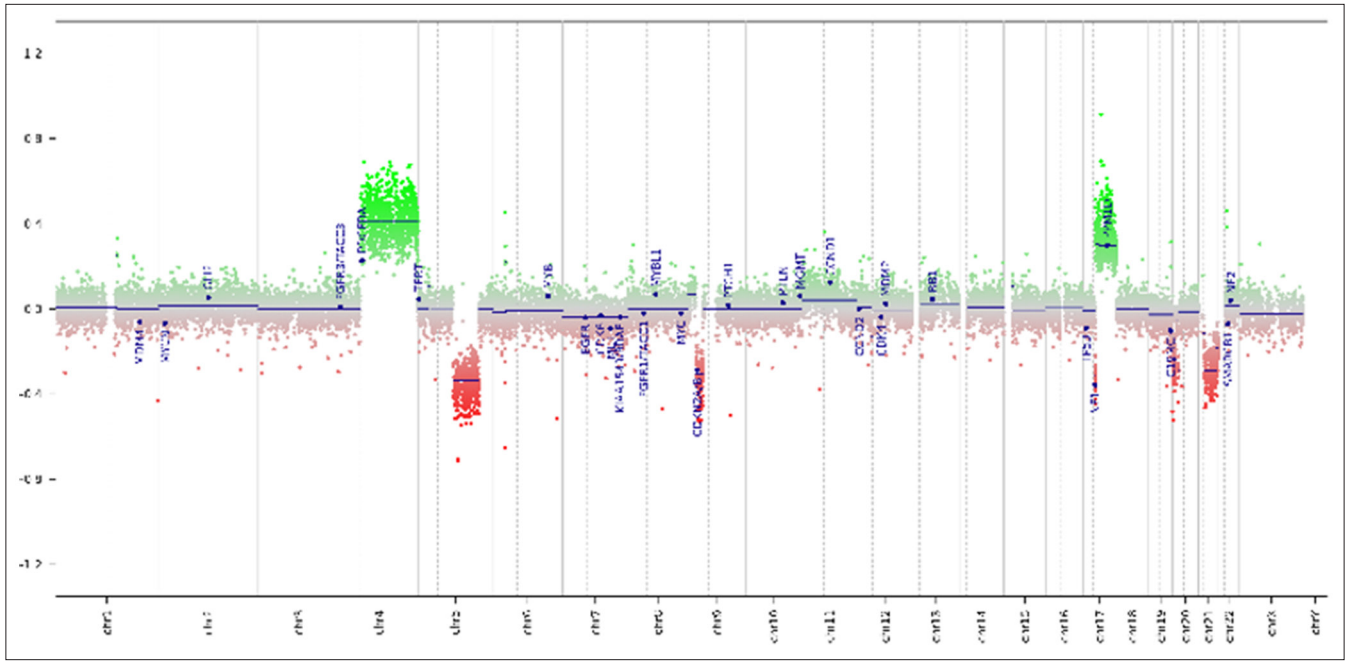

Figure 4: High-grade astrocytoma with piloid features. The DNA copy number profile derived from the Illumina array data shows several alterations, including characteristic CDKN2A/B deletion. Green: Gains/amplifications represent positive deviation from the baseline. Red/pink: chromosome losses/deletions negative deviations from the baseline.

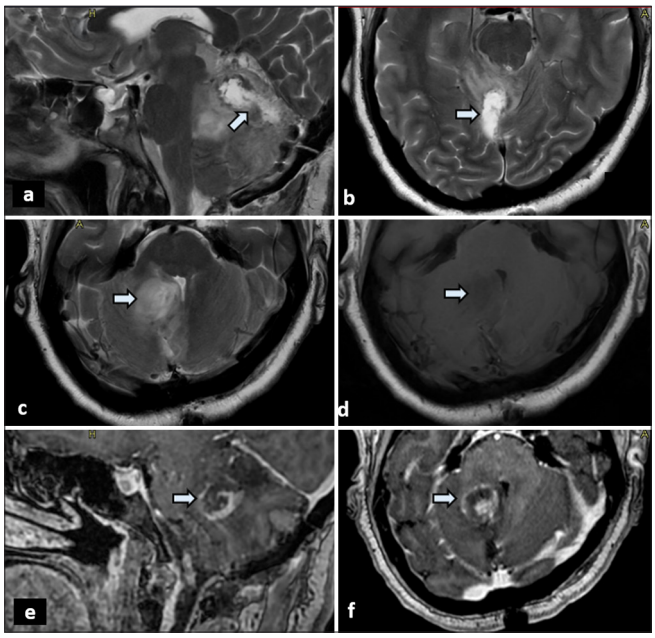

Figure 5: Postoperative magnetic resonance imaging findings after the first surgery. (a). Sagittal T2-weighted image reveals a resection cavity (arrow). (b). Axial T2-weighted image shows the resection cavity (arrow). (c). Axial T2-weighted image displays a rounded hyperintense lesion with a hypointense rim in the right cerebellar hemisphere paravermian location (arrow).(d). Axial T1-weighted image shows the lesion appearing hypointense (arrow). (e). Sagittal T1 postcontrast image demonstrates nodular peripheral enhancement of the lesion (arrow). (f). Axial T1 postcontrast image also shows nodular peripheral enhancement of the same lesion (arrow), suggestive of residual disease.

mutations, and NF1 mutations in the gNF1 subtype, along with rarer alterations such as TP53 mutations (5.4%) and NTRK2 fusions (1 case). They emphasized the poorer progression-free survival of the gNF1 subtype, often associated with midline tumors in the posterior fossa.[4] Bender *et al.* reported a single-center experience involving six cases, demonstrating diverse tumor locations, including the brainstem, cerebellar peduncle, and diencephalon. Imaging typically revealed T1 hypo- to isointensity and T2 hyperintensity with inhomogeneous contrast enhancement. Molecular profiling identified a DNA methylation signature unique to HGAP. Despite aggressive treatment approaches, including surgical resection and adjuvant radiochemotherapy in three cases, the outcomes were dismal, with 4 patients dying within 2 years of diagnosis and only one patient surviving beyond 14.6 months.[1] Table 1 summarizes the findings of these studies, reflecting the heterogeneity and aggressiveness of HGAP, highlighting the critical need for further research into tailored diagnostic and therapeutic strategies for this challenging tumor type.

The clinical presentation of HGAP in our patient aligns with the typical manifestations observed in previously reported cases. The patient, a 57-year-old woman, presented with symptoms of tremors, vertigo, and cerebellar signs, which are consistent with the tumor's predilection for the posterior fossa and midline structures. Such presentations are common, especially in tumors affecting the cerebellum, where the proximity to critical brainstem structures can result in a broad range of neurological deficits.

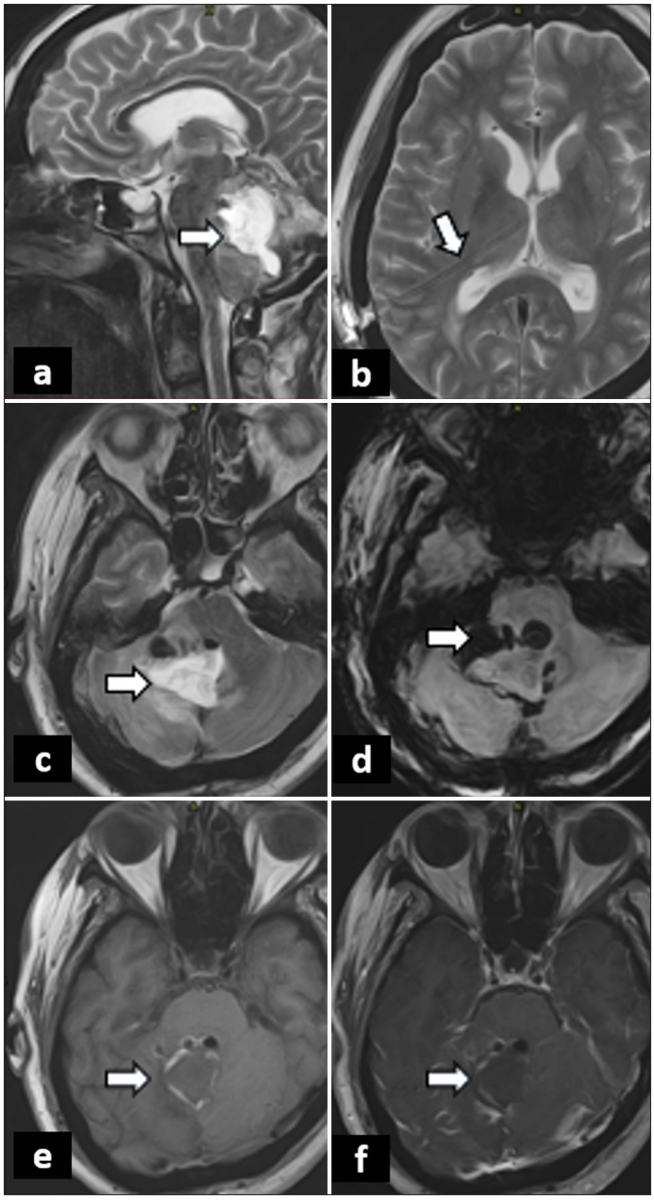

Figure 6: Postoperative magnetic resonance imaging findings after the second surgery. (a). Sagittal T2-weighted image reveals a resection cavity (arrow). (b). Axial T2-weighted image shows a ventricular drain in place (arrow). (c). Axial T2-weighted image also reveals a resection cavity (arrow). (d). Susceptibility-weighted image (SWI) shows marginal susceptibility and pneumocephalus (arrow). (e). Axial T1-weighted image shows marginal hyperintensity, indicating hemorrhage (arrow). (f). Axial T1 postcontrast image shows subtle reactive enhancement along the resection cavity (arrow), representing postsurgical changes. No discrete residual disease was appreciated on imaging.

The presence of NF1 is a significant factor in the pathogenesis of HGAP, with many cases reported in the literature occurring in patients with NF1.[4] However, our patient had no history of NF1, suggesting that HGAP can also occur sporadically. This observation is consistent with other reports that have identified HGAP in patients without NF1, further complicating the understanding of its pathogenesis.

The initial histopathological examination suggested a low-grade glioma, specifically a pilocytic astrocytoma, based on the presence of bipolar cytoplasmic processes, Rosenthal fibers, eosinophilic granular bodies, and the absence of significant mitotic activity or necrosis. However, the high cellularity and proliferation index raised concerns about a higher-grade lesion, prompting advanced molecular testing. This case underscores the diagnostic challenges associated with HGAP, particularly in distinguishing it from other astrocytomas on histopathological grounds alone.

The use of methylation array analysis proved pivotal in arriving at the correct diagnosis. This technique has become increasingly important in the classification of CNS tumors, allowing for the identification of characteristic DNA-methylation profiles complementing histology or immunohistochemistry. The identification of a CDKN2A/B deletion, in this case, is particularly noteworthy, as this genetic alteration is frequently associated with more aggressive tumor behavior and poorer prognosis. The final diagnosis of HGAP in this case, supported by a highly calibrated score from the DKFZ brain tumor methylation classifier, emphasizes the necessity of integrating molecular diagnostics into routine practice for the accurate classification of rare CNS tumors.

Treatment for HGAP, as with other high-grade gliomas, generally involves maximal safe surgical resection followed by adjuvant chemoradiotherapy. However, the prognosis remains poor, with a high likelihood of disease progression, as evidenced in this case by the recurrence of the tumor within a year of the initial surgery. The decision to pursue a second surgical intervention following disease progression highlights the aggressive nature of HGAP and the limited effectiveness of current therapeutic strategies. The patient's subsequent deterioration, despite multimodal treatment, reflects the dismal prognosis associated with HGAP and underscores the urgent need for novel therapeutic approaches.

Table 1: Summary of the existing studies on HGAP.

Study	Patients (*n*)	Age	Location of tumor	Imaging features	Molecular alterations	Treatment	Outcome
Soni *et al.* (2024)[9]	8	Mean: 45.5 years	Posterior fossa (*n*=4), Diencephalon/ Thalamus (*n*=2), Spinal cord (*n*=2)	T1 hypointense, T2 hyperintense, mostly without diffusion restriction, peripheral irregular enhancement with central necrosis (*n*=3), mixed heterogeneous enhancement (*n*=2)	IDH1 wild-type, ATRX, CDKN2A/B, NF1 mutation in NF1-associated cases	Surgical resection, adjuvant chemoradiation	6 alive, 2 died
Cimino *et al.* (2022)[4]	144 out of which 83 had HGAP	Median: 43.5–47 years	Posterior fossa (gNF1 subtype), midline structures	T1 hypo- to isointense, T2 hyperintense, inhomogeneous contrast enhancement	CDKN2A/B homozygous deletion, ATRX mutation, NF1 mutation (gNF1 subtype), TP53 mutation (5.4% of cases), NTRK2 fusion (1 case)	Not specified	Subtype gNF1 shows decreased progression-free survival
Bender *et al.* (2021)[1]	6	Not specified	Brainstem, Cerebellar peduncle, Diencephalon, Mesencephalon, Cerebrum, Thoracic spinal cord	T1 hypo- to isointense, T2 hyperintense, inhomogeneous contrast enhancement	DNA methylation profile specific to HGAP	Surgical resection, adjuvant radiochemotherapy (*n*=3), radiotherapy alone (*n*=1)	4 died (1.8, 9.1, 14.8, 18.1 months), 1 alive (14.6 months), 1 lost to follow-up

HGAP: High-grade astrocytoma with piloid features, NF1: Neurofibromatosis type 1, IDH1: Isocitrate Dehydrogenase 1, ATRX: Alpha-Thalassemia/Mental Retardation Syndrome X-Linked, CKDN: Cyclin-Dependent Kinase Inhibitor, NF: Neurofibromatosis

CONCLUSION

This case report contributes to the growing body of knowledge on HGAP, particularly in the context of South Asian populations. It highlights the critical role of advanced molecular diagnostics in the accurate classification of CNS tumors and the challenges associated with the diagnosis and management of such aggressive neoplasms. Given the rarity and poor prognosis of HGAP, there is a pressing need for further research into its molecular underpinnings and the development of more effective treatment strategies.

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

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