

Well-differentiated Astroblastoma with Both Focal Anaplastic Features and a Meningioma 1 Gene Alteration

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A 6-year-old female was incidentally found to have a brain tumor. Magnetic resonance imaging (MRI) demonstrated a gadolinium-enhanced mass in the left parietal lobe. We performed gross total resection with the assistance of fluorescent guidance by 5-aminolevulinic acid (5-ALA). A histological examination of the tumor specimen showed well-differentiated astroblastic features with focal anaplasia. Fluorescence *in situ* hybridization (FISH) revealed meningioma 1 (*MN1*) gene alteration and supported our diagnosis. She received local radiotherapy and oral temozolomide followed by maintenance temozolomide chemotherapy, and the tumor was well controlled without any neurological deficit for 27 months. Our case is considered to be valuable since it describes a patient who is diagnosed to have a well-differentiated astroblastoma with both focal anaplastic features and *MN1* gene rearrangement. A larger study is warranted to establish evidence supporting the diagnosis and treatment of astroblastoma with molecular characteristic features. *MN1* alteration will be a diagnostic marker for astroblastoma in the future.

Keywords: astroblastoma, anaplastic, Meningioma 1 gene, brain neoplasms, child

Introduction

Astroblastoma usually occurs in bimodal distribution, with a peak between the ages of 5- to 10-years old and another between the ages of 21- to 30-years old. It shows a female predominance and is thought to arise from astroblastic cells.¹⁾ The most recent WHO classification of brain tumors classified this tumor as “other glioma” and did not establish a WHO grade because of the absence of sufficient clinicopathological data.²⁾ Recent literature has suggested a new molecular characteristic feature of meningioma 1 (*MN1*) gene rearrangement.³⁾ However, the clinical course of astroblastoma with *MN1* alteration

has been unclear, and evidence supporting the appropriate treatment has been insufficient.

We encountered a patient with well-differentiated astroblastoma showing focal anaplastic features with meningioma 1 gene alteration. We herein report this rare case and discuss the pathogenesis and prognosis.

Case Report

A 6-year-old girl complained of a painful head bruise and was examined at the closest hospital. A neurological examination revealed no deficit. Computed tomography (CT) showed an iso-density mass lesion with a calcified node on the left parietal lobe (Fig. 1A). She had a history of varicella and exanthema subitum. She was admitted to our department for treatment.

Magnetic resonance imaging (MRI) demonstrated a lobulated lesion with a small cystic component that showed iso-intensity on T1- and T2-weighted imaging and heterogeneous enhancement (Figs. 1B–1E). The enhanced lesion showed a high uptake on L-[methyl-11C] methionine (MET)-positron emission tomography (PET)/CT (Fig. 1F). Left parietal osteoplastic craniotomy was performed. On dissection of the cerebral cortex, the tumor was gray and well-circumscribed, and gross total resection was performed under fluorescent guidance with 5-aminolevulinic acid (5-ALA). On day 10 postoperatively, she was discharged from the hospital without neurological deficit.

After the histological diagnosis was obtained, concomitant chemoradiation therapy was performed, including extended local irradiation (54 Gy/30 Fr) and oral temozolomide (75 mg/m²). After 10 cycles of maintenance therapy using temozolomide, she was free from recurrence at 27 months after the initial treatment.

Pathological findings

The tumor tissue showed relative homogeneity and several characteristic morphological findings. The main part showed high cellularity with perivascular hyalinization, a pseudopapillary pattern, and astroblastic pseudorosette with low nuclear mitosis (2/10 high-power fields [HPFs]) (Fig. 2A). There were no microvascular proliferations or necrosis. The immunohistochemical findings revealed oligodendrocyte transcription factor 2 (Olig2) positivity, multi-focal positivity for glial fibrillary acidic protein (GFAP), and dot-like positivity for epithelial membrane antigen (EMA) (Figs. 2B–2D). Cytokeratin markers, such as AE1/AE3, MNF116, and CAM5.2, were

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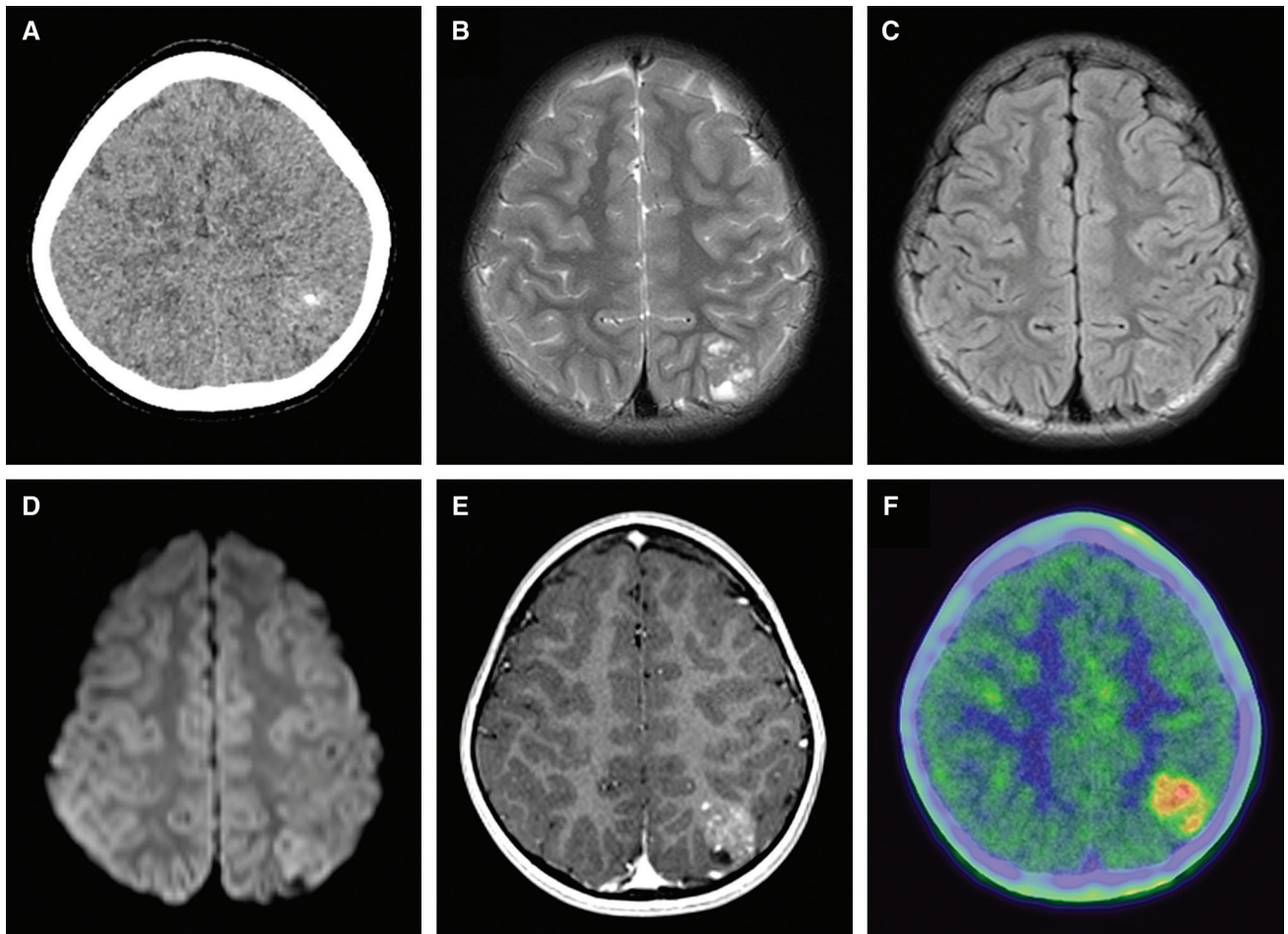


Fig. 1 CT revealed a calcified node in the parietal lobe (A). The lesions presented iso-intensity signals on T2-weighted and FLAIR imaging and slightly high-intensity signals on diffusion weighted imaging (B–D). Gadolinium-enhanced T1-weighted imaging showed a tumor on the left superior parietal lobule with heterogeneous enhancement and a small cystic component (E). L-[methyl-11C] methionine-positron emission tomography/CT showed a high tumor-to-normal ratio (F). CT: computed tomography.

negative. Podoplanin, Vimentin, S-100 protein, ATRX, CD99, transthyretin, and CD56 were positive, while IDH1 R132H, p53, BRAF V600E, and LICAM were negative. The Ki-67 labeling index was 6.2%. The other area was composed of epithelial-like cells with large and irregular nuclei (Fig. 2E). Tumor cells were also seen along the Virchow-Robin spaces. This part of the tumor showed a Ki-67 labeling index of 13.6% (Fig. 2F). Based on the presence of perivascular hyalinization and an astroblastic pseudorosette without high-mitosis nuclei, this main component of the tumor was identified as well-differentiated astroblastoma. However, this tumor specimen had marked nuclear anaplasia and a focally high mitotic rate. We also analyzed the *MNI* gene alteration using break-apart fluorescence *in situ* hybridization (FISH), as described previously.³⁾ The FISH analysis revealed *MNI* rearrangement, characterized with two to three fused red/green signals and one to three isolated red or green signals in each tumor cell in well-differentiated lesions (Fig. 3). These multiple fused red/green signals suggested the gains of the *MNI* locus and the separated red and green signals were considered to have a disrupting effect on the *MNI* locus.³⁾

Based on these findings, we finally diagnosed the patient with well-differentiated astroblastoma showing focal anaplastic features with *MNI* alteration.

Discussion

Astroblastoma was not given a tumor grade in the 2016 WHO classification of CNS tumor and is sorted into high-(anaplastic) and low-grade lesions (well-differentiated) histologically.²⁾ High-grade lesions show high cellularity, anaplastic nuclear features, high mitotic rates, vascular proliferation, and necrosis with pseudopalisading, while low-grade lesions show the uniform perivascular arrangement of pseudorosettes, low-to-moderate numbers of mitotic figures, minimal cellular atypia, minimal-to-no vascular endothelial proliferation, and predominant sclerosis of the vascular walls. In addition, the WHO guideline suggested the cut-off for the Ki-67 labeling index of high grade astroblastoma be set at over 10%.²⁾

Thus far, our case could not be defined as high grade or not, because the pathological findings showed well differentiated astroblastic features with focal anaplasia. Two

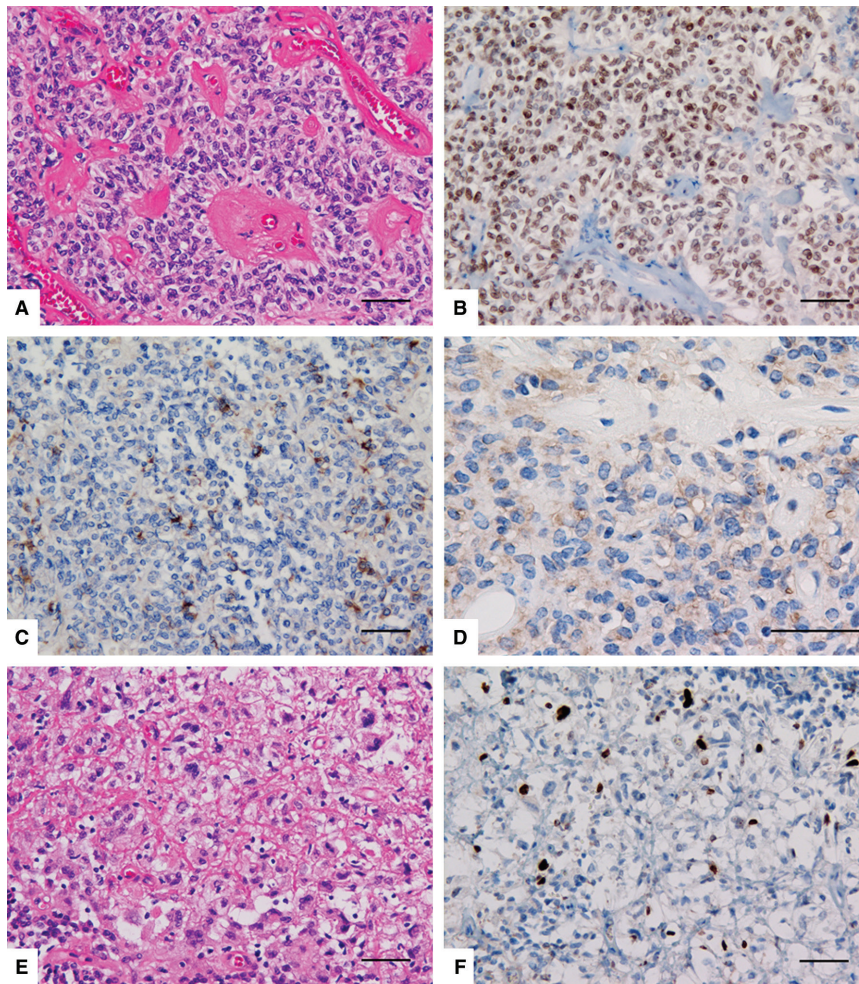


Fig. 2 The main part of the tumor had small tumor cells showing irregularly shaped nuclei and eosinophilic cytoplasm with remarkable vascular hyalinization and astroblastic pseudorosettes, consistent with well-differentiated astroblastoma (A: HE). This area was positive for oligodendrocyte transcription factor 2 (Olig2) (B), multi-focally positive for GFAP (C), and dot-like positive for epithelial membrane antigen (D). The focal anaplastic component of the tumor showed epithelial-like cells with irregular enlarged or small nuclei against cancellous collagen fiber (E: HE). The Ki-67 labeling index of the anaplastic area was 13.6% (F). Scale bars: 50 micrometers. GFAP: glial fibrillary acidic protein.

major studies have mentioned the origin of astroblastoma. One suggested the theory of dedifferentiation from mature astroglial cells, and the other proposed that astroblastic cells are intermediate cells between astrocytes and ependymal cells.^{4,5} Since our patient was diagnosed incidentally based on CT findings, we carefully investigated the pathological findings to determine the manner of malignant transformation or dedifferentiation of the astroblastic cells to an anaplastic pattern.

Table 1 shows the literature review of the 20 astroblastoma cases with *MNI* rearrangement and survival information.^{3,6-10} Almost all patients had lesions in the cerebrum, with one patients showing a lesion in the spinal cord and another showing a lesion in the brainstem.^{7,8} As in our case, Shin et al.⁸ reported a patient with brainstem astroblastoma with focal anaplasia. The radiological findings of astroblastoma with *MNI* translocation showed the tumors to be well-demarcated, lobular or nodular, and located superficially in the cerebral hemisphere. Occasionally, a tumor had calcified

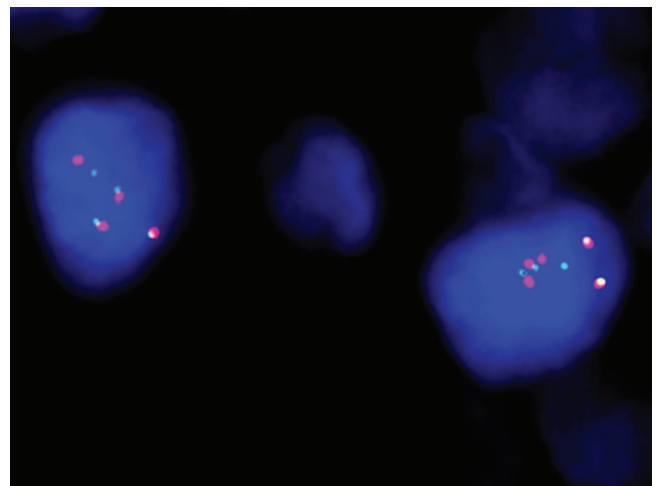


Fig. 3 FISH using the *MNI* break-apart probe showed that each tumor cell had two to three fused red/green signals and one to three isolated red or green signals. FISH: fluorescence *in situ* hybridization.

Table 1 Reported cases of primary astroblastoma with MN1 rearrangement and follow-up information

Reference	Cases	Age(years)/sex	Symptom	Location	Grade	Radiology	Treatment	Prognosis
Wood, et al. ⁶	1	10/F	NA	Left parietal	High	NA	Resection, radiation, chemotherapy (TMZ)	AWSD (2 yrs and 8 mos)
	2	31/F	NA	Left parietal	High	NA	Resection, radiation, chemotherapy (TMZ)	AWSD (1 yr)
Yamada, et al. ⁷	1	20/F	Weakness, hypesthesia	Spinal cord (T1-2)	Low	Contrast-enhancing intramedullary spinal cord lesion	Biopsy, radiation (52Gy), chemotherapy (TMZ and BEV)	NED (1 yr)
Hirose, et al. ³	1	6/F	Generated convulsion	Left frontal	Low	Well-demarcated, contrast-enhancing lesion with calcified foci	GTR	NED (3 yrs and 3 mos)
	2	6/F	Headache	Occipital	Low	Well-demarcated, contrast-enhancing solid lesion	GTR	NED (6 yrs and 4 mos)
	3	18/F	Headache, nausea	Right frontal	Low	Well-demarcated, contrast enhancing solid cystic lesion	GTR	NED (6 mos)
	4	24/F	Weakness, seizures	Left frontal	High	Well-demarcated, contrast enhancing lesion	GTR, radiation (50Gy)	NED (5 yrs)
	5	37/F	Headache, vomiting	Left occipital	High	Ill-defined, contrast enhancing lesion	GTR, radiation, chemotherapy	NED (2 yrs)
Shin, et al. ⁸	1	11/M	Headache, dizziness, photophobia, gait disturbances	Brainstem	unclear	Exophytic, solid, cystic contrast enhancing lesion	NTR, radiation (54Gy), chemotherapy (carboplatin and vincristine)	NA
Lehman, et al. ⁹	1	16/F	NA	Left parieto-occipital	High	NA	Resection	AWSD (11 yrs and 6 mos)
	2	33/F	NA	Left temporal	High	NA	Resection	NED (10 yrs)
	3	12/F	NA	Right fronto-parietal	Low	NA	Resection	AWSD (12 yrs and 3 mos)
	4	9/F	NA	Right fronto-parietal	High	NA	Resection	NED (5 yrs and 8 mos)
	5	18/F	NA	Left parietal	Low	NA	GTR, radiation at recurrence	AWSD (18 yrs and 11 mos)
	6	8/M	NA	Left temporal	Low	NA	Resection	NED (12 yrs)
	7	4/F	NA	Left parieto-occipital	High	NA	Resection	NED (10 yrs and 11 mos)
Mhatre, et al. ¹⁰	1	16/F	Headache, vomiting	Fronto-parietal	Low	Lobulated, heterogeneous enhancing lesion	Resection, radiation	AWSD (5 yrs)

Table 1 Continued

Reference	Cases	Age(years)/sex	Symptom	Location	Grade	Radiology	Treatment	Prognosis
	2	27/F	Headache, seizures	Frontal	High	Multilobulated, contrast enhancing solid cystic lesion	Resection, radiation	AWSD (6 yrs and 4 mos)
	3	10/F	Weakness, decreased sensation	Parietal	High	Lobulated, heterogeneous enhancing lesion with blooming	Resection, radiation	AWSD (7 yrs)
Present case	1	6/F	None	Left parietal	unclear	Lobulated, heterogeneous enhancing solid cystic lesion	GTR, radiation (54Gy), chemotherapy (TMZ)	NED (2 yrs and 3 mos)

AWSD: alive with stable disease, BEV: bevacizumab, F: female, GTR: gross total resection, M: male, mo: month, NA: not available, NED: no evidence of disease, NTR: near total resection, TMZ: temozolomide, yr: year.

foci or cystic components. All patients underwent removal and survived, and eight cases remain alive with stable disease despite histological malignancy. Our case was able to be resected totally under fluorescent guidance with 5-ALA. At surgery, the tumor margin and residual specimen included cyst wall were clearly identified on fluorescence excitation. Other recent studies have described similar cases of fluorescence-guided surgery for astroblastoma.¹¹ Although the standard adjuvant procedure for high-grade astroblastoma has not been confirmed, Mallick et al.¹² advocated maximal surgical resection followed by adjuvant temozolomide and local radiotherapy and described a case treated according to their recommendation, as the case had potential malignant transformation or dedifferentiation of the astroblastic cells to an anaplastic pattern. Another previously reported case of focal anaplasia underwent near total resection and was administered combined chemotherapy with daily carboplatin plus weekly vincristine and radiotherapy (54 Gy/30 Fr).⁸ Astroblastoma with *MNI* rearrangement seems to have a longer survival clinical course than anaplastic pleomorphic xanthoastrocytoma or IDH-wild-type glioblastoma. Lheman et al.⁹ reported in their genomic analysis of histologically diagnosed astroblastoma that *MNI*-rearranged cases showed a significantly better survival than BRAF-V600E mutant astroblastomas.

A recent molecular analysis revealed a new classification of primitive neuroectodermal tumors of central nervous system (CNS-PNETs).¹³ CNS-PNETs have been classified into four new entities: “CNS neuroblastoma with *FOXR2* activation (CNS NB-*FOXR2*),” “CNS Ewing sarcoma family tumor with *CIC* alteration (CNS EFT-*CIC*),” “CNS high-grade neuroepithelial tumor with *MNI* alteration (CNS HGNET-*MNI*),” and “CNS high-grade neuroepithelial tumor with *BCOR* alteration (CNS HGNET-*BCOR*).” Among these new entities, CNS HGNET-*MNI*, which is characterized by *MNI* gene rearrangements on DNA methylation profiling, has frequently shown astroblastic features, such as pseudopapillary patterns and dense pericellular hyalinization. The authors found that nearly 40% of tumors histologically diagnosed as astroblastoma belong to this category. *MNI* rearrangements along with

alterations of the X chromosome have also been reported as features of astroblastoma.³ The histopathological findings of astroblastoma are similar to those of ependymoma, which typically have rosette-forming tumor cells. Olig2 positivity is a useful diagnostic marker, since ependymoma generally does not express that molecule.¹⁴ In addition, *RELA* fusion on a FISH analysis or immunohistochemistry for p65/*RELA* and/or *LICAM* is also useful for making a diagnosis of ependymoma.⁹ Other studies have described cases in which *MNI* rearrangement detected by a FISH analysis was useful for diagnosing astroblastoma and differentiating from ependymoma.³ Astroblastoma histology is not specific for CNS-HGNET-*MNI*. Wood et al.⁶ reported a case of astroblastoma diagnosed histologically without *MNI* alteration showing genetic features of either anaplastic pleomorphic xanthoastrocytoma (*BRAF* p.V600E mutation, *CDKN2A/B* homozygous deletion and *TERT* promoter mutation) or IDH-wild-type glioblastoma (trisomy 7, monosomy 10, *CDK4* amplification and *TP53*, *NRAS*, and *TERT* promoter mutations). Lucas et al.¹⁵ proposed that astroblastomas with *MNI* fusions represent “true” astroblastomas and recommended the terminology “astroblastoma, *MNI* fusion-positive.”

Our present report was limited by the short follow-up duration. The diagnosis and evaluation of malignancy for astroblastoma are made histologically, while no molecular diagnosis was made at this time; therefore, further molecular-based and larger-scale cases studies will be needed to determine whether or not *MNI* alteration is a suitable diagnostic marker for astroblastoma.

Conclusion

We reported a case of well-differentiated astroblastoma with focal anaplastic features and *MNI* alteration that was treated with gross total resection (GTR) and chemoradiotherapy. A larger-scale study is warranted to establish evidence supporting the diagnosis and treatment of astroblastoma with molecular characteristic features.

Conflicts of Interest Disclosure

The authors declare there are no conflicts of interest.

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