

True anaplastic oligoastrocytoma with dual genotype: illustrative case

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BACKGROUND The revised fourth edition of the World Health Organization classification of central nervous system tumors was published in 2016. Based on this classification, one of the infiltrating glioma entities named “oligoastrocytoma/anaplastic oligoastrocytoma” is discouraged. It is proposed that these mixed gliomas should be classified as diffuse astrocytoma/anaplastic astrocytoma or oligodendroglioma/anaplastic oligodendroglioma when analyzing their genetic alteration.

OBSERVATIONS A 78-year-old female underwent brain computed tomography (CT) because of a traffic accident. Cranial CT revealed a brain tumor in the left temporoparietal lobe; therefore, she was hospitalized. She underwent awake craniotomy. After the operation, she was treated with only local radiotherapy; the authors could not prescribe temozolomide, because she had had levetiracetam-induced pancytopenia. The remaining tumor neuroradiologically disappeared, and she was alive 40 months after the operation without tumor recurrence.

LESSONS Histopathologically, this tumor was diagnosed as an anaplastic oligoastrocytoma with a distinct dual phenotype of astrocytoma and oligodendroglioma components. Genetically, these two components revealed astrocytoma and oligodendroglioma genotypes, respectively. Therefore, the authors considered the integrated diagnosis of the temporal tumor as a true anaplastic oligoastrocytoma with a dual genotype. Interestingly, this case also included an area composed of spindle to oval neoplastic cells that revealed intermediate genetic alterations between astrocytomas and oligodendrogliomas.

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KEYWORDS anaplastic oligodendroglioma; anaplastic oligoastrocytoma; WHO classification

Oligoastrocytoma is a glial neoplasm characterized by a mixture of astrocytic and oligodendroglial neoplasms. This glial tumor entity was considered as one of the neuroepithelial tumors and classified as an “oligoastrocytic tumor” in the fourth edition of World Health Organization (WHO) classification of central nervous system (CNS) tumors published in 2007.^{1,2} However, after the revised fourth edition of the WHO classification of CNS tumors was published in 2016, use of the term “oligoastrocytoma/anaplastic oligoastrocytoma (AOA)” was discouraged, and it is proposed that these mixed gliomas should be classified as diffuse astrocytoma/anaplastic astrocytoma (DA/AA) or oligodendroglioma/anaplastic oligodendroglioma (OD/AOD) when analyzing their genetic alteration: IDH1/2 mutation

and 1p/19q codeletion.³ Although fewer than 10 cases have been reported, oligoastrocytic neoplasms with dual genotypes have been reported.^{4–7} This case report describes in detail the clinical, pathological, and genetic features of true AOA showing a dual genotype, and a literature review is provided.

Illustrative Case

A 78-year-old female without any medical history underwent brain computed tomography (CT) at a local hospital because she had experienced a traffic accident while driving her car. Cranial CT revealed a brain tumor in the left temporoparietal lobe; therefore, she was hospitalized in January 2018. Neurological examination

ABBREVIATIONS AA = anaplastic astrocytoma; AOA = anaplastic oligoastrocytoma; AOD = anaplastic oligodendroglioma; CNS = central nervous system; CT = computed tomography; DA = diffuse astrocytoma; DWI = diffusion-weighted imaging; GFAP = glial fibrillary acidic protein; inf-A = infiltrating astrocytoma; LI = labeling index; OD = oligodendroglioma; Olig2 = oligodendrocyte transcription factor 2; WHO = World Health Organization.

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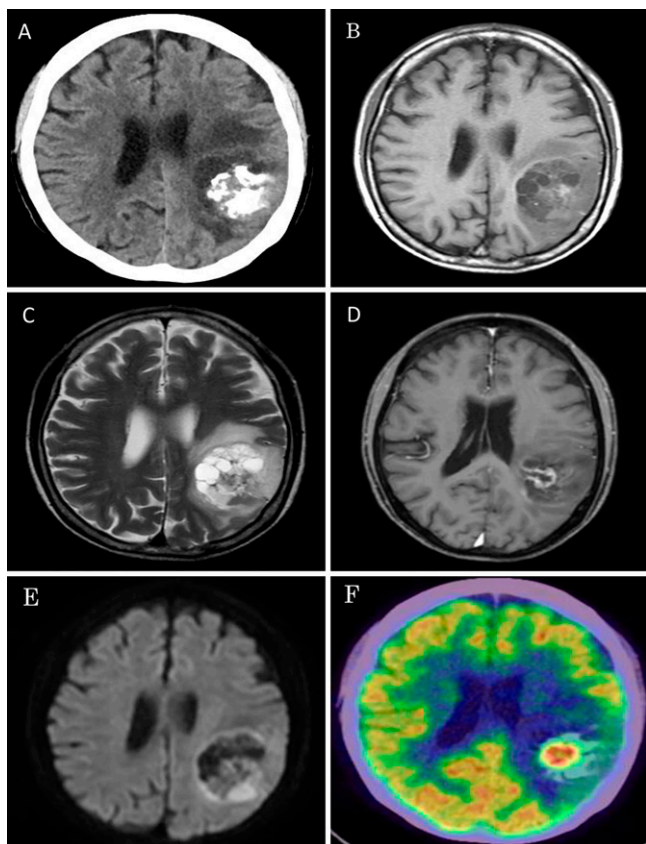


FIG. 1. Preoperative images. **A:** CT showing a mass with hypercalcification in the right temporoparietal lobe. **B:** On MRI, the T1-weighted image showed a hypointense temporoparietal multicystic mass. **C:** On MRI, the T2-weighted image shows a hyperintense temporoparietal multicystic mass. **D:** The DWI hyperintensity area was enhanced on the T1-weighted gadolinium-enhanced image. **E:** DWI showing that the major area of the mass revealed hypointensity but focal hyperintensity. **F:** Fluorodeoxyglucose positron emission tomography showing high intake on the DWI hyperintensity area.

revealed motor aphasia, Gerstman syndrome (finger agnosia and left–right disorientation), and cognitive dysfunction (Mini Mental State Examination score 23/30; Raven’s Colored Progressive Matrices 25/36). Cranial CT showed a mass with hypercalcification in the left temporoparietal lobe (Fig. 1A). Brain magnetic resonance imaging revealed the temporoparietal mass as a large multicystic tumor measuring $36 \times 49 \times 49$ mm. It was hypo-/hyperintense on the T1- and T2-weighted images, respectively (Fig. 1B and C). The diffusion-weighted imaging (DWI) hyperintense area was enhanced on T1-weighted gadolinium-enhanced images (Fig. 1D). DWI revealed that most of the mass was hypointense but focally hyperintense (Fig. 1E).

Furthermore, the DWI hyperintensity area revealed a high intake on fluorodeoxyglucose positron emission tomography (Fig. 1F). On the 12th day after admission, she underwent awake craniotomy, and the tumor was partially resected. After the operation, she was treated with local radiotherapy only, with a total dose of 40.05 Gy in 15 fractions (2.67 Gy per day); she could not receive temozolomide, because she had had levetiracetam-induced pancytopenia. The remaining tumor neuroradiologically disappeared after postoperative therapy. Subsequently, the patient returned home without additional

neurological impairment. She was alive 40 months after the operation without tumor recurrence.

Pathological Findings

Histopathologically, the resected brain tumor was a hypercellular neoplasm with foci of microvascular proliferation and ischemic necrosis. The neoplastic parenchyma was characterized by the following three components (Fig. 2A): an oligo area, composed of neoplastic cells with round nuclei and clear perinuclear haloes, with the growth pattern of honeycomb appearance, rich branching capillary network, with psammoma bodies, morphologically compatible with OD (Fig. 2B); an astro area, composed of neoplastic cells with hyperchromatic oval to spindled nuclei and eosinophilic fibrillary cytoplasm, morphologically compatible with infiltrating astrocytoma (Fig. 2C); and a mixed area, composed of a mixture of neoplastic cells with oval to round nuclei and eosinophilic, relatively rich fibrillary cytoplasm resembling astrocytoma morphology (Fig. 2D, white arrow), with irregular oval to round nuclei and light eosinophilic to clear round cytoplasm resembling nonclassic OD morphology (Fig. 2D, black arrow). In the tumor, neoplastic cells in the mixed area revealed anaplasia, namely high cellularity, nuclear atypia with hyperchromatin, and high mitotic activity (4 per 10 high-power fields). Furthermore, microvascular proliferation and ischemic necrosis were observed in the mixed areas.

The results of the immunohistochemical and genetic analyses are summarized in Table 1. In the oligo area, neoplastic cells were prominently positive for oligodendrocyte transcription factor 2 (Olig2) (Fig. 2E) but less frequently positive for nestin, S100, and glial fibrillary acidic protein (GFAP) (Fig. 2H). In contrast, in the astro and mixed areas, neoplastic cells were positive for nestin, S100 protein, and GFAP (Fig. 2I and J) and rarely positive or almost negative for Olig2 (Fig. 2F and G). Neoplastic cells in these areas showed diffuse immunoreactivity against GFAP. MIB-1 labeling index (LI) was highest in the mixed areas compared with the other two areas, and its MIB-1 LI was 27.6% at the hotspot.

Interestingly, there were distinctive genetic alterations between the oligo area and astro area. Both astrocyte-like and oligodendroglia-like neoplastic cells in the oligo and astro areas showed mutant IDH1-R132H expression (Fig. 3A and B). However, α -thalassaemia/mental retardation syndrome X-linked (*ATR*X) nuclear expression was lost in the astro area but was retained in the oligo area (Fig. 3D and E). Furthermore, the oligo area revealed loss of heterozygosity on chromosome 1p and 19q (1p/19q codeletion) by fluorescence in situ hybridization (Fig. 3G and H), but no 1p/19q codeletion in the astro area (Fig. 3I and J). *TERT* gene mutations were detected in the oligo area but not in the astro area (Table 1). In the mixed area, neoplastic cells showed mutant IDH1-R132H expression (Fig. 3C), retained *ATR*X nuclear expression (Fig. 3F), and *TERT* gene mutation (Table 1), but no distinct 1p/19q codeletion (Fig. 3K and L).

Discussion

Observations

AOA is a high-grade mixed glioma morphologically characterized by a mixture of OD and infiltrating astrocytoma (inf-A) components, with focal or diffuse anaplasia.³ However, in the revised fourth edition of the WHO classification of CNS tumors published in 2016, diagnoses of CNS tumors by integrating both phenotype and genotype have been proposed; therefore, tumor genotypes are

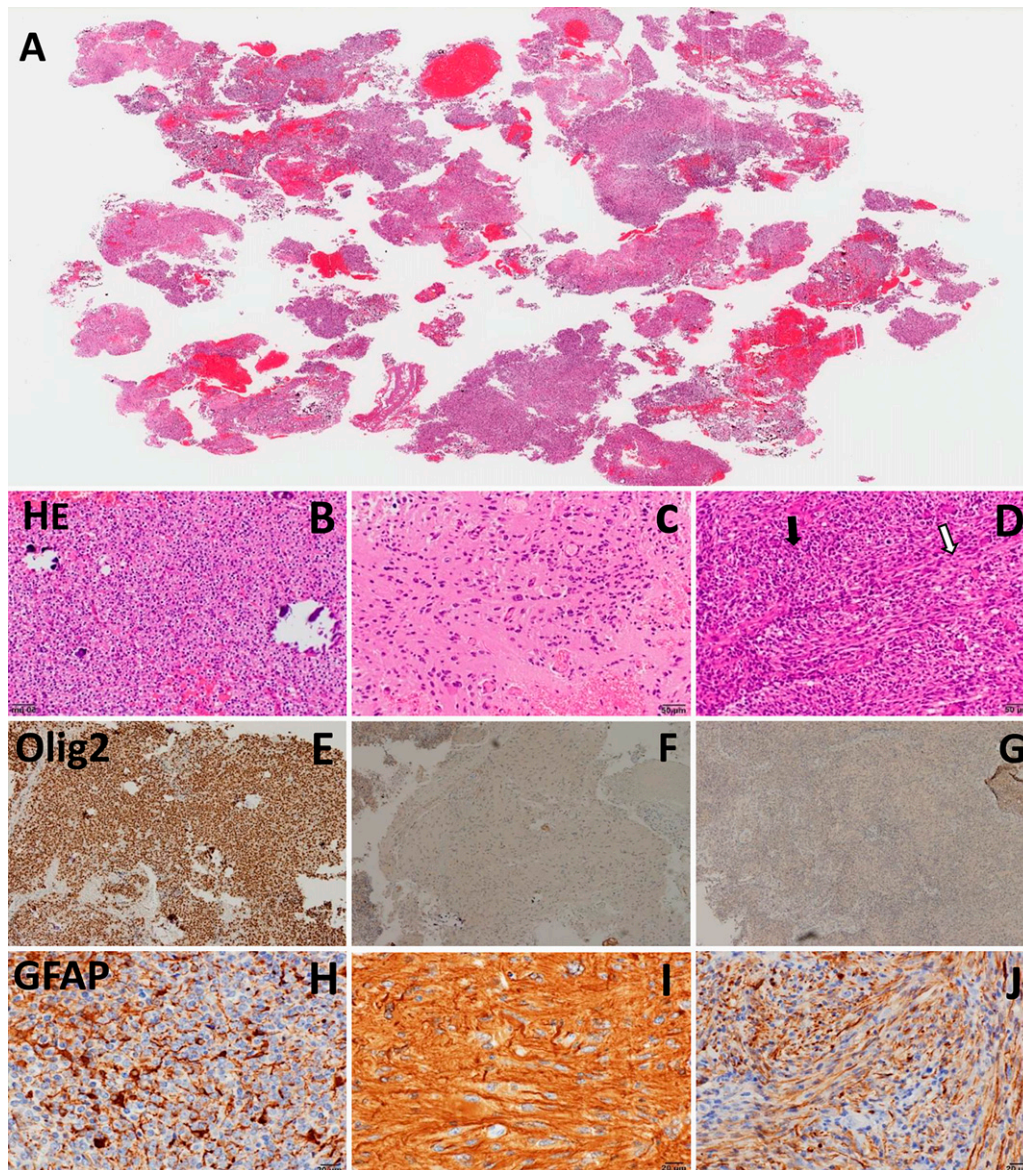


FIG. 2. **A:** Low-power field of the neoplastic parenchyma. **B:** Oligo area, composed of neoplastic cells with round nuclei and clear perinuclear haloes, with the growth pattern of honeycomb appearance, rich branching capillary network, with psammoma bodies. HE, hematoxylin and eosin. **C:** Astro area, composed of neoplastic cells with hyperchromatic oval to spindled nuclei and eosinophilic fibrillary cytoplasm. **D:** Mixed area, composed of a mixture of neoplastic cells with oval to round nuclei and eosinophilic, relatively rich fibrillary cytoplasm resembling astrocytoma morphology (*white arrow*) and with irregular oval to round nuclei and light eosinophilic to clear round cytoplasm resembling nonclassic oligodendroglioma morphology (*black arrow*). **E:** In the oligo area, neoplastic cells were prominently positive for Olig2. **F:** In the astro area, rarely positive or almost negative for Olig2. **G:** In the mixed area, rarely positive or almost negative for Olig2. **H:** In the oligo area, less frequently positive for GFAP. **I:** In the astro area, neoplastic cells were positive for GFAP. **J:** In the mixed area, neoplastic cells were positive for GFAP.

considered as important factors for tumor classification, in addition to tumor phenotypes, for CNS tumor diagnosis.^{8,9} In particular, diffuse gliomas are distinctly classified as DA/AA or OD/AOD according to two genetic alterations: *IDH1/2* mutation and 1p/19q codeletion.^{8,9} According to such background, the revised 2016 WHO classification of the CNS tumors discourages the name “OA/AOA,” and genetic analyses of *IDH1/2* mutation and 1p/19q codeletion are recommended for classifying OA/AOA to astrocytic or

oligodendroglial tumors, although not otherwise specified categories can be used for the diagnosis of OA/AOA only when genetic examination cannot be performed.^{8,9} In fact, previous reports described that when two phenotypes (inf-A phenotype and OD phenotype) can be detected, most oligoastrocytic tumors genetically reveal the pattern of astrocytic tumors or oligodendroglial tumors.^{10–12} Dong et al.¹⁰ suggested in their study that oligoastrocytic tumors predominantly originate from monoclonal precursor glial neoplastic cells.

TABLE 1. Morphological, immunohistochemical, and genetic differences among three areas of the presented brain tumor

Variable	Oligo Area	Mixed Area	Astro Area
Morphology			
Cell morphology	O ₁	Mixed	A
Mitotic figures (/10 HPF)	0	4	2
Microvascular proliferation	—	+	—
Necrosis	—	+	—
Immunohistochemistry			
Nestin	±	+	++
S100 protein	±	++	+
GFAP	+	++	+++
Olig2	+++	—	—
MIB-1 LI (%)	10.4%	27.6%	20.0%
Genetic alteration			
mIDH1-R132H	+	+	+
ATRX nuclear expression	—	—	+
P53 nuclear expression	—	+/-	+
1p/19q codeletion (1p/19q)	+/+	±/±	-/-
TERT mutation	+	+	—
Fraction of <i>TERT</i> mutant allele analyzed using ddPCR assay	31.40%	—	0%

+++ = strong positive; ++ = between +++ and +; + = positive; — = negative; ± = partially positive and partially negative; A = astrocytoma-like cells; ATRX = α -thalassemia/mental retardation syndrome X-linked; ddPCR = droplet digital polymerase chain reaction; HPF = high-power field; mIDH1-R132H = mutant isocitrate dehydrogenase 1-R132H; Mixed = mixed oligodendroglioma-like cells and astrocytoma-like cells; O = oligodendroglioma-like cells.

However, to the best of our knowledge, five studies have described the presence of OA/AOA with distinct dual genotypes.^{4–7} In addition, we present a case of dual-genotype AOA in this report, with a detailed description of the histopathological, immunohistochemical, and genetic features. Table 2 summarizes the clinical, pathological, and genetic features of five previously reported dual-genotype OA/AOA cases^{4–7} and our presented AOA case. The mean age at disease onset was 48.6 years (standard deviation 21.55), and the temporal lobe was the most affected region (5 of 6; 83.3%). All OA/AOA cases were histopathologically composed of inf-A and OD components. In addition, the inf-A component showed a genetic alteration characterized by an *IDH1/2* mutation, loss of ATRX nuclear expression, prominent p53 protein nuclear expression, and no 1p19q codeletion. In contrast, the OD component showed a genetic alteration characterized by an *IDH1/2* mutation, retained ATRX nuclear expression, weak or no p53 protein nuclear expression, and 1p19q codeletion. Furthermore, *TERT* mutation analyses were performed in three of the five reported cases, and all of them showed a *TERT* mutation in the OD component but not in the inf-A component. Therefore, we can propose dual-genotype OA/AOA as a distinct entity of mixed glioma according to the following clinical, pathological, and genetic characteristics: (1) The temporal area of middle-aged patients is mainly affected; (2) two distinct phenotypes, inf-A component and OD component, compose the tumor; (3) the presence of anaplasia varies, and the criteria of anaplasia should be decided by the criteria of AA or AOD; (4) the inf-A component reveals *IDH1/2* mutation, loss of ATRX nuclear expression, prominent p53 protein nuclear expression, no 1p19q codeletion, and no *TERT* mutation; and (5) the OD component reveals *IDH1/2*

mutation, retained ATRX nuclear expression, weak or no p53 protein nuclear expression, 1p19q codeletion, and *TERT* mutation.

In the present case, there was a mixed area composed of a mixture of neoplastic cells resembling inf-A morphology and OD morphology. Wilcox et al.⁷ also described mixed areas in one of their two cases. Interestingly, genetic alterations in these mixed areas resulted in both the inf-A and OD genetic features. It is difficult to determine the distinct meanings of these mixed areas in the dual-genotype OA/AOA. However, we can raise some possibilities from these mixed areas in dual-genotype OA/AOA as follows: (1) the presence of common precursor neoplastic cells of both inf-A and OD components in dual-genotype OA/AOA and (2) only intermingled lesions of inf-A and OD components. If the former, we can rerecognize “OA/AOA” as the third entity of diffuse astrocytic and oligodendroglial tumors. Further morphological and genetic analyses are needed to clarify the meaning of the mixed areas of dual-genotype OA/AOA.

Lessons

In summary, we have described the detailed clinicopathological and genetic features of AOA with a dual genotype. Furthermore, we described the presence of mixed areas revealing the intermediate genetic alteration in the presented AOA with a dual genotype. Although extremely rare, we believe that “OA/AOA with dual genotype” exists, and the likewise is true for glioblastoma with an OD component arising from OA/AOA with a dual genotype.

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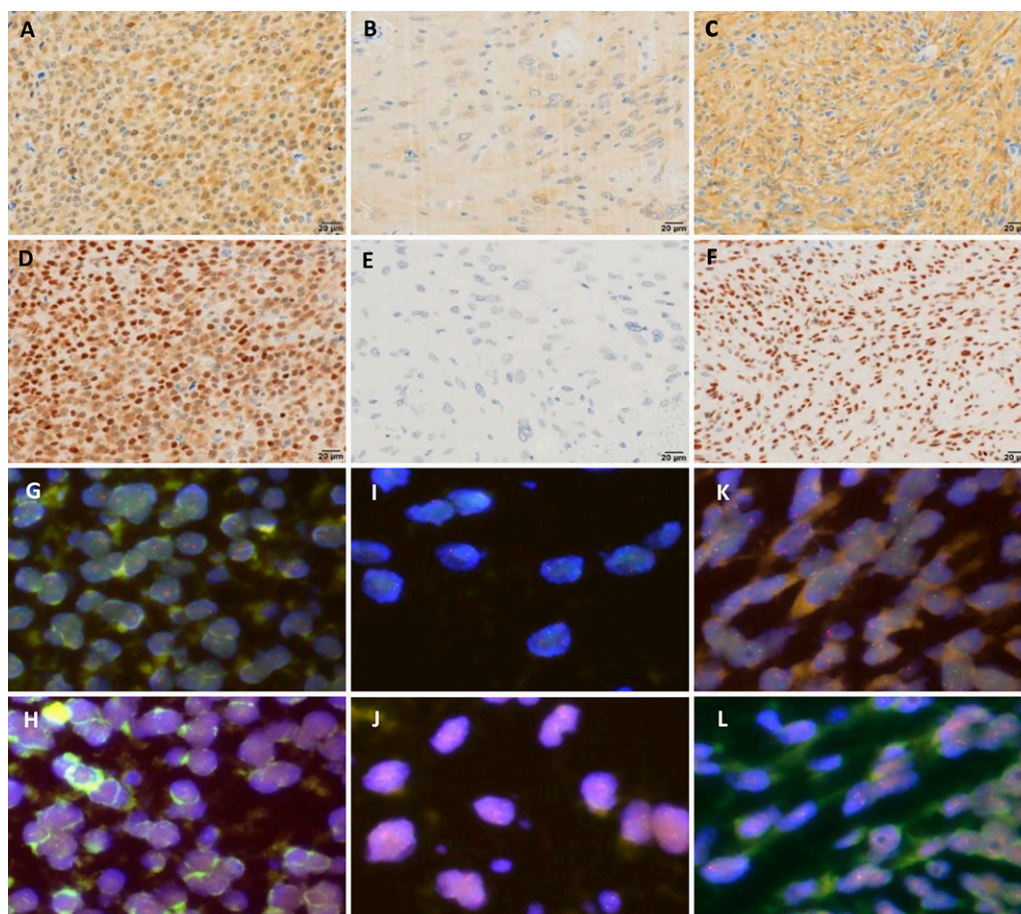


FIG. 3. A–C: In the oligo area (A), astro area (B), and mixed area (C), mutant IDH-R132H expression was detectable. **D:** In the oligo area, nuclear expression of ATRX was retained. **E:** In the astro area, loss of immunohistochemical reactivity for ATRX protein is shown. **F:** Nuclear expression of ATRX was retained in mixed areas. **G and H:** The oligo area showing 1p-19q codeletion. **I and J:** Astro area showing no 1p-19q codeletions. **K and L:** Mixed area, no distinct 1p-19q codeletion.

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TABLE 2. Clinical, pathological, and genetic features of six oligoastrocytic tumors with dual genotype

Authors & Year	Age at Onset (yrs)	Sex	Tumor Location	Recurrence	Path Dx	Component	Genetic Alteration: IDH1/2 Mutation	ATRX Nuclear Expression	P53 Nuclear Expression	1p/19q Codeletion	TERT Mutation
Qu et al., 2007 ⁴	44	M	Temporal	ND	OA	Astro	ND	ND	—	—	ND
						Oligo	ND	ND	—	+	ND
Huse et al., 2015 ⁶	53	F	Frontal	+ (2 mos, GB)	AOA	Astro	IDH1 R132H	+	+	—	ND
						Oligo	IDH1 R132H	—	±	+	ND
Wilcox et al., 2015 ⁷	30	M	Temporal	—	AOA	Astro	IDH1 R132H	+	+	—	—
						Mixed	IDH1 R132H	+/-	±	±	C250T
						Oligo	IDH1 R132H	—	—	+	C250T
	57	M	Temporal	+ (24 mos, A)	OA	Astro	IDH1 R132H	+	ND	—	ND
						Oligo	IDH1 R132H	—	ND	+	ND
Barresi et al., 2017 ⁵	25	M	Temporal	—	OA	Astro	IDH2 R172M	+	+	—	—
						Oligo	IDH2 R172M	—	—	+	C228T
Present case	78	F	Temporoparietal	—	AOA	Astro	IDH1 R132H	+	+	—	—
						Mixed	IDH1 R132H	—	±	±	+
						Oligo	IDH1 R132H	—	±	+	+

+ = positive; — = negative; ± = partially positive; Path Dx = pathological diagnosis.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Mizuno, Homma, Adachi, Suzuki. Acquisition of data: Mizuno, Homma, Adachi, Mishima. Analysis and interpretation of data: Mizuno, Homma, Adachi, Suzuki, Atsushi. Drafting the article: Mizuno, Homma, Adachi, Suzuki. Critically revising the article: Mizuno, Homma, Adachi, Suzuki, Atsushi. Reviewed submitted version of

manuscript: Mizuno, Homma, Adachi, Suzuki, Shirahata, Nishikawa, Atsushi. Approved the final version of the manuscript on behalf of all authors: Mizuno. Statistical analysis: Mizuno, Homma. Administrative/technical/material support: Mizuno, Homma, Adachi, Suzuki, Nishikawa. Study supervision: Mizuno, Homma, Adachi, Suzuki, Nishikawa.

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