True anaplastic oligoastrocytoma with dual genotype: illustrative case

Reina Mizuno, MD,1 Taku Homma, MD, PhD,2 Jun-ichi Adachi, MD, PhD,1 Kazuhiko Mishima, MD, PhD,1 Tomonari Suzuki, MD, PhD,1 Mitsuaki Shirahata, MD, PhD,1 Ryo Nishikawa, MD, PhD,1 and Sasaki Atushi, MD, PhD3

Departments of 1Craniospinal Tumor and 2Pathology, Saitama International Medical Center, Saitama, Japan; and 3Department of Pathology, Hospital of Saitama Medical University, Saitama, Japan

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.

https://thejns.org/doi/abs/10.3171/CASE22146

KEYWORDS anaplastic oligodendroglioma; anaplastic oligoastrocytoma; WHO classification

Oligoastrocytoma is a glial neoplasm characterized by a mixture of astrocytic and oligodendrogial 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...
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 × 49 × 49 mm. It was hypointense 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 oligodendrogli-like neoplastic cells in the oligo and astro areas showed mutant IDH1-R132H expression (Fig. 3A and B). However, in the mixed area, mutant IDH1-R132H 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 chromosomes 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 ATRX 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. 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...
considered as important factors for tumor classification, in addition
to tumor phenotypes, for CNS tumor diagnosis.\textsuperscript{8,9} In particular, diffuse gliomas are distinctly classified as DA/AA or OD/AOD according to two genetic alterations: \textit{IDH1/2} mutation and 1p/19q codeletion.\textsuperscript{8,9} According to such background, the revised 2016 WHO classification of the CNS tumors discourages the name “OA/AOA,” and genetic analyses of \textit{IDH1/2} mutation and 1p/19q codeletion are recommended for classifying OA/AOA to astrocytic or oligodendrogial tumors, although not otherwise specified categories can be used for the diagnosis of OA/AOA only when genetic examination cannot be performed.\textsuperscript{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 oligodendrogial tumors.\textsuperscript{10–12} Dong et al.\textsuperscript{10} suggested in their study that oligoastrocytic tumors predominantly originate from monoclonal precursor glial neoplastic cells.
However, to the best of our knowledge, five studies have described the presence of OA/OA with distinct dual genotypes. In addition, we present a case of dual-genotype OA in this report, with a detailed description of the histopathological, immunohistochemical, and genetic features. Table 2 summarizes the clinical, pathological, and genetic characteristics: (1) The temporal area of middle-aged patients is mainly affected; (2) The presence of common precursor neoplastic cells of both inf-A and OD components in dual-genotype OA/OA. However, we can raise some possibilities from these mixed areas in dual-genotype OA/OA as follows: (1) the presence of common precursor neoplastic cells of both inf-A and OD components in dual-genotype OA/OA; (2) the presence of common precursor neoplastic cells of both inf-A and OD components in dual-genotype OA/OA.

**Lessons**

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

**Acknowledgments**

This work was supported by a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (JSPS).
KAKENHI Grant 18K09003), 2018-2020. We express our sincere thanks to Kaoru Katsura and Ayako Kubota for their technical assistance.

References

1. von Deimling A, Reifenberger G, Kros JM, Louis DN, Collins VP. Oligoastrocytoma. In: Louis DN, Ohgaki H, Wiestler OD, et al., eds. WHO Classification of Tumours of the Central Nervous System. 4th ed. IARC Press; 2007:63–65.
2. von Deimling A, Reifenberger G, Kros JM, Louis DN, Collins VP. Anaplastic oligoastrocytoma. In: Louis DN, Ohgaki H, Wiestler OD, et al., eds. WHO Classification of Tumours of the Central Nervous System. 4th ed. IARC Press; 2007:66–67.
3. Reifenberger G, Cairncross JG, Collins VP, et al. Oligoastrocytoma, NOS. In: Louis DN, Ohgaki H, and Wiestler OD, eds. WHO Classification of Tumours of the Central Nervous System. 4th ed. IARC Press; 2016:75–77.
4. Qu M, Olofsson T, Sigurdardottir S, et al. Genetically distinct astrocytic and oligodendroglial components in oligoastrocytomas. Acta Neuropathol. 2007;113(2):129–136.
5. Barresi V, Lionti S, Valori L, Gallina G, Caffo M, Rossi S. Dual-genotype diffuse low-grade glioma: is it really time to abandon oligoastrocytoma as a distinct entity? J Neuropathol Exp Neurol. 2017;76(5):342–346.
6. Huse JT, Diamond EL, Wang L, Rosenblum MK. Mixed glioma with molecular features of composite oligodendroglioma and astrocytoma: a true “oligoastrocytoma”? Acta Neuropathol. 2015;129(1):147–149.
7. Wilcox P, Li CC, Lee M, et al. Oligoastrocytomas: throwing the baby out with the bathwater? Acta Neuropathol. 2015;129(1):147–149.
8. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803–820.
9. Wesseling P, Capper D. WHO 2016 classification of gliomas. Neuropathol Appl Neurobiol. 2018;44(2):139–150.
10. Dong ZQ, Pang JC, Tong CY, Zhou LF, Ng HK. Clonality of oligoastrocytomas. Hum Pathol. 2002;33(5):526–535.
11. Okamoto Y, Di Patre PL, Burkhard C, et al. Population-based study on incidence, survival rates, and genetic alterations of low-grade diffuse astrocytomas and oligodendrogliomas. Acta Neuropathol. 2004;108(1):49–56.
12. Smith JS, Aldrete B, Minn Y, et al. Localization of common deletion regions on 1p and 19q in human gliomas and their association with histological subtype. Oncogene. 1999;18(28):4144–4152.
### 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 | 44                  | M   | Temporal       | ND         | OA      | Astro     | ND/ND                                | ND/ND                  | ND/ND               | ND              | ND           |
| Huse et al., 2015 | 53                  | F   | Frontal        | + (2 mos, GB) | AOA     | Astro     | IDH1 R132H/ND                         | +/ND                   | ND                  | ND              | ND           |
| Wilcox et al., 2015 | 30                 | M   | Temporal       | —          | AOA     | Astro     | IDH1 R132H/ND                         | +/ND                   | ND                  | ND              | ND           |
| Wilcox et al., 2015 | 57                 | M   | Temporal       | + (24 mos, A) | OA      | Astro     | IDH1 R132H/ND                         | +/ND                   | ND                  | ND              | ND           |
| Barresi et al., 2017 | 25                 | M   | Temporal       | —          | OA      | Astro     | IDH2 R172M/ND                         | +/ND                   | ND                  | ND              | ND           |
| Present case    | 78                  | F   | Temporoparietal| —          | AOA     | Astro     | IDH1 R132H/ND                         | +/ND                   | ND                  | ND              | ND           |

+ = 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.

### Correspondence
Reina Mizuno: Saitama International Medical Center, Saitama, Japan. m8sk11@yahoo.co.jp.