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Short communication

# A dual-genotype IDH-mutant infiltrating glioma, a real oligoastrocytoma in cerebral hemisphere

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ABSTRACT

Since the 5th edition of CNS WHO classification. the categorization of oligoastrocytoma has been discontinued. It is now understood that the majority of tumors previously identified as oligoastrocytomas can be reclassified into either astrocytomas or oligodendrogliomas based on molecular characteristics. In this report, we present a rare case of true oligoastrocytoma characterized by the coexistence of two distinct cell types within a single tumor mass, as evidenced in imaging findings and histological examination. The left frontal infiltrating glioma displayed calcification, and histological analysis revealed two morphologically distinct regions corresponding to oligodendroglioma and astrocytoma. Immunohistochemical and molecular pathology analyses, including IDH1, ATRX, TP53 mutations, H3K27me3 status, Tert promoter mutations, and 1p/19q co-deletion, are consistent with oligodendroglioma and astrocytoma, respectively. Post-surgery, the patient opted against radiotherapy and chemotherapy and showed no signs of recurrence at a 4-month follow-up, but was subsequently lost to follow-up. This case prompts questions about the prognosis and potential grading criteria for true oligoastrocytoma. It underscores the need for further case studies to potentially re-establish it as a distinct tumor type in future CNS WHO classifications.

## Introduction

In 1935, Cooper first identified the mixed oligoastrocytoma, establishing a foundation for its classification (Feiden and Feiden, 2008). The fourth edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System characterizes it as a diffuse neoplasm exhibiting cell morphologies akin to both WHO grade II oligodendroglioma and diffuse astrocytoma (Feiden and Feiden, 2008). Diagnostic criteria are primarily histological, requiring the presence of both oligodendroglioma and significant fibrillary, protoplasmic, or gemistocytic astrocytic components for a diagnosis. Rare or absent mitotic figures, along with potential calcification and microcystic degeneration, are noted; however, microvascular proliferation and necrosis are typically absent.

Despite its initial recognition, the 2021 5th edition of the CNS WHO classification no longer acknowledge oligoastrocytoma as a distinct entity. They suggest that, with molecular testing, most cases can be reclassified as either astrocytoma or oligodendroglioma. Although oligoastrocytoma is not classified as an independent tumor type or subtype, it has been described in both the 2016 revised 4th edition of WHO's mention of oligoastrocytoma, dual-genotype and the 2021 5th edition of WHO's mention of dual-genotype IDH-mutant glioma (Louis et al., 2016; Figarella et al., 2022). Dual-gene phenotype IDH-mutant gliomas can exhibit the morphology of oligodendroglioma, IDH mutation and 1p/19q co-deletion in some regions, while other regions exhibit astrocytoma morphology, IDH mutation, ATRX deletion, and TP53 mutation. It can also be manifested as a unified morphology of all tumor regions, ATRX deficiency, TP53 mutation, and 1p/19q co-deletion. This type of tumor is relatively rare, but it indicates that the decisive molecular changes in IDH mutant astrocytoma and oligodendroglioma are not absolutely mutually exclusive. Given the scarcity of cases and lack of a precise classification, it's advised to diagnose these tumors based on a combination of morphological and molecular characteristics, using 'NEC' (not elsewhere classified) for unambiguous identification.

Herein, we report a case of true oligoastrocytoma with two distinct histological components.

*Abbreviations:* CNS, Central Nervous System; WHO, World Health Organization; NEC, not elsewhere classified; MRI, Magnetic resonance imaging.

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## Clinical summary

A 41-year-old female presented to our hospital's neurosurgery department with a persistent headache lasting over five days, devoid of specific triggers, nausea, vomiting, or convulsive movements. A physical examination revealed no significant findings. Magnetic resonance imaging (MRI) identified a tumor in the left frontal lobe (Fig. 1A–D), which was fully excised. Post-surgical follow-up until June 2022 has shown no recurrence, indicating successful management of the condition.

## Pathological findings

Histological analysis of the surgical specimen demonstrated diffuse proliferation of tumor cells across the cerebral cortex, with significant calcification. Microscopic examination revealed two distinct morphological regions. Areas resembling astrocytoma displayed gemistocytic morphology with abundant cytoplasm staining red and displaced nuclei. Features such as microcystic or mucinous degeneration, visible nuclear division, and swollen vascular endothelium were noted, without evidence of microvascular proliferation or necrosis (Fig. 1E and 1G). Conversely, regions with oligodendroglioma morphology showed cells with a characteristic "fried egg" appearance, featuring clear cytoplasm and centrally located nuclei, alongside branching vascular proliferation in the interstitium but no microvascular proliferation or necrosis (Fig. 1F and 1H).

Both cells with different morphological regions express GFAP (MXB, MX047; 1:200) and Olig-2 (MXB, EP112), did not express Braf V600E (Roche, VE1) and H3K27M (MXB, RM192). Astrocytoma regions showed diffuse positivity for IDH1 R132H (MXB, MX031), ATRX (MXB, MX071; 1:200) loss, 50 % nuclear TP53 (MXB, MX008) positivity, retention of H3K27me3 (MXB, RM175), and a Ki-67 (MXB, MXR002) proliferation index of approximately 15 % (Fig. 2A-2E). Oligodendroglioma regions exhibited similar IDH1 R132H positivity, ATRX positivity, 5 % TP53 nuclear positivity, H3K27me3 loss, and a Ki-67 proliferation index of about 10 % (Fig. 2F-2J).

## Genetic findings

Molecular testing identified an IDH1 mutation (R132H mutant-type), wild-type IDH2, and BRAF V600E, with MGMT methylation and without CDKN2A homozygous deletion in both astrocytoma and oligodendroglioma components. The astrocytoma region lacked 1p/19q co-deletion and tert promoter mutation, which were present in the oligodendroglioma region. Next-generation sequencing of predominantly

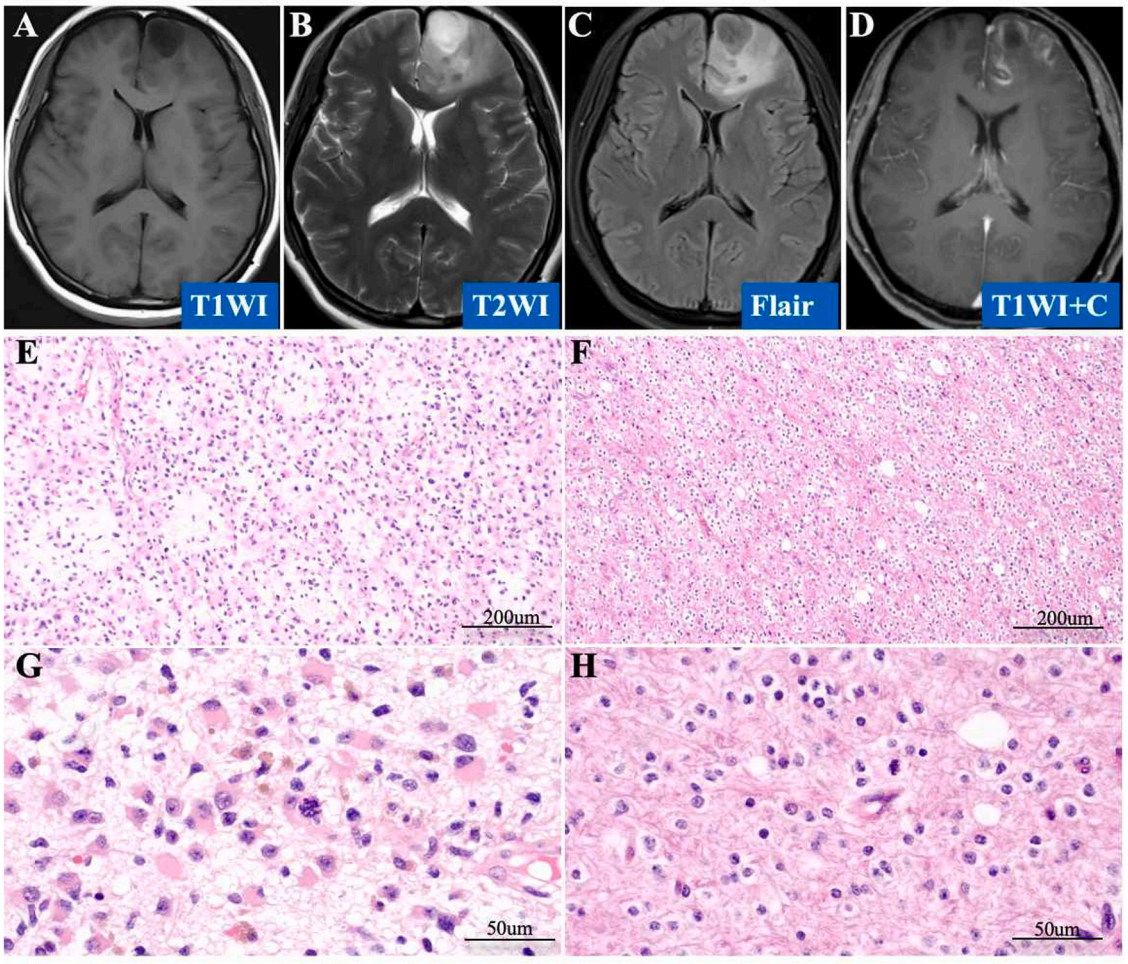


**Fig. 1.** Imaging and Histopathological Characteristics of a Dual-Genotype IDH-Mutant Infiltrating Glioma. A–D) Cross-sectional MRI reveals the tumor's radiological features in the left frontal lobe: T1-weighted images (T1WI) display extensive hypo-intense areas; T2-weighted images (T2WI) indicate hyperintense signals; FLAIR imaging shows mixed hypo-intense signals; and T1WI post-contrast (T1WI+C) highlights linear, mainly subcortical enhancement. E–H) Histological sections stained with hematoxylin and eosin differentiate two distinct morphological tumor regions. E and G: Astrocytoma regions are characterized by gemistocytic cells with abundant, red-staining cytoplasm and eccentric nuclei, alongside features such as interstitial microcystic or mucinous degeneration, evident nuclear division, and swollen vascular endothelium, without microvascular proliferation or necrosis. F and H: Oligodendroglioma regions show cells with a "fried egg" appearance, featuring clear cytoplasm and centrally located nuclei, visible nuclear division, and branching vascular proliferation in the interstitium, also without microvascular proliferation or necrosis.

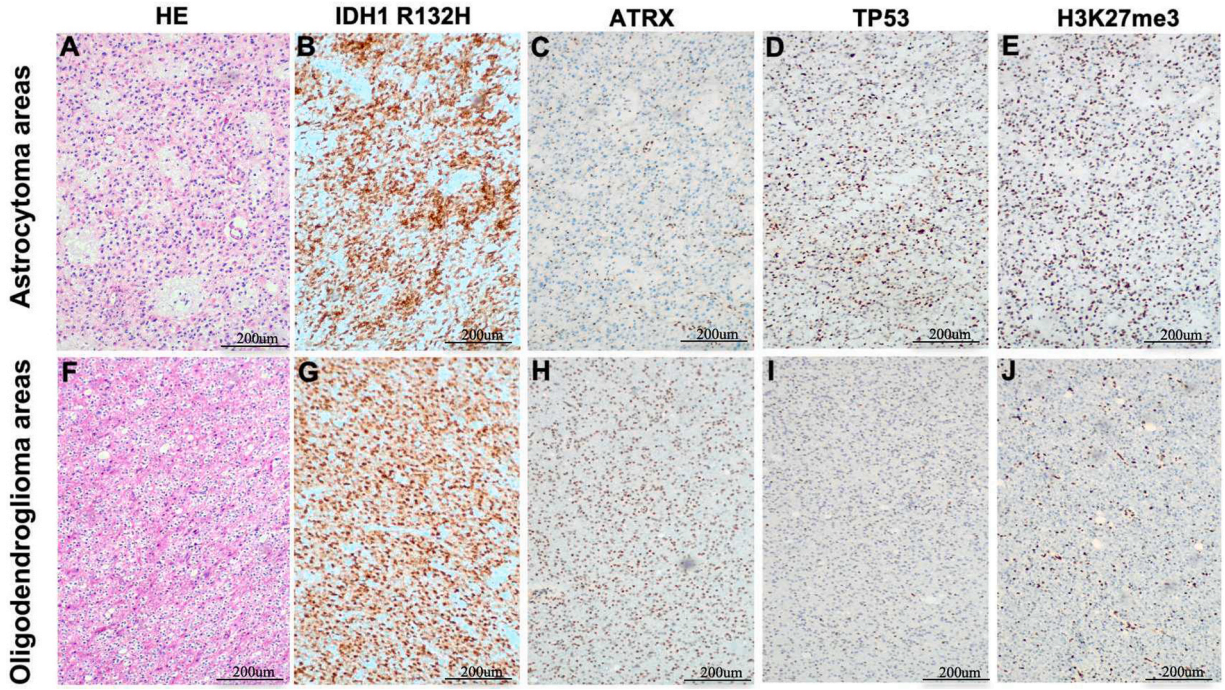


**Fig. 2.** Immunohistochemical Profiling of a Dual-Genotype IDH-Mutant Infiltrating Glioma. A–E) In astrocytoma regions, immunohistochemical analysis reveals IDH1 R132H mutation positivity, ATRX protein loss, TP53 positive in 50 % of nuclei, and predominant retention of H3K27me3 expression. F-J) In oligodendroglioma regions, findings include IDH1 R132H mutation positivity, preserved ATRX expression, TP53 positive in 5 % of nuclei, and a deficiency in H3K27me3 expression.

astrocytoma tissues detected 33 gene variations across 32 genes, including mutations in IDH1 (37.3 % frequency), ATRX (35.4 %), and TP53 (67.4 %), along with low-frequency tert promoter mutation (5.12 %) and 1p/19q co-deletions. The next-generation sequencing results indicate that there is also a small amount of oligodendroglioma components mixed in the tissues dominated by astrocytoma. Therefore, this case demonstrates true oligoastrocytoma in terms of morphology, immunophenotype, and molecular pathology. Distinct regions within these tumors have oligodendroglioma morphology and 1p/19q codeletion, while other regions have astrocytic morphology, ATRX loss, and TP53 mutations. Although the 5th edition of the CNS WHO Classification no longer recognizes oligoastrocytoma as a separate entity, it acknowledges tumors with this dual-genotype phenotype, recommending classification as dual-genotype IDH-mutant glioma, NEC.

## Discussion

The phenomenon of dual-genotype IDH-mutant oligoastrocytomas, featuring two distinct cell types within a single tumor mass, has garnered attention in recent literature. Nasrallah et al. (2020) and Mizuno et al. (2022) each reported cases that mirror our findings, with tumors composed of distinct astrocytoma and oligodendroglioma components and corresponding molecular signatures (Nasrallah et al., 2020; Mizuno et al., 2022). In 2024, Isabella and Sutherland *et al.* reported two new cases of true "oligoastrocytoma," while Sumanta and Das *et al.* reported one additional case. They also reviewed the previously documented cases (Sutherland et al., 2024; Das et al., 2024). These reports suggest such tumors may originate from two clonal cell populations, challenging previous notions of glioma pathogenesis.

Further complicating the classification, some studies propose that dual-genotype IDH-mutant gliomas might arise from a single clonal event, exhibiting two types of molecular alterations. For instance, Zepeda M CJ et al. identified gliomas with uniform morphology but harboring molecular features of both oligodendroglioma (IDH1/2 mutation and 1p/19q loss) and astrocytoma (ATRX and TP53 mutations) within what appears to be a single tumor clone (Zepeda-Mendoza et al., 2020). In fact, as early as 2017, Barresi V et al. reported a case of dual-genotype IDH-mutant oligoastrocytoma with two clones characterized by IDH2 gene mutation (Barresi et al., 2017). Therefore, they raised the question of whether oligodendrocytes should be removed as an independent tumor type at that time. As more cases are documented, the possibility of re-acknowledging dual-genotype IDH-mutant oligoastrocytoma as a distinct entity in future CNS WHO classifications is becoming increasingly plausible.

In summary, detailed histological examination, coupled with targeted immunohistochemical and molecular analyses, facilitates the identification of dual-genotype IDH-mutant oligoastrocytomas. Given the absence of specific grading criteria for this tumor type, it is prudent to assess astrocytoma and oligodendroglioma components according to their respective grading standards. This approach can guide clinicians in devising treatment strategies that reflect the most aggressive component of the tumor.

## Disclosure of ethical statements

Approval of the research protocol: N/A.
Informed Consent: Yes.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.
Research involving recombinant DNA: N/A.

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## CRediT authorship contribution statement

**Liu Jing:** Writing – original draft, Investigation, Data curation. **Liu Xia:** Writing – review & editing, Conceptualization. **Sun Yanhua:** Data curation. **Lin Fan:** Data curation.

## Declaration of Competing Interest

Authors declare no Conflict of Interests for this article.

## Authorship and Acknowledgement

Xia Liu and Jing Liu: conception and design of the work; Jing Liu: drafting and revising the work; Fan Lin and Yanhua Sun: analysis and interpretation of data for the work. All authors approve the final version of the manuscript to be published and agree to be accountable for all aspects of the work.

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