Journal of Neuropathology & Experimental Neurology, 2023, 1–3
https://doi.org/10.1093/jnen/nlad088
Letter to the Editor

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Synchronous contralateral low-grade oligodendroglioma and high-grade IDH-mutant astrocytoma

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To the Editor:

Multicentric gliomas are rare and there has been much debate about their origin. New advents in molecular testing and more rigorous reporting of cases in the literature provide us with an opportunity to more completely elucidate the pathogenesis of these rare tumors. Even rarer are multicentric gliomas with mixed high and low grades, with only 4 cases being reported in the literature (1).

Herein, we report the case of a 39-year-old man who presented with a focal right-hand tonic-clonic seizure that progressed to involve the whole body. There was no significant past medical history including the absence of stigmata of Ollier disease or Maffucci syndrome. Initial magnetic resonance imaging (MRI) showed 2 hyperintense non-enhancing T2 fluid-attenuated inversion recovery (FLAIR) infiltrative lesions, 1 in the left parietal lobe and the other in the right insula (Fig. 1). Functional MRI revealed sparing of language and motor areas by the lesions and left hemisphere language dominance. Tractography showed a slight deviation of the left cortical spinal tract and superior longitudinal fascicle by the left parietal lesion. The left lesion, unlike the contralateral lesion, also showed areas of increased perfusion on the arterial spin-labeling sequence suggesting higher-grade neoplasm. Although both lesions were abutting eloquent areas, the left parietal one was in need of a more urgent intervention. The patient underwent resection of the left parietal lesion and made a full recovery after transient post-operative right upper extremity paresthesia. An image-guided stereotactic biopsy was obtained of the right insular lesion followed by consolidation radiation therapy to the left parietal lesion (volumetric modulated arc therapy, 59.40 Gy of total dose in over 33 fractions). Lastly, the patient underwent a resection for his right insular lesion followed by 12 more cycles of adjuvant chemotherapy with temozolomide, both of which he tolerated well.

Upon neuropathological review, the left parietal brain mass demonstrated an infiltrating glioma with mild nuclear atypia (Fig. 2A). Necrosis and microvascular proliferation were not identified; however, the tumor had significant mitotic activity. Immunohistochemical staining demonstrated the neoplastic cells to be positive for GFAP, Olig2, and IDH1(R132H) mutation. ATRX expression was lost. Approximately 40% of the tumor cells showed strong p53 protein expression. Mismatch repair enzymes including MSH2, MLH1, MSH6, and PMS2 showed preserved expression. A formally quantified Ki-67 proliferation index was 7.1%. Cytogenetic evaluation of the tumor revealed a copy neural loss of heterozygosity of 17p suggesting biallelic *TP53* gene mutation, a 300-kb loss on Xq21.1 resulting in the deletion of the 5′ end of the *ATRX* gene, and loss of 9p resulting in loss of 1 copy of the *CDKN2A* gene. Other copy number alterations include losses on 4q, 5q, and 11p, and a gain of 10p. 1p/19q codeletion was not detected.

Histology of the right insular mass was consistent with an infiltrating glioma with uniform nuclei and perinuclear clearing (Fig. 2B). There was no evidence of mitotic activity, microvascular proliferation, or necrosis. Immunohistochemistry showed the neoplastic cells to be positive for GFAP, Olig2, and IDH1(R132H) mutation. ATRX expression was retained. Less than 10% of cells had strong p53 protein expression. Mismatch repair enzymes including MSH2, MLH1, MSH6, and PMS2 showed preserved expression. A formally quantified Ki-67 proliferation index was 5.1%. Cytogenetic evaluation of the tumor revealed 1p/19q codeletion. In addition, the neoplastic cells displayed a gain of 17q and a loss of the distal half of 4p and most of 4q.

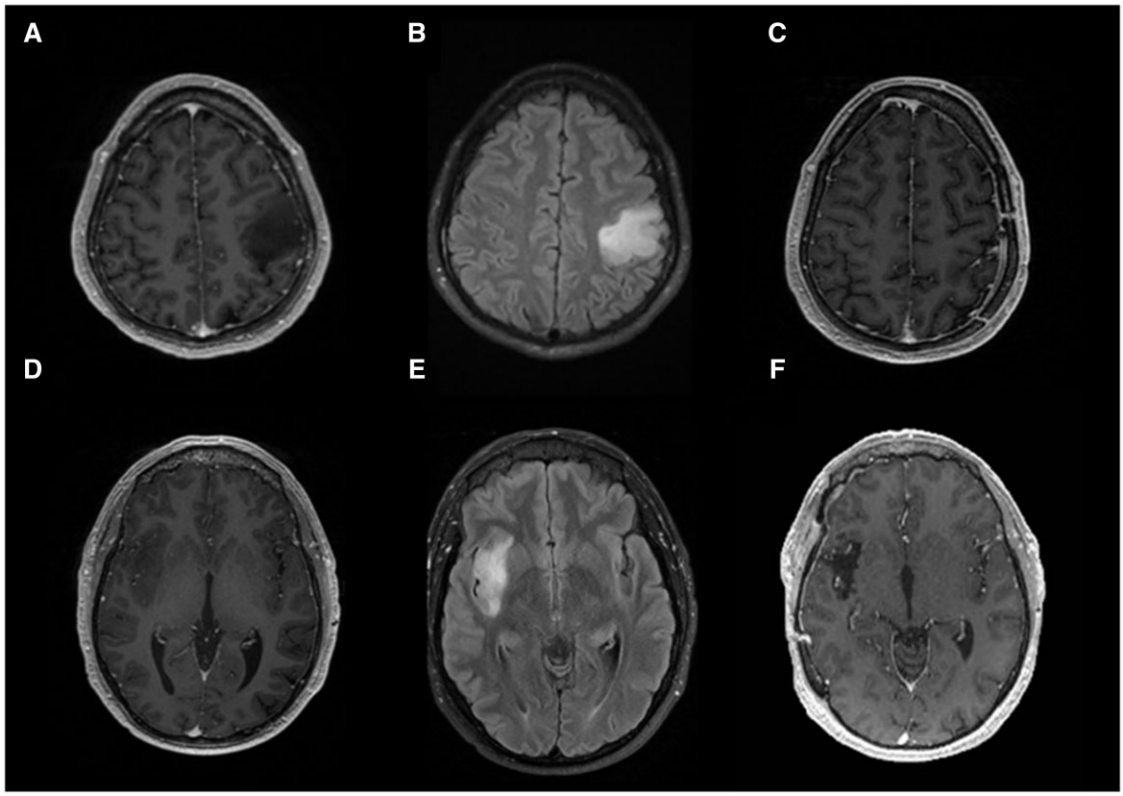

Figure 1. Magnetic resonance images of the multicentric gliomas. **(A)** Axial T1 post-contrast image of the left parietal tumor immediately pre-op. **(B)** Axial T2 FLAIR image of the left parietal tumor immediately pre-op. **(C)** Axial T1 post-contrast image of the left parietal tumor 4 months post-op. **(D)** Axial T1 post-contrast image of the right insular tumor immediately pre-op. **(E)** Axial T2 FLAIR image of the right insular tumor immediately pre-op. **(F)** Axial T1 post-contrast image of the right insular tumor 4 months post-op.

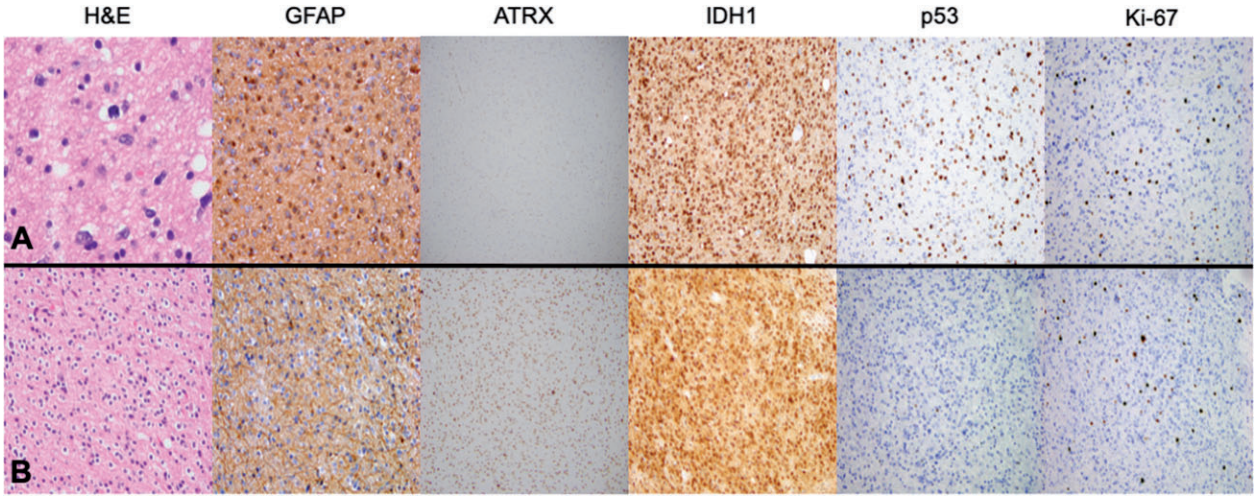

Figure 2. Histology of the patient's astrocytoma **(A)** and oligodendroglioma **(B)**. **(A)** Hematoxylin and eosin (H&E) stain shows cellular atypia and a mitotic figure. GFAP stain shows positive expression in neoplastic cells. ATRX stain reveals loss of nuclear expression. IDH1 (R132H) stain shows the presence of mutant protein in neoplastic cells. p53 stain demonstrates mutant staining pattern. Ki-67 stain; the proliferative index is 7.1%. **(B)** H&E stain shows cellular morphology with perinuclear clearing. GFAP stain shows positive expression in neoplastic cells. ATRX stain demonstrates that expression is retained with strong nuclear positivity. IDH1 (R132H) stain shows the presence of mutant protein in neoplastic cells. p53 stain demonstrates a wild-type staining pattern. Ki-67 stain; the proliferative index is 5.1%.

The IDH1(R132H) mutant protein was the link between the patient's tumors. Notably, the *IDH1* mutation associated with this protein has been reported to be present in about 80% of anaplastic astrocytomas and 60–80% of oligodendrogliomas in the literature (2). This commonality supports the notion that *IDH1* mutation is the driver of tumorigenesis resulting in both an IDH-mutant oligodendroglioma with 1p/19q codeletion and *CIC/FUBP1* mutations as well as an IDH-mutant astrocytoma with *ATRX/TP53* mutations (3, 4). This assumption of a novel progenitor is further supported by the absence of the stigmata typical of syndromic IDH mutation syndromes such as Ollier disease or Maffucci syndrome as well as preservation of the mismatch repair machinery associated with Lynch syndrome.

There have been reports of histologically and molecularly defined biphasic oligodendroglial and IDH-mutant astrocytic diffuse gliomas (5–7). There are also cases with mixed molecular and histologic findings such as a clonal population with overlapping 1p19q codeletion, *IDH* mutation, *ATRX* mutation, and *p53* mutations (8–10). There is a spectrum of heterogeneity amongst these tumors ranging from 1 clone having characteristics of both subtypes, to 1 tumor having distinct morphological regions of the 2 subtypes, to 1 patient with multicentric gliomas of each subtype as is the case with our patient. Interestingly, 7 out of 8 reported tumors with available molecular analysis data had the *IDH1(R132H)* mutation. The aggregate of these tumors (loosely defined by IDH mutation status) may represent a group of related tumors from a shared progenitor.

Our patient's concurrent contralateral tumors may provide insight into the pathogenesis of multicentric gliomas. There have been many proposed theories for the pathogenesis of these tumors, with the stem cell origin theory seeming to have the most support (1, 11, 12). A common cellular ancestor in one of the neural stem cell pools such as the subventricular zone and subgranular zone might have developed an initial mutation then the subsequent progenitor cells could have migrated to the location of the distinct tumors and acquired their respective subsequent mutations. In our patient's case, the initial mutation might have been the *IDH1(R132H)* mutation or another mutation that predisposes the progenitors to acquire the rest of the mutations. Jenkins et al. found that single nucleotide polymorphisms in the 8q24 chromosome region may be associated with *IDH* mutations (1).

To our knowledge, our patient's tumors were the first reported instance of a multicentric contralateral low-grade oligodendroglioma and high-grade IDH-mutated anaplastic astrocytoma in the literature. This case also provides support for a single-cell progenitor origin theory for multicentric gliomas. Further understanding of the pathogenesis of these tumors would significantly advance our understanding of gliomas at large and provide subsequent avenues for therapy development.

CONFLICT OF INTEREST

The authors have no duality or conflicts of interest to declare.

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