A novel isocitrate dehydrogenase 1 G131D mutation in glioblastoma

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To the Editor: A 68-year-old man presented with a 2-month aphasia. Magnetic resonance imaging scan revealed an abnormal signal in the left temporal lobe with heterogenous enhancement [Figure 1A]. Glioma was considered, and the patient underwent total tumor resection. Microscopic examination of the resected tumor showed a high-grade glial tumor with pleomorphic cells, elevated mitotic activity, microvascular proliferation, and pseudopalisading necrosis [Figure 1B and 1C]. Part of the lesion contained round cells with perinuclear halos. Tumor cells also grew around neurons, forming secondary structures [Figure 1D]. On immunohistochemical investigation, the tumor cells expressed glial fibrillary acidic protein and oligodendrocyte transcription factor 2 [Figure 1E]. There was only focal positivity for p53 protein (about 5% of tumor cells), while alpha-thalassemia/mental retardation syndrome X-linked protein expression was positive. The tumor cells were negative for isocitrate dehydrogenase 1 (IDH1) R132H, NeuN, and H3 K27M. The Ki-67 index was approximately 20%. Next-generation sequencing analysis (Simcere Diagnostics, Nanjing, China) was performed on the formalin-fixed paraffin-embedded tumor tissues. The results showed a heterozygous IDH1 CGT>AGT G131D mutation, epidermal growth factor receptor (*EGFR*) amplification, cyclin-dependent kinase inhibitors 2A/B (*CDKN2A/B)* deletion, loss of chromosome 10 as well as 1p loss of heterozygosity [Figure 1F and 1G], while chromosome 19q was intact. Mutations of *IDH2, H3F3A, HIST1H3B, BRAF,* and *TERT* promoters were absent. *IDH1* G131D mutation was confirmed by sanger sequencing [Figure 1H]. The presence of 1p /19q [Figure 1I and 1J] and *EGFR* amplification [Figure 1K] was confirmed via fluorescence *in situ* hybridization (Guangzhou LBP Pharmaceutical Technology Co. Ltd, China). The tumor was finally diagnosed as glioblastoma, *IDH*-mutant (*IDH1* G131D mutation), World Health Organization grade IV. Post-operatively, the patient received combination of radiotherapy and chemotherapy (temozolomide, 140 mg, qd). No recurrence or progression was observed from a follow-up of 2 months. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (No. [2019]004) and with the 1964 *Helsinki Declaration* and its later amendments or comparable ethical standards. The authors have obtained the appropriate patient's consent form.

IDH mutations are known to be a favorable prognostic factor in patients with diffuse gliomas.[1] Mutations in the *IDH1* gene are heterozygous and virtually always affect only a single residue (arginine 132) which is replaced by histidine in approximately 90% of tumors (c.395G>A resulting in *IDH1* R132H).[2] Although some new *IDH1* mutations have been reported, they mostly also change the R132 residue.[3] Here, we present a case of *IDH1* G131D mutant glioblastoma diagnosed based on histopathological and molecular genetic findings. To the best of our knowledge, the *IDH1* G131D mutation has not been reported in gliomas to date. Although there were some oligodendroglioma-like cells in the present case, chromosome 19q was intact and there was no mutation of the *TERT* promoter. Moreover, the tumor had an *EGFR* amplification, *CDKN2A/B* deletion, and loss of chromosome 10. Therefore, these results support the integrated diagnosis of glioblastoma or "Astrocytoma, *IDH*-mutant, grade 4."[4,5] Our findings suggest that the *IDH1* G131D mutation may also be a pathogenic event in the gliomas mutagenesis cascade leading to glioma, which expands the spectrum of known pathogenic *IDH* mutations. Given that *IDH1* mutations are often associated with less aggressive behavior and favorable outcomes in brain tumors in adults, the effect of this novel *IDH1* G131D mutation on prognosis in the present case requires longer follow-up.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001172

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Chinese Medical Journal 2021;134(4)
Received: 25-07-2020 **Edited by:** Peng Lyu

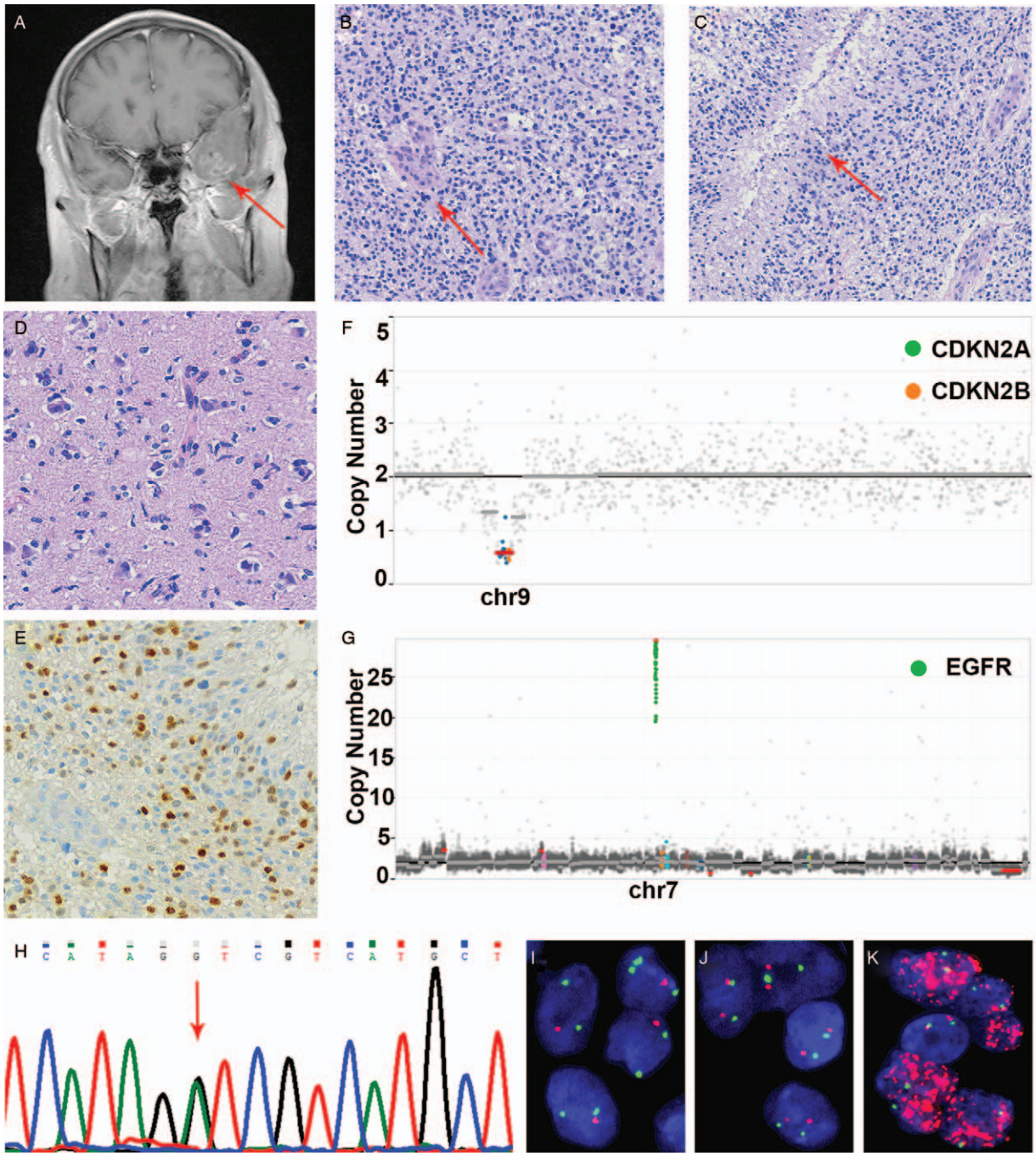

Figure 1: Radiologic and pathologic features of isocitrate dehydrogenase 1 (*IDH1)* G131D mutant-glioblastoma. (A) T1-weighted, post-contrast imaging shows a heterogenous-enhancing mass in the left temporal lobe (arrow). (B–D) Histologic features showed a high-grade glial tumor including round cells with perinuclear halos microvascular proliferation (arrow) (B, original magnification ×200), necrosis (arrow) (C, original magnification ×200), and some tumor cells growing around neurons (D, original magnification ×400). (E) Immunohistochemical stain showed the tumor cells were positive for oligodendrocyte transcription factor 2 (Olig-2) (original magnification, ×400). (F and G) Next-generation sequencing revealed cyclin-dependent kinase inhibitors 2A/B (*CDKN2A/B)* deletion (F) and epidermal growth factor receptor (*EGFR)* amplification (G). (H) Sanger sequencing of IDH1 exon 4 demonstrated IDH1 (c.392G-A, p.G131D) mutation (arrow). (I–K) 1p loss of heterozygosity (LOH) (I), 19q intact (J), and *EGFR* amplification (K) were confirmed with fluorescence *in situ* hybridization (FISH, original magnification, ×1000).

Funding

This work was supported by the Beijing Excellent Talents Training Project, China (No. 201600026833ZK07) and the Beijing Higher Education Young Elite Teacher Project, China (No. CIT&TCD201904091).

Conflicts of interest

None.

References

1. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al*. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131:803–820. doi: 10.1007/s00401-016-1545-1.
2. Wang LM, Li Z, Piao YS, Cai YN, Zhang LY, Ge HJ, *et al*. Clinico-neuropathological features of isocitrate dehydrogenase 2 gene mutations in lower-grade gliomas. Chin Med J 2019;132:2920–2926. doi: 10.1097/CM9.0000000000000565.

3. Visani M, Acquaviva G, Marucci G, Paccapelo A, Mura A, Franceschi E, *et al*. Non-canonical IDH1 and IDH2 mutations: a clonal and relevant event in an Italian cohort of gliomas classified according to the 2016 World Health Organization (WHO) criteria. J Neurooncol 2017;135:245–254. doi: 10.1007/s11060-017-2571-0.
4. Brat DJ, Aldape K, Colman H, Holland EC, Louis DN, Jenkins RB, *et al*. cIMPACT-NOW update 3: recommended diagnostic criteria for "diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". Acta Neuropathol 2018;136:805–810. doi: 10.1007/s00401-018-1913-0.
5. Brat DJ, Aldape K, Colman H, Figrarella-Branger D, Fuller GN, Giannini C, *et al*. cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH-mutant astrocytomas. Acta Neuropathol 2020;139:603–608. doi: 10.1007/s00401-020-02127-9.

How to cite this article: Wang LM, Song C, Li YX, Zhang XD, Ji YH, Wen WJ. A novel isocitrate dehydrogenase 1 G131D mutation in glioblastoma. Chin Med J 2021;134:486–488. doi: 10.1097/CM9.0000000000001172