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Letter to the Editor

Major response to temozolomide as first-line treatment for newly-diagnosed *DDR2*-mutated glioblastoma: A case report

1. Case report

A 58-year old patient, without significant medical history, had a supratentorial intracerebral lesion revealed by temporal seizure. Cerebral magnetic resonance imaging (MRI) identified a large, heterogeneous contrast-enhanced lesion in the left frontotemporal region. The lesion extended to the hippocampus and both thalami in T2-weighted FLAIR sequence. A thoraco-abdomino-pelvic computed tomography was performed and found no suspicious lesion, particularly in the pulmonary parenchyma. Open surgical biopsy was performed in the temporal region. Glioblastoma multiforme (GBM) was diagnosed according to the 2016 WHO classification, Fig. 1b. Next-generation sequencing was performed using a custom panel. One missense mutation on *Discoidin Domain Receptor 2* (*DDR2*) was identified: c.1012C > T (p.Leu338Phe) with a variant allele frequency of 33.4%. This variant induces a modification in the extracellular domain of the DDR2 RTK (Fig. 1a) and is considered as a probably damaging (Polyphen2®) missense mutation. No mutation on *H3F3A*, *HIST1H3B*, *BRAF*, *IDH1/2* or *FGFR2/3* was identified. Pyrosequencing identified *MGMT* promoter (*MGMT*p) methylation (mean 28% of tumor cells). Immunohistochemistry detected expression of p53 protein in 60% of tumor cells.

3D-conformational radiotherapy (RT) was not performed regarding the risk of severe neurocognitive impairment due to the involvement of both thalami. Temozolomide (TMZ) was prescribed as first-line treatment. TMZ dose was set at 125 mg/m^2 due to occurrence of TMZ-induced hematological toxicities at first cycle. At 3 months a drastic response on the contrast-enhanced lesion was observed while the T2-weighted FLAIR lesion remained stable (Fig. 1c). The 6-month MRI exhibited a new 16 mm contrast-enhanced lesion in the left medial temporal lobe. This relapse was managed by hypofractionated stereotactic RT (36 Gray in six fractions) and TMZ was continued for a total duration of 12 cycles (11 months). Along the treatment schedule, corticosteroids were reduced and the patient remained clinically stable without quality of life deterioration. At 11 months a new lesion in the left frontal lobe was observed. The patient received a second-line treatment by lomustine and bevacizumab. Unfortunately, the patient developed leptomeningeal involvement after 5 months of treatment.

2. Discussion

This case is the first reported *DDR2*-mutated GBM. The initial presentation with the involvement of two lobes and both thalami is unusual in GBM. Binding collagen activates *DDR2* expression. The overexpression of *DDR2* plays a role in tumor cell migration [1] and is associated with metastatic/nodal dissemination in several cancers. Interestingly, *DDR2* driver mutations may contribute to the development of central nervous system metastases in non-small-cell lung cancer [2]. Somatic mutations occur on the whole gene, both in and out of the two coding regions for discoidin domain and protein kinase domain. The majority of them confer gain-of-function and oncogenic phenotype. The impact of the p.L338F variant on protein function is unknown. Collagen architecture contributes to tumor cells proliferation in the GBM xenografts mouse model [3]. Regarding our case, the implication of altered DDR2 protein on initial presentation and therapeutic response remains speculative. We hypothesize that the p.L338F mutation probably contributed to tumor invasion in the cerebral parenchyma by enhancing the interaction between extracellular matrix and tumor cells. Moreover, the drastic response to TMZ monotherapy as first-line treatment is exceptional, even in methylated *MGMT*p GBM. TMZ may have stopped tumor proliferation and induced tumor cell apoptosis by acting on the microenvironment.

The role of DDR2 protein on high-grade glioma growth and proliferation, as well as its incidence and survival impact should be explored in future studies; especially considering that in lung cancer the theranostic impact remains debatable. Nevertheless, *DDR2* mutations could be sought in GBM with atypical large initial extension.

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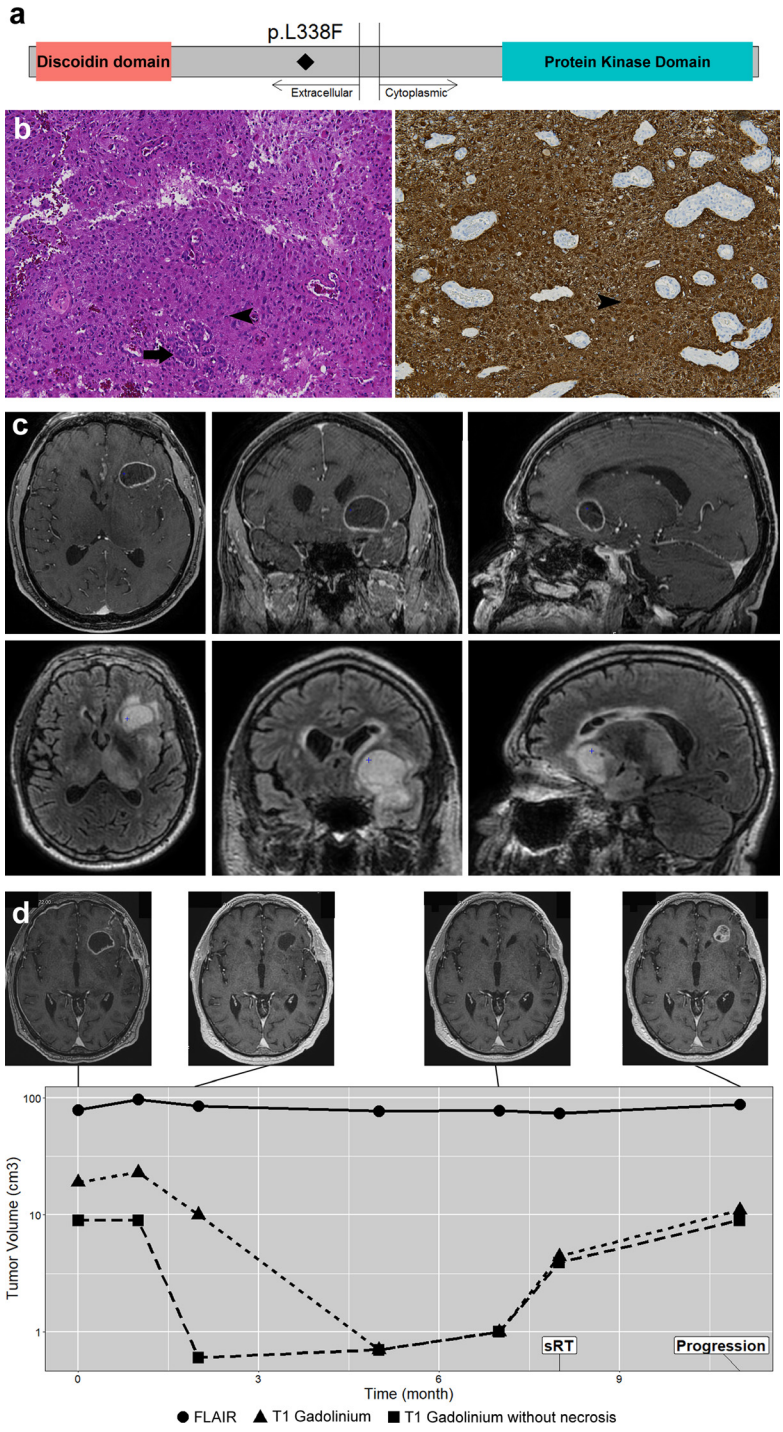

Fig. 1 – a: Schematic representation of the DDR2 protein with its two active regions: extracellular discoidin domain and intracellular protein kinase domain. After binding collagen, DDR2 autophosphorylation leads to signal transduction and contributes to interaction between the cell and its microenvironment. The somatic mutation c.1012C > T induces the change of a leucine to a phenylalanine in the extracellular domain; b: The histological and immunohistochemical presentation is common of GBM with atypical glial cell proliferation, mitosis (black arrowhead) and endotheliocapillary proliferation (black arrow) in the left picture (hemalum-eosin staining × 100); and GFAP positive cells with cytoplasmic staining (black arrowhead) in the right picture; c: Initial morphological MRI presentation (T0) in three dimensions, from left to right axial, frontal and sagittal; for each dimension, T1-weighted with gadolinium (upper image) and FLAIR sequences (lower image) are presented; d: Evolution of tumor volume along treatment schedule: FLAIR volume (filled line with dots) remained stable whereas T1 tumor volume including necrosis (dotted line with triangles) rapidly decreased after TMZ initiation, especially when ignoring the non-gadolinium enhancing component (dotted line with squares). sRT: stereotactic radiotherapy.

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Disclosure of interest

The authors declare that they have no competing interest.

Authors' contributions

KEH wrote the manuscript and collected the data.
FM performed histological and immunochemistry analyses.
AL performed molecular biology analyses.
MF contributed to the patient's treatment and follow-up.
NM performed imagery analysis.
NM, FM, KEH and MF contributed to figure conception.
MF supervised the redaction.
All authors reviewed and contributed to the final version of the manuscript.

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