



## Malignant Transformation of a Rosette-Forming Glioneuronal Tumor with IDH1 Mutation: A Case Report and Literature Review

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### Key words

- Glioblastoma IDH mutant
- IDH 1 mutation
- Malignant transformation
- RGNT

### Abbreviations and Acronyms

**IDH 1:** Isocitrate dehydrogenase 1

**MRI:** Magnetic resonance imaging

**RGNT:** Rosette-forming glioneuronal tumor

**WHO:** World Health Organization

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Citation: *World Neurosurg.* X (2019) 2:100006.  
<https://doi.org/10.1016/j.wnsx.2018.100006>

Journal homepage: [www.journals.elsevier.com/world-neurosurgery-x](http://www.journals.elsevier.com/world-neurosurgery-x)

Available online: [www.sciencedirect.com](http://www.sciencedirect.com)

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### INTRODUCTION

Rosette-forming glioneuronal tumor (RGNT) is a tumor with neuronal and glial components.<sup>1</sup> It is a rare World Health Organization (WHO) grade I tumor, associated with a favorable clinical outcome. Owing to its rarity, the clinical progression and malignant potential of this tumor is not well established.<sup>2,3</sup>

Nonetheless, there had been several case reports describing an aggressive clinical course with unfavorable outcomes, but no reports of RGNT malignant transformation to date.<sup>4-6</sup> Here, we report a unique case of a 42-year-old man who was diagnosed with RGNT of the fourth ventricle, which progressed to an isocitrate dehydrogenase (IDH)-mutant glioblastoma (WHO grade 4) 6 years later.

### CASE REPORT

A 42-year-old man presented in 2010 with symptoms of unsteady gait and headache for 2 months. Physical examination revealed

■ **BACKGROUND:** Rosette-forming glioneuronal tumor (World Health Organization grade I) is considered as a benign tumor with very low potential for progression. The potential for malignant transformation of this tumor is not known and has never been reported before in literature.

■ **CASE DESCRIPTION:** We report a 42-year-old man, diagnosed with rosette-forming glioneuronal tumor of the fourth ventricle with a positive isocitrate dehydrogenase 1 mutation, progressed to glioblastoma after 6 years from diagnosis. We discuss the clinical history, radiological findings, and histopathological characteristic with immunohistochemistry findings observed in this unique case.

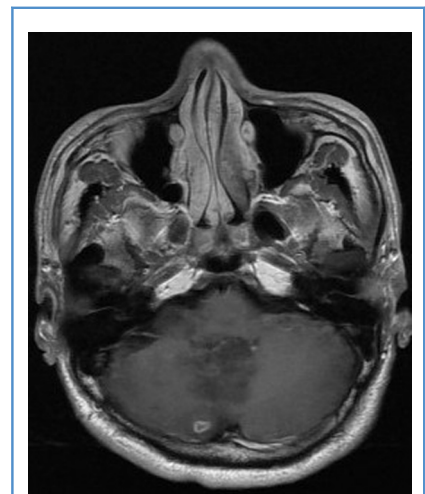
■ **CONCLUSIONS:** Despite being acceptable as benign, based on our observations in this case, there is a potential for malignant transformation of rosette-forming glioneuronal tumor. The role of isocitrate dehydrogenase 1 mutation leading to malignant transformation could not be established as our finding is novel and further prospective studies are required to prove this association.

significant ataxia and right-sided cerebellar signs. Magnetic resonance imaging (MRI) of brain revealed a midline, patchy, and minimally enhancing tumor in the vermis with extension into the right cerebellar hemisphere and fourth ventricle associated with hydrocephalus (Figure 1). With an initial impression of a low-grade glioma, the tumor was partially resected and an external ventricular drain inserted for hydrocephalus.

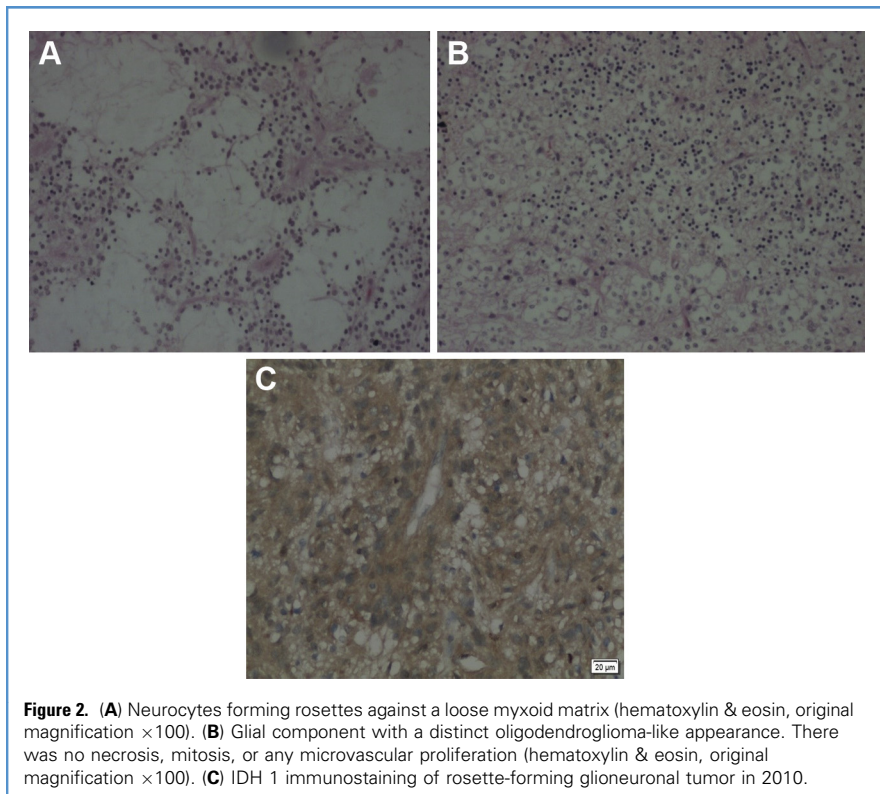
The friable whitish tumor tissue biopsied was submitted entirely for routine processing and histopathology examination. The result showed normal cerebellar tissues infiltrated by a biphasic neurocytic and glial tumor. The neurocytes were uniform and formed rosettes and perivascular pseudorosettes (Figure 2A). In other areas, oligodendroglia-like cells and occasional ganglion cells were observed. There was no necrosis, mitosis, or microvascular proliferation (Figure 2B). Immunohistochemistry showed positivity for glial fibrillary acidic protein, synaptophysin, and IDH 1, whilst the Ki67 proliferative index was less than 1% (Figure 2C). Together, a diagnosis of RGNT was made.

Postoperatively, his symptoms and signs resolved and he resumed his work

shortly thereafter. He was not given adjuvant chemotherapy or radiotherapy. For the next 2 years, he was closely monitored with serial brain MRIs, which showed a



**Figure 1.** Initial magnetic resonance imaging in 2010-axial post-contrast T1-weighted images showing a small enhancing lesion with much larger areas of hypointensity along the cerebellar vermis and fourth ventricle.

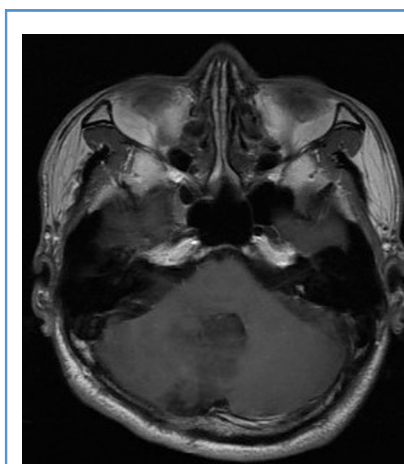


stable residual tumor over cerebellar vermis (Figures 3 and 4). He was lost to follow-up until he presented again in 2016, approximately 6 years from first presentation, with severe giddiness and diplopia. The MRI of brain revealed a large ( $4.7 \times 4.0 \times 3.8$  cm) heterogeneous solid mass over cerebellar vermis, with avid uptake of gadolinium contrast and areas of central necrosis within (Figure 5). An urgent posterior fossa craniotomy and excision of a vascular tumor with extensive adjacent cerebellar parenchymal invasion was performed. Postoperative MRI of the brain showed gross total tumor resection (Figure 6).

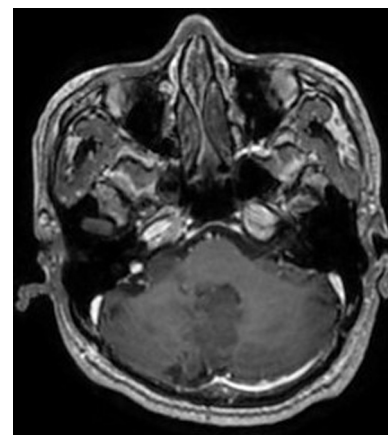
Microscopy of the soft, whitish hemorrhagic tumor tissues showed a polymorphous tumor composed of moderately to markedly pleomorphic glial cells with increased mitosis (Figure 7A), areas of geographic necrosis (Figure 7B), and foci of microvascular proliferation (Figure 7C). Scattered gemistocytes were also seen. The IDH 1 immunostaining was positive (Figure 7D). Based on these findings, a diagnosis of glioblastoma, IDH mutant (WHO grade 4), was made.

## DISCUSSION

Approximately 155 RGNT cases had been reported in the literature since its inception in 2007, but these were mostly on clinico-radiological findings, salient histopathological



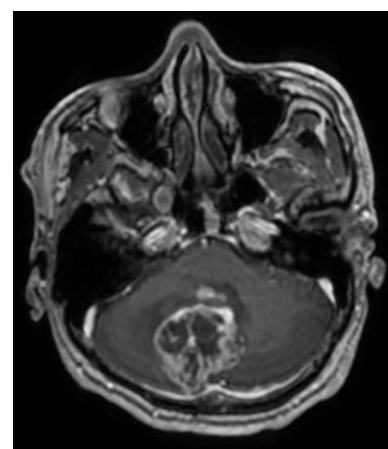
**Figure 3.** Magnetic resonance imaging in 2011—showing residual tumor postoperative period at 6 months.



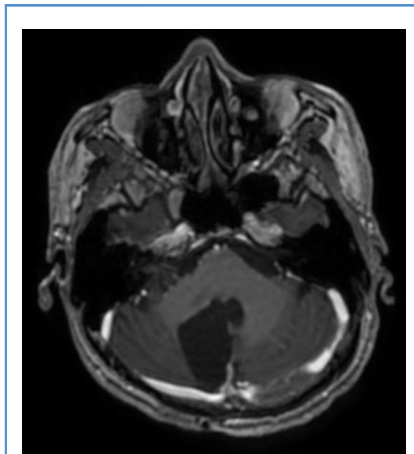
**Figure 4.** Magnetic resonance imaging in 2012—unchanged appearance of residual tumor at 2 years after surgery.

characteristics, and genetic mutations.<sup>3,7-9</sup> As far as we know, there is no description of malignant transformation from RGNT of the fourth ventricle to glioblastoma.

Our case initially presented with ataxia and headache, common but nonspecific symptoms for RGNT. The radiological findings were consistent with the diagnosis.<sup>3</sup> A partial resection was performed leaving behind residual tumor, and although no adjuvant therapy was given, the MRI of the brain surveillance for the first 2 postoperative years did not show any



**Figure 5.** Magnetic resonance imaging in 2016—on recurrence of symptoms, T1-weighted post-contrast images showing an enhancing mass with central necrosis.



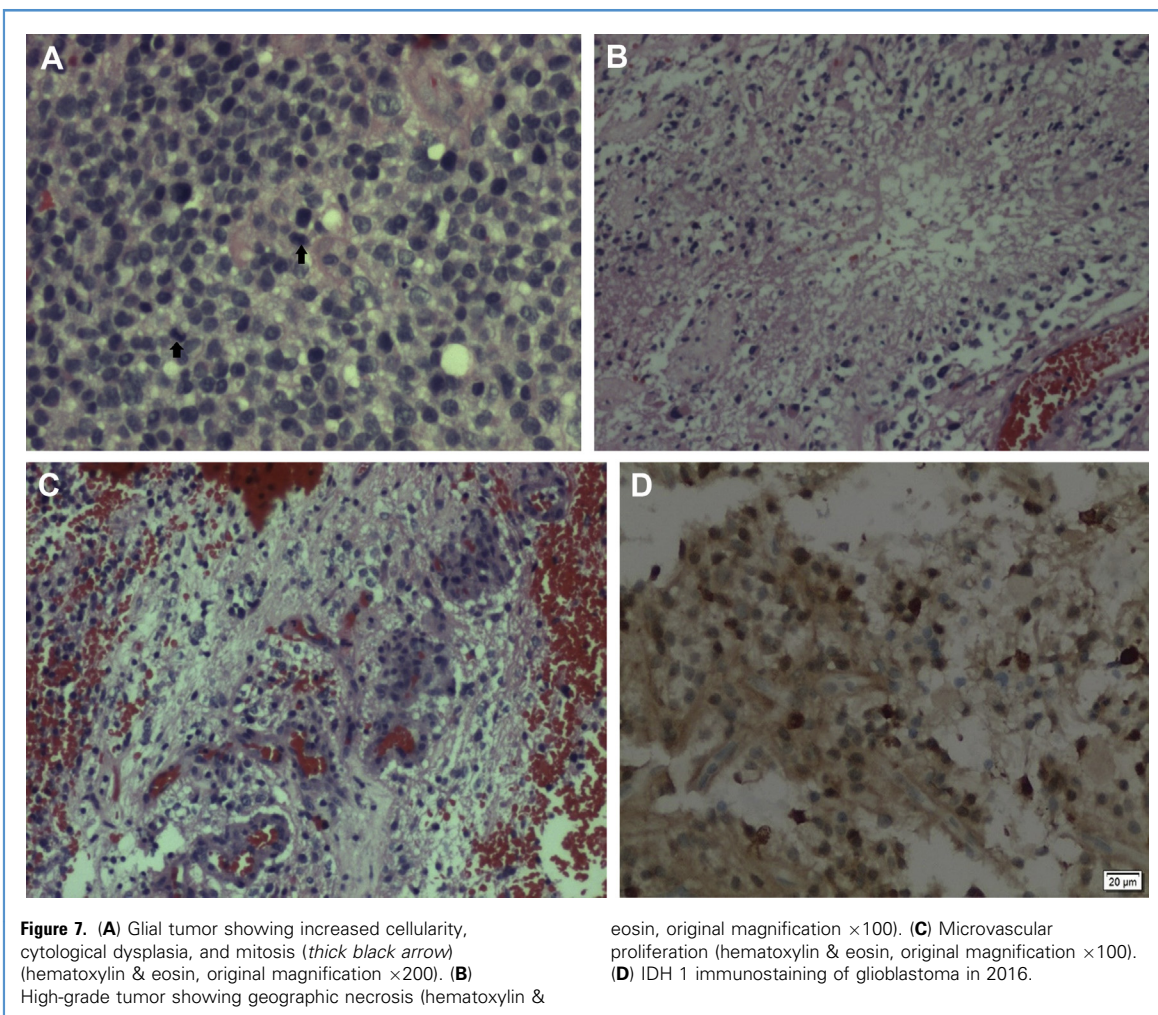
**Figure 6.** Postoperative magnetic resonance imaging after gross total resection in 2016.

radiological progression. The longest follow-up for RGNT remains at 13.5 years (median of 1.2 years) as reported by a meta-

analysis by Schlamann et al<sup>2</sup> indicated a favorable prognosis. The authors concluded that the overall survival of RGNT stands at 100% at 1.5 years, with gross total resection being the primary mode of treatment without adjuvant chemotherapy or radiotherapy.<sup>2</sup> Thus, the standard of care for nondisseminated RGNT is still gross total resection followed by expectant management with no adjuvant therapy.<sup>2,3,7-10</sup> Our case did not receive gross total resection as the initial intent of the first surgery was to obtain a tissue diagnosis. Adjuvant therapy was not given as RGNT is a low-grade tumor, and subsequent MRI findings did not show progression until approximately 6 years after initial presentation.

RGNT progression is rare but literature suggested that this occurred more frequently in the pediatric population (5 of 8 cases published) than adults.<sup>11</sup> Morris

et al<sup>11</sup> inferred that RGNT tumorigenesis in pediatrics may be distinct from that of adult population, but this association was not well established because of the small study population. The largest literature review of RGNT to date, an analysis of 155 reported cases in 2017, found that inadequate resection and solid tumor had higher risks of progression.<sup>3</sup> However, it is unknown if these risk factors do apply for malignant transformation of RGNT as well. Infrequently, there are sporadic reports about RGNTs with an aggressive course (with leptomeningeal spread or intraventricular dissemination and progression of symptoms), but the causes were not well established.<sup>4-6</sup> Matyja et al<sup>12</sup> reported an unusual case of RGNT with advanced microproliferation without marked nuclear atypia. But the authors concluded that these findings were of unknown significance.<sup>12</sup> To the best of



**Figure 7.** (A) Glioma showing increased cellularity, cytological dysplasia, and mitosis (*thick black arrow*) (hematoxylin & eosin, original magnification  $\times 200$ ). (B) High-grade tumor showing geographic necrosis (hematoxylin &

eosin, original magnification  $\times 100$ ). (C) Microvascular proliferation (hematoxylin & eosin, original magnification  $\times 100$ ). (D) IDH 1 immunostaining of glioblastoma in 2016.

our knowledge, definite biopsy-proven, malignant transformation of RGNT to glioblastoma has not been described in the literature before, and this case may be represented as the first reported case.

IDH 1 mutation is understood as an early genetic alteration that ultimately predispose to formation of diffuse gliomas in the central nervous system.<sup>13-15</sup> The first description of IDH 1 mutation in RGNT was by Solis et al<sup>7</sup> in a case of pineal region RGNT; however, they were unable to conclude if this finding is pertinent to pineal RGNT or RGNT occurring elsewhere. Makita et al<sup>16</sup> described the only other case of IDH 1 mutation in RGNT.<sup>3</sup> Thus in our case, a positive IDH 1 immunohistochemistry, a strong surrogate marker of the mutation, is indeed very rare. Recent data also suggest that IDH 1 mutation may not be specific only to gliomas alone, as they can be found in a variety of other extracranial neoplasms as well.<sup>13</sup> IDH 1 mutations are not found in pilocytic astrocytoma, which is the closest entity resembling RGNT in terms of both clinical history and histology.<sup>13-15,17,18</sup> Hence, detection of IDH 1 mutation may become handy in distinguishing RGNT from pilocytic astrocytoma in cases where histopathological characteristics are inconclusive.<sup>13,17,18</sup>

In our case, both the primary RGNT and the secondary glioblastoma were tested positive for IDH 1 immunohistochemistry. Yan et al<sup>15</sup> described IDH 1 mutation in differentiating primary glioblastomas from secondary glioblastomas that are due to malignant transformation of the low-grade gliomas. Secondary glioblastomas that comprise only approximately 10% of all glioblastomas have recently been reclassified into glioblastoma IDH mutant in the 2016 WHO classification for CNS tumors.<sup>1</sup> The findings of IDH 1 mutation in both RGNT and glioblastoma in this case indicate that the glioblastoma must have progressed from its precursor lesion, the RGNT.<sup>19-21</sup> We postulate that the glial component of the RGNT may possibly follow the natural course of low-grade gliomas, eventually undergoing malignant transformation, especially in cases with IDH 1 mutation.<sup>19-22</sup> Recent evidence also suggests that when IDH 1 mutation is coupled with other genetic mutations such

as O-6-methylguanine-DNA methyltransferase methylation and tumor protein p53, it potentially carries higher risk of malignant transformation, as concluded by Murphy et al.<sup>23</sup>

On the basis of our observations, we speculate that other than the presence of a residual tumor, the IDH 1 mutation may have a role in malignant transformation.<sup>2,3,7-9,18</sup> IDH 1 mutation as a biomarker for malignant transformation needs further investigations. Routine IDH 1 mutation testing for future cases of RGNT may shed more light on this potential association.

## CONCLUSIONS

Malignant transformation of RGNT has never been reported in the literature. The observations made in this case are novel. Further prospective studies are needed to consolidate more evidence to our findings. We conclude that in RGNT, the presence of a solid, residual tumor with IDH1 mutation needs close observation with radiological surveillance for potential progression and malignant transformation.

## REFERENCES

- 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;131:803-820.
- Schlamann A, O von Bueren A, Hagel C, et al. An individual patient data meta-analysis on characteristics and outcome of patients with papillary glioneuronal tumor, rosette glioneuronal tumor with neuropil-like islands and rosette forming glioneuronal tumor of the fourth ventricle. *PLoS One.* 2014;9:e101211.
- Yang C, Fang J, Li G, et al. Histopathological, molecular, clinical and radiological characterization of rosette-forming glioneuronal tumor in the central nervous system. *Oncotarget.* 2017;8:109175-109190.
- Allinson KS, O'Donovan DG, Jena R, Cross JJ, Santarius TS. Rosette-forming glioneuronal tumor with dissemination throughout the ventricular system: a case report. *Clin Neuropathol.* 2015;34:64-69.
- Wang Y, Xiong J, Chu SG, et al. Rosette-forming glioneuronal tumor: report of an unusual case with intraventricular dissemination. *Acta Neuropathol.* 2009;118:813-819.
- García Cabezas S, Serrano Blanch R, Sanchez-Sanchez R, Palacios Eito A. Rosette-forming glioneuronal tumour (RGNT) of the fourth ventricle: a highly aggressive case. *Brain Tumor Pathol.* 2015;32:124-130.
- Solis OE, Mehta RI, Lai A, et al. Rosette-forming glioneuronal tumor: a pineal region case with IDH1 and IDH2 mutation analyses and literature review of 43 cases. *J Neurooncol.* 2011;102:477-484.
- Ellezam B, Theeler BJ, Luthra R, Adesina AM, Aldape KD, Gilbert MR. Recurrent PIK3CA mutations in rosette-forming glioneuronal tumor. *Acta Neuropathol.* 2012;123:285-287.
- Bidinotto LT, Scapulatempo-Neto C, Mackay A, et al. Molecular profiling of a rare rosette-forming glioneuronal tumor arising in the spinal cord. *PLoS One.* 2015;10:e0137690.
- Zhang J, Babu R, McLendon RE, Friedman AH, Adamson C. A comprehensive analysis of 41 patients with rosette-forming glioneuronal tumors of the fourth ventricle. *J Clin Neurosci.* 2013;20:335-341.
- Morris C, Prudowsky ZD, Shetty V, et al. Rosette-forming glioneuronal tumor of the fourth ventricle in children: case report and literature review. *World Neurosurg.* 2017;107:1045.e9-1045.e16.
- Matyja E, Grajkowska W, Nauman P, Ozieblo A, Bonicki W. Rosette-forming glioneuronal tumor of the fourth ventricle with advanced microvascular proliferation—a case report. *Neuropathology.* 2011;31:427-432.
- Hodges TR, Choi BD, Bigner DD, Yan H, Sampson JH. Isocitrate dehydrogenase 1 (IDH1): what it means to the neurosurgeon. *J Neurosurg.* 2013;118:1176-1180.
- Ichimura K, Pearson DM, Kocalkowski S, et al. IDH1 mutations are present in the majority of common adult gliomas but rare in primary glioblastomas. *Neuro Oncol.* 2009;11:341-347.
- Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med.* 2009;360:765-773.
- Makita K, Ohta T, Yamamuro S, et al. Gene alteration of rosette-forming glioneuronal tumor in a suprasellar lesion. *Int J Clin Exp Med.* 2016;9:6873-6881.
- Bera G, Das A, Chatterjee S, Chatterjee U. Rosette-forming glioneuronal tumor: a rare posterior fossa tumor in an adolescent. *J Pediatr Neurosci.* 2017;12:168-171.
- Gessi M, Moneim YA, Hammes J, et al. FGFR1 mutations in rosette-forming glioneuronal tumors of the fourth ventricle. *J Neuropathol Exp Neurol.* 2014;73:580-584.
- Mu L, Xu W, Li Q, et al. IDH1 R132H mutation is accompanied with malignant progression of paired primary-recurrent astrocytic tumours. *J Cancer.* 2017;8:2704-2712.

20. Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutamate. *Nature*. 2009;462:739-744.
21. Lee SM, Koh HJ, Park DC, Song BJ, Huh TL, Park JW. Cytosolic NADP(+)-dependent isocitrate dehydrogenase status modulates oxidative damage to cells. *Free Radic Biol Med*. 2002;32:1185-1196.
22. Chen JR, Yao Y, Xu HZ, et al. Isocitrate dehydrogenase (IDH) 1/2 mutations as prognostic markers in patients with glioblastomas. *Medicine (Baltimore)*. 2016;95:e2583.

23. Murphy ES, Leyrer CM, Parsons M, et al. Risk factors for malignant transformation of low-grade glioma. *Int J Radiat Oncol Biol Phys*. 2018;100:965-971.

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*Received 22 September 2018; accepted 23 December 2018*

*Citation: World Neurosurg. X (2019) 2:100006.*

*<https://doi.org/10.1016/j.wnsx.2018.100006>*

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