Scientific Journal of
Neurology & Neurosurgery

Case Report

Incidental IDH1 Mutant Low-grade Astrocytoma Mimicking TBI Later Transforming into Aggressive Glioblastoma: Diagnostic and Serial Surgical Challenges in Gliomas -

Alphonce M. K Nyalali[2-4#], Angela U. Leonard[5,7#], Tibera K. Rugambwa[6,8#], Piniel A. Kambey[9], Kailiang Zhang[2*] and Feng Li[1,2*]

[1]*Department of Neurosurgery, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China*

[2]*Department of Neurosurgery, Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan 250012, China*

[3]*Department of Surgery, Songwe Regional Referral Hospital, Songwe 23, Mbeya, Tanzania*

[4]*Department of Orthopedics and Neurosurgery, Mbeya Zonal Referral Hospital and Mbeya College of Health and Allied Sciences, University of Dar Es Salaam, Mbeya 419, Tanzania*

[5]*Department of Pediatrics and Child Health, Mbeya Zonal Referral Hospital and Mbeya College of Health and Allied Sciences, University of Dar Es Salaam, Mbeya 419, Tanzania*

[6]*Department of Internal Medicine, Mbeya Zonal Referral Hospital and Mbeya College of Health and Allied Sciences, University of Dar Es Salaam, Mbeya 419, Tanzania*

[7]*Department of Pediatrics and Child Health, Muhimbili University of Health and Allied Sciences, United Nations Road, Dar es Salaam 65001, Tanzania.*

[8]*Department of Oncology, Xiangya Hospital, Central South University, Changsha, Hunan, 410008, China*

[9]*Department of Neurobiology and Anatomy, Xuzhou Medical University, Xuzhou, China*

[#]*These authors contributed equally for this work.*

***Address for Correspondence:** Feng Li, Department of Neurosurgery, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China, Tel: +86-185-600-857-29; ORCID ID: orcid.org/0000-0001-6949-1504; E-mail: lifeng@sdfmu.edu.cn

Kailiang Zhang, Qilu Hospital of Shandong University and Brain Science Research Institute, Shandong University, Jinan 250012, China, Tel: +86-185-600-088-183; E-mail: kailiang-zhang@email.sdu.edu.cn

Submitted: 13 May 2022; **Approved:** 20 May 2022; **Published:** 21 May 2022

ISSN: 2640-5733

Scientific Journal of Neurology & Neurosurgery

ISSN: 2640-5733

Cite this article: Nyalali AMK, Leonard AU, Rugambwa TK, Kambey PA, Zhang K, Li F. Incidental IDH1 Mutant Low-grade Astrocytoma Mimicking TBI Later Transforming into Aggressive Glioblastoma: Diagnostic and Serial Surgical Challenges in Gliomas. Sci J Neurol Neurosurg. 2022; May 21; 8(1): 001-006. doi: 10.37871/sjnn.id46

ABSTRACT

Low grade gliomas have better outcomes following intervention compared to high grade gliomas including glioblastomas. About 14.4% of diffuse astrocytoma (WHO II) transform and progress into high grade malignant subtypes. Early diagnosis and intervention can therefore warrant halted transformation and progression and prolong survival with improved quality of life. However, asymptomatic low-grade astrocytoma lesions are difficult to diagnose, ascertain, and differentiate from other non-enhancing lesions including brain contusion. We report a case of grade II astrocytoma that was missed for three years on incidental intra-cranial imaging following two incidences of trauma.

A 30-year-old female was involved in motor traffic crash and lost consciousness for less than 20 minutes, with no other neurological complaints or deficits. CT and follow up MR imaging revealed a low density, non-enhancing left frontal lesion that was thought to be non-hemorrhagic cerebral contusion sequela. Brain imaging done three years later following another accident showed the initial lesion had significantly increased in size. Astrocytoma was then suspected, and the patient underwent tumor resection with histological diagnosis of diffuse astrocytoma. There was tumor recurrence after two years with features of malignancy. Secondary resection was done with immunohistochemical and genetic analysis revealing an Isocitrate Dehydrogenase 1 (IDH1) Mutant Glioblastoma (WHO IV). Along the course of the surgical and medical interventions, the patient again underwent an additional third surgical intervention with autografting dura repair following cerebrospinal fluid effusion through the previously repaired dura.

High index of suspicion is paramount for early diagnosis and intervention of asymptomatic low-grade gliomas. Along with the known hypothesis that traumatic brain injury can induce malignant transformation in the astrocytic cells, incidental findings that are synchronous with events such as trauma can also mask-off already occurring malignant changes that would otherwise require advanced diagnostic skills, experience, and techniques including structural and functional imaging.

Keywords: Incidental low-grade astrocytoma; Diffuse astrocytoma; Secondary glioblastoma multiforme; IDH1 mutation; Traumatic brain injury; Diagnostic challenges

INTRODUCTION

Glioblastoma is the most prevalent primary malignant tumor of the central nervous system in adults and remains to carry the worst prognosis and aggressiveness despite the current advances made in cancer research and interventions [1,2]. About 90% of glioblastomas occur as de novo high grade primary lesions without preceding low grade (primary glioblastoma) and are known to be the most aggressive subtype. The remaining portion are secondary glioblastomas that progress from low grade gliomas such as diffuse astrocytoma and anaplastic astrocytoma [3]. Molecular studies on neoplasms including astrocytoma and glioblastoma have reported several molecules whose genetic integrity and expression, or epigenetic modification serve a prognostic function in malignancy. Some of these molecules are chromosome 1p/19q, cytoplasmic Isocitrate Dehydrogenase Enzyme (IDH1), mitochondrial Isocitrate Dehydrogenase Enzyme (IDH2), tumor suppressor gene P53, and expression of MKI67 gene (ki-67), a marker for actively growing and dividing cells [4]. IDH enzymes are cellular metabolic enzymes that facilitate conversion of isocitrate to α-ketoglutarate, a substrate in cellular energy production, and generation of NADPH from NADP+ where NADPH serve as an antioxidant against intracellular reactive oxygen species. In gliomas, IDH mutations commonly occur in low grade gliomas and secondary glioblastomas. These mutations such as the R132H mutation found in IDH1 are associated with better prognosis and prolonged survival than the IDH1-wildtype counterparts. Also, presence of IDH1 mutation coupled with hypermethylation of CpG islands (promoter regions) of the O6-methylguanine DNA Methyltransferase Gene (MGMT) and acquired TP53 mutations, are associated with development of astrocytoma and progression to secondary glioblastoma [5]. In addition to that, presence of MGMT gene hypermethylation with eventual decreased production of MGMT enzyme in glioblastoma serves as a marker for better response to treatment with Temozolomide (TMZ) [4].

Low grade gliomas have better outcomes even with less aggressive interventions compared to high grade gliomas including glioblastomas [6]. However, low-grade astrocytoma (diffuse astrocytoma, WHO II) carries an about 14.4% potency to transform and progress into high grade malignant gliomas, about 53% of which are glioblastomas [7]. Early diagnosis and appropriate intervention are required to ensure prolonged survival and minimize the possibility of transformation into malignancy [6]. One of the major challenges against properly timed diagnosis and intervention of low-grade astrocytoma is the difficulty to ascertain and differentiate them from other non-enhancing intra-axial lesions including those arising from infections or acute and subacute traumatic brain injuries [8-10]. Also, traumatic brain injury itself is thought to carry a potential of inducing astrocytic malignant transformation [11]. We report a case of diffuse astrocytoma that was diagnosed at three years after incidental observation of a lesion on the same location during intra-cranial imaging following two incidences of trauma.

CASE REPORT

A 30-year-old female was involved in motor traffic crash and sustained abrasion to the forehead with reported loss of consciousness for less than 20 minutes. Physical examination revealed no other lesion or neurological deficits. CT imaging was done at the primary health facility and was reported to show an intra-axial left frontal lobe hypodense lesion. The lesion was suspected to be brain contusion. The patient was discharged after 48 hours of observation and scheduled for follow up imaging. Magnetic resonance imaging at four weeks post-trauma showed persistence of the lesion in the left frontal lobe, which was hypointense on T1-weighted MRI, long T2 and FLAIR signal intensity, and non-enhancing with gadolinium contrast. (Figures 1A-D). Post-traumatic brain gliosis or encephalomalacia was one of the differentials along with other intra-axial brain lesions such as astrocytoma. Therefore, the patient was referred to a neurosurgical center at convenience. However, due to absence of any progressive symptoms, the patient never had any other visit to hospital until three years later when she sustained another accident after slipping and hitting the head. Brain CT and MR imaging revealed persistence of the left frontal lesion which had significantly increased in size but with no change in radiological features from the previous three years (Figures 1E-H). Low grade glioma was then suspected. The patient was referred to a neuro-oncology center where maximum safe tumor resection was done. Immunohistochemical analysis confirmed for diffuse astrocytoma (WHO II). She then received TMZ-based adjuvant chemoradiotherapy.

Follow up imaging at six- and 18-months post-surgery did no show obvious progression (Figures 2A-D). At two years after the first surgery the patient developed progressive headache with behavioral changes and impaired speech. CT and MR imaging showed an extensive progression of the lesion to involve the left frontal and parietal lobes, and right frontal lobe (Figures 2E-H). The tumor was now heterogeneously enhancing on T1 weighted contrast MRI. Progression into high grade glioma was suspected and a second resection was agreed upon. Second tumor debulking surgery was then done. Immunohistochemical and genetic analysis revealed malignant glioma (Glioblastoma Multiforme) with R132H IDH1 mutation, positive P53 and 70% ki-67 reactivities. There was no alteration in MGMT methylation, IDH2, TERT, and BRAF gene expressions or the integrity of 1p and 19q chromosomes (Figure 3A). Multidisciplinary team resolution recommended the patient for adjuvant combined radiation therapy and chemotherapy when stable, with option for enrollment into clinical trial therapies. However, seven weeks after the second surgery, the patient developed scalp swelling which was diagnosed to be cerebrospinal fluid effusion. Intraoperatively, the two-times repaired dura with artificial dura membrane was leaking. To ensure efficacy of the third dura repair, autograft was done with tissue harvested from the thigh (Figures 3C-G). After recovery from the third surgery the patient and relatives requested discharge for palliative care.

DISCUSSION

Asymptomatic astrocytic lesions can be diagnosed incidentally during brain imaging in incidences like traumatic brain injury. A 2021 systemic meta-analytical study showed a prevalence of 0.064

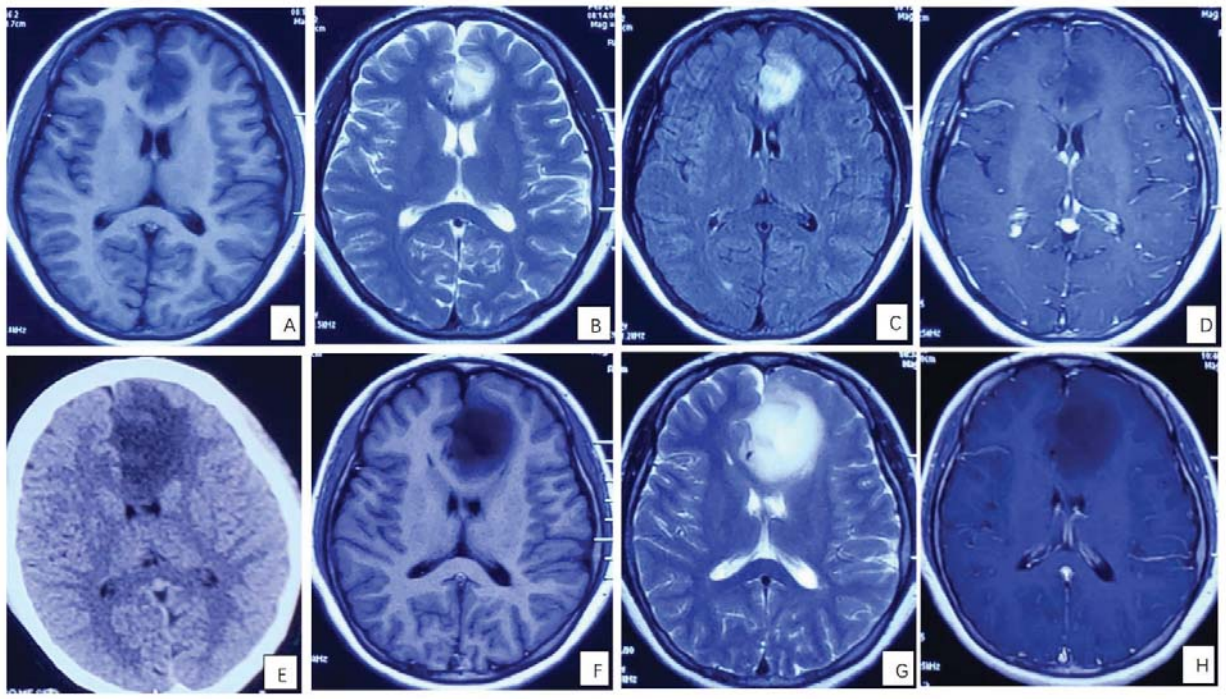

Figure 1: Three year interval imaging following the first and second head trauma.
Axial view MR images taken at four weeks post first trauma showing non-contrast T1-weighted A) T2-weighted B) FLAIR C) and T1-weighted with gadolinium contrast D) They show a hypodense non-enhancing lesion involving the medial aspect of the left superior frontal gyrus, extending to the cingulate gyrus. Axial CT image E) T1-weighted F) T2-weighted G) and T1-weighted with contrast H) MR images taken three years after the first incident, shows an increase in size of the lesion to involve large part of the superior frontal gyrus.

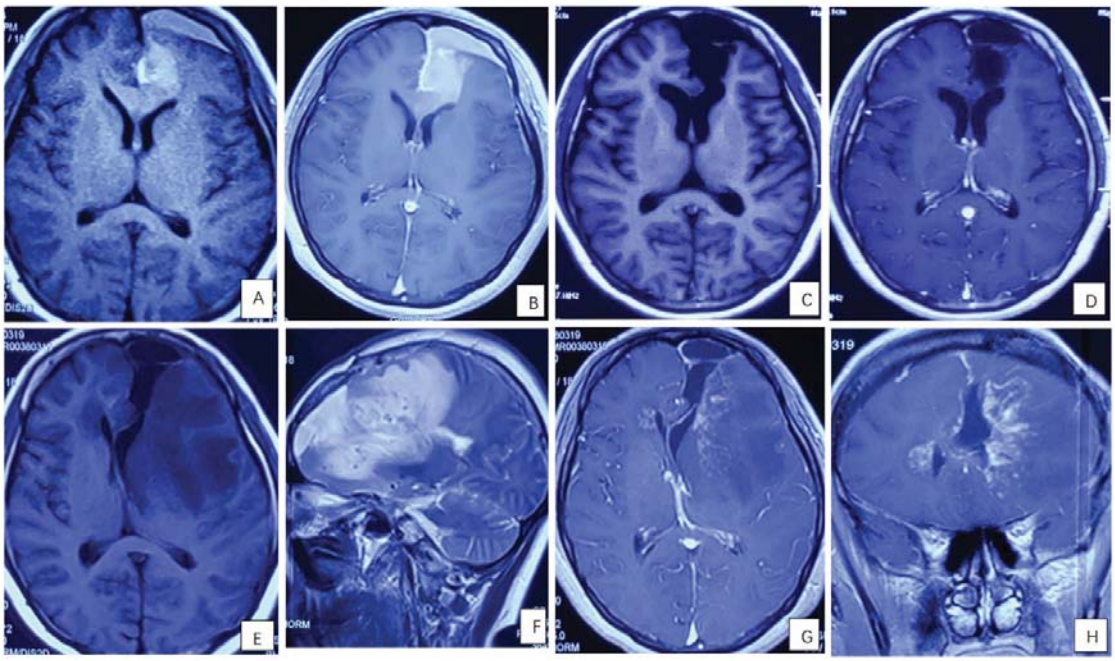

Figure 2: Post resection of diffuse astrocytoma follow-up imaging up to 30 months.
Axial T1-weighted MRI without contrast A) and with contrast B) taken six months after the first tumor resection showing hyperintensity around the resection margins. These were features of post-resection brain gliosis which later resolved and cannot be observed in the T1-weighted images without contrast C) and with contrast D) taken 18 months after surgery. Figure E-H shows MR images taken at 30 months post-surgery. The T1-weighted, axial view without contrast E) T2-weighted sagittal view F) T1-weighted with contrast axial G) and coronal view H) shows an edematous, contrast-enhancing malignant lesion involving the whole left frontal lobe and part of the parietal lobe as well as the medial aspect of the right frontal lobe extending to the medial wall of the frontal horn of the right lateral ventricle.

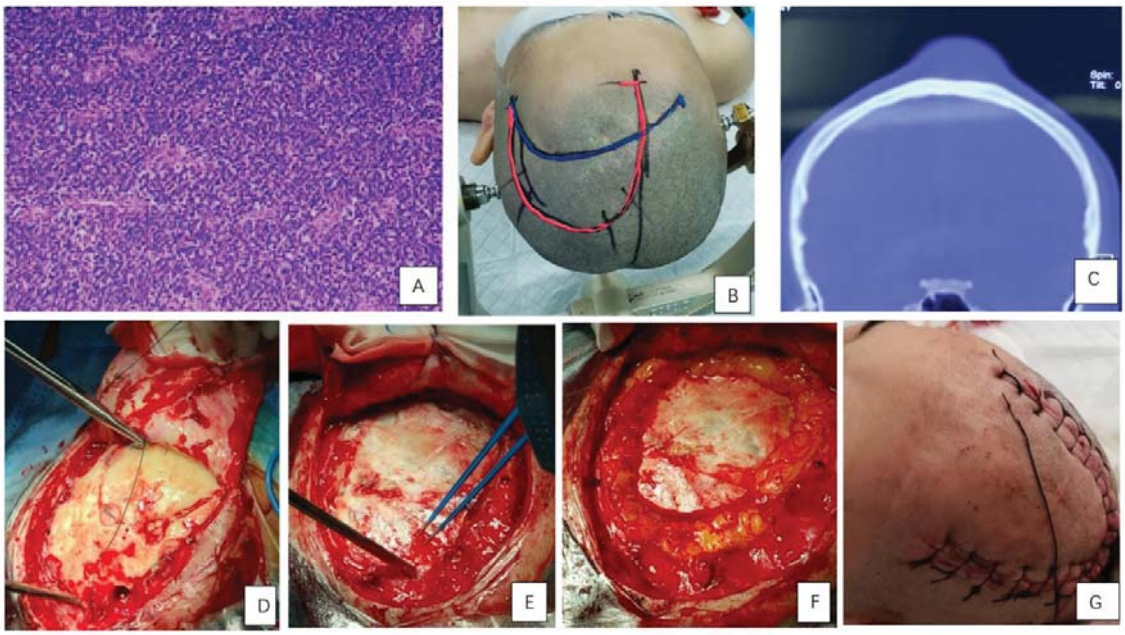

Figure 3: Secondary glioblastoma multiforme histology and condecutive surgeries.
A) shows histological section of glioblastoma with features of hypercellularity, nuclear atypia and palisading cells around areas of necrosis. B) shows curved frontotemporal incisions during the first (blue) and second surgeries (red line) for frontal unilateral craniotomies. C) Bone window CT image showing extracranial mass which was a collection of extracranial cerebrospinal fluid effusion. D-G) are intraoperative images for tertiary repair of the defective dura using fatty-tissue F). There were no signs of wound infection even during the third operation G).

and 0.026% incidental gliomas on MR imaging and histological confirmation, respectively [12]. Loss of consciousness can occur in both incidences of mild TBI (concussion) and severe TBI including cerebral contusion [13]. In that light, the low prevalence of incidental gliomas coupled with the presence of symptoms suggestive of possible brain tissue damage, could have masked-off the suspicion and attention for possible astrocytic tumor by the initial care provider and even the patient during the first encounter, during follow up imaging, and throughout the uneventful period that followed until the second trauma. Absence of neurological deficits that could be directly identified as sequelae from the head trauma, and the radiological features of the left frontal lobe lesion that are consistent from the first trauma incidence to the confirmation of diffuse astrocytoma (three-year period), suggest the presence of the same astrocytic pathology (glioma) even prior to the trauma incident. We also speculate that, involvement of the patient in multiple incidents of trauma could be associated with presence of the brain pathology that impaired her judgement while observing traffics and personal safety. To ensure definitive diagnosis for incidental lesions that mimic but not pathognomonic for traumatic brain injury, brain imaging should go beyond structural analysis to include functional imaging for circulation and metabolic characterization of the lesion. Again, search for and establishment of causations that enable recategorization of incidences like trauma as secondary manifestations of an underlying pathology with mental or physical impairment are crucial for exhaustive differential diagnoses and screening for common malignancies.

In management of gliomas, cytoreductive surgery and safely possible maximum resection are critical for enhanced outcome of adjuvant therapies, prevention of recurrencies and progression into high grade lesions [3,14]. In that case, early detection of low-grade gliomas could warrant gross resection of the tumor beyond the tumor margins hence lower prevalence of radiologically detectable remnant lesions and smaller residual volumes [15]. This in turn could ensure efficacy from relatively less aggressive adjuvant radiation and medical therapies with consequently lower risk of neurological or multisystemic sequelae from the surgical and adjuvant therapies. Strategies to enhance early diagnosis of gliomas especially in the challenging subsets could encompass inclusion of imaging techniques with high sensitivity to cellular density (DWI and ADC), blood flow and metabolic characterization (functional CT/MRI), and minimally invasive diagnostic biopsy (stereotactic biopsy). On the other hand, delayed confirmation, and tumor resection as in this case could therefore be associated with significant remnant of tumor cells seeded beyond the safely possible surgical margins. The progression into high grade glioma (glioblastoma) rendered this lesion even more aggressively invasive with both local and distant metastasis to involve the right cerebral hemisphere. Moreover, multiple necessary craniotomies for brain resection not only presented challenges to maintenance of vital neurological functions, but also difficulty to achieve a functional dura repair and prevent CSF effusion which otherwise impairs surgical wound healing. Use of tissue autograft rather than artificial dura alone during the third surgery was therefore necessary to achieve an impermeable dura thus enhance wound healing.

In reviewing the molecular characteristics of this case, presence of IDH1 and TP53 mutations and the observed course and evolution of the disease in a period of over five years in this case, correlates with the established significance of the molecules in low-grade gliomas, some of which progress into secondary glioblastoma as seen in this case. Also, absence of MGMT gene methylation hence normal cellular MGMT enzyme level tallies with the observed short progression free survival following TMZ adjuvant treatment after the first surgery. In that regard, although IDH1 mutation is indicative for good prognosis, presence of TP53 mutation and absence of MGMT gene hypermethylation suggest an obviously aggressive glioblastoma (marked with high Ki-67 cellular proliferation index) with poor response to TMZ-based conventional therapies.

CONCLUSION

High index of suspicion is paramount for early diagnosis and timely intervention of asymptomatic low-grade gliomas. To delineate incidental gliomas in events such as traumatic brain injury, thorough physical and radiological assessment together with proper counselling, close follow up, and referral to centers with specialized neuro-oncological care are critical.

STATEMENTS

Conflict of interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This study was supported by the National Natural Science Foundation of China (Grant No. 81702470, to Kailiang Zhang) and the Key Technology Research and Development Program of Shandong (Grant No. 2017GSF218028, to Feng Li).

Ethics statement

This report involving human participants was reviewed and approved by Ethics Committee of Cheeloo College of Medicine, Shandong University. The written consent for participation and publication of all data including any potentially identifiable human images or data was obtained from the participant's relatives.

REFERENCES

1. Alexander BM, Cloughesy TF. Adult Glioblastoma. J Clin Oncol. 2017 Jul 20;35(21):2402-2409. doi: 10.1200/JCO.2017.73.0119. Epub 2017 Jun 22. PMID: 28640706.

2. Birzu C, French P, Caccese M, Cerretti G, Idbaih A, Zagonel V, Lombardi G. Recurrent Glioblastoma: From Molecular Landscape to New Treatment Perspectives. Cancers (Basel). 2020 Dec 26;13(1):47. doi: 10.3390/cancers13010047. PMID: 33375286; PMCID: PMC7794906.

3. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res. 2013 Feb 15;19(4):764-72. doi: 10.1158/1078-0432.CCR-12-3002. Epub 2012 Dec 3. PMID: 23209033.

4. Ludwig K, Kornblum HI. Molecular markers in glioma. J Neurooncol. 2017 Sep;134(3):505-512. doi: 10.1007/s11060-017-2379-y. Epub 2017 Feb 23. PMID: 28233083; PMCID: PMC5568999.

5. Aldape K, Zadeh G, Mansouri S, Reifenberger G, von Deimling A. Glioblastoma: pathology, molecular mechanisms and markers. Acta Neuropathol. 2015 Jun;129(6):829-48. doi: 10.1007/s00401-015-1432-1. Epub 2015 May 6. PMID: 25943888.

6. Campos B, Olsen LR, Urup T, Poulsen HS. A comprehensive profile of recurrent glioblastoma. Oncogene. 2016 Nov 10;35(45):5819-5825. doi: 10.1038/onc.2016.85. Epub 2016 Apr 4. PMID: 27041580.

7. Tunthanathip T, Sangkhathat S, Kanjanapradit K. Risk Factors Associated

with Malignant Transformation of Astrocytoma: Competing Risk Regression Analysis. Asian J Neurosurg. 2021 Dec 18;16(4):777-784. doi: 10.4103/ajns.ajns_159_21. PMID: 35071077; PMCID: PMC8751501.

8. Çelik S, Öven BB, Demir MK, Yılmaz EÇ, Kanan D, Özdamarlar U, Emirzeoglu L, Yapıcıer Ö, Kılıç T. Magnetic resonance imaging criteria for prediction of isocitrate dehydrogenase (IDH) mutation status in patients with grade II-III astrocytoma and oligodendroglioma. Clin Neurol Neurosurg. 2021 Aug;207:106745. doi: 10.1016/j.clineuro.2021.106745. Epub 2021 Jun 8. PMID: 34146841.

9. Patel JB, Wilson SH, Oakes TR, Santhanam P, Weaver LK. Structural and Volumetric Brain MRI Findings in Mild Traumatic Brain Injury. AJNR Am J Neuroradiol. 2020 Jan;41(1):92-99. doi: 10.3174/ajnr.A6346. Epub 2020 Jan 2. PMID: 31896572; PMCID: PMC6975320.

10. Liu C, Xu W, Liu P, Wei Y. A Mistaken Diagnosis of Secondary Glioblastoma as Parasitosis. Front Neurol. 2019 Sep 6;10:952. doi: 10.3389/fneur.2019.00952. PMID: 31555204; PMCID: PMC6742723.

11. Munch TN, Gørtz S, Wohlfahrt J, Melbye M. The long-term risk of malignant astrocytic tumors after structural brain injury--a nationwide cohort study. Neuro Oncol. 2015 May;17(5):718-24. doi: 10.1093/neuonc/nou312. Epub 2014 Nov 21. PMID: 25416827; PMCID: PMC4482857.

12. Nakasu S, Notsu A, Nakasu Y. Prevalence of incidental meningiomas and gliomas on MRI: a meta-analysis and meta-regression analysis. Acta Neurochir (Wien). 2021 Dec;163(12):3401-3415. doi: 10.1007/s00701-021-04919-8. Epub 2021 Jul 6. PMID: 34227013.

13. Lizzo JM, Waseem M. Brain Trauma. StatPearls. StatPearls Publishing LLC; 2022. https://bit.ly/3sJ2jLW

14. Moliterno JA, Patel TR, Piepmeier JM. Neurosurgical approach. Cancer J. 2012 Jan-Feb;18(1):20-5. doi: 10.1097/PPO.0b013e3183243f6e3. PMID: 22290253.

15. Gogos AJ, Young JS, Pereira MP, Morshed RA, Potts MB, Hervey-Jumper SL, Berger MS. Surgical management of incidentally discovered low-grade gliomas. J Neurosurg. 2020 Oct 2:1-8. doi: 10.3171/2020.6.JNS201296. Epub ahead of print. PMID: 33007758.