

CASE REPORT

Development of a low-grade glioma in an ischemic brain territory that evolved into a glioblastoma. A case report and brief literature review

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Introduction: Glioblastoma is one of the most common and aggressive brain tumours with a very high mortality rate. It often evolves from a late or misdiagnosed astrocytoma. Stroke is one of the most common pathologies of the brain, affecting approximately 1.1 million Europeans each year. This article presents the sequential development of a low-grade astrocytoma in an ischemic brain territory into a high-grade glioblastoma. **Case presentation:** A 59-year-old patient presented to our hospital with severe headache and transient loss of balance and vision. Clinical findings and control imaging revealed the presence of an ischemic brain area in the left temporal lobe of the brain. Monthly brain magnetic resonance imaging (MRI) follow-up revealed the development of a low-grade astrocytoma in the ischemic territory, which later evolved into a glioblastoma. **Conclusions:** Patients who suffer from a stroke should be closely monitored via MRI to prevent the rare development of tumour pathology in the affected territory.

Keywords: glioblastoma, stroke, magnetic resonance imaging, astrocytoma

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Introduction

Glioblastoma is the most common and rapidly growing primary malignancy of the brain; it has a very poor prognosis despite continuous improvements in diagnostic and therapeutic strategies in recent years. MRI is widely used in the diagnosis and postoperative management of patients with glioblastoma [1]. Despite aggressive multimodal treatment, the prognosis of this neoplasm remains poor. Even with the latest MRI diagnostic techniques, the assessment of post-treatment response remains challenging [2]. Astrocytomas, a slowly growing neoplasm, represents the most frequent cerebral tumour in paediatric and young adult patients. Low-grade astrocytomas account for about 45% of all paediatric brain tumours and 25% of all adult brain tumours. These tumours develop most frequently during the first 4 decades of life, and their most common localisations are the cerebellum, the temporal and parietal lobes, and the hypothalamic pathways. The most common MRI sequences used for diagnosing gliomas are native and post-contrast T1-weighted (T1w), T2-weighted (T2w), T2-fluid-attenuated inversion recovery (T2-FLAIR), and diffusion-weighted (DWI) associated with apparent diffusion coefficient of water (ADC) [3,4].

The aim of this article is to present a rare case of a 59-year-old female patient who was initially considered to have an ischemic stroke, but subsequent MRI follow-up

and histological examination detected the presence of a glioblastoma.

Case presentation

A 59-year-old female patient presented to the hospital complaining of the onset of unspecific neurological symptoms, including severe headache and transient loss of balance and vision. A computer tomography (CT) examination of the head was performed, and the presence of a hypodense ischemic area in the left temporal level was described. The D-dimer level was slightly elevated. Following the persistence of the symptoms, after 2 days, a head MRI examination was performed (Figure 1). The MRI revealed a lesion appearing hyperintense on T2 and FLAIR sequences, measuring 42/27/46 mm (AP/LL/CC), located at the left temporo-occipital junction, parapeduncular, tangent to the ipsilateral optic tract, including the tail of the caudate nucleus, with minimal compressive oedema on the lateral ventricle. The lesion had slight diffusion restriction that was visible on DWI, no cystic, haemorrhagic, necrotic, or calcified areas, no contrast-enhancement, and no areas of stenosis or intraluminal thrombi of the middle cerebral artery were visible on the ANGIO 3D TOF sequence. Following the investigations, a possible differential diagnosis of grade I or II astrocytoma was considered; however, considering the MRI and CT imaging characteristics and the absence of the pathognomic T2 FLAIR mismatch sign, the diagnosis was determined as a sub-acute ischemic stroke in

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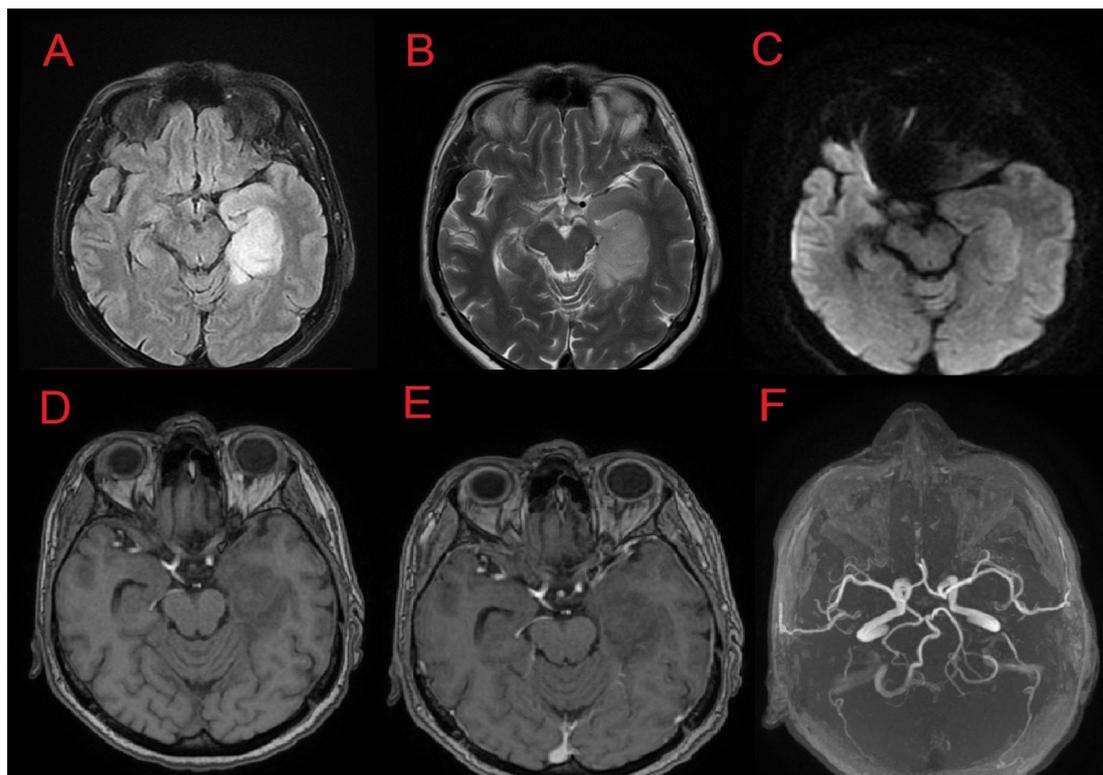


Fig. 1. Head MRI showing a lesion in the left temporal lobe of the brain, parapeduncular, with slight diffusion restriction and no contrast-enhancement, A-T2 FLAIR; B-T2; C-DWI; D-T1; E-T1+Contrast; F-ANGIO 3D TOF

the distribution area of the left middle cerebral artery. It was recommended that the patient should return for MRI re-evaluation. The next MRI examination was performed after approximately 2 months, and the patient stated that she had no changes in her functional or sensory-motor symptoms between the two evaluations. The lesion had similar dimensions and location as in the previous examination, but with moderate contrast enhancement, visible calcifications and haemorrhages, and a discrete T2 FLAIR mismatch sign (Figure 2). Following this investigation, neurosurgery was performed after 3 weeks, where an attempt was made to ablate and remove the tumour. The patient returned after 1 month for another MRI follow-up. Tumour recurrence was observed, with identical localisation to that of the previous examinations. The tumour measured 17/45/31 mm (CC/AP/LL), with multiple areas of intralesional haemorrhage and necrosis, inhomogeneous contrast enhancement, a 'ring of fire' appearance of the cystic and solid components that is pathognomonic for glioblastoma, perilesional oedema, no mass effect on the left ponto-mesencephalic junction, and no meningeal or cerebellar extension (Figure 3 A, B, C).

Histopathological examination revealed atypical glial cells with large hyperchromic nuclei, marked nuclear pleomorphism, and atypical mitotic figures. In addition microvascular proliferation with endothelial hyperplasia and microscopic foci of palisading necrosis were observed (Figure 3D,E,F). The small vessels had intraluminal hyaline thrombi. Immunohistochemically (IHC) the tumour cells were positive for glial fibrillary acidic protein (GFAP), and negative for IDH1-R132H, showed loss of ATRX expres-

sion, and nuclear overexpression of p53. The Ki-67 proliferative index was 25%.

Discussion

The correlation between cerebral ischemia and glioma remains inconclusive based on molecular components; however, numerous clinical reports and case studies have suggested that glioma and cerebral ischemia can ease each other. It has been described that the location and size of the tumour and repetitive resections throughout glioma therapy can upsurge the risk of ischemic injuries and additional neurological deficits [5]. A recent statement founded on clinical cohort studies established that the likelihood of the diseases developing simultaneously was 11% compared with 3% in the control population, and the risk of developing glioma was further increased in stroke patients [6]. In our case, CT and MRI performed at the first evaluation in addition to the patient's laboratory D-dimer values indicated the presence of an ischemic stroke that evolved within 2 months into a high-grade glioblastoma, with IHC features of a de novo tumour.

Classic features of astrocytomas are the preferred localisation in the frontal lobe followed by the temporal lobe, thalamus, and cerebellum [7]. These tumours occur mainly in young patients; they are rarely found in adults between 30 and 40 years old. Astrocytomas classically appear iso- to hypo-intense to grey matter, T2 hyperintense, T2 FLAIR with pathognomonic mismatch sign, and no contrast enhancement. Furthermore, cysts and calcification can be seen [8,9]. Uncommon features found in our case were the absence of the T2 FLAIR mismatch sign, cysts, and cal-

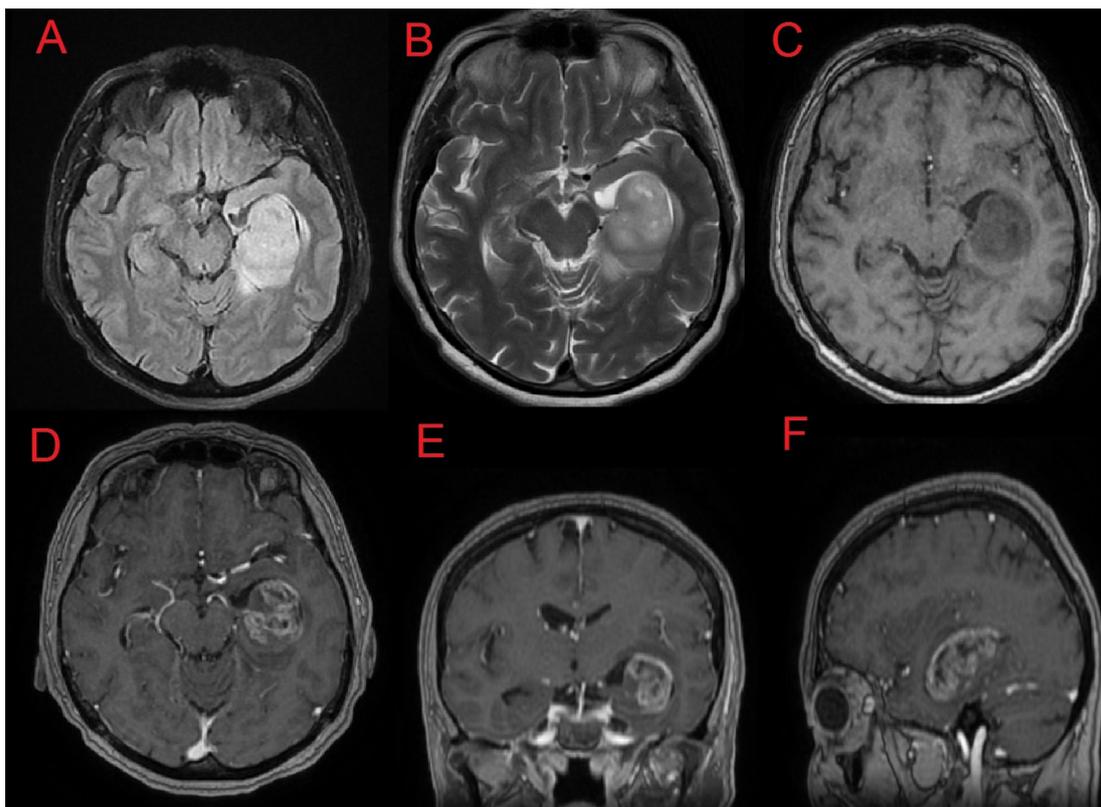


Fig. 2. Head MRI showing the same lesion with contrast enhancement, microcalcifications and haemorrhagic areas, A-T2 FLAIR; B-T2; C-AXIAL T1; D-AXIAL T1+C; E-CORONAL T1+C; F-SAGITAL T1+C

cifications at the first evaluation, the advanced age of the patient, and rapid evolution of the pathology.

The most widely acknowledged model that consociates glioma and ischemia is based on the prevalent hypoxic

conditions that occur in both conditions. Cerebral ischemia due to blockage of the vasculature causes low oxygen perfusion in the ischemic areas and results in hypoxia, whereas an exceedingly proliferating glioma cell mass has

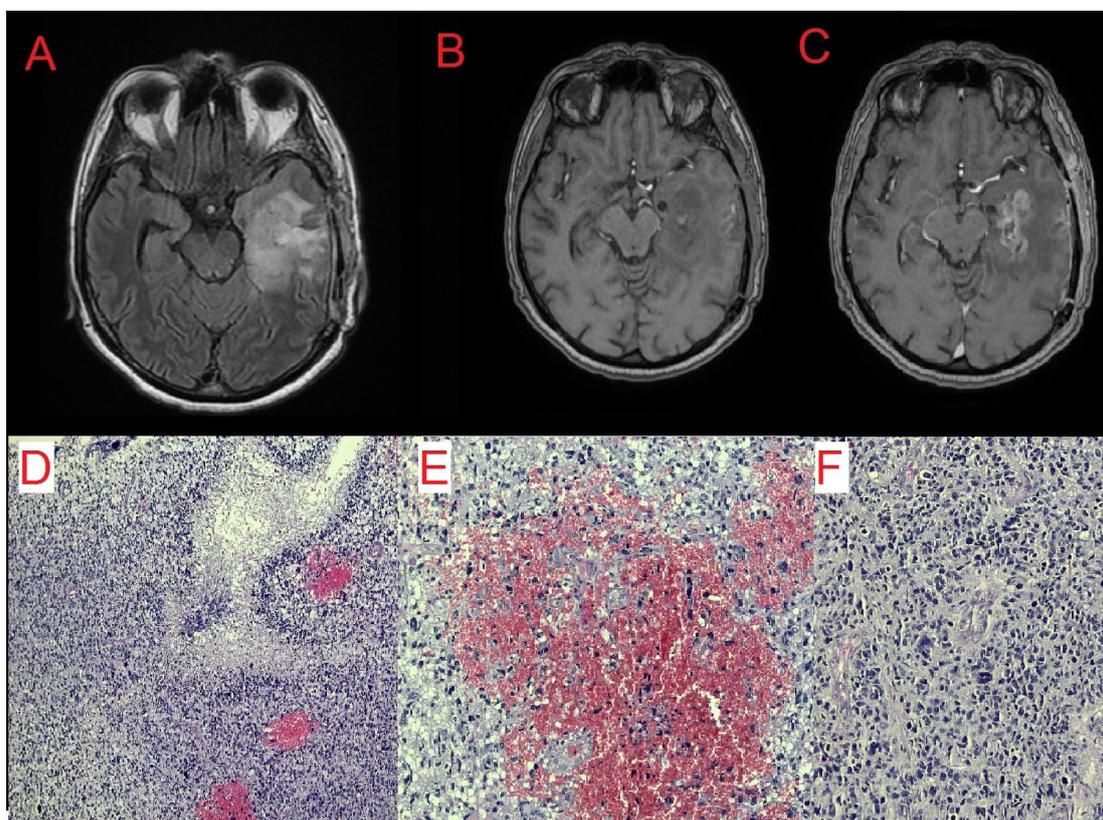


Fig. 3. Head MRI showing tumour recurrence, A-T2 FLAIR; B-AXIAL T1; C-AXIAL T1+C; Histological examination, D-palisading necrosis,hematoxylin eosin, Ob10x; E-haemorrhagic area,hematoxylin eosin, Ob10x; F-nuclear pleomorfism,hematoxylin eosin, Ob20x

poor vascularisation inside its core, causing a hypoxic core region that is deprived of oxygen [10]. The precise mechanism of this interplay remains unclear; however, potential mechanisms, such as reactive gliosis, angiogenesis, astrocyte activation, and changes in perinecrotic and perivascular areas as a result of cerebral ischemia, are described as a result of glioma development [11]. Similar to our study, the rare cases where glioblastomas developed in a previously infarcted territory were reported in patients over 50 years old, where immunostaining was negative for IDH1, positive for GFAP and the Ki-67 proliferative index was estimated to be 20% [11]. In cerebral ischemia, as a result of oxygen and glucose deficiency, dramatic changes (e.g., cytoplasmic hypertrophy in addition to accumulation of GFAP) occur in astrocytes, leading to the development of a metabolically activated reactive form [12,13]. A meshwork of the cytoplasmic processes of activated astroglia develop a glial scar surrounding the area of the ischemic lesions. This activation process and consequent mutations of numerous genes in reactive gliosis leads to gliomagenesis due to both glial progenitor and reactive astrocyte cell lineages having the same proposed origins [14,15].

The unique aspect of the case presented in this article was the development of a low-grade glioma with imaging features identical to those of an ischemic stroke, which later evolved into a glioblastoma in a brain territory previously subjected to an ischemic lesion. Few such cases of fulminant evolution of brain lesions have been reported in the literature.

Conclusions

The exact mechanisms responsible of glioma development in stroke patients have not yet clearly been defined, but patients who suffer from both stroke and cancer are certainly more difficult to treat. It is recommended that patients suffering from an ischemic injury or from an injury with distinguished imaging features be closely monitored at short time intervals via MRI to prevent the development of further incurable complications.

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Authors' contribution

A.C.F (Conceptualization, Data curation, Investigation, Methodology, Formal Analysis, Visualization, Writing – original draft, Writing – review&editing), *Z.O* (Conceptualization, Supervision, Validation, Formal Analysis, Writing – review&editing), *E.F.F* (Conceptualization, Data curation, Supervision), *I.G.G* (Conceptualization, Investigation, Project administration, Writing – original draft), *R.S* (Conceptualization, Data curation, Methodology), *A.K* (Conceptualization, Data curation, Investigation).

Informed consent

The patient signed an informed consent for the publication of this manuscript.

Conflict of interest

The authors declare no competing interests.

References

- Li Y, Ma Y, Wu Z, et al. Advanced Imaging Techniques for Differentiating Pseudoprogression and Tumor Recurrence After Immunotherapy for Glioblastoma. *Front Immunol.* 2021;12:790674. Published 2021 Nov 25. doi:10.3389/fimmu.2021.790674.
- Shukla G, Alexander GS, Bakas S, Nikam R, Talekar K, Palmer JD, Shi W. Advanced magnetic resonance imaging in glioblastoma: a review. *Chin Clin Oncol.* 2017 Aug;6(4):40. doi: 10.21037/cco.2017.06.28. PMID:28841802.
- Gonçalves FG, Chawla S, Mohan S. Emerging MRI Techniques to Redefine Treatment Response in Patients With Glioblastoma. *J Magn Reson Imaging.* 2020 Oct;52(4):978-997. doi: 10.1002/jmri.27105. Epub 2020 Mar 19. PMID: 32190946; PMCID: PMC7492394.
- Dützmann S, Geßler F, Bink A, Quick J, Franz K, Seifert V, Senft C. Risk of ischemia in glioma surgery: comparison of first and repeat procedures. *J Neurooncol.* 2012 May;107(3):599-607. doi:10.1007/s11060-011-0784-1. Epub 2012 Jan 17. PMID: 22249690.
- Chen CW, Cheng TJ, Ho CH, Wang JJ, Weng SF, Hou YC, Cheng HC, Chio CC, Shan YS, Chang WT. Increased risk of brain cancer incidence in stroke patients: a clinical case series, population-based and longitudinal follow-up study. *Oncotarget.* 2017 Nov 15;8(65):108989-108999. doi: 10.18632/oncotarget.22480. PMID: 29312585; PMCID: PMC5752498.
- Gaudino S, Martucci M, Russo R, Visconti E, Gangemi E, D'Argento F, Verdolotti T, Lauriola L, Colosimo C. MR imaging of brain pilocytic astrocytoma: beyond the stereotype of benign astrocytoma. *Childs Nerv Syst.* 2017 Jan;33(1):35-54. doi:10.1007/s00381-016-3262-4. Epub 2016 Oct 18. PMID:27757570.
- Kee HJ, Ahn KY, Choi KC, Won Song J, Heo T, Jung S, Kim JK, Bae CS, Kim KK. Expression of brain-specific angiogenesis inhibitor 3 (BAI3) in normal brain and implications for BAI3 in ischemia-induced brain angiogenesis and malignant glioma. *FEBS Lett.* 2004 Jul 2;569(1-3):307-16. doi: 10.1016/j.febslet.2004.06.011. PMID:15225653.
- 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.
- Chawla S, Shehu V, Gupta PK, Nath K, Poptani H. Physiological Imaging Methods for Evaluating Response to Immunotherapies in Glioblastomas. *Int J Mol Sci.* 2021 Apr 8;22(8):3867. doi: 10.3390/ijms22083867. PMID: 33918043; PMCID: PMC8069140.
- Berghoff AS, Hainfellner JA, Marosi C, Preusser M. Assessing MGMT methylation status and its current impact on treatment in glioblastoma. *CNS Oncol.* 2015;4(1):47-52. doi: 10.2217/cns.14.50. PMID: 25586425; PMCID: PMC6093023.
- Wojtasiewicz, Teresa J et al. "De novo glioblastoma in the territory of a prior middle cerebral artery infarct." Case reports in neurological medicine vol. 2013 (2013):356526. doi:10.1155/2013/356526.
- Colman H. Adult Gliomas. *Continuum (Minneapolis, Minn).* 2020 Dec;26(6):1452-1475. doi: 10.1212/CON.0000000000000935. PMID: 33273168.
- Haque A, Banik NL, Ray SK. Molecular alterations in glioblastoma: potential targets for immunotherapy. *Prog Mol Biol Transl Sci.* 2011;98:187-234. doi:10.1016/B978-0-12-385506-0.00005-3. PMID: 21199773; PMCID: PMC4287208.
- Teresa J. Wojtasiewicz, Andrew F. Ducruet, "De Novo Glioblastoma in the Territory of a Prior Middle Cerebral Artery Infarct", *Case Reports in Neurological Medicine*, vol. 2013, Article ID 356526, 5 pages, 2013. <https://doi.org/10.1155/2013/356526>
- Odjéle A, Charest D, Morin P Jr. miRNAs as important drivers of glioblastomas: a no-brainer? *Cancer Biomark.* 2012;11(6):245-52. doi:10.3233/CBM-2012-0271. PMID: 23248182.