

Neoplasm

Rapid malignant transformation of low-grade astrocytomas: report of 2 cases and review of the literature

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Abstract

Background: Low-grade gliomas have been documented to undergo transformation into high-grade astrocytomas, and the time interval of this transformation has been reported to generally occur within 5 years in about 50% of patients harboring these low-grade lesions. Several studies have investigated the evolution of low-grade gliomas into malignant gliomas by CT and MRI characteristics, but many have not documented the timing of these transformation processes.

Case Description: The authors discuss the cases of 2 patients with histopathologically confirmed grade II astrocytomas after craniotomies that underwent rapid evolution into malignant gliomas within 13 weeks. Interestingly, both low-grade astrocytomas were positive with immunostaining for the epidermal growth factor receptor, in which its amplification has been implicated as a molecular marker of malignant gliomas. In addition, the grade II astrocytomas were negative for p53 in both patients but were found to be positive upon transformation into malignant gliomas.

Conclusions: To our knowledge, this is the first report of rapid malignant transformation of low-grade gliomas, which were proven by histology, within 13 weeks. There may be patients with a subtype of low-grade astrocytomas that may warrant molecular characterization to determine if aggressive adjuvant therapy would be of benefit.

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Keywords: Low-grade glioma; Malignant transformation; High-grade glioma; Glioblastoma; Histopathology; Grade II astrocytoma

1. Introduction

Malignant gliomas have been reported to arise from either secondary transformation from low-grade gliomas or de novo lesions [1,36]. Non-enhancing low-grade gliomas can transform into malignant tumors, and the timing of these interval changes is variable, ranging from 4 months to more than 3 years [8,33,39]. High-grade gliomas demonstrate

heterogeneous patterns of enhancement on MRI and are typically associated with necrosis and/or edema [15,37]. Low-grade gliomas usually lack contrast enhancement, but some non-enhancing gliomas may be high grade as a result of histologic examination [3,9,15,25,34,41]. Clinical studies suggest that patients with low-grade gliomas will undergo anaplastic transformation within 5 years in approximately 50% of cases [1,36]. Several studies have provided evidence that there is variation in enhancement patterns and time intervals in the course of disease progression of non-enhancing gliomas [3,8,33,39].

Studies have been conducted in an attempt to discover molecular markers for GBM. Epidermal growth factor receptor has been shown to be expressed in approximately 40% of GBM cases, and reports provided data that EGFR

Abbreviations: CT, computed tomography; EGFR, epidermal growth factor receptor; FLAIR, fluid-attenuated inversion recovery; GBM, glioblastoma multiforme; MRI, magnetic resonance imaging

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amplification in patients younger than 60 years had a worse prognosis [4,19,43,44]. Loss of heterozygosity on chromosome 10 has also been implicated as a molecular marker [14,24,45]. Furthermore, p53 expression has been found in GBMs and may play a role in secondary GBM formation. A study found 75% of secondary GBMs to express p53 [30].

We discuss the first documented cases of 2 patients with histopathologically confirmed grade II astrocytomas that underwent rapid evolution into malignant gliomas within 13 weeks and provide a review of the literature.

2. Case reports

2.1. Case 1

A 54-year-old woman presented to the emergency room with speech difficulty. Neurologic examination revealed a mild expressive and receptive aphasia. A head CT study was unremarkable, and she was admitted for further workup. A brain MRI revealed a FLAIR and T2 hyperintense lesion in the left temporal lobe (Fig. 1A and B).

The patient underwent a craniotomy with frameless stereotactic guidance for resection of the lesion, in which there was residual tumor posteriorly (Fig. 1C), and histopathologic examination of tumor specimens was consistent with a low-grade astrocytoma, including a low proliferative index with Ki-67 immunostaining and negative for p53 (Fig. 2A-C). EGFR immunostaining was diffusely positive (Fig. 2D).

Postoperatively, the patient had improvement in her speech and was discharged home after an uneventful hospital stay. Adjuvant treatment in the form of chemotherapy and radiotherapy was not administered. Approximately 12 weeks after the first surgery, she began to develop speech difficulty again. The patient exhibited a mild receptive and expressive aphasia along with poor recall and concentration upon neurologic examination. A repeat MRI revealed a ring-enhancing lesion in the left temporal lobe (Fig. 3A). She underwent a craniotomy for surgical resection of this lesion, and GBM was confirmed by pathology, including a high proliferative index with Ki-67 immunostaining and positive p53 (Fig. 4A-D). Postoperative MRI demonstrated gross total resection of the ring-enhancing lesion (Fig. 3B).

2.2. Case 2

This patient is a 45-year-old man who was evaluated for simple partial seizures with speech difficulties, mainly difficulty finding words. Neurologic examination was unremarkable. A brain MRI revealed a FLAIR and T2 hyperintense lesion in the left temporal lobe and insula (Fig. 5A and B). A functional MRI revealed close proximity of the lesion to Broca area.

A craniotomy while the patient was awake was performed with speech arrest mapping. The Ojemann stimulator probe was used for standard cortical mapping of the brain surface. For expressive speech, speech arrest was based on blocking

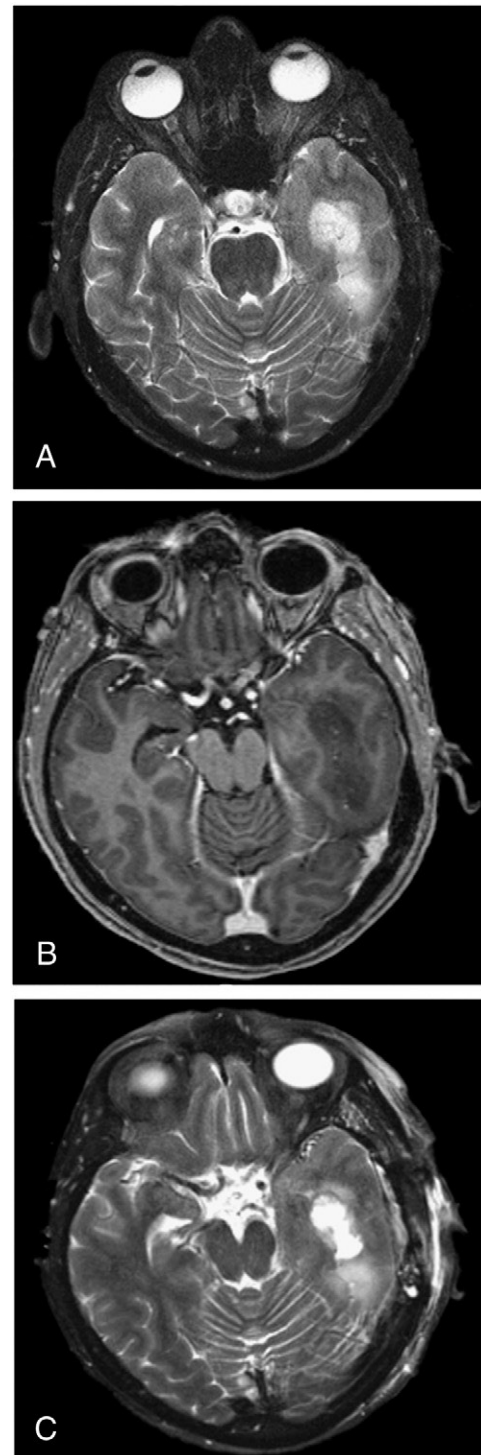


Fig. 1. Patient 1, preoperative and postoperative MR images after detection of the initial lesion. A: Preoperative axial T2-weighted MR image revealing a hyperintense left temporal lesion. B: Preoperative axial T1-weighted MR image with contrast administration revealing no contrast enhancement of the left temporal lesion. C: Postoperative T2 MR image showing resection of the lesion with residual tumor posteriorly.

number counting without simultaneous motor responses in the mouth or pharynx, that is, Broca area. A near total gross resection was achieved, but a small residual amount of tumor

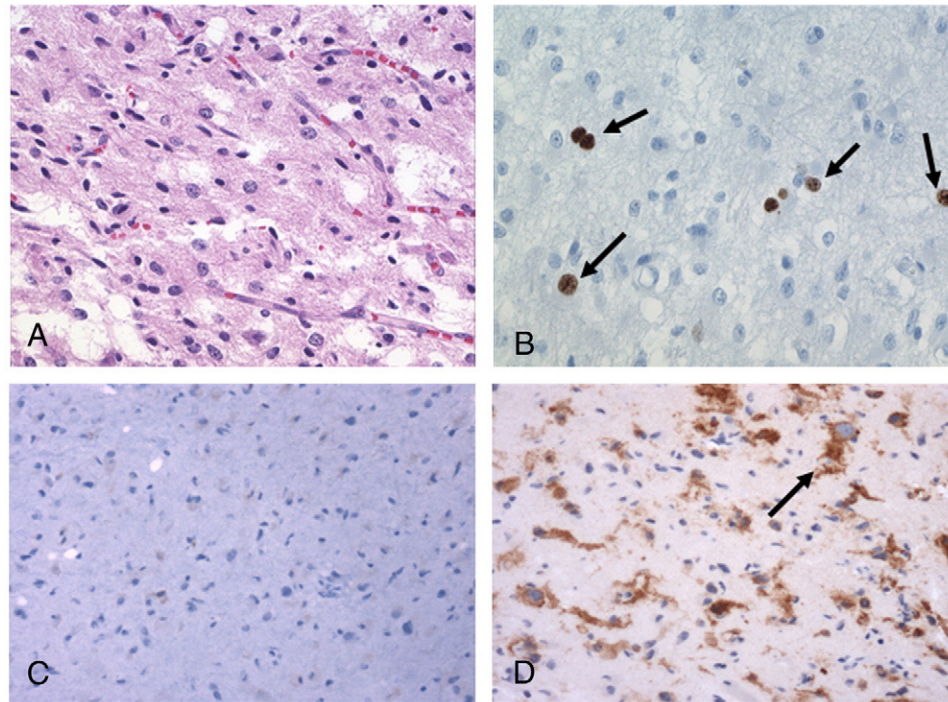


Fig. 2. Histopathology of specimens at the time of diagnosis of the low-grade astrocytoma for the patient in case 1. A: Well-differentiated grade II astrocytoma demonstrating low cellularity in the absence of increased mitotic activity or vascular proliferation. B: Ki-67 immunostaining (arrows) revealing a low proliferative index of the grade II astrocytoma. C: Specimen negative for p53 staining. D: EGFR staining is diffusely positive.

was left in the frontal operculum as a result of proximity to Broca area that was confirmed by intraoperative speech arrest mapping. Histopathologic examination was consistent with a low-grade astrocytoma, including a low proliferative index with Ki-67 immunostaining and negative p53 staining (Fig. 6A and B). The specimen was positive for EGFR (Fig. 6C). The postoperative MRI demonstrated resection of the lesion with residual tumor (Fig. 5C).

Postoperatively, the patient remained free of seizures and was discharged home after an uneventful hospital course. Neither radiotherapy nor chemotherapy was administered as adjuvant treatment. Thirteen weeks later, he began having frequent simple partial seizures. A repeat MRI demonstrated a ring-enhancing lesion in the same area corresponding to the MRI before his first operation (Fig. 7A). A second craniotomy while the patient was awake was performed for surgical resection of the lesion, which was confirmed to be a GBM by histopathology. Staining for Ki-67 revealed a high proliferative index, and p53 and EGFR immunostaining was positive (Fig. 6D-F). Postoperative MRI demonstrated gross total resection of the ring-enhancing lesion (Fig. 7B).

3. Discussion

Magnetic resonance imaging is an important diagnostic tool used for the demonstration of gliomas in affected patients. The degree of contrast enhancement has been used as a determinant of malignancy, and the absence of contrast

enhancement may be suggestive of a low-grade glioma, although some non-enhancing lesions can be malignant as proven by histology [2,9,13,15-17,25,27,33,34,37,41,47]. Therefore, MRI has been beneficial in detecting gliomas in early stages of their natural history in most cases. In the case of non-enhancing gliomas, previous studies have attempted to provide some evidence that there is variation in the time course of disease progression, in which a ring-enhancing lesion is detected on subsequent imaging studies (Table 1) [3,8,33,36,39].

A study by Barker et al [3] prospectively assessed the incidence of anaplastic tumors in a consecutive series of 31 patients who initially presented with a non-enhancing lesion over a 5-month period. Their investigation found that 2 of 31 patients with non-enhancing gliomas developed contrast enhancement during the preoperative period, but the interval timing was not reported [3]. The 2 patients' lesions were determined to be GBM at the time of surgical resection. Another study by Recht et al [39] demonstrated that 3 of 26 patients with non-enhancing lesions suggestive of low-grade gliomas on MRI developed contrast enhancement at intervals ranging from 4 to 123 months. All 26 patients in this group underwent an initial observation period, and 15 of the 26 patients had surgical resection after subsequent MRI revealed contrast enhancement [39]. Of these 15 patients, 7 had high-grade gliomas confirmed by histopathologic examination, whereas 3 tumor specimens were inconclusive [39]. The remaining 11 patients remained in an observation period [39]. Okamoto et al [33] retrospectively reviewed the

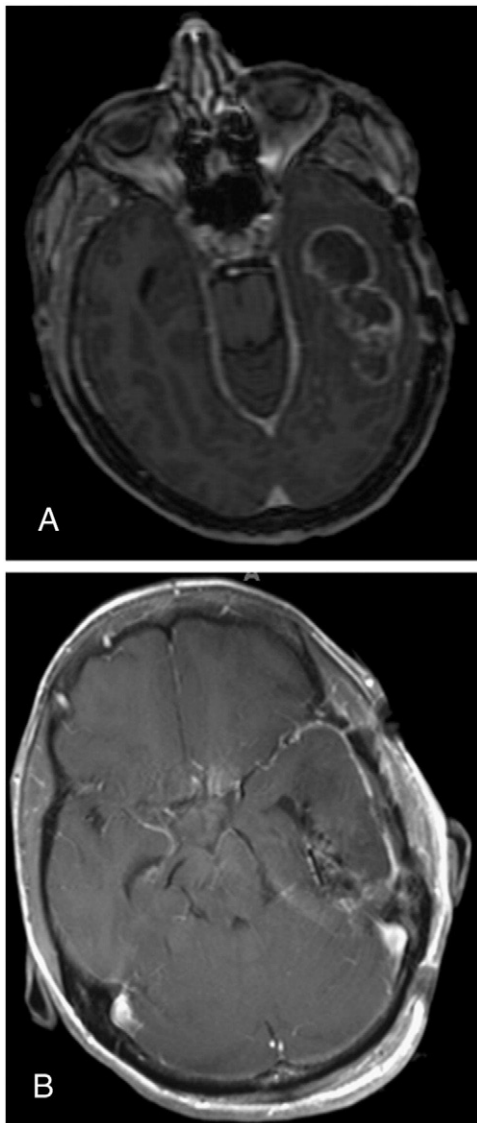


Fig. 3. Patient 1, preoperative and postoperative MR images after detection of the ring-enhancing lesion, around the second craniotomy. A: Twelve weeks after surgery, another postoperative axial T1-weighted MR image acquired after contrast administration demonstrating a ring-enhancing lesion. B: Postoperative T1-weighted MR image demonstrating resection of the lesion.

cases of 5 patients with high-grade gliomas that were diagnosed 4 months to 3 years and 3 months after initial MRIs demonstrated T2 hyperintensities in 3 patients and no detectable lesions in 2 patients. The 3 patients with T2 hyperintensities had their lesions misinterpreted as an ischemic lesion, infarction, or demyelinating process [33]. All lesions demonstrated contrast enhancement on subsequent MRI, and tissue diagnosis revealed malignant glioma [33]. During the CT era, Bolender et al [8] published a case series of 8 patients who were symptomatic with seizures, headaches, or visual disturbances and had normal head CTs after initial evaluation. Subsequent CT scans, ranging from 2 to 9 months later, revealed contrast-enhancing lesions [8].

Tissue obtained at surgery was confirmed to be GBM in all 8 cases [8]. The patients likely had initial “false-negative” CT scans, and MRIs may have demonstrated T2-weighted signal changes. A more recent report by Cohen-Gadol et al [12] documented an interval time of 17 weeks in 2 patients for radiographic progression from non-enhancing, T2 hyperintense lesions to ring-enhancing lesions on repeat MRI. In the first patient, stereotactic biopsy of a non-enhancing lesion in the right primary motor cortex, which was confirmed by functional MRI, revealed anaplastic astrocytoma [12]. A repeat MRI in this patient demonstrated progression to a ring-enhancing lesion, and radiotherapy followed by chemotherapy was administered without surgery because of the lesion’s location [12]. In the second patient, the non-enhancing lesion was followed expectantly and subsequently resected after a repeat MRI demonstrated contrast enhancement. Histopathologic examination was consistent with GBM [12]. We provide in this report 2 examples of rapid malignant transformation within 13 weeks of 2 histopathologically proven low-grade gliomas in 2 patients.

These 2 cases illustrate the potential risk of rapid evolution of histopathologically proven, non-enhancing low-grade gliomas into malignant gliomas. Magnetic resonance imaging has been used to document the evolutionary stages of gliomas, and malignant gliomas are usually identified by the degree of contrast enhancement. Although some anaplastic astrocytomas may not demonstrate contrast enhancement, especially patients in their fifth and sixth decades of life, the pathologic specimens, which were obtained after first surgical resection, in the 2 cases presented in this report were proven to be low-grade astrocytomas. The subtotal resection of tumor in both cases could have possibly led to an absence of sampling of an area of tumor with a higher pathologic grade. In both cases, the lesions subsequently underwent rapid transformation into a malignant glioma. Moreover, there remains much debate over the surgical management of low-grade gliomas, the timing of surgery, and the impact of the extent of resection on patient outcome [5-7,10,11,20-23,26,29,31,32,35,38,40,42,46,49]. In addition, effects of the extent of surgical resection on the timing of malignant transformation have not been investigated. Molecular characterization of this subtype of tumors is warranted to identify patients with low-grade gliomas who may undergo rapid malignant transformation and benefit from more aggressive adjuvant therapy. There have been reports of molecular studies that attempt to find a potential correlation between low-grade gliomas and GBMs, in terms of secondary malignant transformation, but no definitive genetic link has been found to date [18,28,48]. Our 2 cases demonstrated p53 to be expressed in the secondary GBMs and not the predecessor grade II astrocytomas, which may implicate a role for p53 in the transformation process. The overexpression of EGFR was found to be expressed in both the grade II astrocytomas and secondary GBMs in these cases, which may provide a molecular clue for the propensity

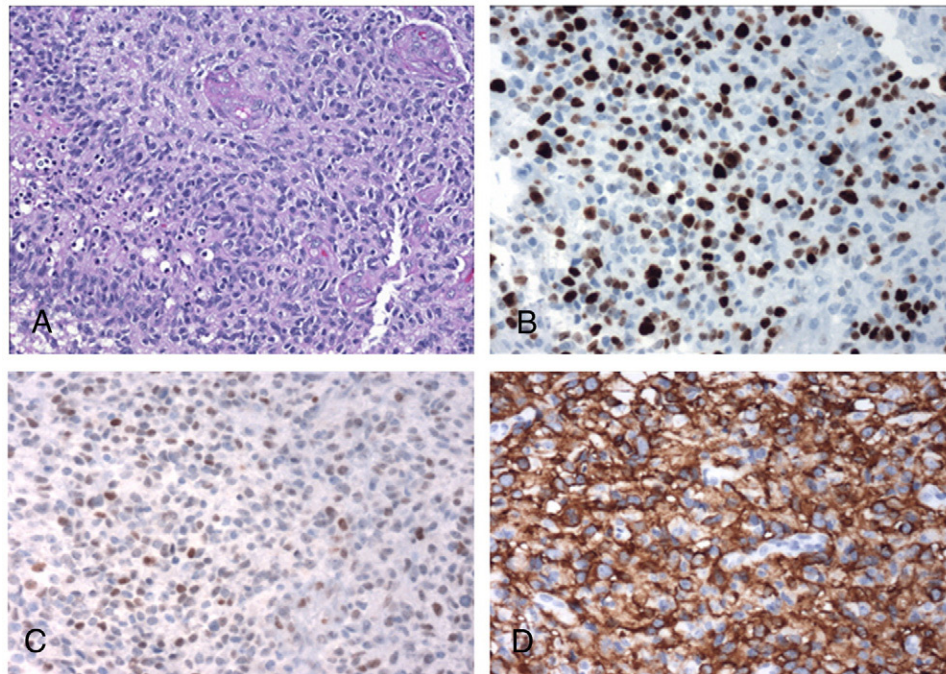


Fig. 4. Histopathology of specimens at the time of diagnosis of GBM for the patient in case 1. A: GBM demonstrating increased cellularity with pseudopalisading necrosis and vascular proliferation. B: Ki-67 immunostaining revealing a high proliferative index. C: p53 staining is positive. D: EGFR staining is diffusely positive.

of low-grade gliomas to transform into malignant gliomas. Further studies need to be conducted to determine if a correlation exists, which may lead to a discussion pertaining to adjuvant treatment in grade II astrocytomas expressing high levels of EGFR.

4. Conclusion

Low-grade astrocytomas may undergo rapid malignant transformation, and molecular and biological variability may exist within the subclassification of low-grade gliomas. Further genotypic studies are needed to ascertain if a subtype of aggressive low-grade gliomas are present at initial biopsy or resection. These tumors may warrant consideration for more aggressive treatment modalities, including radiation and chemotherapy.

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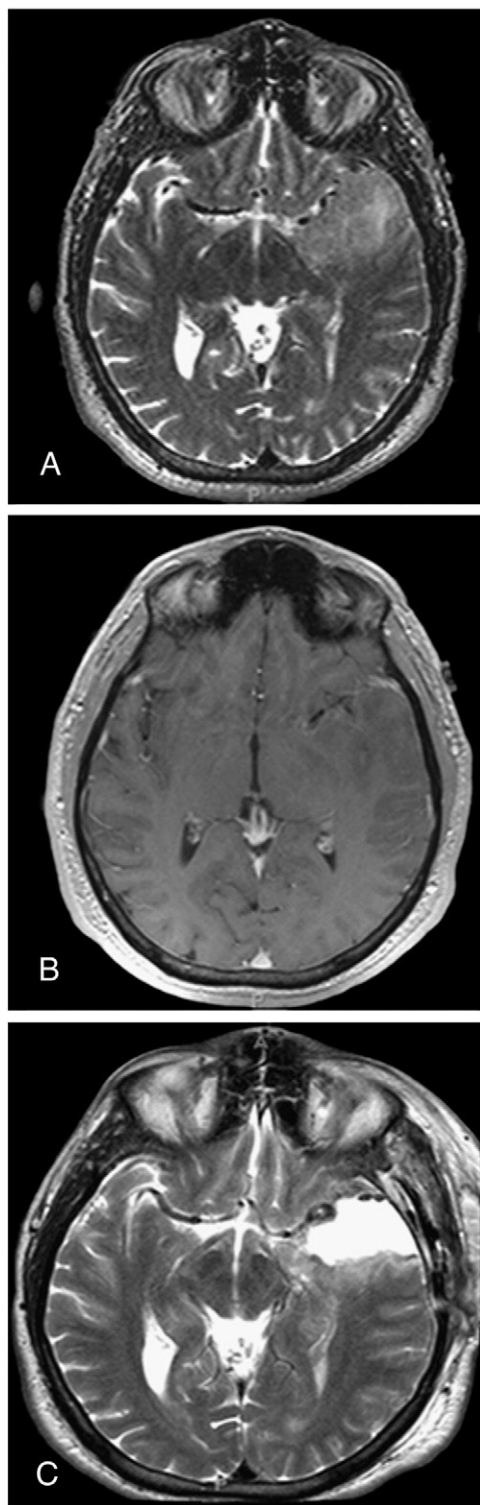


Fig. 5. Patient 2, preoperative and postoperative MR images after detection of the initial lesion. A: Preoperative axial T2-weighted MR image revealing a hyperintense left temporal and insular lesion. B: Preoperative axial T1-weighted MR image demonstrating no enhancement of the lesion. C: Postoperative T2 MR image showing resection of the lesion with residual tumor in the uncus and parahippocampal area.

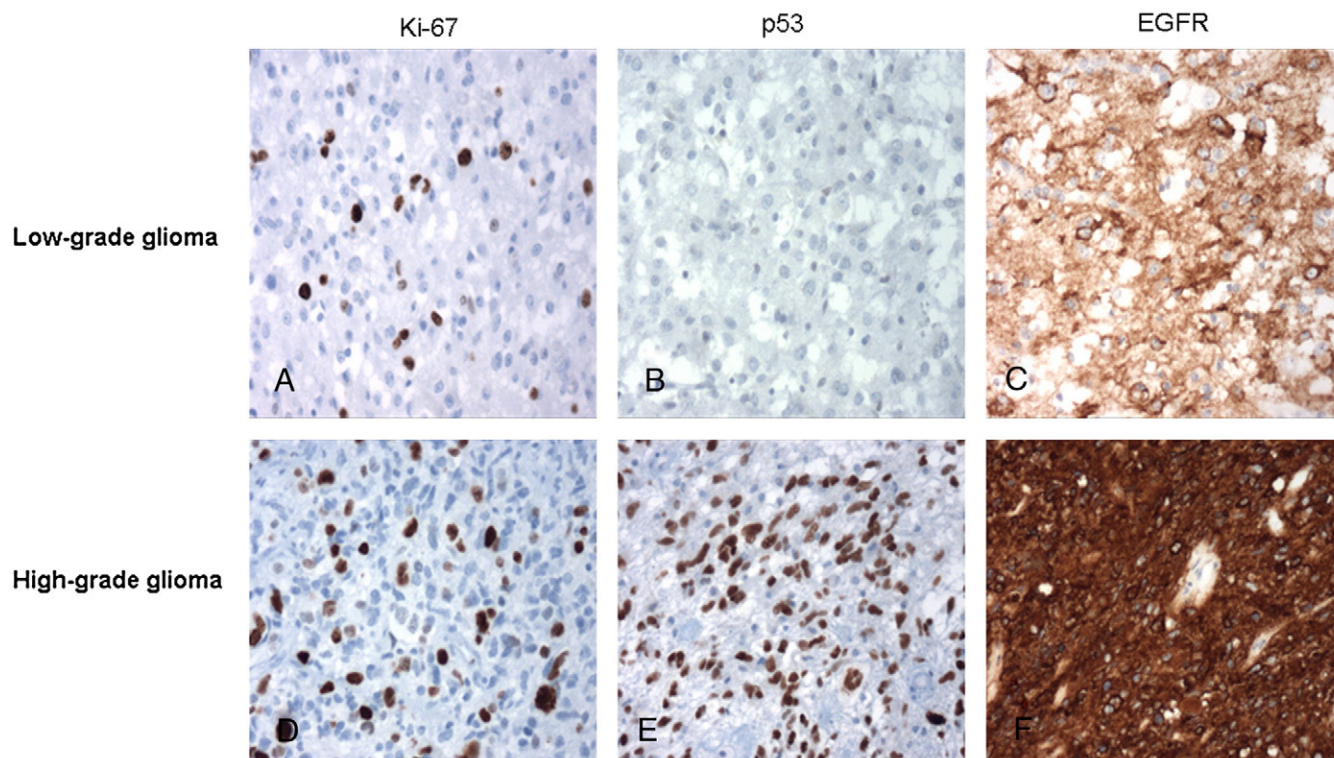


Fig. 6. A to C and D to F represent the low-grade and high-grade astrocytoma diagnoses, respectively, for the patient in case 2. A: Ki-67 staining revealing a low proliferative index. B: Immunostaining negative for p53. C: Immunostaining demonstrating positive EGFR. D: High proliferative index with Ki-67 staining. E: p53-positive. F: EGFR immunostaining diffusely positive.

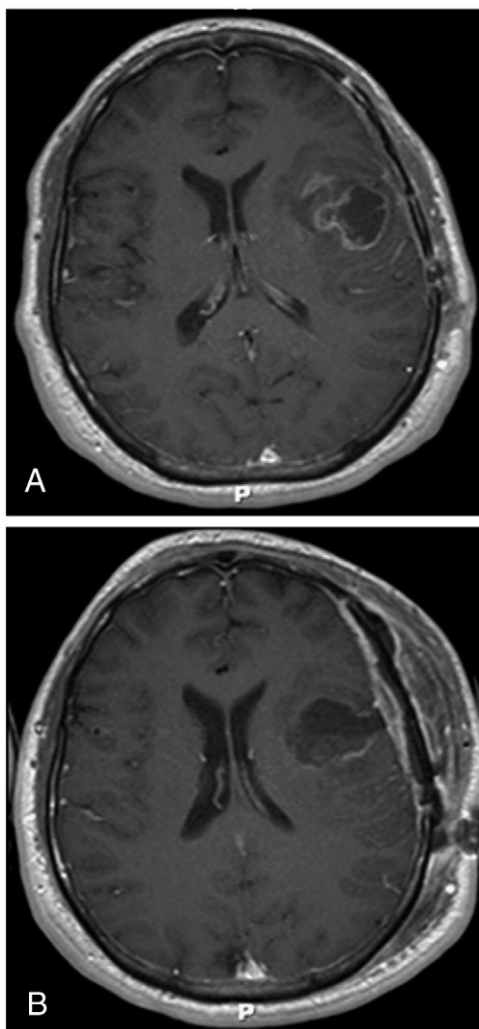


Fig. 7. Patient 2, preoperative and postoperative MR images in patient 2 after detection of the ring-enhancing lesion, around the second craniotomy. A: Thirteen weeks after surgery, another postoperative axial T1-weighted MR image acquired after contrast administration demonstrating a ring-enhancing lesion. B: Postoperative T1-weighted MR image demonstrating resection of the lesion.

Table 1

Summary of studies demonstrating the variable time course of transformation from a non-enhancing brain lesion to a ring-enhancing lesion on imaging studies

Authors and year	No. of patients	MRI/CT findings	Initial biopsy/surgery	Initial pathology results	Time interval	Repeat MRI/CT findings	Surgical/biopsy pathology
Bolender et al [8]	8	Patient 1: normal CT	None		9 mo	CT: ring-enhancing lesion in left parietal lobe	Surgery: GBM
		Patient 2: normal CT	None		4 mo	CT: ring-enhancing lesion in right parietal lobe	Surgery: GBM
		Patient 3: normal CT	None		2.5 mo	CT: ring-enhancing lesion in left frontal lobe	Surgery: GBM
		Patient 4: subarachnoid cyst in right frontotemporal area	None		3 mo	CT: ring-enhancing lesion left temporal lobe	Surgery: GBM
		Patient 5: normal CT	None		3 mo	CT: ring-enhancing lesion in right temporoparietal region	Surgery: GBM
		Patient 6: normal CT	None		4 mo	CT: ring-enhancing lesion left occipital lobe	Surgery: GBM
		Patient 7: normal CT	None		3 mo	CT: ring-enhancing lesion right frontoparietal region	Surgery: GBM
		Patient 8: normal CT	None		3 mo	CT: ring-enhancing lesion left frontal lobe	Surgery: GBM
Barker et al [3]	31	All had supratentorial non-enhancing masses	Biopsy: 8	DNET: 2		2 patients developed enhancement within their lesions	Surgery: GBM in both cases
			STR: 15	Low-grade astrocytoma: 1 (Grade III) Mixed oligoastrocytoma: 12 Oligodendroglioma: 4 AA: 5 (Grade III) Mixed oligoastrocytoma: 4		Timing not documented	
			GTR: 5				
Okamoto et al [33]	5	Patient 1: normal MRI	None		4 mo	T1 multicentric ring-enhancing lesions	Biopsy: GBM
		Patient 2: T2 hyperintensity in left parietal lobe	None	Presumed demyelination	10 mo	T1 ring-enhancing lesion in left parietal lobe	Surgery: GBM
		Patient 3: Multiple small T2 hyperintensities in left frontal lobe	None	Presumed ischemic lesions	39 mo	T1 enhancing lesion in left frontal lobe	Biopsy: AA
		Patient 4: T2 hyperintensity in right frontal lobe	None	Presumed cerebral infarction	5 mo	T1 ring-enhancing lesion in right frontal lobe	Surgery: AA
		Patient 5: subtle T2 hyperintensity in left temporal lobe	None	Presumed ischemic lesion	9 mo	T1 ring-enhancing lesion in left temporal lobe	Biopsy: AA
Cohen-Gadol et al [12]	2	Patient 1: T2 hyperintensity in right precentral area	Biopsy	AA	17 wk	T1 ring-enhancing lesion in right precentral area	Radiation and chemotherapy
		Patient 2: T2 hyperintensity in right medial temporal lobe	None		17 wk	T1 ring-enhancing lesion in right medial temporal lobe	Surgery: GBM
Frazier et al (this study)	2	Patient 1: T2 hyperintensity in left temporal lobe	GTR	Grade II astrocytoma	12 wk	T1 ring-enhancing lesion in left temporal lobe	Surgery: GBM
		Patient 2: T2 hyperintensity in left temporal lobe and insula	GTR	Grade II astrocytoma	13 wk	T1 ring-enhancing lesion in left temporal lobe and insula	Surgery: GBM

AA indicates anaplastic astrocytoma; DNET, dysembryoplastic neuroepithelial tumor; STR, subtotal resection; GTR, gross total resection.