News Release

Title

Imaging features of localized *IDH* wild-type histologically diffuse astrocytomas: a single-institution case series

Key Points

•*IDH* wild-type histologically diffuse astrocytomas are very rare and its pathophysiology and clinical outcome is still unknown.

• Although localized types of *IDH*wt astrocytomas are rarer than the infiltrative type, it is not clear whether this radiographic feature affects the clinical prognosis of *IDH*wt LrGGs.

• The authors assessed clinical cases of localized *IDH*wt histologically diffuse astrocytomas that resulted in malignant recurrence and a poor clinical prognosis similar to that of glioblastomas.

Summary

This work is mainly from the team of Yuji Kibe (Doctoral student) and Kazuya Motomura (Associated professor, Department of Neurosurgery) in Nagoya University Graduate School of Medicine (Dean: Hiroshi Kimura).

Isocitrate dehydrogenase wild-type (*IDH*wt) diffuse astrocytomas feature highly infiltrative patterns, such as a gliomatosis cerebri growth pattern with widespread involvement. Among these tumors, localized *IDH*wt histologically diffuse astrocytomas are rarer than the infiltrative type. We retrospectively analyzed the records of five patients with localized *IDH*wt histologically diffuse astrocytomas.

All patients were female, and their mean age at the time of the initial treatment was 55.0 years. All patients had focal disease that did not include gliomatosis cerebri or multifocal disease. All patients received a histopathological diagnosis of diffuse astrocytomas at the time of the initial treatment. For recurrent tumors, second surgeries were performed at a mean of 12.4 months after the initial surgery. A histopathological diagnosis of glioblastoma was made in four patients and one of gliosarcoma in one patient. The initial status of *IDH1*, *IDH2* was “wild-type” in all patients. *TERT* promoter mutations (C250T or C228T) were detected in four patients.

We assessed clinical cases of localized *IDH*wt histologically diffuse astrocytomas that resulted in malignant recurrence and a poor clinical prognosis similar to that of glioblastomas. Our case series suggests that even in patients with histologically diffuse astrocytomas and those who present with radiographic imaging findings suggestive of a localized tumor mass, physicians should consider the possibility of *IDH*wt histologically diffuse astrocytomas.

Research Background

2021 WHO classification of central nervous system tumors has proposed that *IDH*wt histologically lower grade gliomas (LrGG: histologically diffuse astrocytoma or anaplastic astrocytoma) with molecular features of glioblastoma, *IDH*wt should be classified in glioblastoma,

*IDH*wt, given their poor survival prospects. However, *IDH*wt histologically diffuse astrocytomas are especially rare, then their exact prognosis remains unknown.

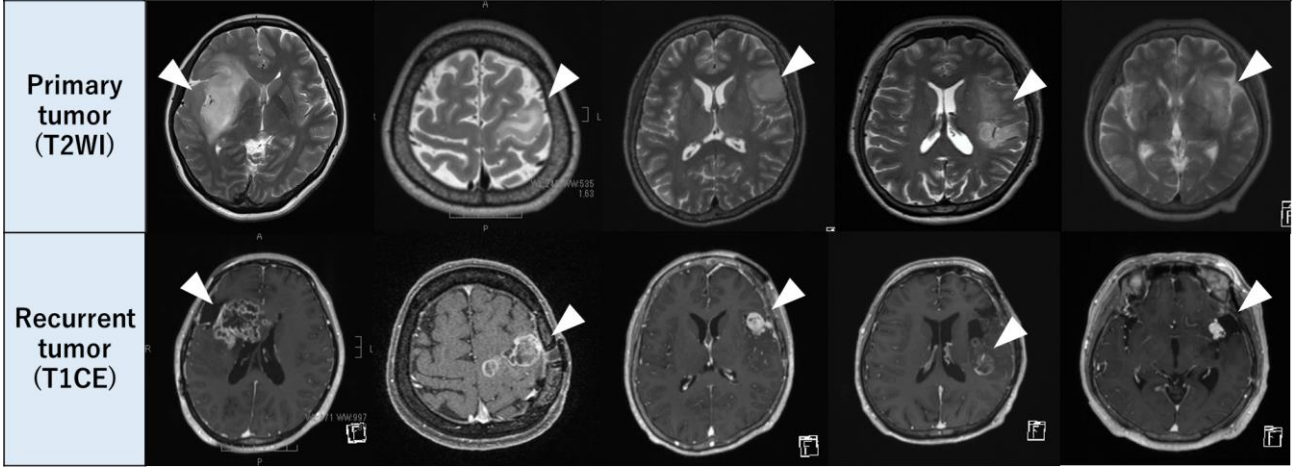
Some studies have reported that *IDH*wt LrGGs possess highly infiltrative patterns, such as gliomatosis cerebri growth patterns with widespread involvement. Although localized tumors are typical in LrGGs, it is not clear whether this radiographic feature affects the clinical prognosis of *IDH*wt LrGGs.

The authors analyzed five cases of localized *IDH*wt histologically diffuse astrocytomas and found that they all resulted in malignant recurrence and a poor clinical prognosis similar to that of GBMs. Although a number of studies have investigated *IDH*wt LrGGs, very few studies have reported detailed information on localized *IDH*wt LrGGs. In the present study, we therefore describe the clinical, radiographic, histopathological, and molecular characteristics of localized *IDH*wt histologically diffuse astrocytomas

Research Results

The five patients' clinical characteristics are summarized in Table 1. All patients were female, and their mean age at the time of the initial treatment was 55.0 years. The tumors were located in the insula in three patients (60.0%), in the precentral gyrus in one patient (20.0%), and in the frontal operculum in one patient (20.0%). All patients had focal disease, not including gliomatosis cerebri or multifocal disease. All initial tumors showed no contrast enhancement on Magnetic Resonance Imaging (MRI) (Fig.1). Gross total resection (GTR) was achieved in three patients and partial resection (PR) in two patients. All histopathological diagnoses at the initial treatment were diffuse astrocytomas. Thus, no adjuvant chemoradiotherapy was performed (Fig.2).

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	female	female	female	female	female
Age	39	57	58	54	67
location	insula	central sulcus	frontal operculum	insula	insula



T2WI; T2 weighted image, T1CE; T1 weighted image with contrast enhancement

Fig.1: Imaging features of primary and recurrent tumors

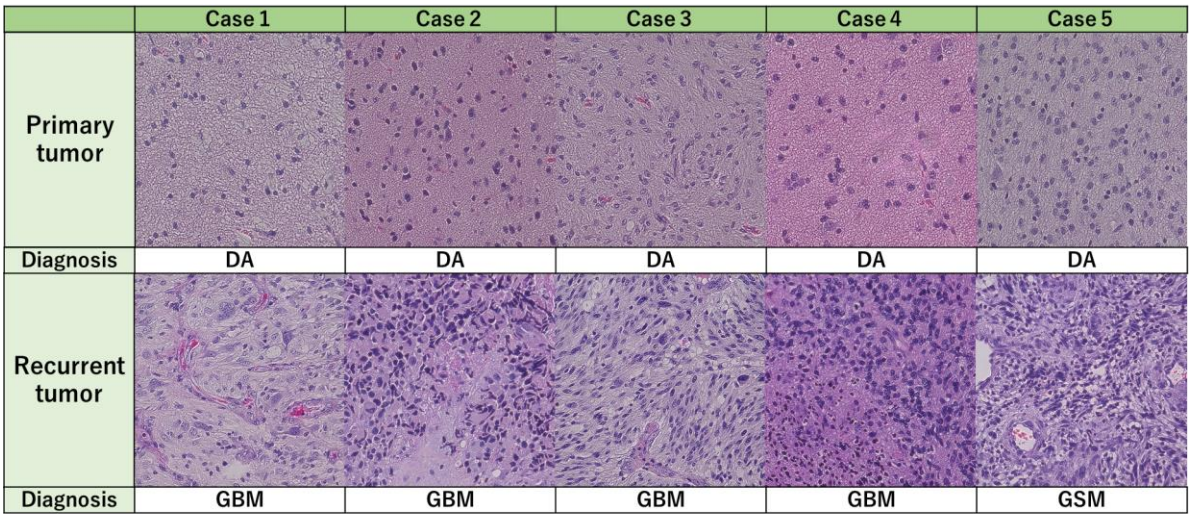


Fig.2 : Hematoxylin and Eosin staining of primary and recurrent tumors

Recurrent tumors developed in or near the surgical defects in all patients, and all tumors showed contrast enhancement on MRI. The second surgery was performed in all patients, at a mean of 12.4 months after the initial surgery (progression-free survival; PFS). The median overall survival (OS) of five patients was 28.7 months (95% CI, 19.0 to 38.4). A histopathological diagnosis of GBM was made in four patients and one of gliosarcoma in one patient. As treatment at recurrence, all patients underwent adjuvant temozolomide and concurrent local radiotherapy or gamma knife radiosurgery.

Genetic analysis was performed for initial and recurrent tumors of all patients. The status of *IDH1*, *IDH2* was "wild-type" in all patients. *TERT* promotor mutations (C250T or C228T), which is characteristic of glioblastoma were detected in four patients. *CDKN2A/B* homozygous was detected in the initial tumor of one patient (Table.1). This patient resulted in shortest PFS (5.8 months) despite gross total resection of initial tumor.

		Case 1		Case 2		Case 3		Case 4		Case 5	
		1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
mutation	*IDH1*	-	-	-	-	-	-	-	-	-	-
	IDH2	-	-	-	-	-	-	-	-	-	-
	H3F3A	-	-	-	-	-	-	-	-	-	-
	HIST1H3B	-	-	-	-	-	-	-	-	-	-
	BRAF	-	-	-	-	-	-	-	-	-	-
	TERTp	C250T	C250T	C250T	C250T	C228T	C228T	-	-	C228T	C228T
Copy number	1p/19q	-	-	-	-	-	-	-	-	-	-
	EGFR	-	-	-		-	-	-	-	-	-
	CDKN2A/B	-	-	-	-			-		-	-
	PTEN	-	-	-	-	-	-	-	-	-	
	p53				-	-					-
	+7/-10	-	-	-	-	-	-	-	-	-	-

mutation amplification Homozygous deletion Heterozygous deletion

Table.1 : Molecular features of primary (1st) and recurrent (2nd) tumors

Research Summary and Future Perspective

Although *IDH*wt histologically diffuse astrocytomas possess highly infiltrative patterns, such as gliomatosis cerebri growth patterns with widespread involvement, we observed clinical cases of localized *IDH*wt histologically diffuse astrocytomas, which resulted in malignant recurrence and a poor clinical prognosis similar to that of GBMs. Even in patients with histologically diffuse astrocytomas and those who present with radiographic imaging findings suggestive of a localized tumor mass, physicians should consider the possibility of *IDH*wt of histologically diffuse astrocytomas.

Publication

Yuji Kibe, Kazuya Motomura, Fumiharu Ohka, Kosuke Aoki, Hiroyuki Shimizu, Junya Yamaguchi, Tomohide Nishikawa, and Ryuta Saito. Imaging features of localized IDH wild-type histologically diffuse astrocytomas: a single-institution case series. Scientific report, published online on January 16, 2023.
DOI:10.1038/s41598-022-25928-2

Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Sci_230116.pdf