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The T2-FLAIR mismatch sign in glioblastoma, isocitrate dehydrogenase wild-type A case report

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Abstract

We present a case of the T2-FLAIR mismatch sign in glioblastoma, *isocitrate dehydrogenase (IDH)*-wild type. The T2-FLAIR mismatch sign is known as a highly specific imaging finding of astrocytoma, *IDH*-mutant. Meanwhile, *IDH*-wildtype diffuse astrocytic gliomas with *telomerase reverse transcriptase* (*TERT*) promoter mutation in adults are defined as glioblastoma in the 2021 World Health Organization Classification of Tumors of the Central Nervous System, fifth edition (2021 WHO classification), which underscores the importance of molecular information in central nervous system tumors. This indicates even glioblastoma, *IDH*-wild type may be masquerading as lower-grade glioma in histology. The reasons for the discrepancy between tumors with less aggressive histology and poor prognosis caused by *telomerase reverse transcriptase* promoter mutation of *IDH*-wildtype diffuse glioma remain unclear. However, glioblastoma, *IDH*-wildtype should be considered as a potential differential diagnosis even in patients with the T2-FLAIR mismatch sign in diffuse gliomas.

Keywords

Glioblastoma, T2-FLAIR mismatch, isocitrate dehydrogenase, glioma

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Introduction

The T2-FLAIR mismatch sign is defined as the presence of a complete/near-complete hyperintensity of the tumor on T2-weighted image in combination with a relative hypointensity except for a hyperintense peripheral rim on FLAIR.[1,2] Studies have shown the T2-FLAIR mismatch sign is a radiogenomic signature for astrocytomas that is considered highly specific and suggestive of *isocitrate dehydrogenase* (*IDH*) mutated 1p19q non-codeleted tumors.[1–6] However, discrepancies between histology and genetic profiles are known for gliomas.[7] The fact indicates that integrated diagnosis of glioblastoma, *IDH*-wild type may be potentially misdiagnosed as lower-grade glioma in histology. This case report describes a case of the T2-FLAIR mismatch sign in glioblastoma, *IDH*-wild type.

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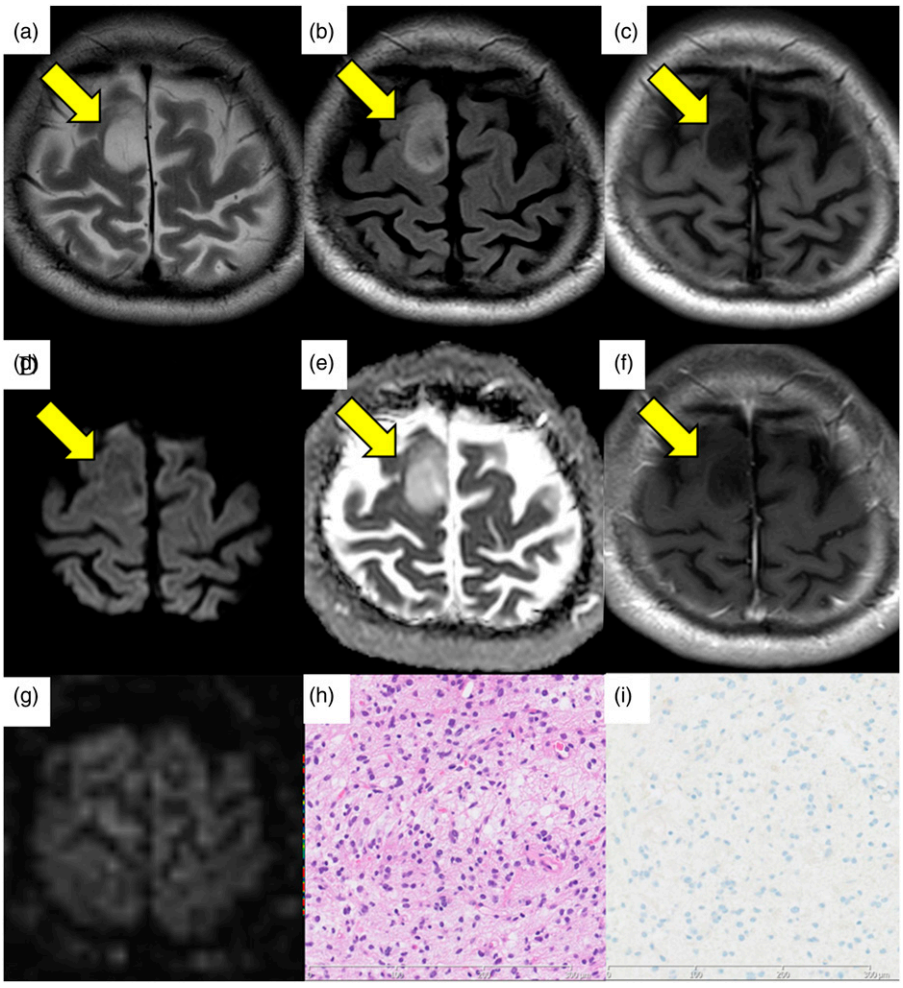

Figure 1. (a) T2-weighted imaging. (b) Fluid-attenuated inversion recovery (FLAIR). (c) Pre-contrast-enhanced T1-weighted imaging. (d) Diffusion-weighted imaging (DWI; b = 1000 s/mm^2) (e) Apparent diffusion coefficient (ADC) map. (f) Post-contrast-enhanced T1-weighted imaging. (g) Arterial spin labeling (post-labeling delay, 2000 ms). (h) Hematoxylin and eosin (HE) staining. (i) *IDH1*-R132H immunohistochemical expression of the right frontal lobe tumor. On MR imaging, the tumor appeared high-intensity on T2-weighted imaging (Figure 1(a)). FLAIR showed low intensity with high-intensity peripheral rim, which indicated positive for the T2-FLAIR mismatch sign (B; arrow). The tumor appeared low-intensity on T1-weighted imaging and iso-intensity on DWI. ADC map showed high mean ADC (1.72×10^{-3} mm^2/s) was demonstrated in the tumor. No contrast enhancement was observed on post-contrast-enhanced T1-weighted imaging. Arterial spin labeling (post-labeling delay, 2000 ms) revealed no increase of tumor blood flow. Histologically, diffuse proliferation of glioma cells with no microcystic changes but edematous changes in the background. *IDH1*-R132H immunohistochemical expression was negative.

Case report

A 57-year-old man had been suffered from transient muscular weakness of the left upper and lower extremities for 6 months. The symptom had improved with the administration of antiepileptic medication by a primary care physician. However, MR imaging showed the right frontal lobe mass, and he was therefore referred to our hospital for further examination and treatment. There was no focal neurological deficit on admission. Routine blood tests were normal, and his family history and medical history were unremarkable.

Computed tomography showed a low-density tumor in the right superior frontal gyrus without calcification or gross hemorrhage (not shown). MR imaging was performed using a 3.0-T scanner (Ingenia Elition X, Philips Medical Systems, Best, The Netherlands). On MR imaging, the tumor appeared high-intensity on T2-weighted imaging (Figure 1(a)). FLAIR showed low intensity with high-intensity peripheral rim, which indicated positive for the T2-FLAIR mismatch sign (Figure 1(b)). The tumor appeared low-intensity on T1-weighted imaging (Figure 1(c)) and iso-intensity on diffusion-weighted imaging (b = 1000 s/mm^2; Figure 1(d)). Apparent diffusion coefficient

(ADC) map showed high mean ADC (1.72×10^{-3} mm^2/s) was demonstrated in the tumor (Figure 1(e)). Arterial spin labeling (post-labeling delay, 2000 ms) revealed no increase of tumor blood flow (Figure 1(f)). No contrast enhancement was observed on post-contrast-enhanced T1-weighted imaging (Figure 1(g)). Astrocytoma, *IDH*-mutant was suspected based on these imaging characteristics.

Total resection of the tumor was performed. Histologically, the diffuse proliferation of glioma cells with no microcystic changes but edematous changes in the background (Figure 1(h)). A low mitotic rate of 2 mitoses in 10 high power fields was noted, while Ki-67 labeling index was about 10% at a hot spot. *IDH1*-R132H immunohistochemical expression was negative (Figure 1(i)) and *IDH*1/2 wild type was confirmed by genetic sequencing. There was no necrosis or microvascular proliferation in histological analysis which corresponds to lower-grade histomorphology, while *TERT* gene mutation and EGFR amplification were found. These features confirmed the integrated diagnosis of glioblastoma, *IDH*-wild type (CNS WHO grade 4) according to the 2021 WHO classification. No neurological symptoms were identified after resection of the tumor, and postoperative intensity modulated radiation therapy combined with temozolomide chemoradiotherapy was administered. A follow-up MR imaging performed 6 months later revealed no evidence of recurrence.

Discussion

The T2-FLAIR mismatch sign is considered a finding that reflects edematous changes or microcystic degeneration in astrocytoma, *IDH*-mutant.[8] Kinoshita et al. suggested that *IDH*-mutant, non-codeleted astrocytomas often contain tumors that exhibit long T1 and T2 effects, which phenomenon could be the leading cause of the T2-FLAIR mismatch sign.[9] In our case, histological features include the diffuse proliferation of glioma cells with no microcystic changes but edematous changes in the background. Taken together, the T2-FLAIR mismatch sign would represent histological features themselves than genetic profiles.

Interestingly, the T2-FLAIR mismatch sign was observed in more than half cases of dysembryoplastic neuroepithelial tumors (DNET) and Onishi et al. stated that the T2-FLAIR mismatch sign is not specific for diffuse astrocytoma, *IDH*-mutant and 1p19q non-codeleted.[10] The T2-FLAIR mismatch sign was defined by the presence of 2 distinct MR imaging features: i) Tumor displays complete or near-complete ad almost homogeneous hyperintense signal on T2-weighted images, ii) Tumor displays relatively hypointense signal on the T2-weighted FLAIR sequence except for a hyperintense peripheral rim.[1,2] *IDH*-wild type gliomas with T2-FLAIR mismatch sign are found in previous literature.[8,11] However, these cases may not be applied to the strict guideline suggested by Patel et al.[1] Thus, we believe our case is the first report of the T2-FLAIR mismatch sign in glioblastoma, *IDH*-wild type.

Imaging findings in this case include high mean ADC without contrast enhancement in addition to the T2-FLAIR mismatch sign, making it difficult to diagnose as glioblastoma, IDH-wild type preoperatively. Indeed, histological findings were consistent with low grade astrocytoma. The reasons for the discrepancy between tumors with less aggressive histology and poor prognosis caused by *TERT* promoter mutation of *IDH*-wildtype diffuse glioma in our case remain unclear. ^{1}H-MR spectroscopy and stretched-exponential model of diffusion-weighted imaging has been reportedly useful for predicting *TERT* promoter mutation status in *IDH*-wildtype diffuse astrocytic glioma preoperatively.[12] Nevertheless, it is crucial to identify imaging features of the T2-FLAIR mismatch sign in glioblastoma, *IDH*-wild type with an increasing number of reported cases.

In conclusion, glioblastoma, *IDH*-wildtype should be considered as a potential differential diagnosis even in patients with the T2-FLAIR mismatch sign in diffuse gliomas.

Declaration of conflicting interests

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