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# IDH-wildtype infiltrative low-grade glial tumor with nodule-like enhancement pattern

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A B S T R A C T

The authors describe a usual case of infiltrative low-grade glial neoplasm with a marked enhanced area which is difficult to diagnose. A 42-year-old man had the diffuse mass lesion partially with apparent enhancement in the right temporal lobe, the insular, and the basal ganglia regions. Final pathological diagnosis from the removed specimens was *IDH-wildtype diffuse astrocytoma* according to 2016 WHO classification, although it had unusual findings including gliomesenchymal reaction. The nodule-like enhancement was thought to be owing to the mesenchymal component. Several molecular analysis including pyrosequence analysis, Ion Torrent™ next-generation sequencing and multiplex ligation-dependent probe amplification analysis detected no genomic abnormality. *IDH-wildtype diffuse astrocytoma* is a heterogeneous category and has a minor subset with a silent genomic landscape like the present case.

## 1. Introduction

A diffuse astrocytoma is a diffusely infiltrative glial tumor occurring at the peak from 30 to 50 years old as the typical age of its diagnosis and mainly locates in the cerebral hemisphere [1]. A magnetic resonance imaging (MRI) of the typical diffuse astrocytoma shows hyperintensity on T2WI and no (or minimal) enhancement by the contrast medium. In a previous paper, only 50 cases (5.4%) of 927 WHO grade II gliomas had nodule-like enhancement pattern [2]. In this report, we describe a case of diffuse astrocytoma with a marked enhanced area which is difficult to diagnose before surgery.

## 2. Case presentation

A 42-year-old man was referred to our hospital because of mild paralysis of the left leg. Six month ago he also developed left upper limb paralysis. MRI showed the lesion was hypo-intense on T1- weighted images (WI), of mixed intensity on T2WI, and hypo-intense on diffusion-WI (DWI) in the right temporal lobe, the insular, and the basal ganglia regions (Fig. 1). A part of the lesion had large nodule-like enhancement after the gadolinium (Gd) injection, and showed hypo-perfusion at the cerebral blood volume study. The patient underwent lesion biopsy for pathological diagnosis. Pathological diagnosis from the biopsy specimen was not classified according to any existing classification and seemed to show a low-grade neoplasm. Both neurological findings, including the paralysis and neuroimaging data improved intensely after oral and intravenous corticosteroids for relieving peritumoral edema (Fig. 2). Despite recommendation of treatment with radiotherapy and/or temozolomide (TMZ) the patient refused any chemo-radiotherapy.

Ten months after the first surgery, the left paresis worsened and MRI showed the increasing tumor in the temporal lobe extending to the frontal lobe (Fig. 2). He underwent partial tumor removal. Pathological diagnosis from the specimen was basically the same as after the first surgery. An infiltrative neoplasm mainly consisted of astrocytic tumor cells (Fig. 3), positive for glial fibrillary acidic protein (GFAP). Neither piloid tumor cell nor degenerative structure such as rosenthal fiber and eosinophilic granular body were shown in the specimen. Additionaly, in the Gd-enhanced area mainly located in the insular cortex, there were spindle-shaped cells near the astrocytic tumor cells, that were positive for reticulin, indicating mesenchymal cells (Fig. 4).

Immunohistochemical staining of synaptophysin, neurofilament, CD34 and Neu-N as neuronal markers showed that they were stained mainly in normal neurons of the gray matter (Figs. 4 and 5). Any part of specimens did not show accumulation of macrophages or perivascular lymphocytic cuffing such as demyelinating disease. Final pathological

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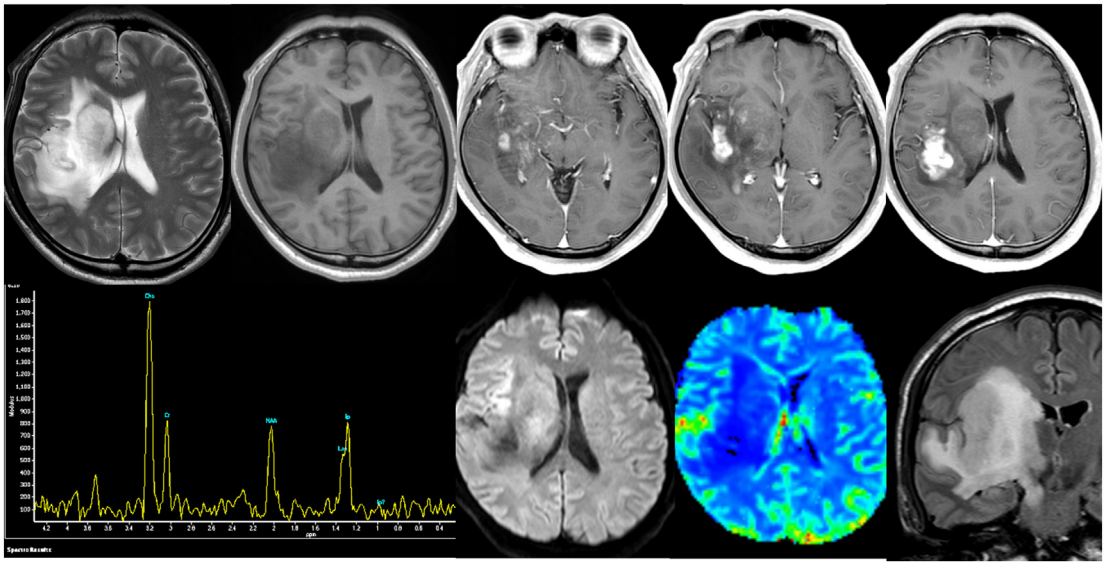

**Fig. 1.** The axial view of magnetic resonance images (MRI) on admission. An area from right temporal region to insula on T2WI, T1WI and T1WI with gadolinium (Gd) enhancement (upper), and MR spectroscopy, diffusion WI, perfusion image, and the coronal view of FLAIR image (lower) is shown.

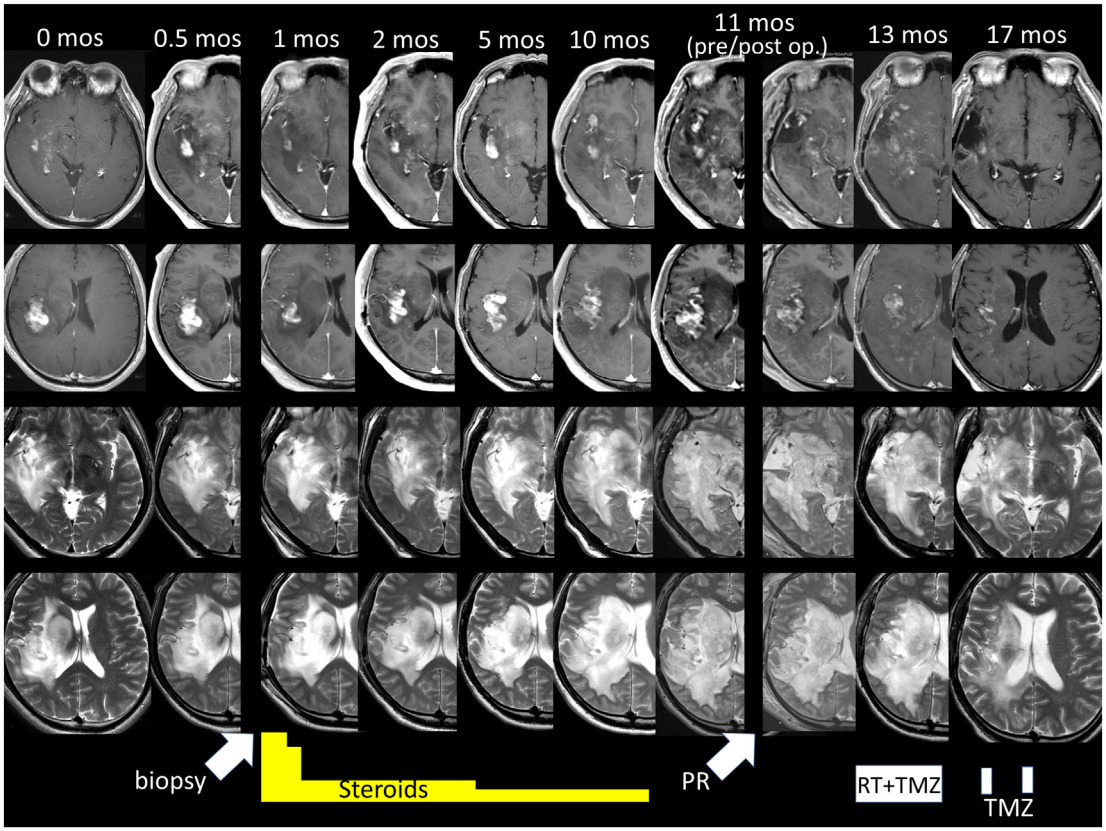


**Fig. 2.** The axial view of MRI (upper and upper middle, T1WI with Gd enhancement; lower and lower middle, T2WI) before and after the biopsy, partial removal (PR) and radiation therapy (RT) concomitant with temozolomide (TMZ) showing the drastic change of tumor lesion.

diagnosis was *IDH-wildtype diffuse astrocytoma* according to 2016 WHO classification, although it had unusual findings including gliomesenchymal reaction. The patient received fractionated radiotherapy (FRT, 61.2Gy/34fr) concomitant with TMZ after the second surgery. As he developed drug eruption on his precordia, legs, so he stopped taking oral drugs including TMZ. Four months after completion of FRT, he restarted maintenance TMZ treatment. Since pyrosequence analysis of the specimen showed wild type of IDH-1/2 R132/R172, BRAF T599/V600, H3F3A K27/G34, TERT C250/C228 genes and the hypo-methylated (unmethylated) MGMT CpG island, the TMZ was stopped after finishing the 2nd cycle of administration. Ion Torrent™ next-generation sequencing also showed no mutational status of *BRAF*, *RB1*, *TP53 and ATRX* in tumor tissue. Multiplex ligation-dependent probe amplification analysis did not detect 1p19 co-deletion, 10q loss (PTEN), 7p amplification (EGFR) or 9p homozygous deletion (CDKN2A). Tumor recurrence was not seen in the patient 24 months after the 1st surgery.

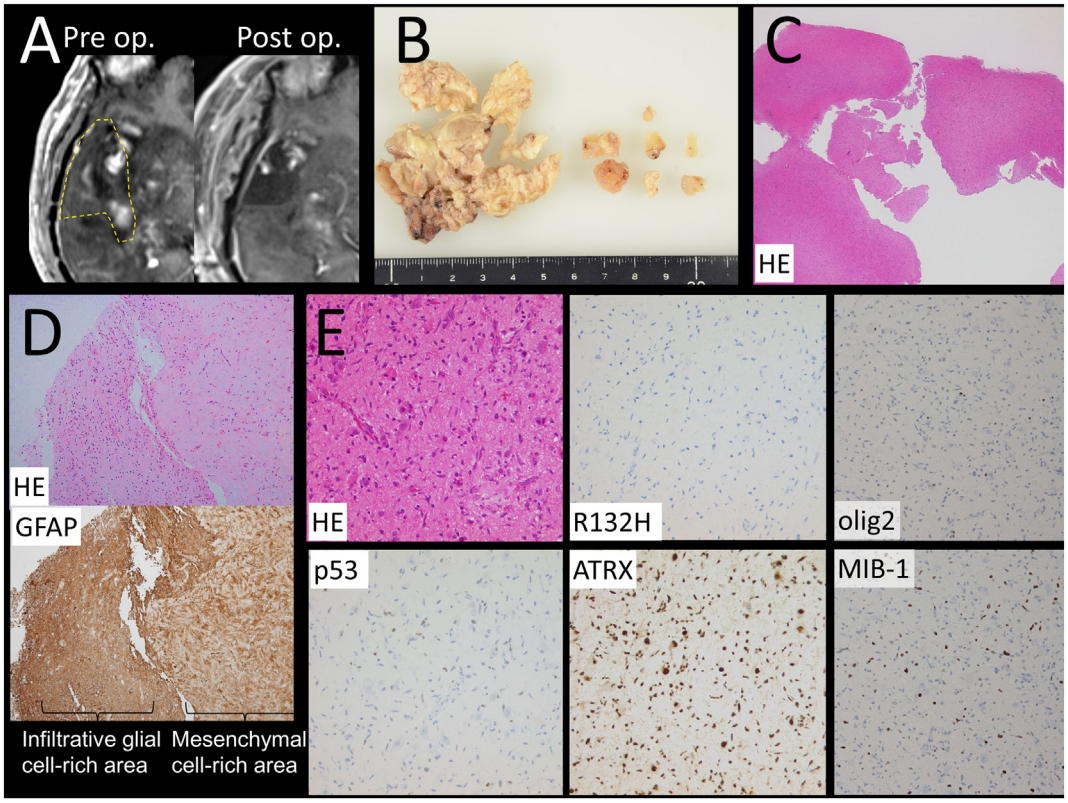


**Fig. 3.** T1WI with Gd enhancement before and just after partial resection of lesion (A), macroscopic image (B) and histopathological images (C–E). C. A histopathological image (Hematoxylin-Eosin (HE) staining (magnification, ×1.25)). D. Infiltrative glial cell-rich area and mesenchymal cell-rich area (HE staining and GFAP staining (magnification, ×100)); E. HE, IDH-R132H, Olig2, p53, ATRX, and MIB-1 staining of infiltrative glial cell-rich area (magnification, ×400).

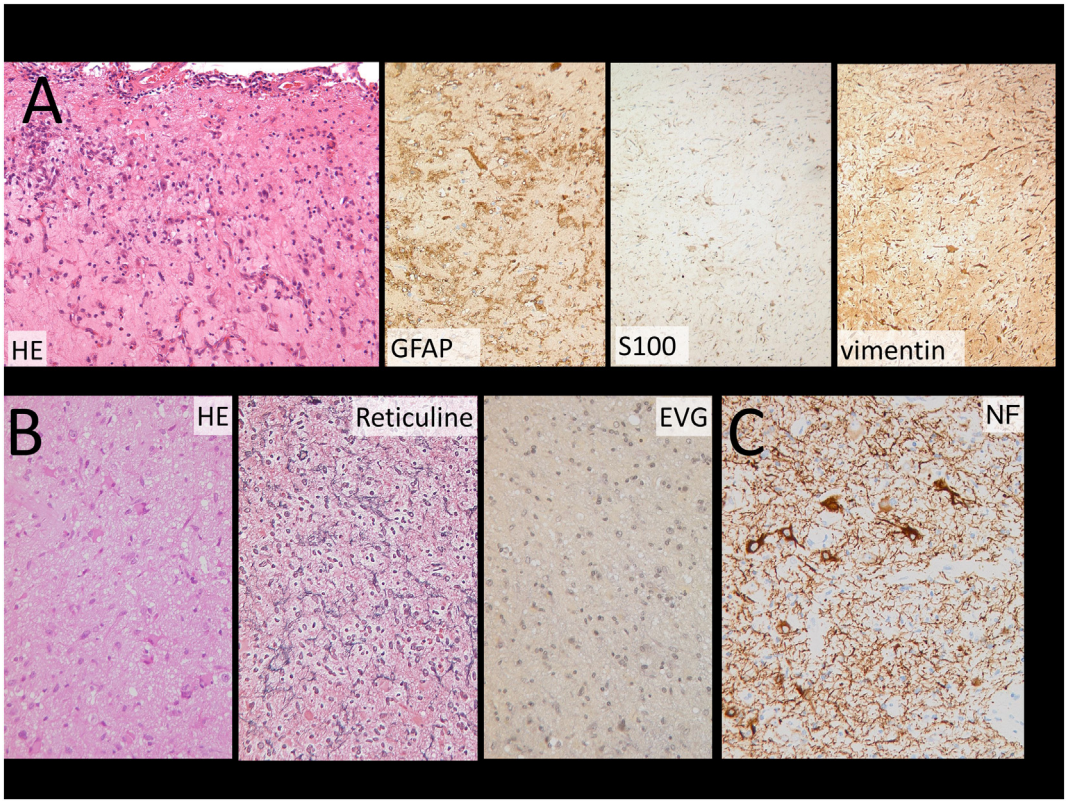


**Fig. 4.** A. Histopathological images of mesenchymal cell-rich area (HE staining (magnification, ×200); GFAP, S-100 protein and vimentin staining (magnification, ×400)). B. The area is positive for reticulin staining and negative for Elastic van Gieson (EVG) staining (magnification, ×200). C. Neurofilament (NF) stain shows diffuse axons and neurons in any part of the tumor tissue (magnification, ×200).

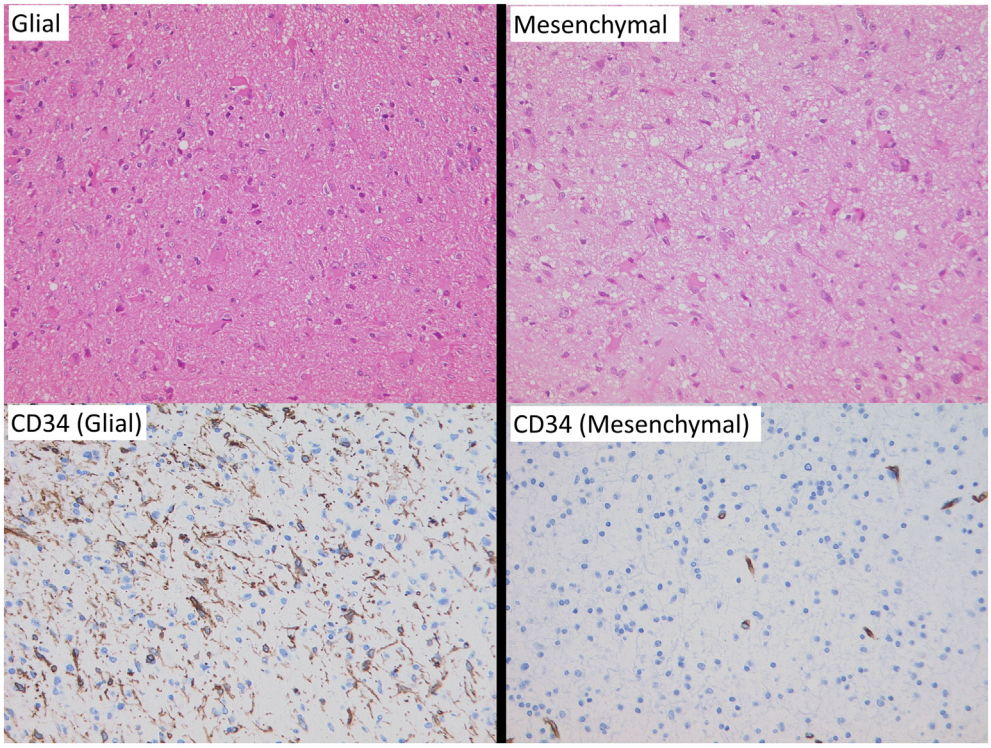


**Fig. 5.** Histopathological images of infiltrative glial cell-rich and mesenchymal cell-rich areas (HE and CD34 staining (magnification, ×200)).

## 3. Discussion

The supratentorial lesion in the present case is a very rare case of diffuse astrocytoma with a nodule-like component. Furthermore steroids were effective for regression of T2 high-intensity area. It may be related to peritumoral edema due to mesenchymal component in these astrocytic tumors. A review of previous reports shows that there is a category named 'gliofibroma' or 'desmo-plastic glioma' that co-existing malignant glia cells and benign mesenchymal cells [3], categorized as a so-called 'gliomesenchymal tumor' [4], although these mixed type tumors are not officially categorized in 2016 WHO classification [5]. In the present case, however, the lesion might not be gliofibroma, since mesenchymal cells positive for reticulin staining were only around the inflammatory vessels in the cortex, indicating secondary changes by the inflammation of vessels but not produced by the tumor. Pleomorphic xanthoastrocytoma, which is another type of astrocytic tumor and has a typical superficial location in the cerebral hemisphere, often has the reticulin fibers as a reactive change [6].

In general, *IDH-wildtype diffuse astrocytoma* has poorer prognosis compared to other types of lower grade gliomas [7]. In addition, nodule-like enhancement pattern is also a risk factor of poorer prognosis in WHO grade II gliomas [2]. However, in more recent paper, adult *IDH-wildtype diffuse gliomas* is prognostically heterogeneous category [8, 9], and has a minor subset with a silent genomic landscape like a pilocytic astrocytoma and favorable prognosis relative to others [8]. TERT promotor mutation, EGFR amplification and H3F3A mutation were associated with poor prognosis, and lacking all of the 3 genomic abnormality was associated with good prognosis in *IDH-wildtype diffuse astrocytoma* [9]. Because the tumor in the present case lacks all of the 3 genomic abnormality, it may belong to the good prognosis group despite having a nodule-like enhancement. In a limitation of this molecular analysis, there is a possibility that the evaluated tissue was not fully representative as only homogenized tissue was studied that lacks morphological control.

In conclusions, we have experienced treating a unique infiltrative low-grade glial neoplasm with gliomesenchymal reactions pathologically and with a nodule-like enhancement on MRI, which was diagnosed as an *IDH-wildtype diffuse astrocytoma* according to the 2016 WHO classification. The clinical course of this tumor and neuroimaging results were unusual for typical diffuse astrocytoma.

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## Conflict of interests

The authors declare that they have no financial or other conflicts of interests in relation to this research and its publication.

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