Anaplastic Ganglioglioma With Malignant Features in Both Neuronal and Glial Components
—Case Report—

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Abstract

A 34-year-old man presented with a case of anaplastic ganglioglioma with malignant features in both neuronal and glial components manifesting as seizure episodes over 11 months. The tumor was subtotally removed, followed by irradiation and chemotherapy. The histological diagnosis was anaplastic ganglioglioma. Atypical cells were morphologically estimated as glial and neuronal cells. Though these cells were weakly positive for synaptophysin and glial fibrillary acidic protein, the neural stem cell marker nestin was extremely expressed in both these cells. The MIB-1 index was 15%. Two months later, the tumor recurred with more pleomorphic appearance and higher cellularity with increased nestin expression level. Mitotic cells and multinucleated cells were found in the neuronal components. Cytological examination found dissemination to the leptomeningeal space. The patient died 6 months after the first surgery. This rare case of anaplastic ganglioglioma with both neuronal and glial components, which were extremely positive for nestin, showed progressive worsening of the clinical course. The expression of nestin may suggest that the origin or malignant transformation in anaplastic gangliogliomas is related to the undifferentiated neural stem cells.

Key words: anaplastic ganglioglioma, dissemination, neuronal mitosis, nestin, malignant transformation
Introduction

Gangliogliomas are rather uncommon tumors of the central nervous system consisting of both neuronal and glial elements, and account for only 0.4–1.0% of all brain tumors. Anaplastic ganglioglioma is an extremely rare malignant variant occurring in 3–5% of cases of ganglioglioma, with the malignant transformation mostly located in the glial element. One large series reported that only 2 of 184 patients with ganglioglioma had pathological diagnoses of anaplastic ganglioglioma. To date, only four cases of ganglioglioma have been reported with anaplastic recurrence in the neuronal element, and two cases involved malignant transformation following radiation therapy. Here, we present a case of anaplastic ganglioglioma with rapidly progressive malignant features in both morphological neuronal and glial components with expression of the neural stem cell marker nestin.

Case Report

A 34-year-old man had suffered seizure episodes over 11 months. On admission, neurological examination was unremarkable except for mild recent memory disturbance. Fluid-attenuated inversion recovery magnetic resonance (MR) imaging revealed a hyperintense area of 2.5-cm diameter in the left medial temporal lobe, and MR imaging with gadolinium-diethylenetriaminepenta-acetic acid showed a ring-like enhanced mass (Fig. 1). Angiography showed tumor staining and early venous filling in the mass lesion. Thallium-201 single photon emission computed tomography revealed high uptake in the same area on the delayed images. In addition, MR spectroscopy showed a relatively higher peak of choline. Our preoperative diagnosis was malignant glioma.

Anterior temporal lobectomy was performed to include the mass lesion. The tumor was subtotally removed. Radiation therapy of 60 Gy and chemotherapy with carboplatin, ACNU, vincristine, and interferon-β were undertaken postoperatively. Two months after the initial resection, follow-up MR imaging demonstrated local recurrence in the left temporal lobe posterior to the initial lesion and the second operation was performed. However, his neurological status progressively worsened. He died 6 months after the initial surgery. No autopsy was performed.

Surgical specimens were fixed in 4% buffered formalin and embedded in paraffin. Histological and immunohistochemical examinations were performed using synaptophysin, neuronal nuclear antigen (NeuN), glial fibrillary acidic protein (GFAP), nestin, and Ki-67 (MIB-1) antibodies.

The first resected tumor from the left temporal lobe revealed a markedly cellular and pleomorphic appearance (Fig. 2A). The tumor consisted of morphologically large neuronal cells and small glial cells (Fig. 2B). Tumor necrosis and vascular proliferation were not observed. The selective neuronal cells were weakly positive for synaptophysin and were presumed to represent neurons entrapped in the tumor tissue (Fig. 2C). GFAP-positive cells were thought to be reactive astrocytes (Fig. 2D). Neural stem cell marker nestin was diffusely expressed in both morphological glial and neuronal atypical cells (Fig. 2E). The MIB-1 proliferation index was 15% (Fig. 2F). MIB-1-positive cells consisted of neuronal components with large nuclei with prominent nucleoli. The histological diagnosis was anaplastic ganglioglioma, World Health Organization classification grade III.

The recurrent tumor specimen showed significant changes. The tumor cells had a more pleomorphic appearance, higher cellularity, and mitosis (Fig. 3A, B). The MIB-1 proliferation index was about 30–40%. Serial sections revealed the same multinucleated or giant nuclear cells which were positive for both MIB-1 and NeuN (Fig. 3C, D). Synaptophysin- and GFAP-positive cells were detected, but expression was weak. However, nestin-positive cells were easily found in both morphological glial and neuronal cells. Nestin expression was significantly increased in the recurrent tumor compared to the first resected tumor (Figs. 2E and 3E).

After the second surgical resection, cerebrospinal fluid (CSF) cytology detected large cells with prominent nucleoli, and relatively small and round cells. Presumably these cells had disseminated from the glial and neuronal components into the CSF (Fig. 3F).
Fig. 2  A, B: Photomicrographs showing the neoplastic neuronal and glial cells in the first resected tumor. Hematoxylin and eosin stain, original magnifications $\times 200$ (A) and $\times 400$ (B).  C–F: Immunohistochemical examinations showing selective morphologically neuronal cells positive for synaptophysin (C, arrows), some reactive astrocytes positive for glial fibrillary acidic protein (D), nestin expression in morphologically glial and neuronal cells (E), and glial and neuronal cells positive for MIB-1 (F, index of 15%). Original magnifications $\times 200$.

Fig. 3  A, B: Photomicrographs showing the recurrent tumor, with morphological changes of nuclei more frequently observed in both ganglion and glial cells (A), and large cells with prominent nucleoli and one mitotic figure (B, arrowhead). Hematoxylin and eosin stain, original magnifications $\times 200$ (A) and $\times 400$ (B).  C–E: Immunohistochemical examinations of serial sections showing the morphologically neuronal cells positive for both MIB-1 (C, arrowheads) and neuronal nuclear antigen (D, arrowheads), and diffuse and strong immunoreactivity for nestin in morphologically glial and neuronal cells (E) compared to the first resected tissue (Fig. 2E). Original magnifications $\times 200$ (E) and $\times 400$ (C, D).  F: Cerebrospinal fluid cytology showing neuronal cells and glial cells. Giemsa stain, original magnification $\times 200$.

Discussion

Gangliogliomas are considered to originate from glioneuronal precursor cells. Most malignant transformation occurs in the glial component. In the present case, the proliferated cells had the morphological appearance of neurons and expressed the neuronal stem cell marker nestin, although synaptophysin expression was weak. To date, only four cases have been described as anaplastic ganglioglioma with malignant components: a spinal cord ganglioglioma with “very few mitoses” in both components; an initially benign ganglioglioma with anaplastic changes in both neuronal and astrocytic cells after radiotherapy; and a benign ganglioglioma with anaplastic recurrence of neuronal elements 3 years after radiotherapy. Only one case was reported as cerebral ganglioglioma with malignant transformation in both astroglial and neuronal cell components and was not associated with radiotherapy.

Malignant transformation is thought to be associated with radiotherapy. One review of a series of low-grade astrocytoma in 55 children who initially received radiation therapy noted that 6 underwent malignant change. The time to anaplastic transformation varied between 2 and 10 years (mean 6.4 years). The present case showed anaplastic changes in both neuronal and glial components in the initial tumor before radiation therapy, and recurrence was observed during radiation therapy. The induction of malignant degeneration of existing tumors by radiation therapy is difficult to prove. However, we presume that the first resected tumor had been malignant since the duration of malignant change was so short.

We examined the immunoreactivity of the tumor cells for the neural stem cell cytoskeletal protein nestin. Interestingly, nestin was expressed diffusely in both morphologically glial and neuronal components. Moreover, the nestin expression was significantly greater in the recurrent tumor tissue. On the other hand, GFAP and synaptophysin were expressed modestly. These findings suggest that the anaplastic ganglioglioma in the present case originated from the undifferentiated stem cell lineage, which is capable of divergent differentiation along both glial and neuronal lines.

Gangliogliomas were first hypothesized to originate...
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from undifferentiated neural stem cells. On the other hand, other studies pointed out that the origin of gangliogliomas is the ectopic neuronal cell nests derived from peripheral autonomic nerve tissue. A previous study demonstrated a different temporal pattern of nestin expression during glial and neuronal differentiation. Nestin expression was found not only in the central nervous system progenitor cells but also in cells in transition from the progenitor stage to becoming neuronal and glial cells. Persistent expression of nestin was reported in both neuronal and glial cells of gangliogliomas, suggesting that persistent expression of nestin within ganglioglioma represents a developmental link between these divergent cell types. Our findings suggest that nestin expression is related to the origin or malignant transformation in ganglioglioma.

CSF cytology found many disseminated cells like anaplastic neurons, suggesting higher invasive activity of anaplastic neuronal cells. The biological nature of anaplastic gangliogliomas is not always correlated with prognosis. In this case, tumor recurred at the primary site for a short period and disseminated into the subarachnoid spaces despite gross total tumor resection followed by chemotherapy and radiotherapy. The biological and morphological findings showed an extremely malignant phenotype from the onset.

MIB-1 indices in 54 cases of histologically diagnosed gangliogliomas ranged from 0 to 10.2 (mean 1.1 ± 1.0), suggesting that mortality did not correlate with MIB-1 index. The highest index was observed in the only case of anaplastic ganglioglioma. In our case, the MIB-1 index was extremely high and the patient died within 6 months of the initial diagnosis. High MIB-1 index may indicate careful follow up and a poor prognosis in patients with anaplastic ganglioglioma.

This rare case of anaplastic ganglioglioma showed malignant features in both neuronal and glial components. The expression of nestin may suggest that the origin or malignant transformation in anaplastic gangliogliomas is related to the undifferentiated neural stem cells. The clinical course was devastating in our patient with recurrence and dissemination within a short period, despite treatment with surgical resection, irradiation, and chemotherapy. The malignant nature was consistent with the clinical and neuroimaging findings, and the histological features including the extremely high MIB-1 index and expression of the neural stem cell marker nestin.

References


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