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Clinicopathological Diagnosis of Gliomatosis Cerebri

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1. Introduction

Regarding the definition of gliomatosis cerebri (hereinafter referred to as "GC"), the 3rd edition of the WHO Classification of Central Nervous System Tumors (hereinafter referred to as "3rd ed.") provides only a five-line description that GC is a diffuse, frequently bilateral, glioma that infiltrates the brain, involving more than two lobes. It often extends to the infratentorial structures and even to the spinal cord. Compared with this, the definition in its 4th edition (hereinafter referred to as "4th ed.") is described in 13 lines, stating that GC involves at least 3 lobes and is usually bilateral, extending from the cerebral white matter, including the deep and subcortical portions, and often infiltrating the brain stem and the spinal cord. In the 4th ed., GC is characterized by a widespread infiltration of the brain by tumor, occurring as bilateral lesions involving commissural fibers, and frequently infiltrating from the brain stem to the spinal cord. Moreover, the 4th ed. states that GC is mainly astrocytic tumor but, in some cases, mainly consists of oligodendroglial tumor cells (Akimoto, 2004; Balko, 1996; Levin, 2004; Sanson, 2004, Taillibert, 2006). Unlike the 3rd ed., which specifies the histological malignancy as Grade III, the 4th ed. rates it basically as Grade III, without specifying it, although recognizing the importance of the evaluation of histological malignancy, in consideration of the possibility that the grade may be underestimated in some cases due to tissue sampling problems (Akimoto, 2004; Nishioka, 1996). These changes in the description of the definition in the WHO Classification have reflected the findings of many clinicopathological researches on GC.

This situation requires us neuro-oncologists to diagnose GC before operation and to provide appropriate treatment. In that sense, it is important to evaluate the extent of tumor progression by imaging diagnosis, mainly using MRI, and to perform adequate tissue sampling to enable accurate histopathological diagnosis, in accordance with the 4th ed. (Akimoto et al., 2004). In addition, it is important to establish a treatment protocol mainly consisting of adjunctive therapy.

2. Clinical cases (Table 1)

We have encountered 8 cases in which GC was suspected based on the neuroradiological definition of the 4th ed. and was diagnosed pathologically. These cases aged 46 to 73 years (median age: 55.5 years) consisted of 3 men and 5 women. The initial symptoms were mainly cognitive impairment and seizure. The symptoms of ordinary brain tumor,

including increased intracranial pressure, as well as focal signs, including hemiparesis, were less frequent. The tumoral topography based on CT or MRI revealed that most of the lesions were diffused in the white matter, often extending to the basal ganglia, brain stem or cerebellum which is unlikely to be invaded by ordinary diffuse glioma. These lesions were characterized by bilateral progression accompanied by hypertrophy of the corpus callosum. Wide resection of tissue, including areas over the white matter and cortical regions, was considered preferable as the surgical procedure to obtain a reliable pathological diagnosis. Therefore, anterior temporal lobectomy and maximally possible tumor resection were performed. Pathological diagnosis was anaplastic astrocytoma (Grade III) in most of the cases. However, GC consisting of oligodendroglial tumor cells was found in 2 cases. Basic treatment was radiation therapy (30 Gy to whole brain and 30 Gy focal boost) combined with chemotherapy (ACNU, Temozolomide). Except for a patient who developed central brain herniation in the early phase after operation, patients receiving sufficient adjunctive therapy tended to maintain partial response or stable disease.

2.1 Case 2

A 46-year old woman. She was admitted with a 2-month history of clumsiness and numbness of the right hand as well as gradual development of disorientation and right hemiparesis. The head MRI on admission revealed a lesion arising primarily in the left corona radiata and extending to the right parietal lobe and frontal lobe white matter through the corpus callosum, showing no obvious contrast enhancement (Fig. 1 A-D). CT-guided stereotactic biopsy of the left frontal lobe white matter was performed to make a definite diagnosis. Infiltration of large cells with abundant cytoplasm and thick processes, suggestive of reactive astrocytes, was observed in the matrix of the edematous white matter. However, a diagnosis of neoplastic lesion was not reached. Triggered by status epileptics, her condition deteriorated. Two months after the operation, she died of brain herniation. Cerebral autopsy revealed a widespread edema over the region from the left corona radiata to the basal ganglia, further extending to the right frontal lobe and the temporal lobe white matter through the corpus callosum. KB staining, Bodian staining, Holtzer staining, etc. demonstrated the extent of the lesion (Fig. 2 A-D). The pathological features of each section showed infiltration of gemistocytic cells, forming parallel rows along the nerve fibers. Although lack of nuclear atypism was noted, most of the nuclei were MIB-1 positive. The degree of myelin destruction varied across sections, being the most severe in the corpus callosum. However, Bodian staining demonstrated that the involved axis cylinder was preserved even in the corpus callosum. (Fig. 2 E, F) The autopsy-based diagnosis was GC consisting of gemistocytic astrocytoma.

2.2 Case 8

A 47-year old women. She was admitted to the hospital because of having abrupt cognitive impairment 1 month previously and gradual development of ataxic gait and urinary incontinence thereafter. Head MRI showed a lesion with enlargement of the corpus callosum in the white matter of the bilateral frontal lobe. Although the lesion extended from the bilateral corona radiata to the white matter of the parietal lobe, no obvious contrast enhancement was observed (Fig. 3 A-D). The partial removal of the tumor was performed to

| Case	Age/Sex	Initial symptom	Tumoral Topography	Surgery	Pathological Dx	Treatment	Prognosis
1	54/ Male	Headache, Depression	White matter, Basal ganglia, Brain Stem, Cerebellum	ATL	Anaplastic oligodendroglioma	RTx	D: 2 months
2	46/ Female	Disorientation, Heminumbness	White matter, Basal ganglia, Corpus callosum	Biopsy	Gemistocytic astrocytoma	None	D: 2 weeks
3	71/ Female	Seizure, Hemiparesis	White matter, Corpus callosum	Partial removal	Glioblastoma	none	D: 8 months
4	50/ Female	Seizure, Cognitive impairment	White matter, Basal ganglia	Biopsy	Anaplastic astrocytoma	RTx, Chemo Tx	D: 26 months
5	66/ Male	Cognitive impairment	White matter, Corpus callosum	Biopsy	Anaplastic astrocytoma	RTx, Chemo Tx	A: 49 months
6	73/ Male	Seizure	White matter, Basal ganglia	ATL	Anaplastic astrocytoma	RTx, Chemo Tx	D: 4 months
7	57/ Female	Cognitive impairment	White matter, Basal ganglia	ATL	Anapalstic astrocytoma	RTx, Chemo Tx	D: 20 months
8	47/ Female	Cognitive impairment	White matter, Corpus callosum	Partial removal	Anaplastic oligodendroglioma	RTx, Chemo Tx	A: 11 months

ATL: anterior temporal lobectomy, RTx: radiation therapy, Chemo Tx: chemotherapy, D: dead, A: alive

Table 1. Case summary

(a)   (b)

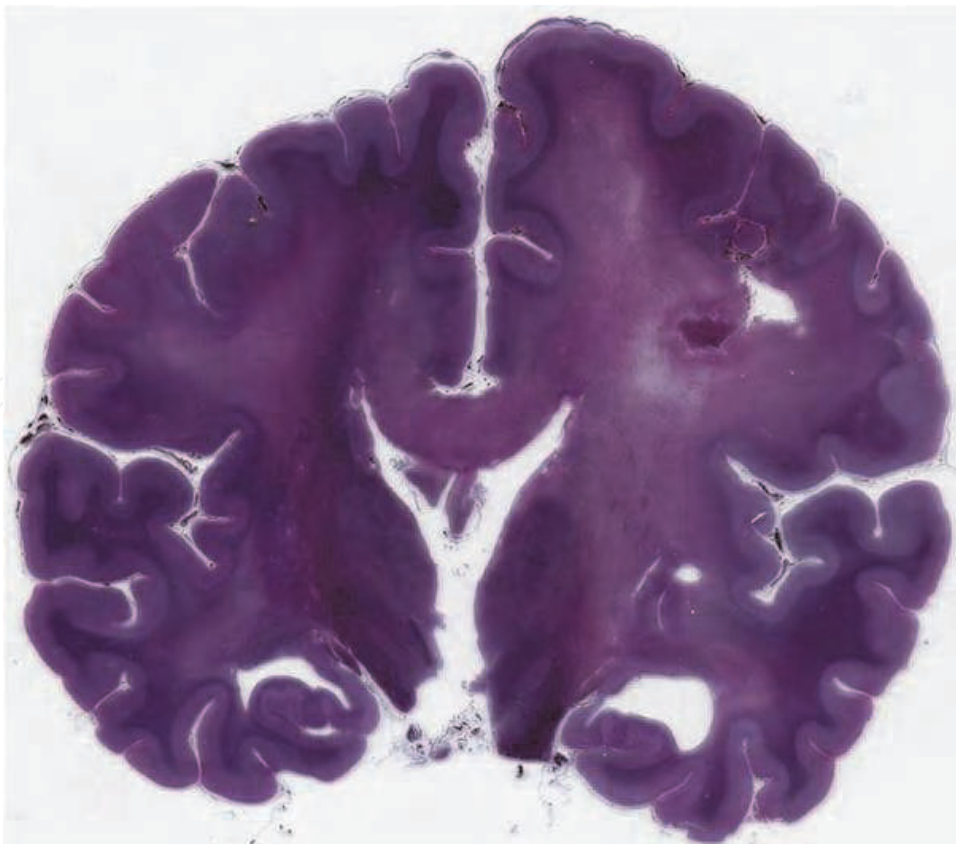(c)   (d)
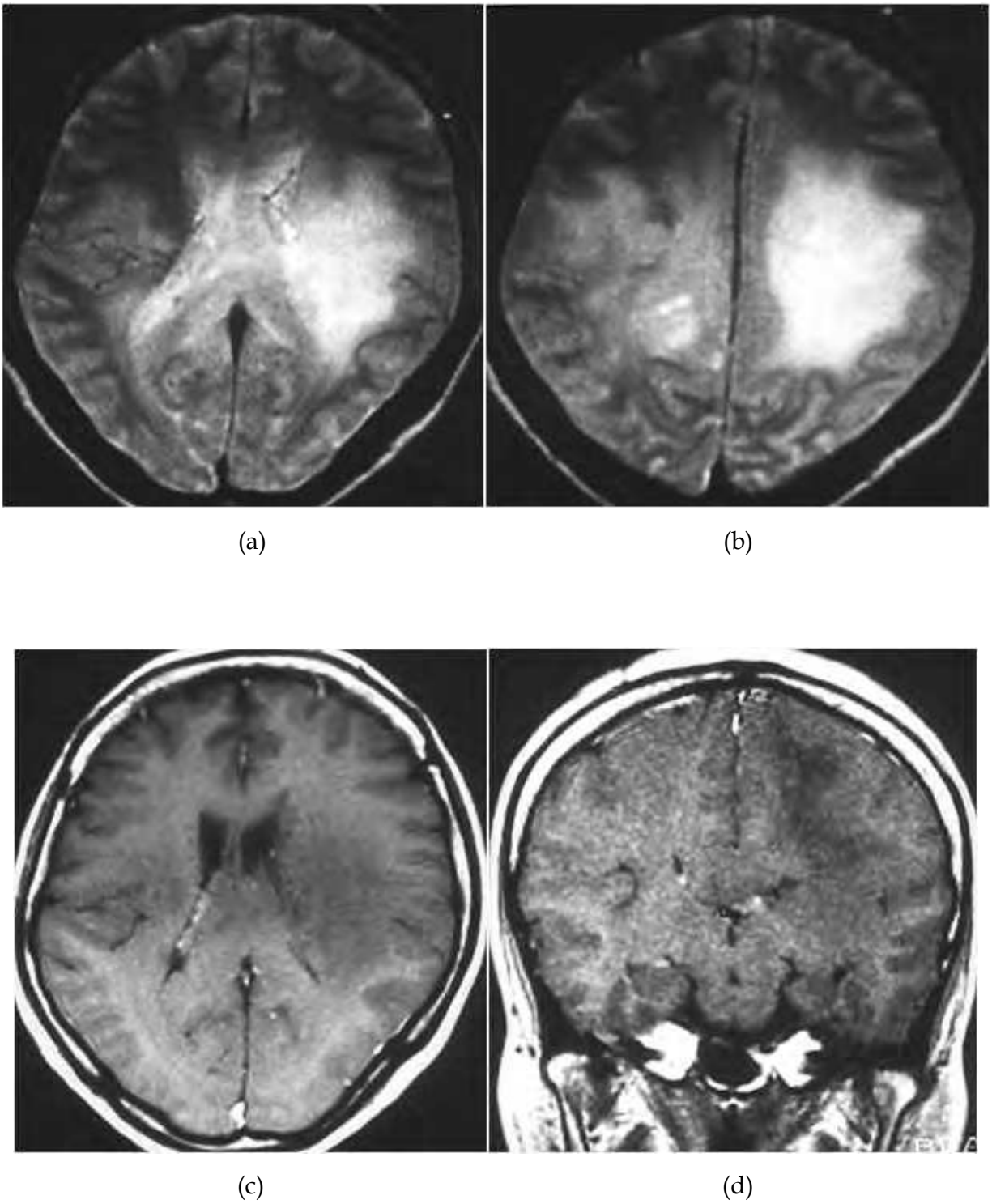
T2-weighted MRI (A, B) demonstrated diffuse high intensity in the white matter of both cerebral hemispheres, with enlargement of the corpus callosum. T1-weighted MRI with Gd-DTPA (C, D) demonstrated slightly low intensity in the white matter without enhancement.
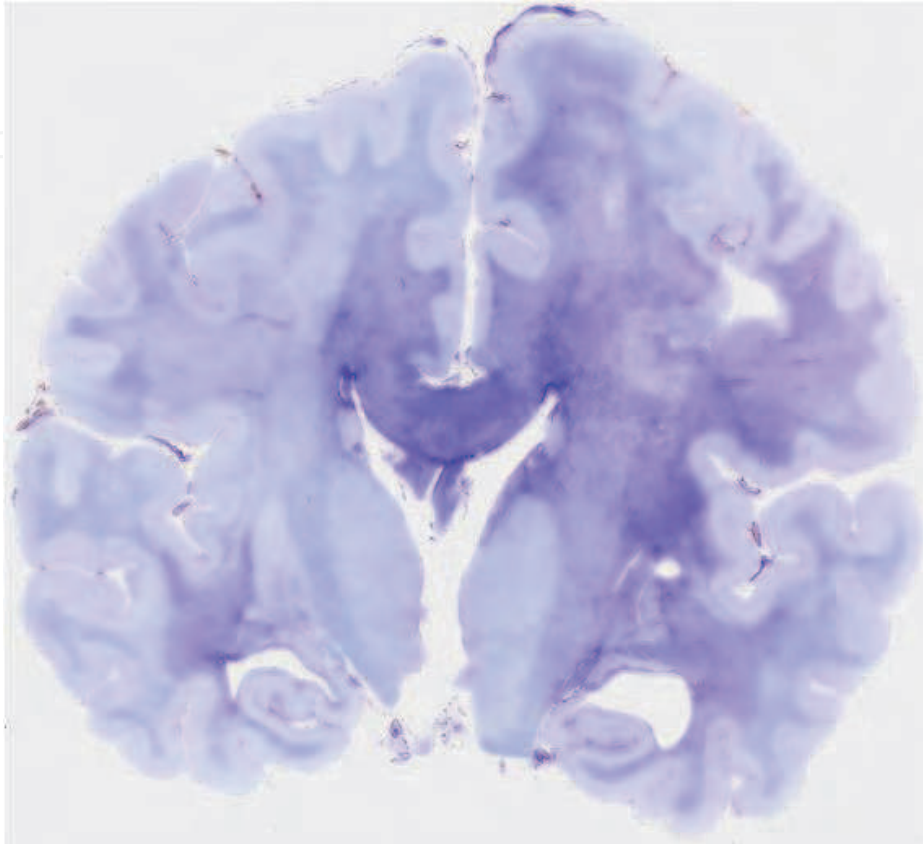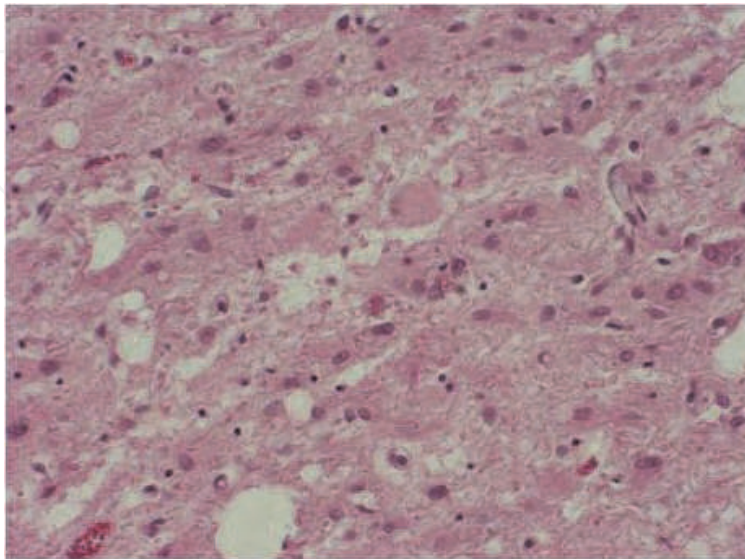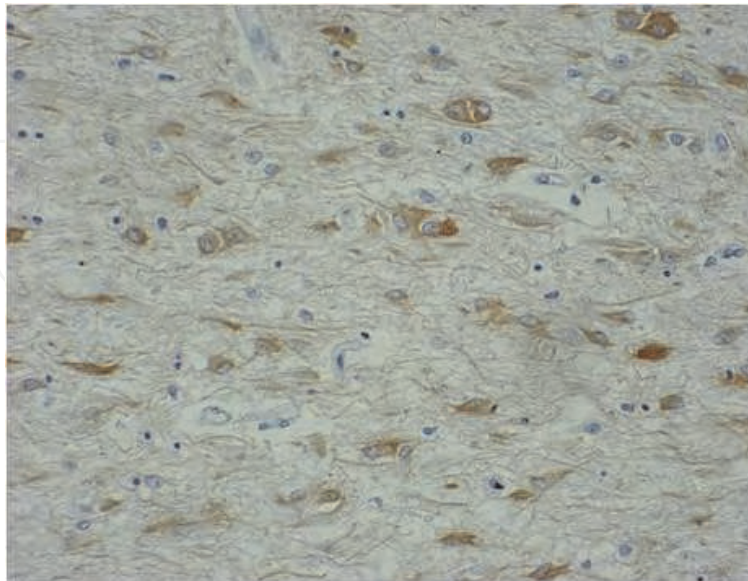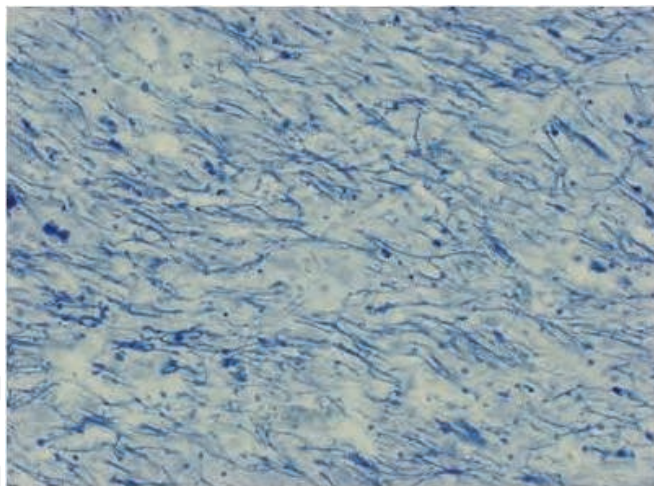
Fig. 1. MRI on admission (A-D)
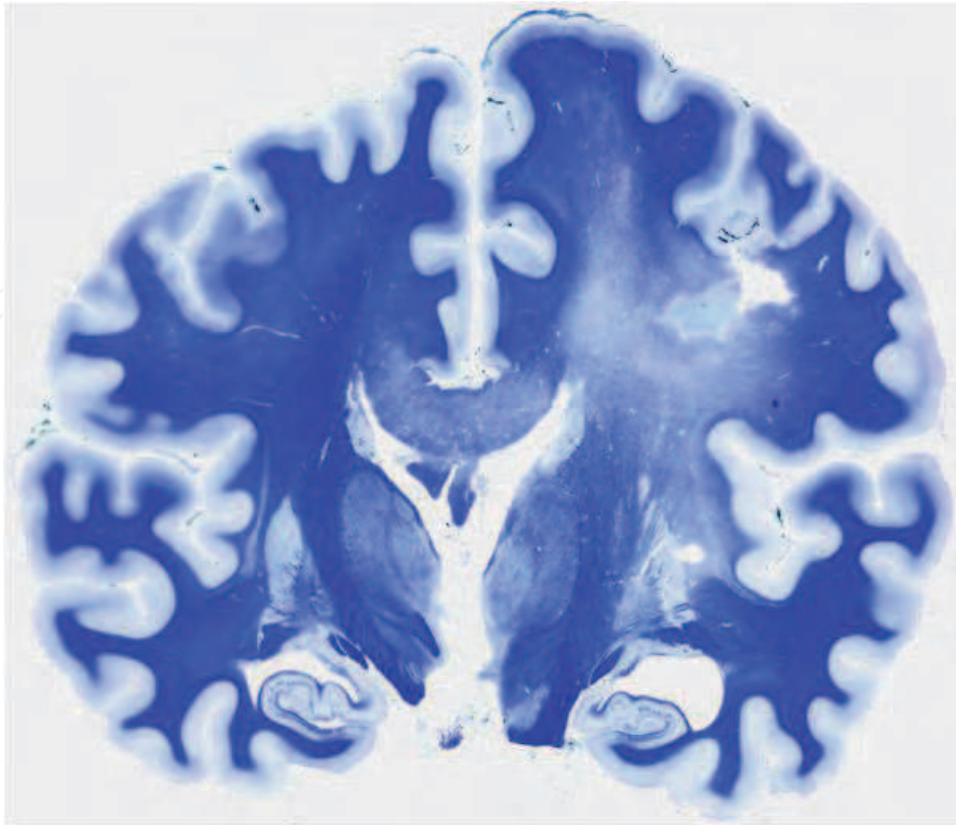
a

b

c

d

e

f

Klüver-Barrera stain (A) demonstrated the affected region to be a broad region of myelin destruction extending from the white matter of the left parietal lobe to the basal ganglia and to the corpus callosum and in a part of the right hemisphere. Bodian stain (B) demonstrated the preservation of axons, but the intensity of staining of the white matter and corpus callosum was slightly decreased owing to edematous change. Holzer stain (C) demonstrated the broad area of reactive gliosis. The region showed increased atypical gemistocyte-like cells of various sizes and forms [D: hematoxylin and eosin (HE) stain, ×100], Immunohistochemically, most tumor cells were positive for GFAP (E). Klüver-Barrera stain (F) showed extensive destruction of myelin.

Fig. 2. Coronal section of the autopsy brain (A-C) and microscopic appearance of autopsy material (D-F)
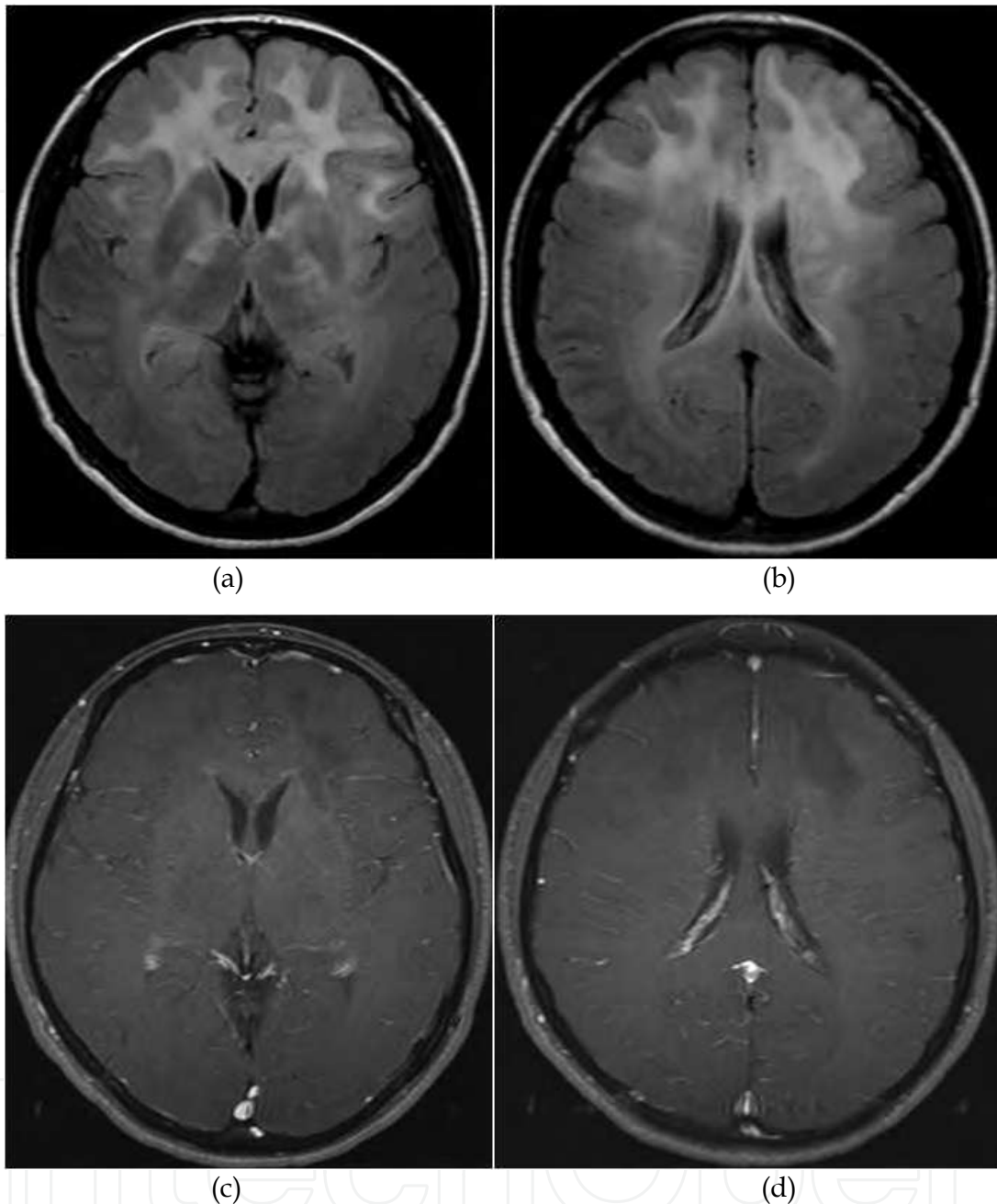
FLAIR MRI (A, B) demonstrated diffuse high intensity in the white matter of both frontal lobe and bilateral corona radiata, with enlargement of the corpus callosum. T1-weighted with Gd-DTPA (C, D) demonstrated low intensity in the white matter of the left frontal lobe without enhancement.

Fig. 3. MRI on admission (A-D)

make a definite diagnosis showed a dense proliferation of tumor cells with round nuclei, scant cytoplasm and perinuclear halo in the left superior frontal gyrus. The perineuronal satellitosis-like infiltration of tumor cells was observed even in the deep layer of the cerebral cortex. Myelin was preserved although partially destroyed by tumor cell infiltration (Fig. 4 A, B). The tumor cells were found to be Olig-2 positive, and the proportion of MIB-1 positive patients was also high. As a result of analysis using

fluorescence in situ hybridization (FISH), she was found to be positive for 1pLOH (1p36) and 19qLOH (19q36) (Fig. 4 C, D). Based on these results, she was diagnosed with GC consisting of anaplastic oligodendroglioma cells. After the operation, she underwent radiation therapy (60 Gy) combined with chemotherapy using oral temozolomide. At 11 months post-operative, a reduction in the lesion size was observed, with an improvement in cognitive function.
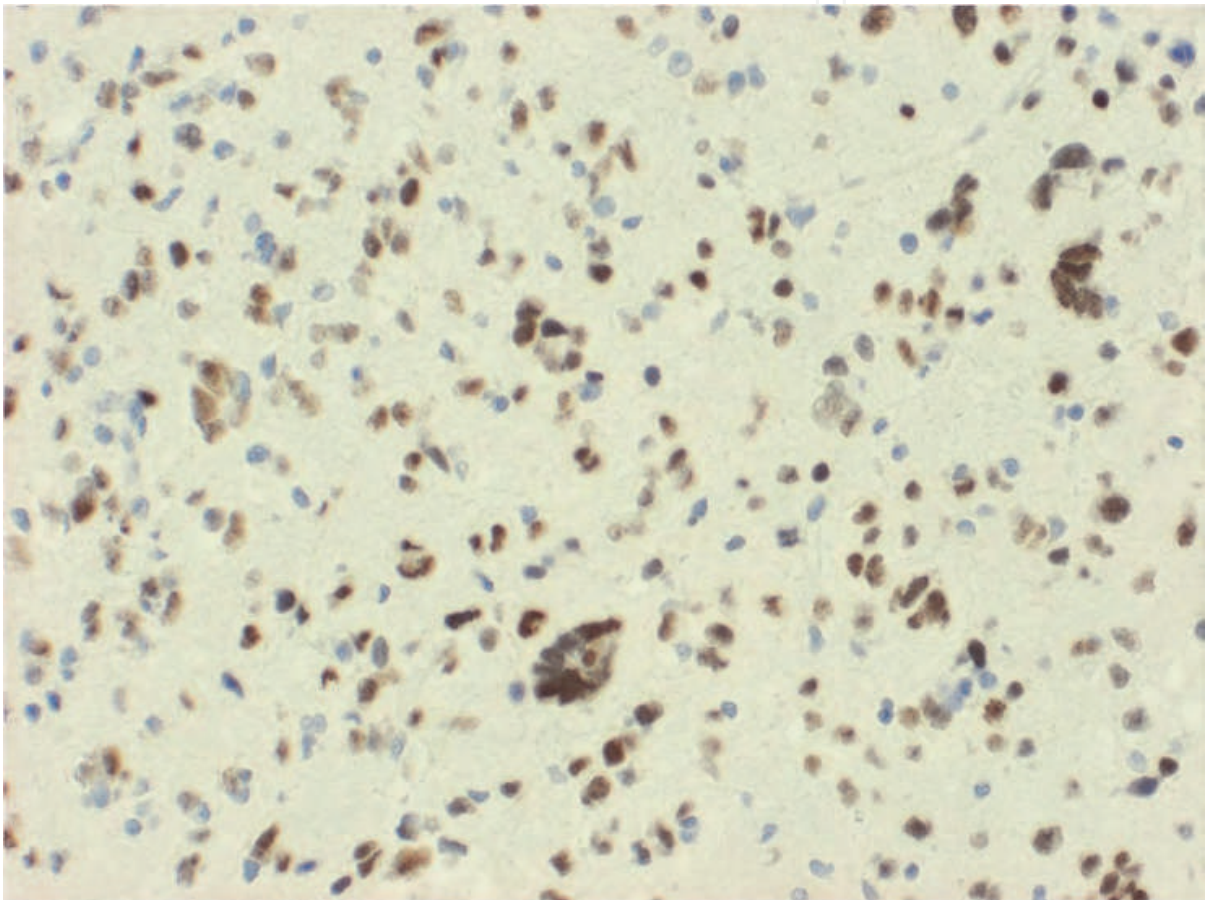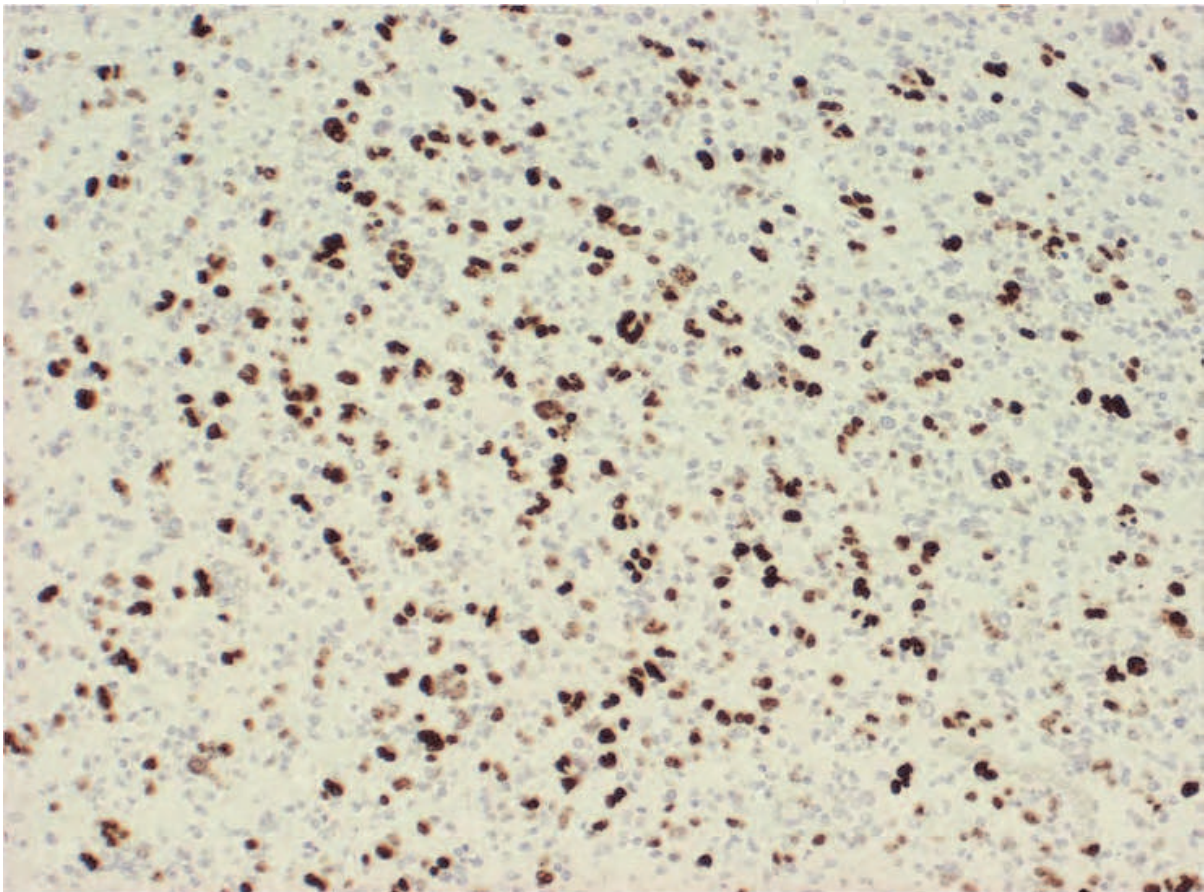

a

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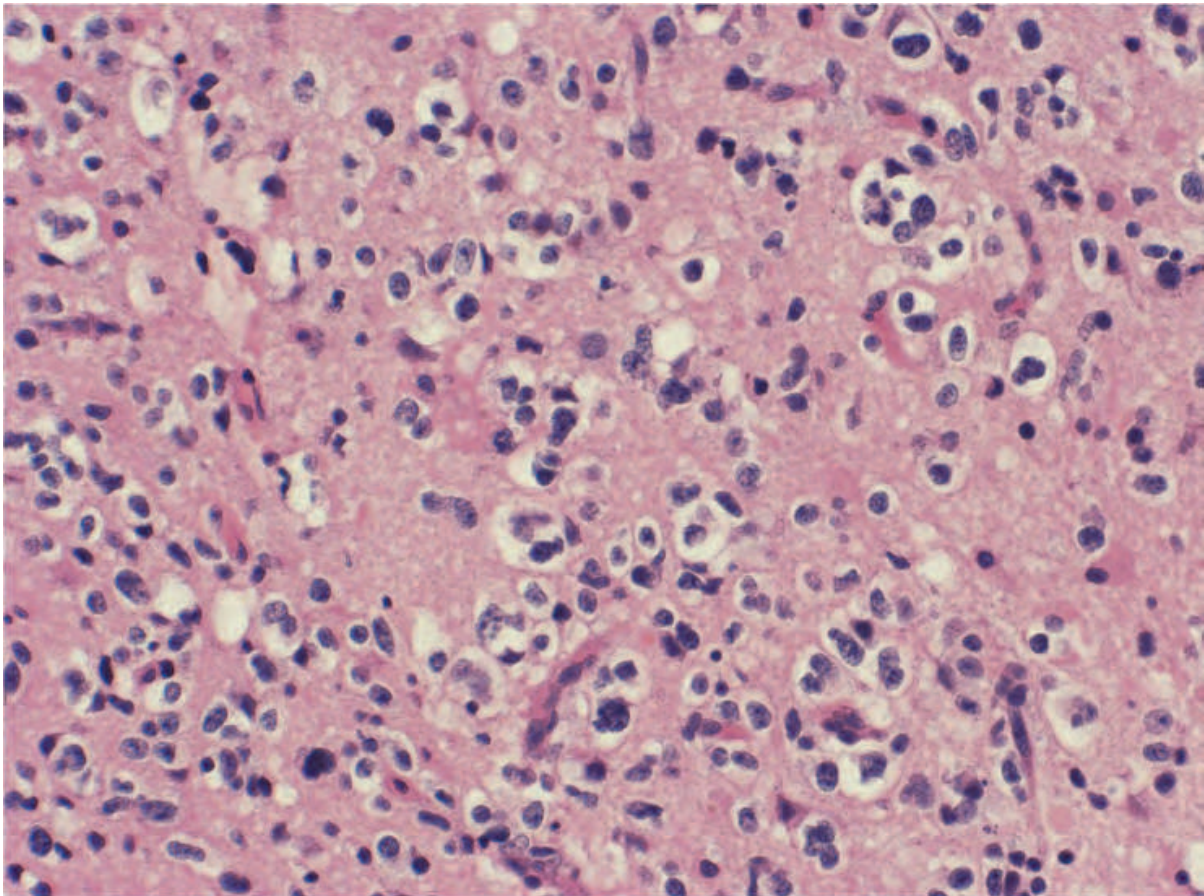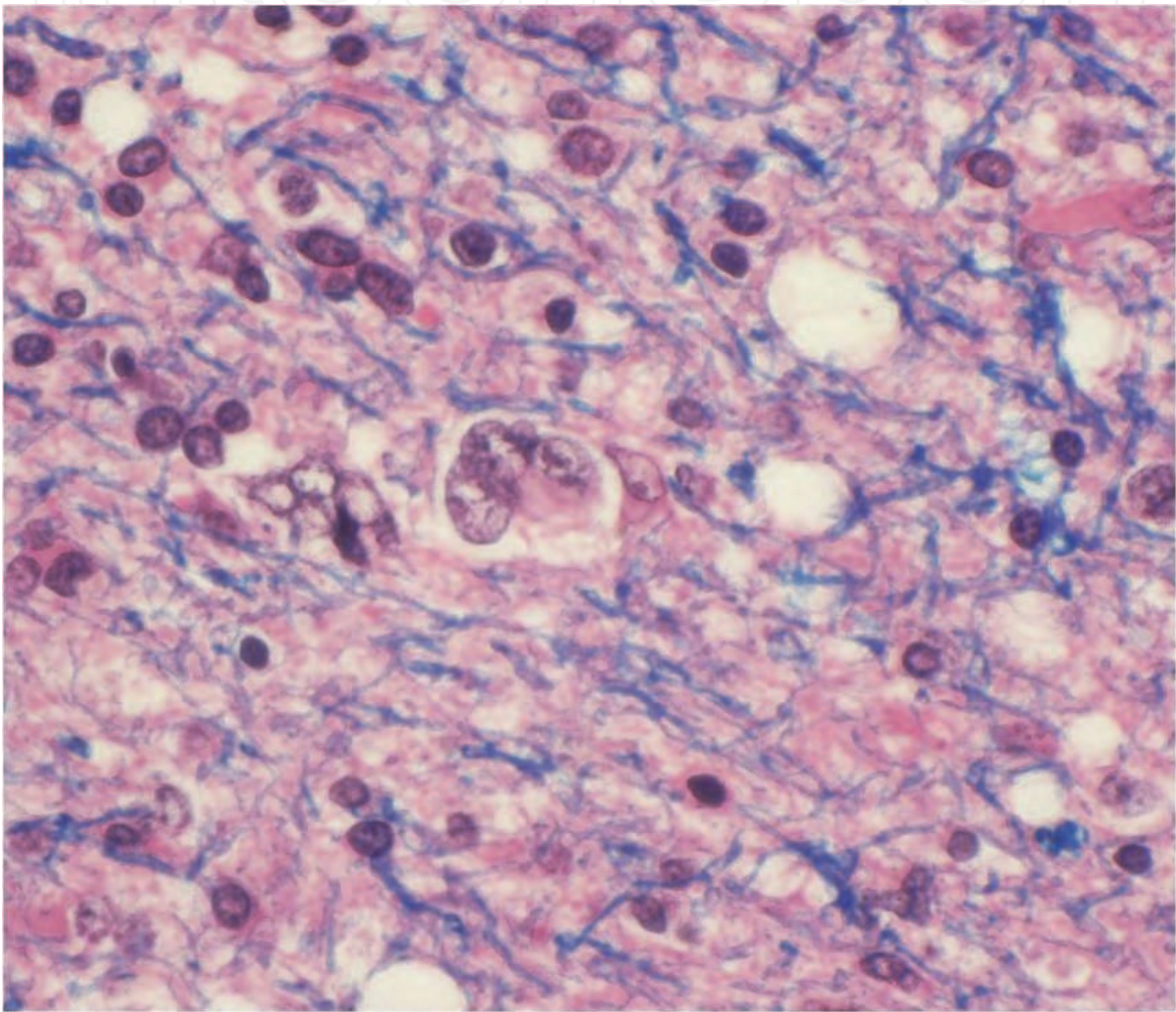
d

The region showed increased atypical oligodendroglial cells of various sizes and forms (A: HE stain, ×100). Luxol fast blue and HE stain showed extensive destruction of myelin (B, ×100). Immunohistochemically, most tumor cells were positive for olig2 (C) and MIB-1 (D).

Fig. 4. Microscopic appearance of resected tissue (A-D)

3. Discussion

3.1 Points to be noted in radiological diagnosis

Based on the definition of the 4th ed., confirmation of the presence of bilateral lesions over at least 3 lobes as well as the absence of an obvious focal tumor mass is considered essential to make an imaging-based diagnosis of GC. In addition, detection of infiltration of the basal ganglia, brain stem, cerebellum and spinal cord lends more confidence to the imaging-based diagnosis of GC. In other words, GC is considered a pathological condition where great emphasis is placed only on the invasive potential among the two growth mechanisms of ordinary glioma, i.e., the proliferative potential and invasive potential (Akimoto, 2004; Peretti-Viton, 2002; Saraf-Lavi, 2003). According to one report (Sanson et al., 2004), factors determining the diagnosis of GC based on MRI are: (1) a high signal area over at least 3 lobes on T2-weighted and FLAIR images; (2) absence of a contrast-enhanced tumor mass of 1 cm or greater; and (3) thickening of the corpus callosum or anterior commissure. These factors are the criteria adopted in the 4th ed. Such a clear definition may make it possible to suspect the presence of GC by performing MRI. However, these imaging findings are also obtained in white matter lesions other than tumors, such as demyelinating disease, encephalitis and venous sinus thrombosis (Essig, 2001; Saraf-Lavi, 2003). Therefore, it becomes necessary to confirm the presence of tumor cells by histological diagnosis. In recent years, studies evaluating GC by MR spectroscopy have been published (Bendszus, 2000; Galanaud, 2003; Saraf-Lavi, 2003). According to these studies, increased choline and decreased NAA levels, which are findings characteristic of glioma, are not necessarily observed in GC, but rather increased NAA levels are often observed. Increased myoinositol (m-Ins), which indicates increased activity of glia cells, has been reported as a finding characteristic of GC. Although the 4th ed. only states that multivoxel MRS is useful for determining the target of biopsy, it appears that biopsy of the sites with increased choline or m-Ins levels lends more confidence to the histological diagnosis of GC.

3.2 Points to be noted in pathological diagnosis

It is important to be faithful to the criteria for the pathological diagnosis of GC (Scheinker & Evans, 1943). More specifically, GC is basically defined as an invasive and tumoral lesion, with no tumor mass centered in the white matter, and the axis cylinder is preserved even when myelin destruction takes place (Akimoto, 2004; Peretto-Viton, 2002; Vates, 2003). To thoroughly carry out these evaluations, stereotactic biopsy sampling is often difficult. We previously reported the need to remove, as much as possible, the cerebral lobes with lesions detectable by imaging (Akimoto, 2004). In other words, not only the evaluation of tumor cells but also the evaluation of normal tissue is necessary for making the pathological diagnosis of GC. The cases presented in this article demonstrate the significance of the additional response evaluation for myelin by KB staining, axis cylinder by Bodian staining and reactive glia by Holtzer staining. The evaluation of tumor cells infiltrating between normal nerve fibers is by no means easy. In addition, the shape of the nuclei varies greatly from elongated-form or fusiform to round-form, and no consistency is found regarding the presence or absence of atypical cells. In fact, there are some reports on cases of GC consisting of oligodendroglioma-like cells, as shown in Case 8 (Akimoto, 2004; Balko, 1996; Benjelloun, 2001; Sanson, 2004; Vates, 2003). Confirmation of the preservation of the axonal structure after evaluation of the proliferative potential of infiltrating cells by MIB-1 and

AgNORs can contribute to the diagnosis of GC (Akimoto, 2004). In the 4th ed., the range of MIB-1 index is specified to be from not more than 1% to 30%, which is difficult to understand. However, it is also the fact that objective calculation of MIB-1 index is extremely difficult in tissues containing responsive glia cells due to normal tissue infiltration (Akimoto, 2004; Nishioka, 1996; Vates, 2003). Therefore, we consider it useful to evaluate the proliferative potential of each cell by AgNORs. However, there have only been two case reports on AgNORs in GC(Hara et al., 1991). A recent study has reported that L1, which is a cell adhesion factor, is expressed more abundantly in GC than in ordinary glioma (Suzuki et al., 2010). Since L1 is a glycoprotein that plays an important role in the migration of the immature neurons in the development stage, L1 might be significantly involved in the invasive potential of GC. In addition, it was reported that the control of L1-functions might contribute to the treatment of GC. Moreover, according to a study (Seiz et al., 2005) evaluating the mutation of IDH1 in GC, the frequency of IDH1 mutations is relatively high in the secondary GC, caused by the progression of diffuse astrocytoma, whereas no IDH1 mutation was observed in primary GC. This suggests the possibility that the evaluation of IDH1 mutations may become important for making the diagnosis of GC, as suggested in the molecular analysis of the development of glioblastoma.

3.3 Topics regarding treatment

According to the 3rd ed., GC has extremely poor prognosis, and 1-, 2- and 3-year survival rates are 48%, 37% and 27%, respectively, being similar to those in glioblastoma. The 3rd ed. specifies only MIB-1 as a prognostic factor. However, the 4th ed. is not intended to provide data, and states only that age, performance status and histological features, especially for grade and subtype (oligodendroglioma), are important as prognostic factors. The deletion of the description on MIB-1 suggests the difficulty of the evaluation (Akimoto, 2004; Nishioka, 1996; Vates, 2003). There are many reports discussing the extremely poor prognosis of GC (Taillibert, 2006; Vates, 2003). However, recent studies have reported some cases with relatively better prognosis due to greater sensitivity to adjuvant therapy (Levin, 2004; Sanson, 2004; Taillibert, 2006). Of these, one report (Taillibert et al., 2006) summarizing 296 cases from the literature showed that the overall survival (OS) in GC was 14.5 months. Examined for each prognostic factor, OS was 27 months and 9 months in KPS of ≥80 and ≤80, respectively, and 20 months and 8.5 months in Grade 2 and 4, respectively, showing significant differences. However, no significant difference was observed between cases with and without radiation therapy, and there was a trend for prolonged OS in patients receiving additional chemotherapy. The most noteworthy was the difference between cases of astrocytic tumor and oligodendroglial tumor: the OS was 11 months for the former and 36 months for the latter, showing a marked difference. Moreover, one study reported (Levin et al., 2004) that, in the use of temozolomide (TMZ), which is regarded as the standard treatment for ordinary glioma, the response rate was 45%, the median TTP to time to progression (TTP) was 13 months, with 1- and 2-year progression-free survival (PFS) rates of 55% and 23%, respectively. In another study (Sanson et al., 2004) where PCV and TMZ were used as first-line treatment in the 63 cases they encountered, no significant difference was observed in the response rate between the two treatment groups. In the study, no significant differences were observed in PFS and OS between patients stratified by age, tumor grade, KPS, etc.

However, in GC consisting of oligodendroglial tumor cells, significantly better responses were observed in both PFS and OS, with PFS of 21.2 months and OS of 33.9 months. Therefore, also for the treatment of GC, it is considered important to determine 1p, 19qLOH and the methylation status of MGMT by adequate tissue sampling in GC, for additional evaluation of the sensitivity to chemotherapy.

4. Conclusion

In terms of diagnosis, we are focusing on the application of chemical shift imaging MR spectroscopy with m-Ins, application of *in vivo* imaging technique using L1 and integrin as markers, and accurate detection of oligodendroglial GC by adequate tissue sampling and detailed evaluations of pathological morphology and gene mutations. In terms of treatment, focus is being placed on the evaluation of sensitivity to chemotherapy and the establishment of a treatment protocol for TMZ. The algorithm from the diagnosis of GC to treatment, we propose currently, is shown in Table 2. The pathological conditions for the diagnosis of GC have been specified in the 4th ed., but GC is still stated as an orphan disease. We believe that a multicenter study on the treatment of patients definitely diagnosed as having GC should be started.

Proposed algorithm for management of gliomatosis cerebri
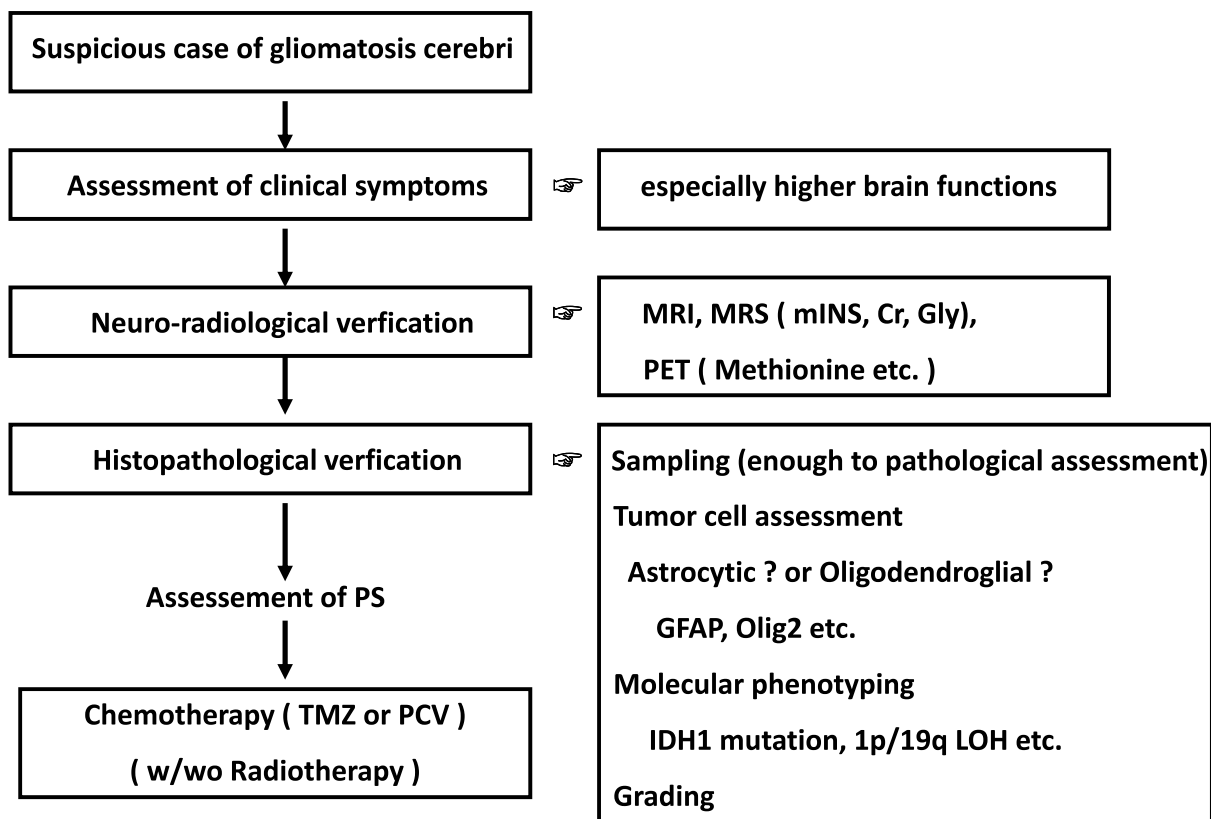

Table 2. Proposed algorithm of the management of gliomatosis cerebri

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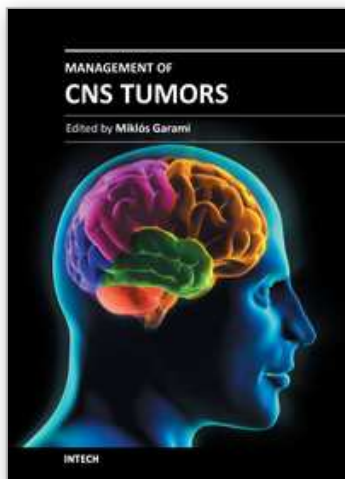
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