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Gliofibroma: A Case Report and Review of the Literature

Gliofibroma is a rare astrocytic tumor, composed of a glial component ranging from benign to high grade of malignancy and a consistently benign mesenchymal component. Its exact biological behavior is not fully known. In addition, histogenesis and prognostic factors are also still debatable. We herein present a rare case of gliofibroma in a 25-yr-old male with seizure. A computed tomographic scan of the brain showed a 1.5 cm-sized, enhancing mass with calcification. Histologically, the tumor consisted of glial fibrillary acidic protein (GFAP)-positive glial cells admixed with a mesenchymal component and extensive collagen lay down. The glial cells displayed variable cellularity, but without mitosis or necrosis. Since the MIB-1 labeling index was up to 35.8% in the cellular areas of the glial component, it could be considered to be a predictor of worse prognosis.

Key Words : *Astrocytoma; Fibroma; Glioma; Brain Neoplasms*

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INTRODUCTION

Gliofibroma is a very rare bimorphic neoplasm composed of both glial and mesenchymal components (1-5). The term, gliofibroma, was first introduced by Friede in 1978 (6). Since this initial report, about 23 cases have been reported (1-17) mostly in the first two decades of life (1). Because of the paucity of the literature with regard to this neoplasm, its exact biological behavior is not fully known (1-4). In the World Health Organization classification of tumors of the nervous system, the gliofibroma was not included as a distinct entity (18).

We herein present a case of gliofibroma involving the left parietal region in a young adult man, describing the histologic findings and immunohistochemical profile including MIB-1 and p53, with a review of the literature. This is the first case report of gliofibroma in Korea.

CASE REPORT

The patient was a 25-yr-old man who had suffered from generalized tonic clonic seizure for 6 months. The seizure was accompanied by tingling sense as a prodromal symptom. A magnetic resonance scan of the brain showed an enhancing mass occupying the left parietal lobe with a central area displaying low signal intensity. Since this lesion showed high attenuation on computed tomographic scan, it was considered to be calcification. He underwent gross total excision of the mass under the clinical and radiological diagnosis of oligodendroglioma or metastatic tumor. At operation, the mass was firmly palpable at the cortical surface and located in the deep cortex. Neither chemotherapy nor radiotherapy was given. For 2 months after the operation, the patient showed no symptoms or signs of recurrence of tumor.

On gross examination, the submitted specimen was a hard mass with attached mucoid tissue, measuring 3.2 × 2.6 × 2.2 cm. On sections, the hard mass measured about 1.5 cm and exhibited calcified areas.

Under the light microscope, the tumor was a relatively well circumscribed mass without encapsulation but showed an infiltrative growth pattern (Fig. 1). The tumor consisted of round-to-oval and spindle cells and abundant extracellular collagenous stroma. Tumor cells were arranged in small groups or islands separated by bundles of fibrous connective tissue in most areas. There was extensive calcification in the sclerotic tumor tissue (Fig. 2). The cellularity of tumor varied from area to area and was closely related with the abundance of collagenous stroma. In areas with abundant hyalinized collagenous stroma, fibroblast-like spindle cells and tumor cells were sparsely scattered (Fig. 3A). The periphery of the tumor showed hypercellular aggregates of small round cells with a scanty collagenous stroma (Fig. 3B). The nuclei of tumor cells were round to oval or elongated with a fine chromatin pattern and perinuclear halo (Fig. 3B). The nuclei were not uniform, and angulated nuclei and nuclear grooves were frequently observed. Some round-to-spindle cells showed wavy cellular processes. Neither mitosis nor necrosis was observed throughout the tumor tissue. The tumor was hypervascular with sclerosis of the vascular wall. The collagenous tissue in the tumor was strongly stained with Masson-trichrome. The reticulin stain showed abundant reticulin

fibers outlining the islands or nests of tumor cells (Fig. 4). The tumor cells lacked periodic acid-Schiff (PAS)-positive mucin or glycogen in their cytoplasm.

Immunohistochemically, most of the round-to-elongated tumor cells were strongly reactive for glial fibrillary acidic protein (GFAP) (dilution 1:3,000; Biogenex, CA, U.S.A.), vimentin (dilution 1:80; DAKO, Glostrup, Denmark), and S-100 protein (dilution 1:2,000; DAKO). Their cellular processes were evident by GFAP immunostain (Fig. 5A, B). None of the tumor cells expressed EMA (dilution 1:50; DAKO) or cytokeratin AE1/AE3 (dilution 1:80; Zymed, San Francisco, CA, U.S.A.). There were some spindle cells that were GFAP-negative but vimentin-positive (Fig. 5C). However, tumor cells were negative for phosphorylated neurofilament (dilu-

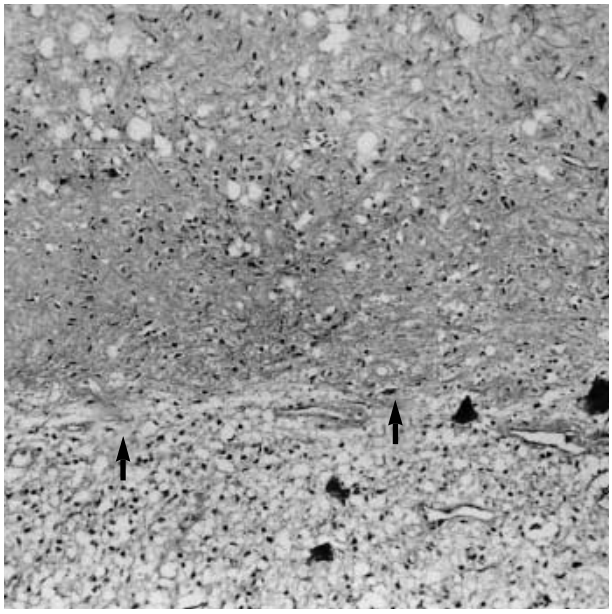

Fig. 1. Histologically, the tumor is relatively well circumscribed (arrows) and shows reactive gliosis in the surrounding brain parenchyma (Masson-trichrome stain, ×200).

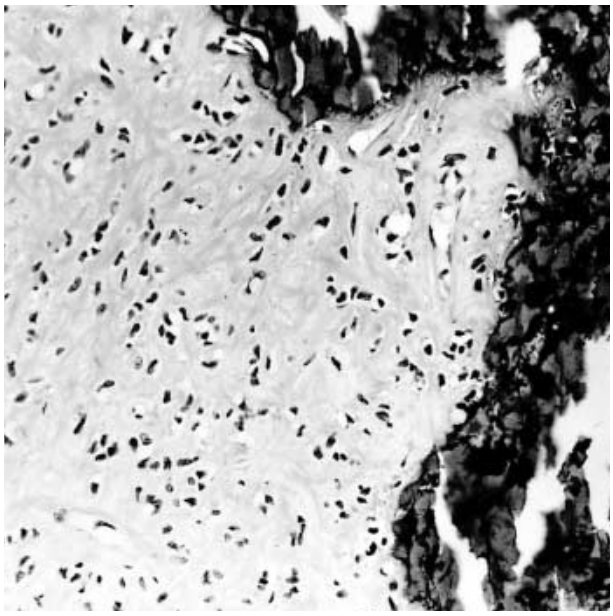

Fig. 2. Tumor cells are arranged in small groups or islands in most areas with abundant collagen deposit and calcification (H&E stain, ×200).

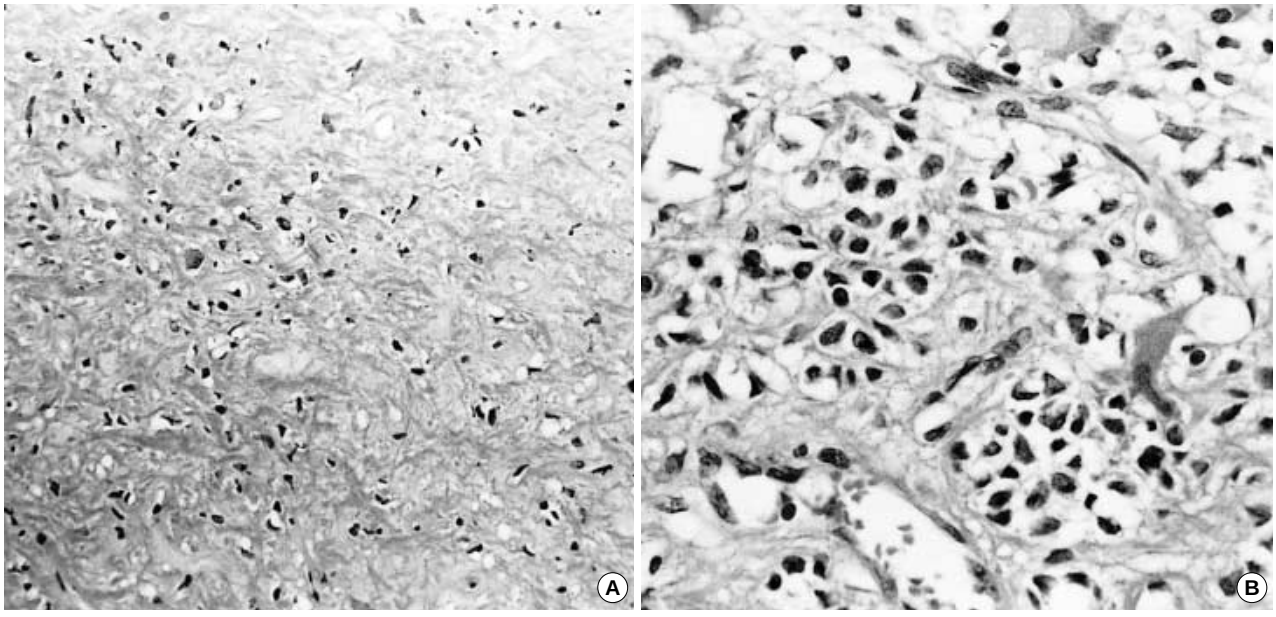

Fig. 3. The tumor contains a sparse population of fibroblast-like spindle cells and glial cells in abundant connective tissue stroma (A, H&E stain, ×200). Hypercellular areas of the tumor with scanty collagenous stroma show round to oval and elongated nuclei with an irregular contour and perinuclear halo (B, H&E stain, ×400).

tion 1:200; Biogenex, CA, U.S.A.) or synaptophysin (dilution 1:40; DAKO), in contrast to the strong expression in the entrapped neurons. p53 (dilution 1:80; Zymed) was not expressed in tumor cells. MIB-1 (dilution 1:50; DAKO) was almost negative in the sclerotic areas of the tumor, but its labeling index was up to 35.8% in the cellular areas of the tumor periphery. These histologic and immunohistochemical findings of the tumor were consistent with a gliofibroma.

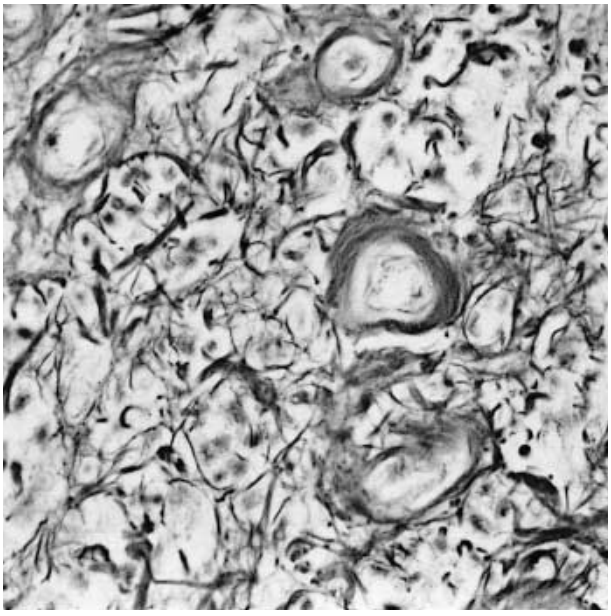

Fig. 4. The tumor contains abundant reticulin fibers outlining the islands or nests of tumor cells (reticulin stain, ×200).

DISCUSSION

Since the first description of gliofibroma in 1978, only sporadic cases of tumors designated as "gliofibroma" have appeared in the literature (1-17). Table 1 summarizes the clinical and histologic findings of the cases. The tumor showed no apparent gender predilection. It has been described as arising both in the supratentorial and infratentorial regions, including several cases developing in the spinal cord. The age at presentation varies, although most patients were in the first two decades of life. There are several adult cases including the present patient. Histologically, the majority of these neoplasms have a benign histology and show no recurrence or metastasis after resection. Necrosis and prominent vascular proliferation are not typical features of gliofibroma (2). However, five cases showed anaplastic or malignant features in their glial component, such as increased mitotic activity and cellularity, abnormal mitosis, and marked nuclear pleomorphism (1, 3, 6, 10, 11). Among them, four patients died of the disease (1, 4, 6, 10).

Gliofibroma display either close intermingling of mesenchymal (fibroblastic) and glial tissues or alternate areas of glial and fibroblastic elements (1, 2). Our case showed the former pattern. The glial cells of the present case showed fried-egg appearance or artifact of oligodendroglioma, but their nuclear features with angulated nuclei and nuclear grooves were reminiscent of astrocytoma. Moreover, astrocytic differentiation of those cells was confirmed by immunohistochemistry for GFAP. Clear cell changes of the glial element and extensive perivascular sclerosis were considered to be unique features of the present case, as compared with previously reported cases (1-7, 10, 11, 13-15, 17).

Among the rare bimorphic neoplasms of mixed mesenchy-

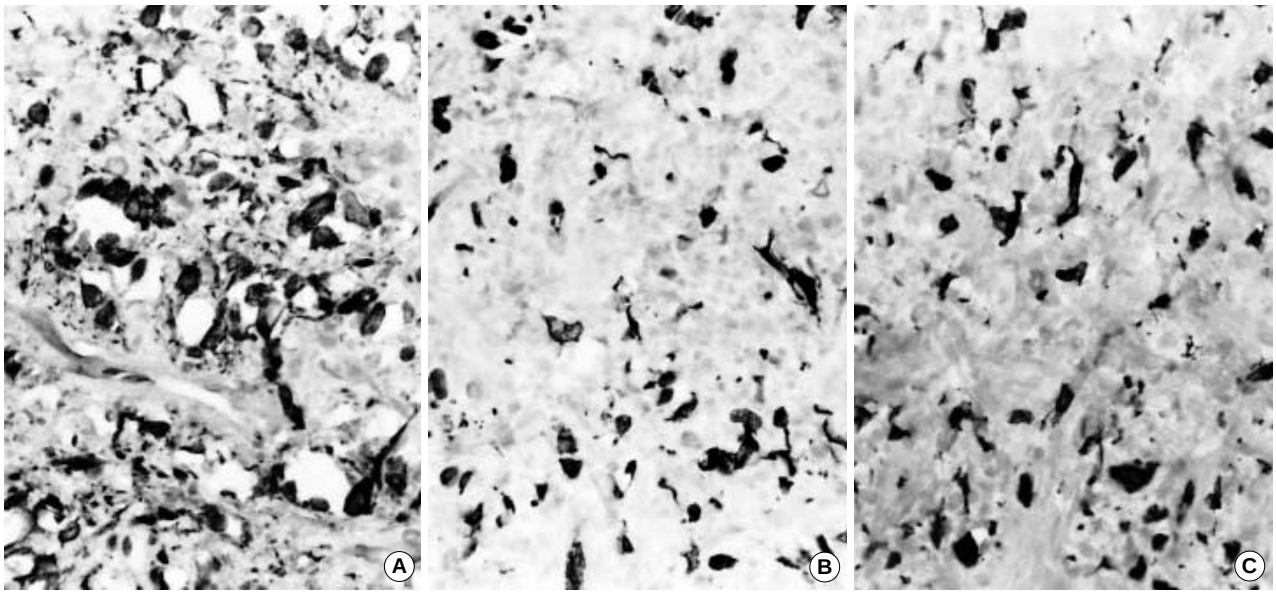

Fig. 5. Results of immunohistochemical stains. (A, B) Most of the tumor cells are strongly reactive for GFAP, and their cellular processes are evident by GFAP immunostains (×400). (C) Some spindle cells are GFAP-negative but vimentin-positive (×400).

Table 1. Clinical findings of gliofibromas reported in the literature

Authors, Year (Reference)	Case No.	Age (yr), Sex	Location of tumor	Pathologic findings	Treatment	Outcome (duration of follow-up)
Friede 1978 (6)	1	3.7, F	Lower medulla	Dedifferentiation in the glial component	RT/chemoT	No surgery Died 3 mos after presentation
Budka and Sunder-Plassmann 1980 (7)	2	45, F	Cervical spinal cord	Moderately increased cellularity in the glial component	Surgery (GTR)	Alive (1 yr)
Iglesias et al. 1984 (5)	3	11 days, M	Thoracic spinal cord	Benign gliofibroma	Surgery (GTR)	Alive (4 yr)
Reinhardt et al. 1984 (8)	4	16, F	Rt temporal lobe	NA	Surgery	Alive (6 mos)
Bonin et al. 1990 (9)	5	32, F	4th ventricle	NA	NA	NA
Snipes et al. 1991 (10)	6	2 mo, F	Thalamus, post. fossa	Increased MFs in the glial component	Surgery (STR)	Died (16 mos)
Vazquez et al. 1991 (4)	7	9, F	spinal cord (C, T)	Benign gliofibroma	Surgery (STR)/RT	Died (1.5 yr)
	8	5.5, M	spinal cord (T, S)	Benign gliofibroma	Surgery (GTR)/RT	Alive (2.5 yr)
	9	11 mo, F	Rt temporal lobe	Foci of pleomorphism and numerous MFs in the glial component	Surgery (GTR)	Alive (2 yr)
Schober et al. 1992 (11)	10	18, M	Rt frontal lobe	Small foci of anaplasia and giant cells in the glial component	Surgery (GTR)	Alive (7 days)
Iglesias-Rozas et al. 1992 (12)	11	14 mo, F	Lt frontoparietal lobe	NA	Surgery	Alive (18 mos)
Rushing et al. 1993 (13)	12	6 mo, F	Posterior fossa	Benign gliofibroma	Surgery (GTR)	Alive (2 yrs)
Cerda-Nicolas et al. 1993 (14)	13	9, M	Lt parietal lobe	Benign gliofibroma	Surgery (GTR)	Alive (5.5 mos)
	14	4, F	4th ventricle	Foci of increased cellularity & giant cells in the glial component	NA	NA
Windisch et al. 1995 (15)	15	5 mo, M	T10-11	Benign gliofibroma, abundant small thick-walled vessels	Surgery (STR)	Alive (7 mos)
Caldemeyer et al. 1995 (3)	16	8, M	Temporal lobe	Numerous MFs and increased cellularity in the glial component	chemoT	NA
	17	6 mo, F	Cerebellum	Benign gliofibroma	Surgery (GTR)	NA
Prayson, 1996 (2)	18	3 mo, M	Lt frontoparietal lobe	Benign gliofibroma 0.9% of PI	Surgery (STR)	Alive (31 mos)
Molenkamp et al. 1998 (16)	19	NA	NA	NA	NA	NA
Sharma et al. 1998 (1)	20	24, F	T6-8	Benign gliofibroma 0% of PI	Surgery (STR)	Alive (2 yr)
	21	10, M	Temporal lobe	Benign gliofibroma 0% of PI	Surgery (GTR)	Alive (3 mos)
	22	54, F	Rt parietal lobe	Increased cellularity and MFs in the glial component, 10.5% of PI	Surgery (GTR)/RT	Died (6 mos)
Matsumura et al. 2002 (17)	23	12, F	Cervical spinal cord	Increased cellularity 1% of PI	Surgery (GTR)	Alive (33 mos)
Present case, 2003	24	25, M	Lt parietal lobe	Foci of increased cellularity up to 35.8% of PI	Surgery (GTR)	Alive (2 mos)

NA: not available, C: cervical, T: thoracic, S: sacral, Rt: right, Lt: left, RT: radiation therapy, chemoT: chemotherapy, GTR: gross total resection, STR: subtotal resection, yr: year, mo: month, MFs: mitotic figures, PI: proliferation index.

mal and glial elements, gliosarcoma is the most common and well-recognized lesion comprised of a malignant astrocytic component (glioblastoma) and also a malignant mesenchymal component (sarcoma) (1, 2). The sarcomatous element is frequently accompanied by an increased deposition of collagen material (2). In gliofibroma with a malignant behavior, the glial component exhibits features of anaplasia, while the histology of mesenchymal component is consistently benign (1). Unfortunately the term "gliofibroma" has been used in the literature for both benign and malignant forms. Actually the prognostic factors of the tumor are still a matter of debate (1). Nevertheless, the MIB-1 or Ki-67 antibody appears to be a marker of cell proliferation (1). The present case showed focal areas with increased celluarity in the glial element of tumor, in which the MIB-1 index was 35.8%. The MIB-1 index of our case is the highest among the gliofibroma cases reported in the literature (1, 2, 17). With existence of high cellular area, the high Ki-67 positivity may be considered to be a possible predictor of worse prognosis.

Histologically, gliofibromas should be distinguished from other collagen-producing tumors of the central nervous system, including clear cell meningioma, gliosarcoma, and desmoplastic infantile astrocytoma and ganglioglioma (DIA/DIG). Clear cell meningioma is easily excluded by the negative EMA staining of the tumor cells. In addition, the cells have no PAS-positive cytoplasmic glycogen. Gliosarcoma can be distinguished by the presence of a malignant mesenchymal element. Gliofibroma may be included under a broader category of desmoplastic astrocytic tumors with DIA/DIG (2, 13, 19). In spite of their striking similarities, there are also several differences,

DIA/DIG are presented as a large cystic lesion in the superficial cortex of the brain and usually affect infancy or early childhood. DIA/DIG is considered to be a benign neoplasm (WHO grade I) with a low MIB-1 labeling index less than 5% (20). In DIA/DIG, the mesenchymal fibroblastic element is absent. In the present case, clear cell features of the glial component resembled those of glioneuronal tumors such as neurocytoma, which prompted us to do immunostain using the neuronal markers and electron microscopic study. However, tumor cells showed no evidence of neuronal differentiation.

The most salient feature of these desmoplastic neoplasms may be their ability to generate connective tissue elements, for which a number of hypotheses have been advanced (2). Friede (6) proposed that collagen was produced by multipotential glial/mesenchymal cells. Iglesias et al. (5) demonstrated that collagen was produced by fibroblasts. On the other hand, there also have been some theories suggesting glial cells as the source of collagen via: 1) fibroblastic metaplasia (13), 2) secondary differentiation (21), or 3) generation of growth factors resulting in a proliferation of certain mesenchymal cell types (2).

Although some authors put gliofibroma in the same category with desmoplastic astrocytic tumors (2, 13, 19), the disease is a distinct entity (1, 22). Depending upon the presence of features of anaplasia in the glial component, this tumor should be labeled as a benign or malignant gliofibroma and treated accordingly (1).

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