INTRODUCTION

Glioblastomas may develop de novo or through progression from low-grade or anaplastic astrocytomas. The term ‘primary glioblastoma’ refers to a glioblastoma that lacks a precursor lesion and has a clinical history of less than three months. On the other hand, the term ‘secondary glioblastoma’ indicates that the glioblastoma has progressed from a low-grade tumor after a long latency period and often manifests in younger patients. These subtypes of glioblastoma develop via different genetic pathways, and they differ in prognosis and response to therapy. Thus, differential diagnosis of these subtypes and prediction of the factors that affect the progression from low-grade diffuse astrocytoma to secondary glioblastoma would be clinically very important. We present a rare case of secondary glioblastoma, which developed only three months after the follow-up imaging evaluations, with a history of low grade glioma, and present the factors that cause rapid progression.

Index terms
Glioblastoma
Secondary
IDH1 Protein, Human
Disease Progression

Case Report

Rapid Progression of Gliomatosis Cerebri to Secondary Glioblastoma, Factors That Affect the Progression Rate: A Case Report

대뇌신경아교종증에서 빠른 진행을 보인 이차성 다형성아교모세포종, 진행속도에 영향을 미친 인자에 대한 증례 보고

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blastoma. We present a rare case of secondary glioblastoma which developed only three months after the initial detection of gliomatosis cerebri and discuss the factors that cause rapid progression.

CASE REPORT

An 80-year-old male presented with syncope and scalp bleeding; he had a history of myocardial infarction, which was treated 7 years ago with coronary angiography and stent insertion, and he has been taking aspirin for cardiovascular disease. His vital signs were stable and there were no abnormal laboratory findings. He complained of symptoms of memory loss at the time of syncope. To identify any traumatic injury or brain lesions, contrast-enhanced multi-detector computed tomography images were obtained with a 32 channel dual source CT scanner (SOMATOM Definition; Siemens Medical Solutions, Forchheim, Germany) and magnetic resonance images (MRI) were obtained with 3T; MRI scanner (MAGNETOM Skyra 3T; Siemens Medical Systems, Erlangen, Germany).

On the CT scan, wide regional, patchy and decreased attenuation lesions involving the left insula, the left subinsula, the left hippocampus, the left anterior temporal lobe, left parahippocampus, and some of the left frontal and high parietal cortices and white matter were detected along with mild gyral effacement. On MRI, these wide, regional and patchy lesions showed high signal intensity (SI) on T2-weighted images (WI) and fluid attenuation inversion recovery (FLAIR) images (Fig. 1A, B) and slightly increased SI on diffusion weighted imaging and apparent diffusion coefficient maps. On contrast-enhanced T1WI images, these lesions showed decreased SI without an enhancing lesion (Fig. 1C, D). On perfusion MRI, the cerebral blood volume (CBV) parameter map did not show increased signal at the level of high SI detected on conventional images (Fig. 1E, F). The spectroscopic findings showed an increased choline peak and a markedly decreased N-acetylaspartate (NAA) peak in the diffuse ill-demarcated patchy lesion involving the left anterior parahippocampal temporal area (Fig. 1G). Diffuse hypoattenuating lesion on CT and bilateral poorly defined areas of high T2SI represent tumor spread and lack of enhancement indicates a preserved blood-brain barrier. This lesion involved three lobes of the brain with preservation of the underlying structures. Increased choline/NAA peak in the tumor as compared with normal brain tissue, supposedly caused by a decrease in NAA, reflects replacement of neurons by neoplastic glial cells. It is consistent with a neoplastic lesion and characteristic findings of WHO grade II glioma. Thus, we suggested that this lesion was gliomatosis cerebri or a multicentric low-grade glioma.

Other noticeable imaging findings were mild chronic ischemic change in the left border zonal frontoparietal white matter area. On CT angiography, total occlusion of the left proximal portion of the middle cerebral artery was detected (Fig. 2A). However, collaterals to the distal run-off were seen faintly. On transfemoral cerebral angiography (TFCA), total occlusion of the middle cerebral artery at the proximal level was seen and collateral flow via the posterior communicating artery through the vertebral artery was detected. Also, there were asymmetrically prominent deep medullary veins in the left hemisphere, suggestive of increased oxygen extraction on susceptibility weighted images (Fig. 2B). On perfusion images, mean transit time (MTT) parameter maps were significantly asymmetric with a large area of increased intensity which indicates prolonged MTT in the left border zone of the frontal, parietal, and temporal periventricular white matter areas in the left middle cerebral artery territory, suggesting the presence of a large penumbra or oligemia (Fig. 2C, D).

We decided to perform conservative treatment without biopsy, and during the follow-up, the patient did not present any other symptoms and there was no change in imaging evaluations.

After three months, our patient visited the emergency department with a complaint of right hemiparesis and fine motor disturbance which had started five days ago. On laboratory examinations, there were no abnormal findings. There were no interval changes in the left anterior temporal, insular, and subinsular areas, which showed a diffuse regional hypodense lesion without enhancement on contrast-enhanced CT and high SI on T2WI. However, a focal, lobulated, unevenly thickened, enhancing lesion with newly developed central necrosis was observed in the left high parietal white matter and cortical areas, previously seen as non-enhancing hyperintense signal on T2WI (Fig. 3A).

Peritumoral edema was prominently visible on the T2WI and FLAIR images (Fig. 3B). There was diffusion restriction in the thickened wall of the mass, but not in the central necrotic portion (Fig. 3C, D). On perfusion MRI, a markedly increased CBV in the newly developed interval enhancing peripheral wall
Fig. 1. Initial contrast-enhanced conventional, perfusion MRI, and MR spectroscopy in an 80-year-old male, suggesting gliomatosis cerebri. A-D. Fluid attenuation inversion recovery (FLAIR) images show diffuse swelling with increased signal intensity and mild gyral effacement involving the left anterior temporal, the left parahippocampal, some of the left frontal cortical and white matter areas (A) as well as the left high parietal white matter and some cortical areas (B). Gadobenate dimeglumine-enhanced T1-weighted MRI shows slightly decreased signal without an enhancing lesion in the corresponding sites (C, D).

E, F. Cerebral blood volume parameter map shows an increased signal at the level of high signal intensity detected on conventional MRI.

G. On MR spectroscopy, an increased choline peak and a markedly decreased N-acetylaspartate peak are seen in the diffuse ill-demarcated patchy high FLAIR signal intensity, poorly enhancing lesions involving the left anterior parahippocampal temporal area, suggesting gliomatosis cerebri.
of the central necrotic mass in the left high parietal white matter and some cortical areas was seen, suggesting a malignant tumor such as a glioblastoma (Fig. 3E). On spectroscopy, increased choline and lactate peaks, suggesting a malignant tumor with central necrosis, were detected (Fig. 3F).

Total resection of the tumor was performed, and the final pathological diagnosis was glioblastoma (WHO grade IV). Photomicrograph of the lesion showed classical features of glioblastoma with foci of glomeruloid proliferation and vascular proliferation (Fig. 4A), the presence of some mitosis, and hemorrhagic necrosis. Surrounding low-grade glioma components supported the diagnosis of secondary glioblastoma because a low-grade gli-
Fig. 3. Follow-up contrast-enhanced, perfusion MRI and MR spectroscopy after 3 months showing a newly developed glioblastoma at the site of the previous gliomatosis cerebri lesion.

A. Contrast-enhanced T1-weighted MRI shows a markedly enhancing wall with uneven thickness of the mass.
B. Fluid attenuation inversion recovery images show a newly developed interval mass, measuring approximately 2.9 × 2.5 × 2.4 cm in dimensions in the left high parietal white matter and some cortical areas. The mass shows a lobulated margin, multiple internal septae, and peripheral edema. Central portion of the mass shows dark signal intensity.
C. Diffusion weighted imaging and (D) apparent diffusion coefficient show diffusion restriction in the thickened wall of the mass, but no increased signal intensity is detected in the central necrotic portion.
E. Perfusion MRI shows a markedly increased cerebral blood volume in the newly developed-interval enhancing-peripheral wall of the central necrotic mass.
F. Increased choline peak and lactate peak (arrow) are seen in the peripheral enhancing wall of the mass with central necrosis in the left high parietal area, suggesting a malignant tumor such as glioblastoma or anaplastic glioma.

Gliomatosis cerebri component is not detected in primary glioblastoma (Fig. 4B). On immunohistochemical staining, positive reaction to GFAP was detected, which indicates the presence of neoplastic cells (Fig. 4C). Immunohistochemical staining of epithelial membrane antigen and synaptophysin showed negative reactivity. Ki67, a marker of cell division and an indicator of the tumor cell proliferation activity, showed high levels, indicating an increased grade of glioma (Fig. 4D). p53 expression, which is considered an early event in glioma progression and is generally associated with secondary glioblastoma, rather than primary glioblastoma, showed moderately positive reactivity (Fig. 4E). Hypoxia-inducible factor 1a (HIF-1α) is a transcriptional factor that activates tumor survival under an unstable hypoxic tumor microenvironment. Some of the tumor cells showed nuclear staining, indicating that the tumor is in a hypoxic environment (Fig. 4F). Isocitrate dehydrogenase (IDH) sequencing was negative for the IDH1 mutation.
DISCUSSION

Glioblastoma is the most common brain tumor. Since the terms ‘primary and secondary glioblastomas’ were first used in 1940 (5), these subtypes have been considered as distinct disease entities that affect different age groups of patients and develop through distinct genetic pathways.

The vast majority of glioblastomas (~90%) which develop rapidly de novo without clinical or histologic evidence of a less malignant precursor lesion were termed as primary glioblastomas (6). Secondary glioblastomas progress from low-grade diffuse astrocytoma or anaplastic astrocytoma and constitute a relatively rare disease when compared with primary glioblastomas. At a population level, it was found that only 5% of all cases were secondary glioblastomas with histopathological evidence of a precursor low-grade or anaplastic astrocytoma (1).

The distinction between primary and secondary glioblastomas is based on clinical observations. The diagnosis of primary glioblastoma is made at the first biopsy, without radiologic or histologic evidence of a preexisting precursor lesion. The diagnosis of secondary glioblastoma requires neuroimaging or histologic evidence to prove progression from a low-grade or anaplastic astrocytoma (6).

These subtypes of glioblastoma affect patients at different ages, and show a different clinical course, prognosis and response to therapy. Primary glioblastoma develops in the elderly compared to secondary glioblastoma. A review of several studies shows a tendency toward a higher male to female ratio in primary glioblastomas than secondary glioblastomas. The development rate is different between these subtypes as well. Primary glioblastoma is characterized by a very rapid development of clinical symptoms. The majority of patients with primary glioblastomas present with symptoms within weeks of the onset of disease, while secondary glioblastomas may progress more slowly over months (6).

Fig. 4. Photomicrograph of the lesion in the left high parietal lobe on hematoxylin and eosin (H&E) staining and immunohistochemical staining. A, B. Photomicrograph of the lesion shows classical features of glioblastoma (A) high grade glioblastoma with glomeruloid proliferation and vascular proliferation (H&E, ×200) and (B) low grade component of the tumor (H&E, ×400). C. Neoplastic glial cells show strong positivity for Glial fibrillary acidic protein immunohistochemical staining (×100). D. Ki67, a marker of cell division and an indicator of tumor cell proliferation activity, shows high levels of reactivity, indicating an increased grade of glioma (×100). E. p53 expression, which is considered an early event in glioma progression and is generally associated with secondary glioblastoma, rather than primary glioblastoma, shows moderately positive reactivity (×100). F. Hypoxia-inducible factor 1α (HIF-1α) is a transcriptional factor that activates tumor survival under an unstable hypoxic tumor microenvironment. Some of the tumor cells show nuclear staining, indicating that the tumor is in a hypoxic environment (×400).
blastomas (68%) had a clinical history of less than three months (1). On the other hand, the course of progression of secondary glioblastomas varies considerably, and Watanabe et al. (2) reported that the mean time for progression from low-grade astrocytoma to secondary glioblastoma was 55 months.

Differential diagnosis of these subtypes of glioblastomas by neuroimaging is difficult, but there are some noticeable features. Primary glioblastomas typically present as large tumors that show central necrosis and extensive peritumoral edema on MRI. Because of the rapid growth rate, sequential neuroimaging that includes early lesions is rarely carried out (7). On the other hand, secondary glioblastomas have a lesser degree of necrosis, and are preferentially located in the frontal lobe (6).

Histologically, primary and secondary glioblastomas are largely indistinguishable. The main reason for this is that both glioblastoma types share similar morphologic features (5). But even with these indistinguishable histological features, primary and secondary glioblastomas differ in their genetic and epigenetic profiles. Epidermal growth factor receptor overexpression and phosphatase and tensin homolog mutations prevail in primary glioblastomas but are rare in secondary glioblastomas (1). TP53 mutations, which are the first genetic alterations identified in astrocytic brain tumors, are rare in secondary glioblastomas (< 10%) and have a high incidence (> 65%) in secondary glioblastomas (3). The incidence of TP53 protein accumulation is significantly higher in secondary glioblastomas (> 90%) than in primary glioblastomas (< 35%) (8). IDH1 mutations, indicating that these tumors are derived from neural precursor cells that differ from those of primary glioblastomas, were first reported in many patients with secondary glioblastomas and were associated with good prognosis (9). It is now agreed that IDH1 mutation is a definitive diagnostic molecular marker of secondary glioblastomas and more reliable and objective than clinical and/or pathologic criteria.

Unlike the characteristics of the subtypes of glioblastomas mentioned above, our case shows a rapidly growing secondary glioblastoma with internal necrotic portions. We suggest that the causes of a rapid growth rate and necrosis in our case are genetic characteristics and previous ischemic injury detected on CT angiography and TFCA as total occlusion of the left middle cerebral artery. The time of progression to anaplastic astrocytoma or glioblastoma is somewhat shorter for low-grade astrocytomas carrying a TP53 mutation (3). This result is in accordance with our case as a high level of p53 expression was observed on immunohistochemical staining. Secondary glioblastomas lacking IDH1 mutations have a shorter clinical history. In a previous study, patients with glioblastomas lacking IDH1 mutations had a mean duration of preceding clinical symptoms of 3.9 months, which was significantly shorter than that in patients with IDH1 mutant glioblastoma (mean, 15.2 months) (4). It is suggested that the absence of extensive necrosis and peritumoral brain swelling in secondary glioblastoma is due to the slow growth rate (5). However, our case showed central necrosis and peritumoral brain swelling which occurred within three months.

In a study for determining the morphologic features of glioblastoma that link vascular pathology and hypoxia, hypoxia-mediated activation of the coagulation system was presented as the cause of intravascular thrombosis, which aggravates intratumoral hypoxia, and this leads to abnormal endothelial cell proliferation and tumor necrosis (10). Intratumoral necrosis is the hallmark of glioblastoma and it is due to rapid cell proliferation and inadequate vascularization leading to insufficient oxygen supply to the tumor. Chronic exposure to low levels of oxygen has been linked to several phenotypic changes, and it frequently produces necrotic zones and induces changes in the proteome of tumor cells that lead to impaired growth or cell death and elaborate microvascular proliferation that heralds a phase of more malignant progression. Hypoxia-inducible factor 1 (HIF-1) is one of the major regulators of tumor cell adaptation to hypoxic stress, lead to the establishment of a vicious circle of hypoxia and malignant progression (10). This can be applied to our case with the findings of CT angiography and sequelae of the previous hypoxic ischemic change detected on conventional MRI and perfusion MRI.

Differential diagnosis of these subtypes of glioblastomas is important to therapeutic approaches. The ability to predict the pace of progression from low-grade diffuse astrocytoma to secondary glioblastoma would be clinically very important. Based on the genetic profiles and previous ischemic injury detected on neuroimaging, rapid progression of secondary glioblastoma can be predicted and it can affect patient prognosis.
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대뇌신경아교종증에서 빠른 진행을 보인 이차성 다형성아교모세포종, 진행속도에 영향을 미친 인자에 대한 증례 보고

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다형성교모세포종은 새롭게 형성될 수도 있고 저등급 교종 혹은 역형성아교모세포종에서 이차적으로 형성될 수도 있다. 일차성 다형성교모세포종은 전구 병변의 증가가 없이 3개월 미만의 임상 증상으로 내원한 환자가 교모세포증으로 진단받은 경우를 의미하지만 이차성 다형성교모세포증은 저등급 병변이 오랜 기간에 걸쳐 악성으로 진행된 경우를 의미하며 좀 더 젊은 환자에게 많이 발생한다. 이러한 하위 유형들은 각각 다른 유전적 경로와 예후를 보이기 때문에 일차성과 이차성 다형성교모세포증을 구별하고 저등급 교종에서 이차성 교모세포증으로의 빠른 진행을 예측할 수 있는 인자를 찾는 것은 임상적으로 매우 중요하다. 우리는 이전 연구에서 알려졌던 특징과는 다르게 저등급 교종이 추적관찰 3개월 만에 이차성 다형성교모세포증으로 진단된 증례를 통해 영상의학적 소견과 함께 빠른 진행을 이기한 요인들에 대해 알아보고자 한다.

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