Rapid Regrowth of Solitary Subependymal Giant Cell Astrocytoma

—Case Report—

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Abstract

A 48-year-old female presented with a subependymal giant cell astrocytoma (SEGA) without tuberous sclerosis manifesting as memory and mental disturbance. Magnetic resonance imaging showed a huge mass which was well-demarcated and extended from the anterior horn of the right lateral ventricle to the septal area on the right side. Surgery was performed with partial removal of the tumor. The histological diagnosis was typical SEGA. One year postoperatively, follow-up magnetic resonance imaging revealed marked regrowth of the tumor. Total resection of the tumor was performed. Microscopic and immunohistochemical studies could not identify the cause of the rapid regrowth. SEGA can regrow rapidly after partial removal of the tumor.

Key words: solitary subependymal giant cell astrocytoma, rapid growth, tuberous sclerosis

Introduction

Subependymal giant cell astrocytoma (SEGA) is a World Health Organization grade I tumor typically arising in the wall of the lateral ventricle, and is the most common central nervous system neoplasm associated with tuberous sclerosis (TS). The incidence is 6% to 16% of confirmed cases of TS.¹³⁾ Whether SEGA occurs in the absence of TS remains unclear, but several cases of SEGA without any obvious features of TS have been reported.^{1,3-6,14,17,19)} SEGA is thought to be slowly progressive.^{11,16)} We describe here a rare case of SEGA without TS which rapidly regrew one year after partial removal.

Case Report

A 48-year-old female presented with memory and mental disturbance in April 1999. She was admitted to our hospital on May 7, 1999. Physical examination found no abnormalities. She had no stigma of TS, such as seizure, mental retardation, or cutaneous lesion. Computed tomography revealed a huge mass appearing as hypo- to isodense relative to the

cortical gray matter, which occupied the anterior horn of the right lateral ventricle. Magnetic resonance (MR) imaging showed a huge mass measuring $4.7 \times 4.2 \times 5.5$ cm with heterogeneous signal intensity. T₁-weighted imaging showed the mass as iso- to hypointense relative to the gray matter (Fig. 1A). T₂-weighted imaging revealed the mass as hyperintense (Fig. 1B). There was no perifocal edema. The mass was well-demarcated and strongly enhanced after administration of contrast material, and extended from the anterior horn of the right lateral ventricle to the septal area on the right side (Fig. 1C). There were no other intracranial abnormalities. Angiography revealed small feeding vessels from the anterior cerebral artery and early venous filling. The draining vein was the internal cerebral vein on the right side.

Surgery was performed via the transcallosal approach with partial removal of the tumor on May 11, 1999. Postoperatively, the patient was discharged without neurological deficits. Postoperative MR imaging showed the tumor size was markedly decreased (Fig. 2A). Follow-up MR imaging on May 8, 2000 disclosed marked regrowth of the tumor, but she had no sign of neurological deficits. MR imaging on June, 2000 revealed a further increase in the

Fig. 1 Magnetic resonance images taken before the first operation showing the tumor occupying the anterior horn of the right lateral ventricle. (A) T₁-weighted image, (B) T₂-weighted image, (C) T₁-weighted image with gadolinium.

Fig. 2 T₁-weighted magnetic resonance images with gadolinium after the first operation. (A) Five months later, a small residual tumor was present at the anterior horn of the right lateral ventricle. (B) One year later, a large tumor occupied the anterior horn of the right lateral ventricle.

tumor size (Fig. 2B). Second surgery was performed via the transcortical approach with complete resection of the tumor on July 17, 2000. Postoperatively, the patient had left hemiparesis, diabetes insipidus, urinary incontinence, and recent memory disorder. Left hemiparesis and diabetes insipidus improved after several days. One year after the second surgery, her recent memory disorder had not improved. Follow-up MR imaging showed no recurrence.

Histological examination showed the tumor was composed of large gemistocytic cells with abundant

cytoplasm and fibrillated spindle cells (Fig. 3A). The diagnosis was SEGA. Immunohistochemical studies showed both the spindle cells and the large cells were strongly positive for glial fibrillary acidic protein (GFAP), S-100 protein, vimentin, and neuron-specific enolase. A small population of polygonal cells was stained positively for synaptophysin. There was no staining for neurofilament in either the spindle cells or the large cells. The histological and immunostaining features were similar in the specimens obtained at the two operations, but the specimen from the second operation included multiple geographic necroses (Fig. 3B). MIB-1 index was less than 1% in both specimens.

Discussion

TS is an autosomal dominant disease characterized by the presence of Vogot's triad of mental retardation, seizures, and facial angiofibroma. Recently, many varieties of clinical expression of TS have been recognized and this triad is no longer considered essential for diagnosis. These 'formes frustes' may present with only epilepsy or mental deficiency, or with solitary adenoma sebaceum, or even with only visceral or retinal tumors.¹⁵⁾ The present and several other cases of SEGA without any obvious features of TS^{1,3-6,14,17,19)} have been described as a 'forme fruste' of TS,^{5,12,16)} but without the genetic studies, whether these neoplasms represent a 'forme fruste' of TS or a spontaneous tumor unrelated to the genetic abnormality that causes TS remains unclear.^{1,17)}

Fig. 3 Photomicrographs of the specimen from the second operation. (A) The tumor was composed of large gemistocytic cells with abundant cytoplasm and fibrillated spindle cells, leading to a diagnosis of subependymal giant cell astrocytoma. HE stain, original magnification $\times 100$. (B) Multiple geographic necroses were observed. HE stain, original magnification $\times 25$.

The recent identification of mutations in two tuberous sclerosis complex (TSC) genes (*TSC1* and *TSC2*) that cause TS has led to rapid progress in understanding the molecular and cellular pathogenesis of this disorder. *TSC1* (chromosome 9q34) and *TSC2* (chromosome 16p13) encode distinct proteins, hamartin and tuberin, respectively, which are widely expressed in the brain and may interact as part of a cascade pathway that modulates cellular differentiation, tumor suppression, and intracellular signaling.²⁾ Changes in tuberin messenger ribonucleic acid or protein expression have been detected in tubers and SEGAs with TS.²⁾ SEGA associated with TS is thought to originate from the subependymal nodule characteristic of the disease.¹⁵⁾ Enlargement of a subependymal nodule in childhood and subsequent transformation into a SEGA has been found.¹⁰⁾ However, the link between the altered functions of

tuberin and hamartin and the genesis of tubers, subependymal nodules, and SEGAs remains unknown. Furthermore, the origin of solitary SEGA is currently obscure. Genetic analysis of SEGA with TS or without TS may elucidate whether the origin and pathogenesis of SEGA with TS and solitary SEGA is similar.

Previous immunohistochemical studies have demonstrated mixed glial and neuronal differentiation in SEGA, suggesting that these lesions arise from multipotent progenitor cells within the germinal mantle of the developing brain.^{1,5,7-9,18)} In our case, astroglial differentiation was demonstrated by positive staining of GFAP, vimentin, and S-100 protein. Neuronal differentiation was demonstrated by positive staining for synaptophysin. These findings contrast with previous demonstrations of predominant astroglial differentiation in cases of SEGA in asymptomatic TS, and both glial and neuronal differentiation in SEGA associated with TS.^{1,7,19)}

Total removal is the recommended treatment for SEGA,¹⁰⁾ and may be curative. Unfortunately, these tumors are invariably large and often exceedingly vascular as in the present case. The benign behavior of the tumor is supported by flow cytometric studies, which have demonstrated that most of these tumors are diploid, and by low Ki-67 (MIB-1) labeling indices.^{8,11,16)} Therefore, partial removal of these tumors may be adequate to prevent the patient from developing new neurological deficits and to preserve neurological symptom-free conditions for several years. This was the reason why the first operation in the present case was performed via the transcallosal approach. However, the tumor in the present patient regrew rapidly one year after the first operation. The transcortical approach was selected at the second operation for complete resection of the tumor. Histological examination found the typical findings of SEGA in the specimen from the first operation, but multiple geographic necroses were seen in the specimen from the second operation. These findings might indicate malignant transformation of SEGA. However, mitoses, necrosis, or vascular proliferation in SEGA do not suggest a worse prognosis.^{3,5,8,16,17)} The MIB-1 labeling index of the specimen from the second operation was less than 1%. Therefore, no adjuvant therapy, such as radiotherapy or chemotherapy, was given after the total removal.

References

- 1) Bonnin JM, Rubinstein LJ, Papasozomenos SC, Marangos PJ: Subependymal giant cell astrocytoma:

- significance and possible cytogenic implications of an immunohistochemical study. *Acta Neuropathol (Berl)* 62: 185-193, 1984
- 2) Crino PB, Henske EP: New developments in the neurobiology of the tuberous sclerosis complex. *Neurology* 53: 1384-1390, 1999
 - 3) Gyure AK, Prayson RA: Subependymal giant cell astrocytoma: a clinicopathologic study with HMB45 and MIB-1 immunohistochemical analysis. *Mod Pathol* 10(4): 313-317, 1997
 - 4) Halmagyi GM, Bignold LP, Allsop JL: Recurrent subependymal giant-cell astrocytoma in absence of tuberous sclerosis. Case report. *J Neurosurg* 50: 106-109, 1979
 - 5) Huang M-C, Kubo O, Tajika Y, Takakura K: Immunohistochemical and electron microscopic study of subependymal giant cell astrocytoma. *Brain Tumor Pathol* 12: 117-123, 1995
 - 6) Kashiwagi N, Yoshihara W, Shimada N, Tanaka H, Fujita N, Hirabuki N, Watanabe Y, Nakamura H: Solitary subependymal giant cell astrocytoma: case report. *Eur J Radiol* 33: 55-58, 2000
 - 7) Kawasaki S, Yamamoto Y, Sunami N, Suga M, Ohtsuki Y: [Subependymal giant cell astrocytoma associated with tuberous sclerosis exhibiting rapid regrowth after 17 years: a case report]. *No Shinkei Geka* 27: 550-556, 1999 (Jpn, with Eng abstract)
 - 8) Kim S-K, Wang K-C, Cho B-K, Jung H-W, Lee YJ, Chung YS, Lee J-Y, Park S-H, Kim Y-M, Choe G, Chi JG: Biological behavior and tumorigenesis of subependymal giant cell astrocytomas. *J Neurooncol* 52: 217-225, 2001
 - 9) Lopes MBS, Altermatt HJ, Scheithauer BW, Shepherd CW, VandenBerg SR: Immunohistochemical characterization of subependymal giant cell astrocytomas. *Acta Neuropathol (Berl)* 91: 368-375, 1996
 - 10) Morimoto K, Mogami H: Sequential CT study of subependymal giant-cell astrocytoma associated with tuberous sclerosis. Case report. *J Neurosurg* 165: 874-877, 1986
 - 11) Nishizaki T, Orita T, Abiko S, Aoki H, Ito H: Subependymal giant cell astrocytoma associated with tuberous sclerosis: with special reference to cell kinetic studies. Case report. *Neurol Med Chir (Tokyo)* 30: 695-697, 1990
 - 12) Osborn AG: *Diagnostic Neuroradiology*. St Louis, Mo, Mosby, 1994, pp 561-563
 - 13) Paulus W, Lopez BS, Crino PB: Tuberous sclerosis complex and subependymal giant cell astrocytoma, in Kleihues P, Cavenee WK (eds): *Pathology and Genetics of Tumours of the Nervous System*. Lyon, International Agency for Research on Cancer (IARC), 1997, pp 182-184
 - 14) Prahlow JA, Teot LA, Lantz PE, Staton CA: Sudden death in epilepsy due to an isolated subependymal giant cell astrocytoma of the septum pellucidum. *Am J Forensic Med Pathol* 16(1): 30-37, 1995
 - 15) Russell DS, Rubinstein LJ: *Pathology of Tumours of the Central Nervous System*, ed 5. London, Edward Arnold, 1989, pp 766-769
 - 16) Shepherd CW, Scheithauer BW, Gomez MR, Altermatt HJ, Katzmman JA: Subependymal giant cell astrocytoma: a clinical, pathological, and flow cytometric study. *Neurosurgery* 28: 864-868, 1991
 - 17) Sinson G, Sutton LN, Yachnis AT, Duharime A-C, Schut L: Subependymal giant cell astrocytoma in children. *Pediatr Neurosurg* 20: 233-239, 1994
 - 18) Tabuchi K: [Histological diagnosis of brain tumors: (17). Subependymal giant cell astrocytoma]. *No Shinkei Geka* 19: 603-609, 1991 (Jpn)
 - 19) Taraszewska A, Kroh H, Majchrowski A: Subependymal giant cell astrocytoma: clinical, histologic and immunohistochemical characteristic of 3 cases. *Folia Neuropathol* 35(3): 181-186, 1997

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