

Subependymal Giant Cell Astrocytoma Presenting with Tumoral Bleeding: A Case Report

Jae-Young Kim¹, Tae-Young Jung¹, Kyung-Hwa Lee², Seoul-Kee Kim³

Departments of ¹Neurosurgery, ²Pathology, ³Radiology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Hwasun, Korea

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Correspondence

Tae-Young Jung
Department of Neurosurgery,
Chonnam National University
Hwasun Hospital, 322 Seoyang-ro,
Hwasun-eup, Hwasun 58128, Korea
Tel: +82-61-379-7666
Fax: +82-61-379-7673
E-mail: jung-ty@chonnam.ac.kr

We report a rare case of subependymal giant cell astrocytoma (SEGA) associated with tumoral bleeding in a pediatric patient without tuberous sclerosis complex (TSC). A 10-year-old girl presented with a 2-week history of an increasingly aggravating headache. Brain magnetic resonance imaging revealed an approximately 3.6-cm, well-defined, heterogeneously enhancing mass with multistage hemorrhages on the right-sided foramen of Monro. The tumor was completely resected using a transcallosal approach. Intraoperatively, the mass presented as a gray-colored firm tumor associated with acute and subacute hemorrhages. The origin of the mass was identified as the ventricular septum adjacent to the foramen of Monro. A pathological analysis revealed pleomorphic multinucleated eosinophilic tumor cells with abundant cytoplasm. These cells showed positive staining for the glial fibrillary acidic protein and S100 protein. A diagnosis of SEGA was established. The patient recovered without any neurological symptoms. There was no evidence of TSC. The radiological follow-up showed no recurrence for 2 years. This was a case of SEGA with intratumoral hemorrhage, for which a favorable outcome was achieved, without any neurological deficit after tumoral resection.

Key Words Hemorrhage; Astrocytoma; Tuberous sclerosis; Surgery.

INTRODUCTION

Subependymal giant cell astrocytoma (SEGA) is a clinically benign tumor that is usually associated with tuberous sclerosis complex (TSC) [1]. TSC is an autosomal dominantly inherited neurocutaneous syndrome that affects any organ system of the body. The prevalence rate of TSC in patients with SEGA ranges from 5% to 20%. Solitary SEGAs in the absence of TSC-related lesions have been reported; these resulted from somatic mosaicism of the TSC gene or *de novo* mutations at the TSC locus [2-5].

SEGA mostly occurs in the first two decades of life [6,7]. This tumor generally arises in the periventricular regions near the foramen of Monro. Therefore, diagnosis of SEGA is relatively easy, unless there is minimal evidence of tuberous sclerosis. Clinical features of SEGA include focal neurological

deficits and symptoms related to increased intracranial pressure accompanying obstructive hydrocephalus. Occasionally, the tumor is associated with intratumoral bleeding [3,6,7]. Intratumoral bleeding causes acute neurological symptoms, and in some cases, the prognosis can be dismal. Here, we present a rare case of SEGA with intratumoral bleeding, without any signs of TSC.

CASE REPORT

A 10-year-old girl presented with a 2-week history of a continuous headache, which was aggravated by accompanying nausea. Brain computed tomography showed acute hemorrhage in the region of the right lateral ventricle and obstructing hydrocephalus (Fig. 1A). Brain magnetic resonance image revealed an approximately 3.6-cm, well-defined mass on the body of the right lateral ventricle. The mass showed mixed low and high signal intensity on T1-weighted (Fig. 1B) and T2-weighted images (Fig. 1C). Following gadolinium administration, a heterogeneous enhancement was observed for the peripheral solid areas (Fig. 1D, E). The cerebral blood volume

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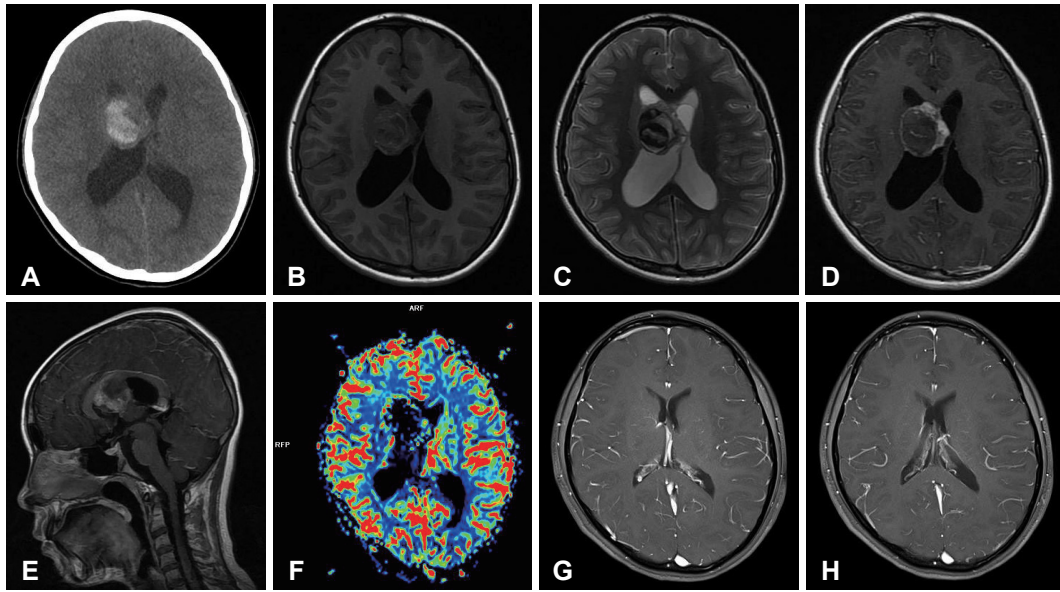


Fig. 1. Preoperative and postoperative radiological findings of subependymal giant cell astrocytoma with bleeding. A: A brain computed tomography scan showing acute hemorrhage on the right lateral ventricle. B: A brain magnetic resonance (MR) image showing an approximately 3.6-cm, well-defined mass in the right-sided foramen of Monro. The mass shows mixed low and high signal intensity on T1-weighted MR images. C: The mass shows mixed low and high signal intensity on T2-weighted MR images. D: Following gadolinium administration, the lesion demonstrates heterogeneous enhancement on axial images. E: The lesion is heterogeneously enhanced on peripheral solid area on sagittal images. F: Cerebral blood volume is focally increased on perfusion MR images. G and H: Recurrence is not observed for 2 years, based on T1-weighted enhanced MR images.

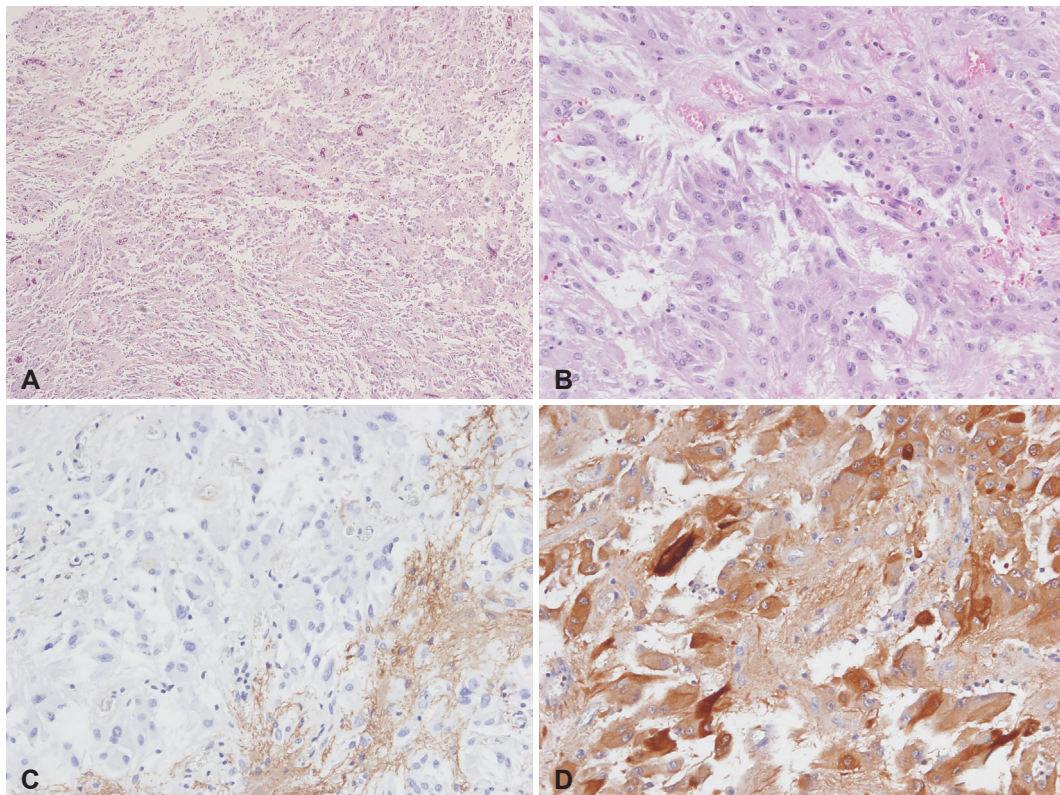


Fig. 2. Pathological findings of subependymal giant cell astrocytoma. A: Pathological analysis revealing tumor cells with many small vessels (hematoxylin and eosin staining, original magnification, $\times 40$). B: The pleomorphic multinucleated eosinophilic tumor cells contain abundant cytoplasm (hematoxylin and eosin staining, original magnification, $\times 200$). C: The tumor cells show focally positive staining for glial fibrillary acidic protein (original magnification, $\times 200$). D: The tumor cells show positive staining for S100 protein (original magnification, $\times 200$).

was focally increased in the MR-enhanced areas (Fig. 1F). The mass was a well-defined, heterogeneously enhanced lesion with mixed cystic and solid components. It contained multi-stage hemorrhages in the right-sided foramen of Monro. The radiological differential diagnoses included high-grade glioma, SEGA, and choroid plexus tumor. The tumor was completely resected via a transcallosal approach. Intraoperatively, the mass presented as a gray-colored, firm tumor associated with acute and subacute hemorrhages. The origin of the mass was the ventricular septum adjacent to the foramen of Monro. A pathological analysis revealed pleomorphic multinucleated eosinophilic tumor cells with abundant cytoplasm, associated with increased vascularity (Fig. 2A, B). The tumor cells showed focal positive staining for the glial fibrillary acidic protein (Fig. 2C) and strong positive staining for the S100 protein (Fig. 2D). The Ki-67 labeling index was less than 1%. A diagnosis of SEGA was established. The patient recovered without any neurological symptoms. On an evaluation of TSC, there is no family history of TSC and there were no cutaneous stigmata of tuberous sclerosis. A clinical evaluation was performed including echocardiography, renal ultrasonography, ophthalmologic examination, and skeletal imaging. No features of TSC were observed. A genetic study was not performed. The radiological follow-up showed no recurrence for 2 years (Fig. 1G, H).

DISCUSSION

SEGA is a rare tumor of the central nervous system with mixed glioneuronal features, most frequently seen in the setting of TSC [1]. The preoperative diagnosis of SEGA takes into account the age and clinical condition of the patient, and the location of the tumor. If clinical signs of TSC are present, an early diagnosis of TSC is possible. Solitary lesions without any clinical or radiographical evidence of tuberous sclerosis have been reported [2-4]. In these cases, the symptoms of SEGA are present with obstructing hydrocephalus, and in most cases, TSC is diagnosed according to the clinical diagnostic criteria, of which the presence of SEGA is the most important [8]. The tumor suppressor genes *TSC1* on chromosome 9q34 and *TSC2* on chromosome 16p13 encode the proteins tuberin and hamartin, respectively. In 20% of patients with clinically diagnosed TSC, mutations in the *TSC1/2* genes are not observed, and the disease in patients without mutations is less severe than in those with *TSC1/2* mutations [9,10]. It has been reported that solitary SEGAs that do not show any clinical evidence of TSC can be the result of somatic mosaicism [5]. Other reports have described solitary SEGAs with isolated somatic *TSC2* mutations or amplification of exons on the *TSC1* gene [2,11]. Solitary cases of SEGA without mutation may be due to epigenetic alteration in tuberin or hamartin [2]. The current

case did not demonstrate any clinical features of TSC, and a genetic study was not performed.

Among primary brain tumors, the incidence of hemorrhage associated with glioma is 3–7%, with cases of low-grade glioma accounting for less than 1% [3,6,7]. Despite their slow-growing nature, tumoral hemorrhage has been reported with low-grade gliomas, and, in some cases, the prognosis has been dismal. The mechanisms of hemorrhage were investigated in malignant lesions [12], and include vascular structural abnormalities, which make the vessels fragile. When there is a change in blood volume or if tumor cells invade the vessels, tumoral hemorrhage or necrosis can easily occur in the fragile vascular structures. Due to the relatively benign and slow-growing nature of low-grade gliomas, vascular proliferation and necrosis are not commonly present. Venous congestion, intravascular thrombosis, or vascular ectasia may represent potential mechanisms of hemorrhage [6,13]. A histological analysis of the current case revealed that the tumor contained many small vessels, which may have caused blood congestion in the tumor. Even though tumor bleeding is rare in low-grade glioma, the presentation of SEGA bleeding may be serious, and was found to be associated with significant morbidity and mortality in the reviewed cases. In three out of six cases of SEGA with tumoral hemorrhage, the patients had died or were in a vegetative state [6]. Perioperatively, one patient died as a result of venous hypothalamic infarction [14]. There is no doubt that doing prompt surgical removal in the acute increase in intracranial pressure due to obstructing hydrocephalus or hemorrhage [6].

For a benign SEGA, total surgical resection can be curative. Surgical treatment of symptomatic SEGA should be offered without debate [3,6,13,14]. However, the appropriate time for surgery is still controversial for small asymptomatic lesions [15-17]. Early surgical treatment for these lesions decreases the potential for surgical morbidity or hemorrhagic events compared with large lesions. However, the surgical treatment itself can cause morbidity, and tumoral hemorrhage is so rare that it may not always be considered. We found previous case reports of SEGA with intratumoral bleeding. As shown in Table 1, most of them underwent surgical treatment in the case of acute deterioration with intratumoral hemorrhage to reduce the mass effect to surrounding [7].

As alternative treatments, it can be considered Gamma Knife radiosurgery (GKR) or the mechanistic target of rapamycin (mTOR) inhibitors which can reduce the size of the mass in TSC-related tumors in not emergent situation like incidentally detected mass. GKR revealed good outcomes for many types of benign brain tumors, including gliomas, with a low incidence of side effects [22]. Out of reported cases of SEGA after GKR, half of them showed tumor volume reduction 70–

Table 1. Summary of published cases of SEGA with intratumoral bleeding

Authors (years)	Patients age (years)	Signs & symptoms	Treatment	Recurrence	Outcome	F/U period
Waga et al. (1977) [18]	11	Hemiparesis	GTR	NA	Vegetative	NA
Barbosa-Coutinho et al. (1991) [19]	13	Headache, nausea Comatose M/S	Tumor resection & HA	NA	Death	NA
Kalina et al. (1995) [20]	17	Seizure, lethargy	Tumor resection	NA	NA	NA
Hamamoto et al. (1994) [13]	19	Headache Comatose M/S	External ventricular drainage	NA	Death	NA
Sinson et al. (1994) [14]	21	Headache, lethargy	Mass debulking	NA	Death	NA
Kim et al. (2001) [21]	9	Headache	NTR	None	Stable	14 month
Stavrinou et al. (2008) [3]	33	Headache	GTR	NA	Stable	NA
Ogiwara and Morota (2013) [7]	5	Headache, vomiting	GTR	None	Stable	6 month
Ogiwara and Morota (2013) [7]	21	Hemiparesis, vomiting lethargy	STR	None	Stable	3 years
This case	10	Headache, nausea	GTR	None	Stable	2 years

F/U, follow up; GTR, gross total resection; NTR, near total resection; STR, subtotal resection; HA, hematoma aspiration; NA, not available; SEGA, subependymal giant cell astrocytoma; M/S, mental state

80% within 6 months, and another shown tumor progression [22-25]. Even though the role of GKR in SEGAs was limited by the sporadic cases, these reported results suggest GKR may be an additional option for SEGAs that are small but progressively enlarging tumors where complete resection has not been safely achieved, residual or recurrent tumors. Recently, with encouraging preliminary results with rapamycin, a phase 2 open-label clinical trial using everolimus to treat SEGAs in 28 patients with TSC showed SEGA volume reduction of at least 30% in 21 patients (75%) and at least 50% in nine patients (32%) within the initial 6 months [26]. The therapy with everolimus was continued for a median duration of 21.5 months with trough concentrations of 5 to 15 ng/mL. Importantly, none of the patients treated with mTOR inhibitors required surgical intervention or developed new lesion during treatment [27]. However, the response has been shown to be temporary, lasting only as long as the medication is used, and the toxicity of the medication may exceed its benefits, due to necessity of long-term use of mTOR inhibitors. The tumor can regrow with the discontinuation of therapy, but it can also regrow with the continuation of therapy [26,28].

In conclusion, hemorrhage is a rare occurrence in benign SEGAs; and, the outcome in such cases may be dismal. We presented an uncommon case of SEGA with intratumoral bleeding, without any signs of TSC. The patient recovered well following prompt surgical resection.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgments

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