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Clinical Observations

# Acute Management of Symptomatic Subependymal Giant Cell Astrocytoma With Everolimus

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ABSTRACT

**BACKGROUND:** Subependymal giant cell astrocytomas (SEGA) are slow-growing tumors, which can cause obstructive hydrocephalus in patients with tuberous sclerosis complex (TSC). These tumors require routine surveillance with magnetic resonance imaging. Current consensus guidelines recommend treatment of asymptomatic SEGAs with an mechanistic target of rapamycin (mTOR) inhibitor because these medications have demonstrated efficacy and safety in multiple prospective clinical trials. For symptomatic SEGAs, standard therapy typically involves surgical resection of the tumor to relieve mass effect and resolve hydrocephalus. However, resection can be associated with significant perioperative morbidity and complications. There are anecdotal reports of using mTOR inhibitors to reduce tumor size in preparation for surgery, but prospective studies comparing sole mTOR inhibitor therapy with surgical management have not been completed. **METHODS:** Here, we present a seven-year-old boy with a large, symptomatic SEGA which was treated acutely with everolimus. **RESULTS:** Everolimus treatment resulted in rapid reduction in tumor size, symptomatic improvement, and decrease in cerebrospinal fluid protein. **CONCLUSIONS:** Everolimus can effectively reduce tumor size, decrease cerebrospinal fluid protein, and allow successful ventriculoperitoneal shunt placement without the need for surgical resection of a symptomatic SEGA.

***Keywords:*** tuberous sclerosis, subependymal giant cell astrocytoma (SEGA), hydrocephalus, mTOR inhibitor, everolimus

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## Introduction

Tuberous sclerosis complex (TSC) is a multisystemic disease resulting from mutations of either of the tumor suppressor genes *TSC1* or *TSC2*, which encode for the protein products hamartin and tuberin. These protein products form a heterodimer, which modulates the mechanistic target of rapamycin (mTOR) pathway in response to growth-promoting hormonal and metabolic signals.[1] Loss of either TSC1 or TSC2 increases activation of mTOR in the absence of these signals, leading to the formation of various tumors including subependymal giant cell astrocytomas (SEGAs) in the brain.

SEGAs can be congenital, but most occur in childhood or adolescence. New onset of SEGA in adulthood is extremely rare.[2] SEGAs tend to arise in the caudothalamic groove adjacent to the foramen of Monro, but they can occur anywhere in the ventricular system and can be bilateral in up to 50% of patients.[3] No uniform definition for SEGA exists, although most commonly they are distinguished from subependymal nodules by size (i.e., >1 cm in longest diameter) or evidence of growth on serial imaging studies. Most SEGAs continue to grow at a typically, but not

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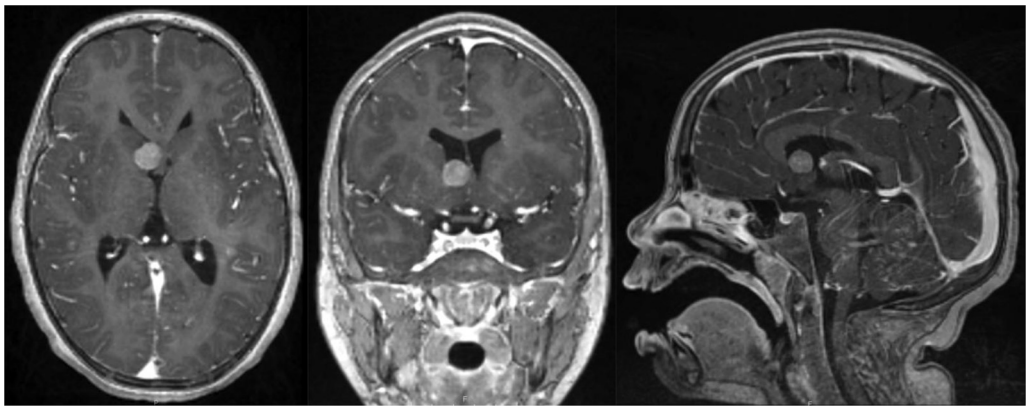

**FIGURE 1.**
MRI at age 4 after initial evaluations revealed a SEGA near the right foramen of Monro (tumor measures 1.4 cm longest diameter). MRI, magnetic resonance imaging; SEGA, subependymal giant cell astrocytoma.

invariably, slow rate until eventually producing symptoms because of the mass effect and/or obstruction of the cerebrospinal fluid (CSF) pathways and subsequent obstructive hydrocephalus. Traditional management has entailed surgical resection of a large or symptomatic SEGA to reduce the mass effect and relieve hydrocephalus, but multiple studies have shown the benefits of mTOR inhibitor therapy (everolimus, sirolimus) in the prevention of tumor growth in asymptomatic patients, with associated reduction in SEGA volume up to 80% and maintenance of the effect for up to five years in clinical trials.[4-6]

Because SEGAs are usually slow-growing tumors, they may become quite large before clinical signs and symptoms of hydrocephalus are evident. Magnetic resonance imaging (MRI) of the brain is recommended for all newly diagnosed patients with TSC, with follow-up every one to three years thereafter until adulthood to monitor for newly emerging SEGA.[7,8] An asymptomatic SEGA may be treated with mTOR inhibitors or surgical resection, but once SEGA becomes symptomatic, urgent neurosurgical evaluation and treatment is most often necessary.[7,8] To date, medical therapy of symptomatic SEGA has not been recommended because of the lack of clinical data supporting mTOR inhibitor treatment in the acute setting, but potential benefit has been suggested to reduce both SEGA volume[9] and SEGA-associated CSF protein burden that can complicate ventriculoperitoneal (VP) shunting.[10,11] We present a child with acute, symptomatic hydrocephalus associated with SEGA who was treated with everolimus and quickly demonstrated a favorable clinical and radiological response to treatment.

## Patient Description

This four-year-old boy with TSC presented to subspecialty clinic in our institution to establish care. The patient had been diagnosed with TSC at age two months when he had a brain MRI revealing cortical tubers as part of evaluation for abdominal gastroschisis. At age four years, he had no history of seizures, development was age-appropriate, and his neurological examination was normal. The only pertinent findings on general examination were hypopigmented macules and café-au-lait spots. Genetic testing revealed a disease-associated mutation in TSC1. He denied having headaches, blurred vision, or early morning vomiting.

Before establishing care, recommended imaging surveillance for SEGA had not been obtained. MRI was obtained after the initial visit (Fig 1), which in addition to TSC-associated tubers, revealed a SEGA near the right foramen of Monro and lateral ventricles that were mildly prominent.

Multiple attempts to have the patient return to clinic and discuss treatment options for his SEGA were unsuccessful. Approximately three years later, at age seven years, the patient presented to his pediatrician with a primary complaint of headaches that had been present for four months. Headache severity and frequency had worsened since onset and were now associated with night-time awakening, early morning vomiting, and dizziness. He was sent to the emergency room where neurological examination revealed papilledema and ataxia. An urgent

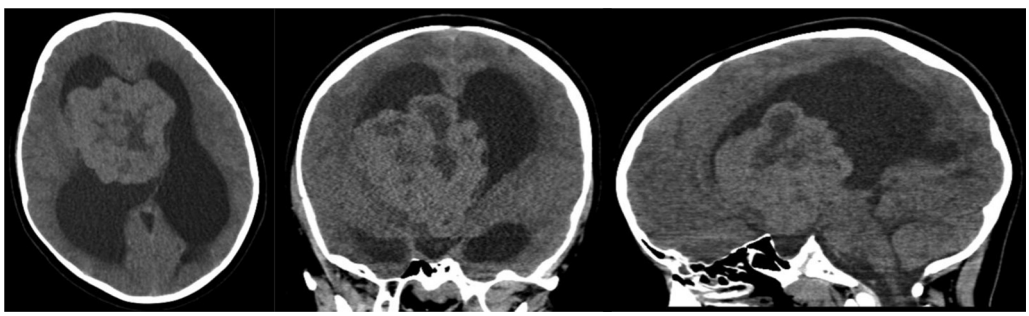

**FIGURE 2.**
Head CT performed three years later showed enlarged SEGA with obstructive hydrocephalus (tumor measures 7.5 × 6.7 × 7.9 cm, 208 $cm^3$). CT, computed tomography; SEGA, subependymal giant cell astrocytoma.

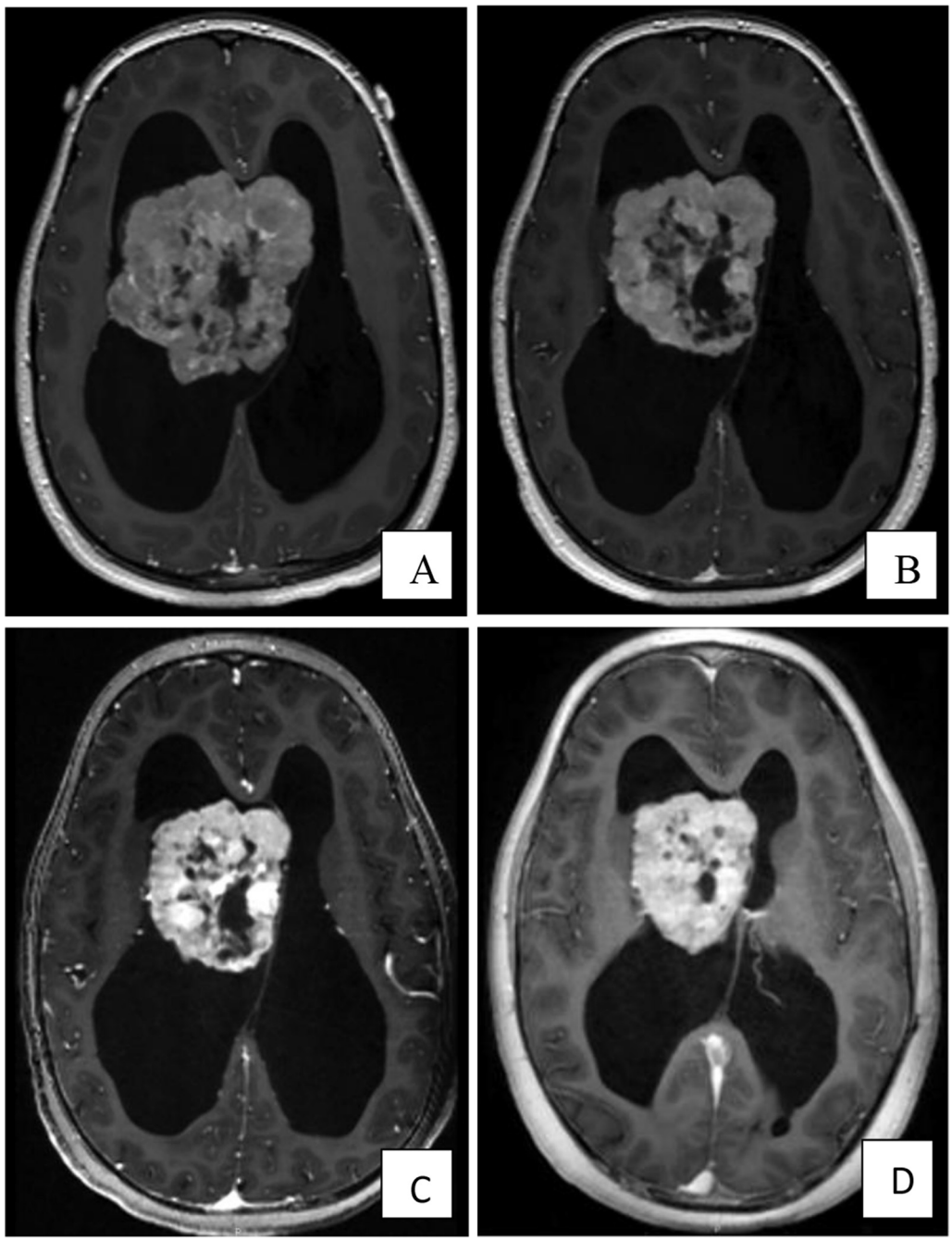


**FIGURE 3.**
(A) MRI brain on initial hospital admission demonstrating large right-sided SEGA (7.3 × 7.1 × 7.7 cm, 209 $cm^3$) with associated bilateral obstructive hydrocephalus. (B) MRI of SEGA after 12 days on everolimus (6.6 × 6.2 × 6.6 cm, 141 $cm^3$, 32% decrease from initial measurement). (C) MRI of SEGA after 20 days treatment with everolimus (5.6 × 5.0 × 5.3 cm, 78 $cm^3$, 63% decrease). (D) MRI of SEGA after 75 days treatment with everolimus and after VP shunt placement (5.1 × 4.4 × 4.9 cm, 58 $cm^3$, 72% decrease from initial measurement). MRI, magnetic resonance imaging; SEGA, subependymal giant cell astrocytoma; VP, ventriculoperitoneal.

head computed tomography (CT) scan was obtained, demonstrating an enlarged SEGA with associated severe obstructive hydrocephalus (Fig 2).

The patient was admitted to the critical care unit and both the neurology and neurosurgery services were consulted. Emergency tumor resection was considered to carry a high risk of morbidity and mortality with little likelihood of an adequate resection. Marked elevation of CSF protein was anticipated, as was the need for bilateral shunting, which would likely limit the utility of ventricular drainage.[11] We therefore elected to start dexamethasone and everolimus (initiated as two initial doses of 5 mg given 12 hours apart followed by a daily regimen of 5 mg, i.e., 4.5 mg/$m^2$/day) upon admission. He was also started on levetiracetam for seizure prophylaxis. Preoperative planning included an MRI of the brain on the second day of admission (Fig 3A), by which time his headaches and nausea had resolved and ventricular size had decreased. Given his clinical improvement and concerns for significant morbidity with resection of such a large tumor, the neurosurgeon, neurologist, and parents deferred neurosurgical intervention and instead elected to

**TABLE.**
CSF Protein Trends According to Days Post EVD Placement

| CSF | Day of EVD | 3 days Post-EVD | 6 days Post-EVD | 12 days Post-EVD | 16 days Post-EVD |
|---|---|---|---|---|---|
| Protein (mg/dL) | 1399 | 735 | 846 | 647 | 650 |
| RBC ($mm^3$) | 115 | 18 | 9 | 154 | 7 |
| Leukocytes ($mm^3$) | 9 | 13 | 2 | 12 | 7 |

Abbreviations:
CSF = Cerebrospinal fluid
EVD = Extraventricular drain
RBC = Red blood cells.
CSF trends according to days post-EVD placement.

continue dexamethasone and everolimus treatment and close inpatient observation.

His ataxia and dizziness improved and had mostly resolved within the first six days of treatment, and a repeat head CT at that time showed a mild decrease in the tumor size. Dexamethasone was gradually tapered, and everolimus further optimized to 10 mg daily (9 mg/$m^2$/day) on hospital day 10. MRI of the brain was repeated on day 12 and showed a significant reduction (32% smaller compared with initial) in the size of SEGA and a decrease in the ventricular size (Fig 3B). He was discharged home with plan to return for repeat MRI and clinical evaluation one week later.

SEGA size continued to decrease (63% smaller), and the extent of his obstructive hydrocephalus also demonstrated improvement on the follow-up MRI (Fig 3C), obtained one week after hospital discharge (day 20 since presentation). He remained symptom free, without headaches or visual symptoms, but on follow-up ophthalmologic examination at two months he was noted to have worsening in visual acuity (20/100 right eye and 20/200 left eye, compared with 20/50 OD and 20/80 OS at initial emergency room visit). Head CT showed further decrease in the size of SEGA, but given vision changes he was taken to the operating room for extraventricular drain (EVD) placement. CSF protein was found to be elevated at 1399 mg/dL (Table). Interestingly, CSF pressure at the time of EVD placement was noted to range from 7 to 11 cm $H_2O$ with a good variation during respiration and negligible (less than 1 mL) loss during catheter insertion. Everolimus was continued and dexamethasone restarted until protein levels were reduced to 650 mg/dL, which took 16 days. The EVD was replaced with a bilateral VP shunt then and he was discharged home two days later without complications. Follow-up MRI obtained 2.5 months after acute presentation showed a 72% decrease in SEGA volume (Fig 3D). Subsequent visual examinations have demonstrated improvement in his visual acuity, and his neurological examination has otherwise remained normal.

## Discussion

Treatment of an acute symptomatic SEGA is considered a medical emergency given the potential fatal complications of obstructive hydrocephalus. As of the most recent TSC surveillance and management consensus recommendations published in 2013,[7,8] tumor resection is considered the gold standard for management of acute symptomatic SEGA. Although treatment of nonacute, asymptomatic SEGA with mTOR inhibitors such as everolimus is considered a safe and effective treatment that is supported by well-designed, prospective clinical trials, reports of their use in treating acutely symptomatic SEGA is extremely limited. Anecdotal reports exist where treatment has been used as an adjunct to surgical resection or alternative when tumor resection is contraindicated or unsuccessful.[9-11] No studies comparing tumor resection with mTOR inhibitors in the management of acute symptomatic SEGA exist.

Our patient had been overtly symptomatic for three to four months when he presented to the emergency room. Because of its massive size, risk of complications from tumor resection was considered significant, including possibility of panhypopituitarism, injury to the optic chiasm, intracerebral hemorrhage, and injury to the frontal lobes. It was therefore elected to initiate treatment with everolimus combined with close inpatient monitoring and neurological examinations while presurgical planning proceeded. Ultimately the need for surgical tumor resection was obviated. This is the first reported patient for whom an acutely symptomatic SEGA has been treated in this fashion and in which demonstrated treatment response was evident clinically within two days and radiologically within six days after initiating medical treatment with everolimus. Everolimus was also effective in reducing CSF pressure to normal at ventriculostomy performed two months after presentation. This finding suggests that our patient's visual changes may have occurred even if surgical resection or ventricular diversion had been undertaken as initial treatment.

Because of uncertainty regarding outcome at the time of initial treatment, we followed this child more aggressively than our standard outpatient management of SEGA patients treated with everolimus. Our standard practice is to start outpatient treatment at 4.5 mg/$m^2$/day once daily, obtain safety laboratory data and serum trough level measurement two weeks later, and perform follow-up clinical examination and MRI imaging at three months. Given the acute nature of our patient's presentation a different dosing schedule was undertaken as opposed to the usual dose or 4.5 mg/$m^2$/day. We administered a loading dose of 4.5 mg/$m^2$ twice on day one, followed by 4.5 mg/$m^2$/day on days two to nine. Everolimus trough serum level obtained on day seven was 7.2 ng/mL (therapeutic range 5 to 15 ng/mL). Everolimus was then increased to 9 mg/$m^2$/day, with a subsequent trough level of 10.4 ng/mL after one month at this dose. Although higher than recommended for initial SEGA management, our patient's dose was determined based on measurements of his trough serum levels. Furthermore, everolimus at 9 mg/$m^2$/day has been used in a placebo-controlled randomized clinical trial.[12] Dexamethasone was given initially with everolimus because of the presence of obstructive hydrocephalus and cerebral edema in the frontal lobes bilaterally. The patient was observed with daily clinical examinations in the inpatient setting until clinical and radiological response could be demonstrated, and follow-up imaging was performed more frequently (daily and weekly at first, then monthly, and then at three-month interval). Whether these precautions ultimately were necessary or need to be repeated for all similar patients remains to be determined.

Our patient displayed rapid symptomatic improvement and reduction in tumor size allowing discharge without the need of neurosurgical intervention. He eventually required shunt because of concern for vision loss, which was not entirely unexpected as CSF diversion is a common occurrence even when SEGA are removed surgically.[13,14] Patients who present with a symptomatic SEGA can also experience optic neuropathy and visual loss, even when surgical resection is the initial therapy. Our patient's findings also provides further evidence that continued treatment with everolimus can decrease CSF protein burden to minimize complications of VP shunt placement.

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## References


1. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. *Cell*. 2012;149:274-293.
2. Jozwiak S, Mandera M, Mlynarski W. Natural history and current treatment options for subependymal giant cell astrocytoma in tuberous sclerosis complex. *Semin Pediatr Neurol*. 2015;22:274-281.
3. Adriaensen ME, Schaefer-Prokop CM, Stijnen T, Duyndam DA, Zonnenberg BA, Prokop M. Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and a review of the literature. *Eur J Neurol*. 2009;16:691-696.
4. Krueger DA, Care MM, Holland K, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N Engl J Med*. 2010;363:1801-1811.
5. Franz D, Belousova E, Sparagana S, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2012;381:125-132.
6. Krueger DA, Wilfong AA, Talley CM, et al. Long-term treatment of epilepsy with eveorlimus in tuberous sclerosis. *Neurology*. 2016;87:2408-2415.
7. Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatr Neurol*. 2013;49:255-265.
8. Roth J, Roach ES, Bartels U, et al. Subependymal giant cell astrocytoma: diagnosis, screening, and treatment. Recommendations from the International Tuberous Sclerosis Complex Consensus Conference 2012. *Pediatr Neurol*. 2013;49:439-444.
9. Moavero R, Carai A, Mastronuzzi A, et al. Everolimus alleviates obstructive hydrocephalus due to subependymal giant cell astrocytomas. *Pediatr Neurol*. 2017;68:59-63.
10. Laviv Y, Jackson S, Rappaport ZH. Persistent communicating hydrocephalus in adult tuberous sclerosis patients: a possible therapeutic role for everolimus. *Acta Neurochir (Wien)*. 2015;157:241-245.
11. Perek-Polnik M, Jóźwiak S, Jurkiewicz E, Perek D, Kotulska K. Effective everolimus treatment of inoperable, life-threatening subependymal giant cell astrocytoma and intractable epilepsy in a patient with tuberous sclerosis complex. *Eur J Paediatr Neurol*. 2012;16:83-85.
12. French JA, Lawson JA, Yapici Z, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet*. 2016;388:2153-2163.
13. De Ribaupierre S, Dorfmüller G, Bulteau C, et al. Subependymal giant-cell astrocytomas in pediatric tuberous sclerosis disease: when should we operate? *Neurosurgery*. 2007;60:83-89.
14. Sun P, Kohrman M, Liu J, Guo A, Rogerio J, Krueger D. Outcomes of resecting subependymal giant cell astrocytoma (SEGA) among patients with SEGA-related tuberous sclerosis complex: a national claims database analysis. *Curr Med Res Opin*. 2012;28:657-663.