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(CASE REPORT)

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Large subependymal giant cell astrocytoma in a young adult with no evidence of Tuberous Sclerosis Complex: A case report of recurrence and complex course

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Abstract

Subependymal giant cell astrocytoma (SEGA) is most associated with tuberous sclerosis complex (TSC); however, its occurrence in adults lacking TSC stigmata presents a considerable diagnostic challenge. A 22-year-old male with a prior subtotal resection of an intraventricular tumor presented with a six-week history of progressive headaches, nausea, vomiting, and visual impairment. Clinical examination identified bilateral papilledema without systemic or cutaneous features of TSC. Contrast-enhanced MRI showed a large (5.2 cm), heterogeneously enhancing, calcified intraventricular mass in the right lateral ventricle and foramen of Monro, causing obstructive hydrocephalus.

Near-total resection was achieved via an interhemispheric transcallosal craniotomy. Histopathological evaluation demonstrated large polygonal cells with abundant eosinophilic cytoplasm. Immunohistochemistry (IHC) confirmed SEGA, showing positive glial fibrillary acidic protein (GFAP) and S-100, focal synaptophysin, and a low Ki-67 index. Molecular analysis of tumor tissue identified a pathogenic TSC2 alteration, whereas peripheral-blood testing was negative for a pathogenic germline TSC1 or TSC2 variant.

Persistent hydrocephalus required postoperative placement of a ventriculoperitoneal shunt. At 18-month follow-up, surveillance MRI detected a recurrent enhancing nodule. Given the recurrent lesion and multidisciplinary assessment of resectability, everolimus was initiated. After 12 months of therapy, substantial tumor reduction and near-baseline functional recovery were achieved. This case demonstrates that mTOR inhibition can effectively control recurrent SEGA in the absence of TSC and points out the possibility of spontaneous SEGA development in individuals without TSC.

Keywords: Subependymal giant cell astrocytoma; Isolated SEGA; Tuberous sclerosis complex; Recurrent; Lateral ventricle; Foramen of Monro; Obstructive hydrocephalus; Pathogenic TSC2 alteration

1. Introduction

Subependymal giant cell astrocytoma (SEGA) is an uncommon circumscribed astrocytic glioma, classically arising near the foramen of Monro in association with TSC. Although assigned CNS WHO grade 1, its consequences are governed by location: enlargement can obstruct cerebrospinal fluid flow, causing hydrocephalus, intracranial hypertension, visual symptoms, and life-threatening deterioration. [1,2,3] The diagnosis of SEGA usually prompts evaluation for TSC, a multisystem disorder caused by pathogenic TSC1 or TSC2 alterations. However, molecularly verified SEGAs rarely occur without clinical diagnostic criteria or a detectable pathogenic germline variant for TSC. [4,7]

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This setting creates an important diagnostic trap. In a young adult with a large lateral-ventricular mass; central neurocytoma, ependymoma, subependymoma, and choroid plexus neoplasms are often favored before considering SEGA. [5] Absence of mucocutaneous stigmata or family history should reduce, but not eliminate, suspicion for SEGA when a lesion is centered at the foramen of Monro and causes obstructive hydrocephalus. Isolated SEGA may be driven by tumor-restricted or mosaic TSC1/TSC2 alterations, with implications for genetic assessment, interpretation of negative blood testing, and pathway-directed therapy. [3,7,8]

We report a young adult with large recurrent intraventricular SEGA, no clinical TSC features, a pathogenic tumor TSC2 alteration, and negative germline testing. The case highlights integrated diagnosis, the morbidity of inadequate surveillance after subtotal resection, and the role of everolimus in unresectable recurrence.

2. Case Presentation

2.1. Clinical Presentation

A 22-year-old man with a history of a subtotally resected intraventricular tumor presented with a six-week history of progressive headaches, nausea, and vomiting. His prior tumor had been diagnosed three years earlier and treated surgically elsewhere, with no known genetic workup or follow-up. He now sought medical attention due to the recurrence of his symptoms, which were more severe than before and accompanied by intermittent blurry vision. He denied any personal or family history of seizures, skin lesions, or renal issues, and there was no known family history of TSC.

2.2. Physical Examination and Imaging Findings

Physical examination revealed bilateral papilledema. Neurological exam was nonfocal. There were no skin findings such as hypomelanotic macules, angiofibromas, or shagreen patches. A comprehensive clinical and multi-organ evaluation including brain, skin, eye, renal, and cardiac imaging revealed no clinical features of TSC. A contrast-enhanced MRI revealed a large, heterogeneously enhancing intraventricular mass measuring 5.2 cm in greatest dimension, occupying the right lateral ventricle and extending through the foramen of Monro, causing significant hydrocephalus. The mass showed calcifications and mixed signal intensity on T1 and T2 sequences. The key differential diagnoses for an intraventricular mass in a young adult included astroblastoma, gemistocytic astrocytoma, ganglioglioma, ependymoma, and Pleomorphic xanthoastrocytoma. With the patient's age and lack of TSC stigmata, SEGA without clinical evidence of TSC was less likely to be initially considered, especially since the prior tumor pathology was unknown.

2.3. Multidisciplinary Tumor Board Discussion and Decision

The tumor board reviewed the case, focusing on the patient's age, the large recurrent tumor burden, and the absence of TSC features. The central discussion centered on the diagnostic uncertainty and the appropriate management strategy to address the symptomatic hydrocephalus and obtain a definitive pathological diagnosis. The team recommended an immediate surgical intervention to both relieve the hydrocephalus and achieve maximal safe resection of the tumor. Given the tumor's size, likely recurrence, and involvement of the foramen of Monro, a gross-total resection was the primary goal. Still, the proximity to critical structures such as the fornix and thalamus necessitated a careful approach to avoid neurological deficits.

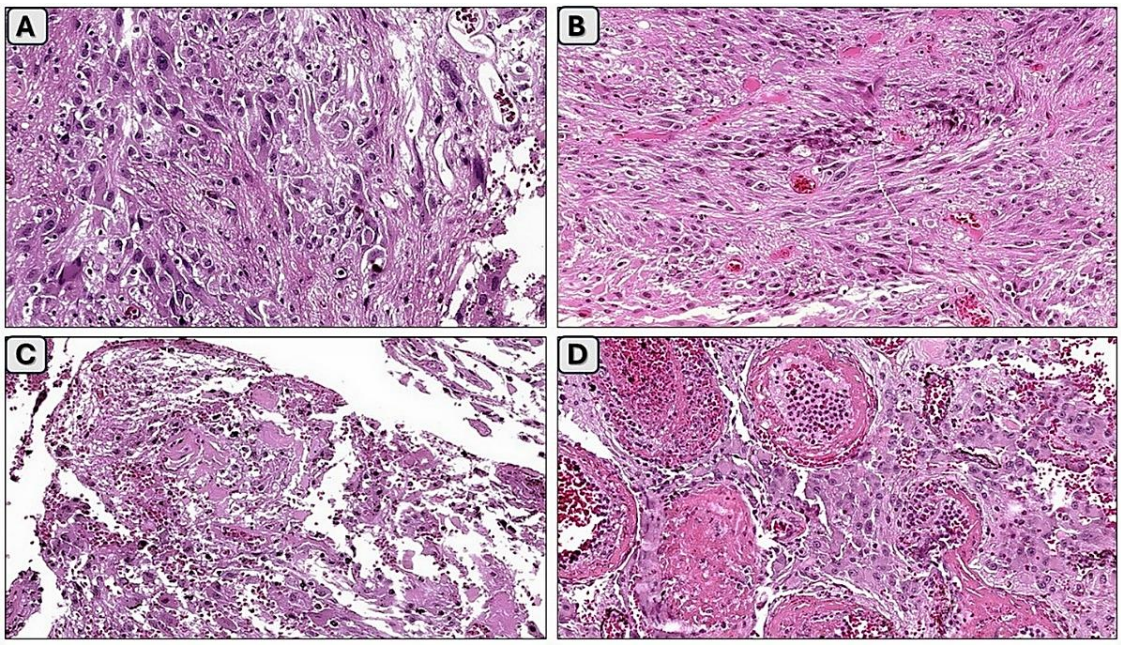
2.4. Special Studies and Pathology

The patient underwent a right frontal craniotomy with an interhemispheric transcallosal approach for tumor resection. A near-total resection was achieved. Histopathological examination showed a moderately cellular tumor composed of large polygonal cells with abundant eosinophilic cytoplasm, characteristic of SEGA. (**Figure 1 A, B, C, D**) Immunohistochemistry (IHC) revealed diffuse positivity for GFAP and S-100 protein, and focal positivity for synaptophysin. TTF-1 was negative. Although TTF-1 is generally a sensitive ancillary marker for SEGA, rare TTF-1-negative SEGAs have been documented; therefore, its absence did not preclude the diagnosis in the context of the characteristic morphology, immunophenotype, location, and tumor molecular findings

The Ki-67 labeling index was low (<2%). Molecular analysis of tumor tissue identified a pathogenic TSC2 alteration, whereas peripheral-blood testing was negative for a pathogenic germline TSC1 or TSC2 variant. The final diagnosis was subependymal giant cell astrocytoma (SEGA) without clinical or germline evidence of tuberous sclerosis complex (TSC), consistent with isolated SEGA.

2.5. Treatment, Outcome, and Follow-up

The postoperative course was complicated by persistent hydrocephalus requiring a ventriculoperitoneal shunt. At 18 months post-surgery, the patient was clinically stable, but a surveillance MRI revealed a small, enhancing nodule in the surgical bed suggestive of a second recurrence. Given the recurrent lesion and multidisciplinary assessment of resectability, everolimus was initiated. Follow-up imaging at 6 and 12 months after starting everolimus demonstrated a significant reduction in residual tumor size and stable hydrocephalus, with the patient reporting a marked improvement in symptoms and a return to near-baseline function.



1A**:** High-power view showing gemistocytic-like cells with abundant eosinophilic cytoplasm and ganglion-like cells with eccentric, vesicular nuclei and prominent nucleoli (H&E X60); 1B**:** High-power view showing spindle cells with elongated nuclei admixed with other types of cells (H&E X60); 1C**:** Low-power view showing fibrillary background (H&E X20); 1D: Intermediate-power view showing thick hyalinized vessels (H&E X40)

Figure 1 Microscopic features of subependymal giant cell astrocytoma (SEGA)

3. Discussion

3.1. Background

SEGA is a rare primary central nervous system tumor, accounting for approximately 1%–2% of pediatric brain tumors and occurring mainly in children, adolescents, and young adults. [1,6,9] It usually develops along the lateral-ventricular wall near the caudothalamic groove/foramen of Monro, sometimes extending into the third ventricle. Obstruction at this site explains the characteristic presentation: headache, nausea, vomiting, papilledema, blurred vision, or other signs of intracranial hypertension may occur despite an initial nonfocal examination. [1,9]

SEGA is most closely linked to TSC (Bourneville–Pringle disease), an autosomal-dominant multisystem disorder in which approximately 5%–20% of affected individuals develop SEGA. [1,10] TSC may be inherited or de novo and has wide phenotypic variability. Assessment should include family history, dermatologic examination, relevant ophthalmologic, renal, and cardiopulmonary evaluation, brain imaging for other TSC features, and germline testing when diagnosis is uncertain. [4] Under the 2021 consensus criteria, a pathogenic constitutional TSC1 or TSC2 variant establishes TSC; clinically, SEGA alone supports possible, rather than definite, TSC. [4]

In the 2021 WHO framework, SEGA is a circumscribed astrocytic glioma, CNS WHO grade 1. Diagnosis rests on the presence of large polygonal or spindle- or gemistocyte-like cells with abundant eosinophilic cytoplasm, glial marker expression, and variable neuronal marker expression. TSC1/TSC2 alterations and a compatible DNA methylation profile are typical but not mandatory when integrated pathology is convincing. [1] The first reported isolated case dates to 1979; the literature remains dominated by case reports and small series, with a recent review identifying 59 documented cases. [9,10]

3.2. Pathogenesis, Pathophysiology

The central molecular event in SEGA is dysregulation of the hamartin–tuberin complex. Hamartin and tuberin, encoded by TSC1 and TSC2, are tumor suppressors that restrain RHEB-dependent activation of mammalian target of rapamycin complex 1 (mTORC1). Loss of this inhibition leads to persistent mTORC1 signaling, increased protein synthesis and cellular growth, and a slow-growing yet expansile lesion. [8,11] In TSC-associated SEGA, biallelic TSC1 or TSC2 inactivation is frequent; whole-exome analysis has shown few additional likely pathogenic somatic alterations, supporting TSC-pathway loss as a principal driver. [11]

The mixed glial and neuronal immunophenotype, GFAP/S-100 positivity with variable synaptophysin expression, is compatible with differentiation from a neuroepithelial progenitor population in the periventricular region. [1,10] A low proliferative index explains the WHO grade 1 designation, but not clinical harmlessness. Growth at the foramen of Monro compromises cerebrospinal-fluid transit, causing hydrocephalus and papilledema before focal deficits emerge. In isolated cases, a pathogenic TSC2 alteration with negative blood testing supports a tumor-restricted event. However, it does not fully exclude low-level mosaicism without considering assay sensitivity and, when justified, additional tissues. [4,8] The pathway provides a rationale for mTOR inhibition in residual or recurrent disease.

3.3. Comparative Analysis of Our Case with Existing Literature.

The patient closely resembles the reported phenotype of isolated SEGA: a young person with a lateral-ventricular/foramen-of-Monro lesion, intracranial-hypertension symptoms, papilledema, hydrocephalus, typical histology, low Ki-67, and no clinical or germline evidence of TSC. In the 2025 systematic review by Ledford et al., the median age was 16 years (interquartile range, 10–22); headache occurred in 43%, visual changes in 38%, and lateral ventricular involvement in 78%. [9] Presentation at age 22 is therefore at the upper end of the reported distribution but compatible with it. The size, calcification, heterogeneous enhancement, and hydrocephalus also overlap with those in recently molecularly documented cases. [7,8]

The clinical course was unusually complex. Prior subtotal resection without documented molecular characterization or structured follow-up preceded a large symptomatic recurrence three years later, followed by a second surgical-bed recurrence after near-total resection. In the pooled review, recurrence was recorded in 9 of 37 resected cases with follow-up (24%), including 4 of 23 after initially reported gross-total resection; heterogeneous case reports and incomplete follow-up limit these estimates. [9] The need for a ventriculoperitoneal shunt is also consistent with the reported cerebrospinal-fluid-diversion burden. [13]

The pathogenic TSC2 alteration provided a biologically plausible rationale for mTOR inhibition. Although the strongest efficacy data for everolimus derive from TSC-associated SEGA, published case reports of isolated SEGA, including tumors with TSC1/TSC2 alterations, also describe radiographic responses to mTOR inhibition. Alassiri et al. described an adolescent without clinical or germline evidence of TSC, with a pathogenic TSC2 tumor alteration, residual/recurrent disease, and a radiographic response to everolimus. [12] A five-patient pediatric series likewise reported recurrence controlled with mTOR inhibition in one molecularly characterized isolated SEGA. [4,7,8].

In the present patient, everolimus was associated with marked clinical improvement and radiographic reduction of the recurrent lesion at 6 and 12 months. Given the absence of detailed dosing, therapeutic drug monitoring, and toxicity data, exposure–response and tolerability could not be assessed. This case presents a young adult with a multiply recurrent course and a meaningful clinical and radiological response.

4. What Have We Learned from This Case?

The principal diagnostic lesson is that absence of TSC stigmata should lower, but not eliminate, suspicion for SEGA. A large or enlarging lesion at the foramen of Monro with hydrocephalus, headache, nausea/vomiting, papilledema, or visual disturbance warrants urgent assessment because symptoms may reflect cerebrospinal-fluid obstruction rather than infiltrative malignancy.

In young adults, the differential remains broad; therefore, interpretation should integrate lesion location and serial growth with histology, IHC, and molecular testing rather than relying on a single clinical feature or marker. In particular, GFAP/S-100 positivity with focal synaptophysin expression and low proliferation may support SEGA, whereas TTF-1 negativity should not be used in isolation to exclude it. A methylation-based classifier may be helpful when morphology, immunophenotype, and conventional sequencing are discordant. [1,14]

The molecular finding should prompt careful, but precise, language. A pathogenic TSC2 variant confined to tumor tissue and absent from peripheral blood supports an isolated, tumor-restricted SEGA; it does not, by itself, completely exclude low-level mosaic TSC. Clinical assessment for subtle TSC manifestations, appropriate genetic counseling, and consideration of testing strategies that can detect mosaicism remain important. [4,8] The exact scope and interval of systemic surveillance for an individual without established TSC should be tailored through multidisciplinary discussion, because evidence for isolated SEGA is limited and its long-term natural history remains incompletely defined. [7,9]

From a management perspective, this case reinforces early maximal safe resection for symptomatic obstructive lesions while respecting the risk to the fornix, thalamus, and other deep structures. It also underscores the value of a documented postoperative imaging plan after subtotal or near-total resection. For residual, recurrent, or surgically high-risk disease with biologic evidence of TSC–mTOR pathway activation, mTOR inhibition offers a rational nonoperative strategy; however, the strongest trial evidence derives from TSC-associated SEGA, so use in isolated disease should be individualized and monitored in a multidisciplinary neuro-oncology setting. [4,15]

Abbreviations

- Subependymal giant cell astrocytoma (SEGA)
- Tuberous sclerosis complex (TSC)
- Glial fibrillary acidic protein (GFAP)
- Immunohistochemistry (IHC)

5. Conclusion

This case demonstrates that SEGA should remain in the differential diagnosis for a large, enhancing intraventricular mass near the foramen of Monro, even when the patient lacks overt features or a family history of TSC. Its contribution lies in the integrated documentation of recurrent, clinically consequential isolated SEGA in a young adult: the tumor exhibited characteristic morphology and immunophenotype; a pathogenic TSC2 alteration was identified in tumor tissue; germline testing was negative; and the unresectable recurrence responded to everolimus. The case also illustrates that CNS WHO grade 1 histology does not preclude major morbidity from hydrocephalus, repeat surgery, and the need for permanent cerebrospinal-fluid diversion. Reporting such cases strengthens the limited literature on the natural history of isolated SEGA, encourages appropriate molecular and systemic evaluation, and supports a multidisciplinary, pathway-informed approach to recurrent disease.

Compliance with ethical standards

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All authors make the following declarations:

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- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

This work did not involve any studies on human or animal subjects performed by the authors. It was a retrospective review of archival pathology material collected during routine clinical care, and all data were fully de-identified before analysis.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

The patient was lost to follow-up, and all attempts to reach the patient were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

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