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The Clinicopathological Features of the Solitary Subependymal Giant Cell Astrocytoma: A Systematic Review

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Abstract:

Subependymal giant cell astrocytoma (SEGA), a circumscribed grade I glioma, is typically associated with tuberous sclerosis complex (TSC). However, "solitary SEGA" has been described. We performed a systematic review of available case reports and case series of solitary SEGA. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used with the following MeSH terms: "Subependymal giant cell astrocytoma," "Sporadic," "Absence," "Non-associated," "Solitary," and "Tuberous Sclerosis." Data sources included PubMed, Google Scholar, Web of Science, and Cochrane from 1979 to June 29, 2023. Of the 546 studies, 20 met the inclusion criteria. Fifty-nine cases were analyzed. The mean age was 19 years (range 4–75), with 29 women (49.1%). Tumor ranged in size from 0.8 to 5.8 cm. Headache was the most frequent initial symptom (75.6%). The lateral ventricles near the foramen of Monro were the most common location (66.10%). Tumors expressed neuroglial (n = 19) or only glial (n = 20) markers. In nine of 59 cases, genetic studies ruled out germinal TSC1/2 mutations; in 13 cases (22.03%), somatic mutations in those genes were identified. "Solitary SEGAs" included tumors with neuroglial profile and classic morphological pattern, and tumors with only glial markers. It is necessary to confirm in SEGA-like tumors, the dual nature with at least glial fibrillary acidic protein (GFAP), neurofilaments, and synaptophysin antibodies. Screening for TSC1/2 mutations, and probably of the NF type 1 gene, is recommended for both germline and somatic mutations. Long-term clinical follow-up is necessary to analyze biological behavior and compare it with genetic and molecular profiles.

Key Words:

Non-associated, solitary, sporadic, subependymal giant cell astrocytoma, tuberous sclerosis complex

Key Messages:

SEGA-like tumors are heterogeneous neoplasms. First, the dual neuroglial profile should be confirmed. Long-term follow-up and the correlation with molecular findings are required in those with only glial markers.

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Subependymal giant cell astrocytoma (SEGA) is a grade I tumor typically associated with tuberous sclerosis complex (TSC), an autosomal dominant disease.[1,2] Germline mutations in TSC1 (9q34.3) encoding hamartin and TSC2 (16p113.3) encoding tuberin affect the regulation of cell growth through the mammalian target of the rapamycin (mTOR) pathway.[3] In recent years, cases of solitary SEGA in the absence of clinical TSC have been reported. Although some tumors represent "forme fruste" of TSC, there are solitary SEGAs in patients without TSC.[4] Therefore, we conducted a systematic review of solitary SEGA cases to identify their clinicopathological characteristics.

Systematic Review and Analysis

Objectives

We sought to systematically review all available case reports and case series of solitary SEGA to comprehensively analyze these tumors including demographic data, clinical manifestations, diagnostic criteria, treatment, and genetic studies.

Search methods

We performed a systematic review searching PubMed, Web of Science, Google Scholar, and

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Cochrane databases using a combination of the following keywords with Boolean operators (OR/AND): "Subependymal giant cell astrocytoma," "Sporadic," "Absence," "Non-associated," "Solitary," "Tuberous Sclerosis." The study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5] Candidate articles from the reference lists of the eligible studies were reviewed.

Inclusion and exclusion criteria

We included all published studies in English, between 1979 and June 29, 2023, that reported at least one case of SEGA not associated with TSC. We included only studies with confirmed histopathological diagnosis and with a negative full examination for stigmata (FES). Autopsy cases compatible with SEGA, in the absence of TSC, were also included.

Selection of studies

All cases were reviewed individually to verify that they met the inclusion criteria. After the initial selection, two reported cases, O'Rawe *et al*. 2020[6] and Suzuki *et al*. 2021,[7] were not included. The first case was a 9-year-old boy with SEGA (major feature) and multiple kidney cysts (minor feature) with a negative germline test for TSC mutations. However, in 15–20% of cases of TSC, patients have no identifiable mutation; therefore, we did not include this case.[6] The second case was a tumor with malignant histological features and a Ki-67 labeling index of 25%, which was not compatible with classic SEGA, plus a short follow-up period of less than one and a half years.[7]

The eligibility of each article identified through the database search was assessed and determined by two independent reviewers by screening titles and abstracts and then reviewing the full-text versions of the articles. All disagreements were resolved by consensus or arbitration by a third reviewer.

Data collection

Extracted data from each eligible article included the following: the number of solitary SEGA or non-associated TSC patients, demographic data, clinical presentation, studies for TSC criteria, absence of TSC features, SEGA location, type of surgery, tumor recurrence, clinical outcome, and genetic study results.

Quality assessment

Two independent reviewers appraised the quality and risk of bias of the included studies. In addition, the quality of the case reports was appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports, which consists of eight yes/no/unclear questions.[8] Of the 16 case reports included in this review, 14 met with an affirmative response to each of the eight checklist questions. Only the articles by Stavrinou *et al*. (2008)[9] and Takei *et al*. (2009)[10] had a single negative response each, in relation to the description of adverse effects and the post-intervention clinical condition, respectively, but even so, they were eligible and included.

The quality of the case series was appraised by the JBI Critical Appraisal Checklist for Case Series, which consists of 10 yes/no/unclear questions.[10] A high risk of bias was considered if a study scored "Yes" less than 49% of the quality criteria, moderate risk of bias if it scored "Yes" between 50% and 74% of the quality criteria, and low risk of bias if it scored "Yes" in at least 75% of the quality criteria. Consensus resolved all disagreements. Of the four case series publications, two met 100% of the criteria (Palsgrove *et al*. (2018)[11] and Fohlen *et al*. (2020)),[12] while the publication by Bonnin *et al*. (1984)[13] covered 70% and that of Sharma *et al*. (2004)[14] 90%.

Systematic Review Results

A total of 547 studies were identified from the selected databases; 181 were removed as duplicates. Among the remaining 366 file studies, 322 were excluded after title/abstract screening, and 24 were excluded after reviewing the full text. Finally, 20 articles that fulfilled the inclusion criteria are included in Figure 1.

Immunohistochemical inclusion criteria

A tumor with neuroglial expression was considered if the neoplastic cells were positive for glial fibrillary acidic protein (GFAP)/Olig2 in at least 20% of the tumor cells, according to the description or what was observed in the representative histological images. Neuronal nature was considered when the neoplastic cells expressed NF, MAP2, or synaptophysin in at least 5% according to the description or what was observed in the representative histological images. If the expression was in isolated neurons (<1%) observed at low magnification, it was not possible to rule out that they were neurons trapped in the tumor, and in these cases, glial tumors were considered. In many cases, the reports did not include histological description with hematoxylin and eosin, nor a description of immunohistochemistry, and these tumors were placed in the group of unspecified nature. Finally, in the tumors of patients with neurofibromatosis type 1 (NF1), the tumors were glial, but with wide morphological and molecular variability; therefore, they were placed separately.

Results

The systematic review identified 20 articles that met the inclusion criteria and was possible to separate tumors with SEGA morphology into four large groups [Figure 2].

The first thing evident was the heterogeneity of the reports in terms of morphological criteria. All 59 cases (100%) shared a tumor morphologically compatible with SEGA and a negative FES. However, there were cases with dual histological expression (glial and neuronal markers) in the tumor (group 1, Table 1), tumors with only glial expression (group 2, Table 2), tumors with a non-specific expression (group 3, Table 3), and finally, cases with proven NF1 (group 4, Table 1). Genetic analysis for TSC1/2 germinal line mutations was performed in nine cases (15.25%), and somatic mutation analysis in the tumor was performed in 13 cases (22.03%).

Demographic data

From 20 articles (16 case reports and four case series), a total of 59 cases with solitary SEGA in the absence of TSC have been identified in the literature, as summarized in Table 3. The mean age at diagnosis was 19 years (range 4–75), with 29 women (49.15%) and 30 men (50.84%).

When analyzing the groups separately, we identified 10 patients (16.94%) in the dual group, 20 patients (33.89%) in the glial group, 20 patients (33.89%) in the non-specified group, and nine cases (15.25%) in the NF1 group [Figure 2].

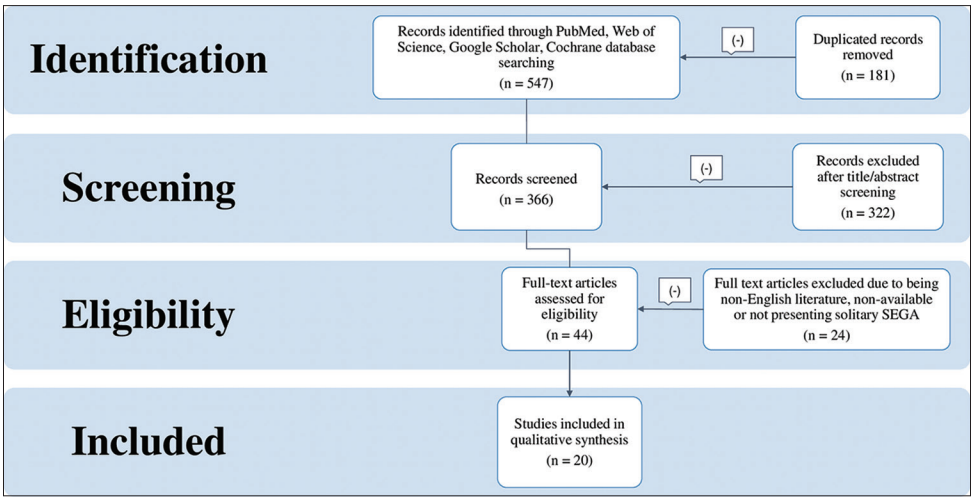

Figure 1: Flowchart diagram of search mechanism in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

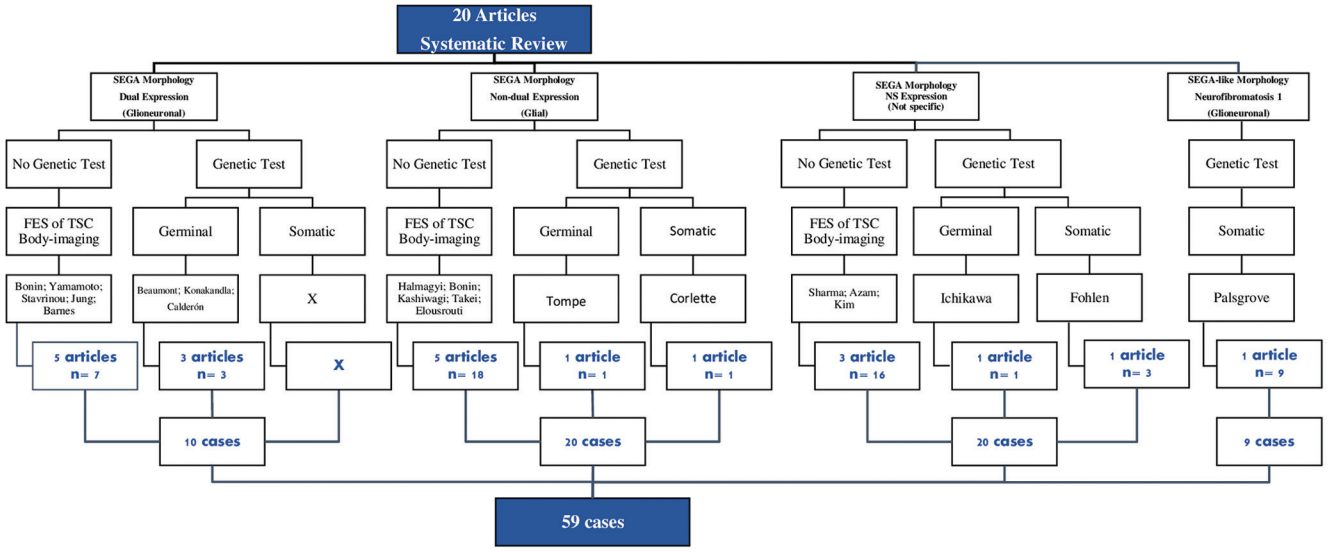

Figure 2: Flowchart diagram of the reviewed articles. SEGA: subependymal giant cell astrocytoma; FES: full examination for stigmata; TSC: tuberous sclerosis complex

Clinical presentation

Of a total of 59 patients, in 18 (30.50%), information about the clinical presentation was not available. In patients with available information (41 = 100%), 31 had headaches (75.6%), four started with seizures (9.7%), one patient (2.4%) had memory and mental disturbances, another patient had both headache and seizure, and one referred diplopia. In three autopsy cases, SEGA was an asymptomatic finding.

No patient presented stigmata of tuberous sclerosis. Forty-seven (79.66%) patients underwent a FES of TSC, and complementary imaging studies confirmed the absence of TSC criteria. However, in 12 cases (20.33%), the type of exploration performed was not specified.

Neuroimaging and pathological characteristics

Tumors ranged in size from 0.8 to 5.8 cm. MRI showed a lobulated, well-defined lesion with solid or cystic components. The tumor was iso-hypointense in T1 sequence and hypointense in T2-weighted images, with occasionally heterogeneous post-contrast enhancement. Four cases had hydrocephalus due to obstruction to CSF flow near the foramen of Monro (FM). MRI confirmed the absence of subependymal nodules and cortical tubers as expected in TSC.

In 39 cases (66.1%), tumors were in the lateral ventricles (18 on the left side, 16 on the right side, four on the unspecified side, and one was bilateral), near the FM. Four cases (6.77%) were in the FM, six cases (10.16%) in the frontal lobe, two cases (3.38%) in the caudate nucleus, two in the third ventricle (3.38%), and six (10.16%) distributed in other locations (thalamus, hypothalamus, non-specified intraventricular location, frontal ventricular horn, and parietal and occipital lobes).

Morphologically [Table 4], the four cases with TSC somatic mutations showed classical SEGA morphology with large rounded giant cells with abundant eosinophilic cytoplasm forming clusters, surrounded by smaller astrocytic type cells either with fibrillary processes or with striped cytoplasm.

Table 1: Reported cases of dual expression SEGA without TSC, in the literature

Article	Case number	Age (years)/ sex	Clinical presentation	Further studies for TSC	TSC features or other	SEGA location	Extent of removal	Outcome/genetic study
Bonnin *et al*. (1984)[13]	1	19/M	NA	FES	None	LV	Biopsy, NS	NA/NA
	2	33/F	NA	FES	None	LV	Biopsy, NS	NA/NA
	3	18/F	NA	FES	None	RLV and 3rd V	Biopsy, NS	NA/NA
Yamamoto *et al*. (2002)[17]	4	48/F	Memory and mental disturbance	FES	None	RLV and anterior horn	STR	Recurrence in 1 year required second surgery with GTR/none
Stavrinou *et al*. (2008)[9]	5	33/M	Headache	FES, ECG, and abdominal CT	None	Left FM	GTR	Good/none
Beaumont *et al*. (2015)[19]	6	14/M	Headache	FES	None	LLV and FM	GTR	Good/DNA sequencing from blood: negative for TSC1/2 mutations
Jung *et al*. (2015)[20]	7	18/M	Headache	NA	None	FM	STR	Recurrence 4 years later required second surgery and NS/NA
Konakondla *et al*. (2016)[22]	8	25/F	Headache	NA	None	LLV and FM	GTR	Good/DNA sequencing from blood: negative for TSC1/2 mutations
Palsgrove *et al*. (2018)[11]	9	20/F	Seizures	NA	NF1	FL	Resection and NS	NA/next-generation sequencing from tumor tissue: NF1 (p. L180Yfs)
	10	17/M	Seizures	NA	NF1	LFL	GTR	Good/next-generation sequencing from tumor tissue: NF1 (p.Y2171X)
	11	24/F	NA	NA	NF1	RFL	NA	NA/next-generation sequencing from tumor tissue: NF1 (p. G1190Afs)
	12	53/F	Headache	NA	NF1	LLV	STR	Death/next-generation sequencing from tumor tissue: NF1 (p. Y2264Tfs and p.G1219R)
	13	20/F	Headache	NA	NF1	LFL	GTR	Good/next-generation sequencing from tumor tissue: NF1 splice mutation (c. 3198-2 A>G)
	14	25/M	NA	NA	NF1	LFL	Resection and NS	NA/next-generation sequencing from tumor tissue: NF1 (p.L2323X)
	15	9/M	Headache	NA	None	Hypothalamus	Endoscopic biopsy and carboplatin–vincristine	NA and chemotherapy/ next-generation sequencing from tumor tissue: NF1 (p.R720Gfs)
	16	25/F	Headache	NA	NF1	LLV	GTR	Good/next-generation sequencing from tumor tissue: NF1 (p. S285Qfs)
	17	60/F	NA	NA	NA	FL	STR	Death, 650 days post-surgery, and NS/next-generation sequencing from tumor tissue: NF1 (p. R815Gfs)
Barnes *et al*. (2020)[25]	18	17/F	Headache	NA	None	RLV	GTR	Good/none
Calderón-Garcidueñas *et al*. (2023)[28]	19	19/M	Headache	FES, ECG, and RUSG	None	LLV and FM	STR	Good/DNA sequencing from blood: negative for TSC1/2 and VUS APC gene

M: male; F: female; NA: not available; NS: not specified; FES: full examination for stigmata (dermatologic and ophthalmologic examinations); CT: computed tomography; RUSG: renal ultrasound; ECG: echocardiography; GTR: gross total resection; STR: subtotal resection; NF1: neurofibromatosis 1; VUS: variation of uncertain significance; RLV: right lateral ventricle; LLV: left lateral ventricle; FM: foramen of Monro; RFL: right frontal lobe; LFL: left frontal lobe; FL: frontal lobe; 3rd V: third ventricle

These tumors showed dual, GFAP, and synaptophysin or neurofilament staining in more than 20% of tumor cells.

The other cases showed a more dispersed fibrillar background composed of glial cells with phenotypes varying from gemistocytic-like cells, ganglion-like cells, and spindle cells. These were arranged in sheets, but not well-defined nests, and showed pseudorosettes. Giant cells measuring 40–120 micrometers with abundant eosinophilic cytoplasm with fibrillar extensions, vesicular eccentric nuclei, and prominent nucleoli were scattered throughout the tumor. Some cases reported the presence of pleomorphic and multinucleated cells. Mitosis, necrosis, and microvascular proliferation were not observed, and only one case reported considerable nuclear atypia. The vessels consisted of wide-lumen capillaries and arterioles

Table 2: Reported cases of glial expression SEGA without TSC, in the literature

Article	Case number	Age (years)/ sex	Clinical presentation	Further studies for TSC	TSC features or other	SEGA location	Extent of removal	Outcome/genetic study
Halmagyi *et al.* (1979)[15]	1	16/M	Headache and seizures	FES	None	Right parietal lobe beneath the motor cortex.	GTR	Recurred 12 and 45 years after initial presentation/none
Bonnin *et al.* (1984)[13]	2	10/F	NA	FES	None	RLV	Biopsy and NS	NA/NA
	3	20/F	NA	FES	None	Bilateral	Biopsy and NS	NA/NA
	4	14/F	NA	FES	None	RLV	Biopsy and NS	NA/NA
	5	5/F	NA	FES	None	RLV and 3rd V	Biopsy and NS	NA/NA
	6	32/M	NA	FES	None	FM	Biopsy and NS	NA/NA
	7	17/M	NA	FES	None	CN	Biopsy and NS	NA/NA
	8	17/F	NA	FES	None	LLV	Biopsy and NS	NA/NA
	9	56/F	Autopsy	FES	None	3rd V	Autopsy	Death/NA
	10	14/M	NA	FES	None	3rd V	Biopsy and NS	NA/NA
	11	43/F	NA	FES	None	LV	Biopsy and NS	NA/NA
	12	28/M	NA	FES	None	Left CN	Biopsy and NS	NA/NA
	13	41/M	NA	FES	None	LLV and 3rd V	Biopsy and NS	NA/NA
	14	20/M	NA	FES	None	LLV and 3rd V	Biopsy and NS	NA/NA
	15	21/M	Autopsy	FES	None	LV	Autopsy	Death/NA
Kashiwagi *et al.* (2000)[16]	16	20/F	Headache	FES and body imaging	None	RLV and FM	GTR	Good/none
Takei *et al.* (2009)[10]	17	75/F	Autopsy	FES	None	LLV and FM	Autopsy	Death not related to SEGA/ none
Elousrouti *et al.* (2016)[21]	18	10/F	Seizures	FES and body imaging	None	LLV	GTR	Good/none
Corlette *et al.* (2020)[26]	19	26/F	Diplopia	FES, RUSG, and MRI spine	None	RLV and FM	Resection and NS.	Good/MLPA on tumor tissue and blood: tumor with deletion of TSC2 gene
Tompe *et al.* (2021)[27]	20	17/M	Seizures	FES, EEG, RUSG, and ECG	None	Left occipital lobe	GTR	Good/DNA sequencing from blood: negative for TSC1/2

M: male; F: female; NA: not available; NS: not specified; FES: full examination for stigmata (dermatologic and ophthalmologic examinations); MRI: magnetic resonance imaging; RUSG: renal ultrasound; ECG: echocardiography, EEG: electroencephalogram; GTR: gross total resection; STR: subtotal resection; MLPA: multiplex ligation-dependent probe amplification; RLV: right lateral ventricle; LLV: left lateral ventricle; FM: foramen of Monro; 3rd V: third ventricle; CN: caudate nucleus

with predominantly perivascular lymphocytic infiltration. Hyalinized vessel walls were observed in seven cases. In some areas, the cells adopt a perivascular arrangement. One case had calcifications. Positive immunohistochemical staining for GFAP, S100, NSE (neuron-specific enolase), SYN (synaptophysin), Olig2, vimentin, neurofilaments (NF), and low Ki-67 labeling index were described. Other markers that were analyzed in some tumors, with negative results, were HMB-45 (melanoma cell marker), p53, MAP2 (microtubule-associated protein 2), EMA (epithelial membrane antigen), BRAFV600E, NeuN (marker of postmitotic neurons), IDH1/2 (isocitrate dehydrogenase 1/2), MGMT (O (6)-methylguanine-DNA-methyltransferase), H3K27M, and ATRX (transcriptional factor, known as ATP-dependent helicase).

Genetic analysis was performed only in recent cases; in nine cases (15.25%), the search for germline TSC1/2 mutations was negative. In the nine patients with NF1, somatic gene mutations were found in this gene. Four patients without stigma of TSC nor NF1 showed somatic mutations in TSC1/2 genes. Corlette *et al*.[26] identified a deletion of the TSC2 gene; Fohlen *et al*. showed a case with TSC1 heterozygous mutation, a case with mutation in TSC2 at the canonical splicing donor site of intron 5, and a TSC2 mutation in exon 9.

Surgical procedures and outcome

Gross total resection (GTR) was achieved in 21 cases (35.59%) and subtotal resection (STR) in 14 cases (23.72%). After the biopsy, one patient received chemotherapy (1.69%), and one patient received radiotherapy (1.69%) after tumor resection. In the other 19 cases (32.20%), biopsy was performed, but the percentage of tumor resection was not specified. In three cases (5.08%), the tumors were autopsy findings.

The clinical outcome in patients with at least 1 year of follow-up after resection was good in 28 cases. The recurrence of tumor was documented in five cases (two GTR and three STR), and death occurred in seven cases [Table 3]. In 19 cases, the outcome was not reported [Tables 1–3].

Discussion

According to the World Health Organization (WHO) 2021 classification of central nervous system (CNS) tumors, SEGA is a "circumscribed astrocytic glioma." The first studies

Table 3: Reported cases of non-specified expression SEGA without TSC, in the literature

Article	Case number	Age (years)/ sex	Clinical presentation	Further studies for TSC	TSC features or other	SEGA location	Extent of removal	Outcome/genetic study
Sharma *et al*. (2004)[14]	1	8/M	Headache	FES	None	FM and 3rd V	GTR	Good/NA
	2	20/M	Headache	FES	None	RLV	STR	Death/NA
	3	14/F	Headache	FES	None	RLV	STR	Death/NA
	4	10/M	Headache	FES	None	RLV and FM	STR	Good/NA
	5	13/M	Headache	FES	None	LLV and FM	GTR	Good/NA
	6	10/M	Headache	FES	None	RLV and FM	STR	Good/NA
	7	37/F	Headache	FES	None	LLV and 3rd V	STR	Recurrence and NS/NA
	8	6/M	Headache	FES	None	LLV	STR	Good/NA
	9	15/F	Headache	FES	None	LLV	STR	Good/NA
	10	21/M	Headache	FES	None	RLV	STR	Good/NA
	11	11/M	Headache	FES	None	RLV	GTR	Good/NA
	12	19/M	Headache	FES	None	RLV	GTR	Good/NA
	13	26/M	Headache	FES	None	LLV	STR	Good/NA
	14	4/M	Headache	FES	None	LLV	GTR	Recurrence and NS/NA
Ichikawa *et al*. (2005)[18]	15	20/F	Headache	FES, ECG, and whole-body CT	None	LLV and FM	GTR	Good/RFLP, and DNA from blood, buccal mucosa swab: negative for TSC1/TSC2 mutations
Azam *et al*. (2017)[23]	16	11/M	Headache	FES	None	Left internal capsule and thalamus	Endoscopic biopsy and radiotherapy	Good/none
Kim *et al*. (2017)[24]	17	10/F	Headache	FES, RUSG, ECG, and skeletal imaging	None	RLV	GTR	Good/none
Fohlen *et al*. (2020)[12]	18	8/F	Headache	FES, RUSG, and ECG	None	Left frontal ventricular horn	GTR	Good/DHPLC sequencing in tumor tissue and blood: tumor with TSC1 heterozygous mutation
	19	5/F	Headache	FES and RUSG	None	Intraventricular and NS	GTR	Good/molecular study from tumor tissue and blood, NS: tumor with mutation in TSC2 at canonical splicing donor site of intron 5
	20	8/M	Headache	FES and RUSG	None	LLV and FM	GTR	Good/molecular study from tumor tissue and blood, NS: tumor with TSC2 mutation in exon 9

M: male; F: female; NA: not available; NS: not specified; FES: full examination for stigmata (dermatologic and ophthalmologic examinations); CT: computed tomography; RUSG: renal ultrasound; ECG: echocardiography; GTR: gross total resection; STR: subtotal resection; RFLP: PCR-restriction fragment length polymorphism; RLV: right lateral ventricle; LLV: left lateral ventricle; FM: foramen of Monro; 3rd V: third ventricle

describing SEGAs suggested an astrocytic nature, but several recent reports demonstrated its glioneuronal nature. SEGAs are composed of three main types of cells with a fibrillary background: fibrillated spindle cells, swollen gemistocytic-like cells, and giant cells with a ganglionic appearance.[29]

SEGA in the context of TSC has a prevalence of 5–20%, and it is related to the subependymal nodules (SENs), hamartomatous lesions present in 90% of TSC patients. SENs and SEGAs are histopathologically indistinguishable, with no marker to differentiate between them, except size. Germline mutations of the TSC1 and TSC2 genes determine the onset of TSC, due to unregulated cell proliferation, abnormal differentiation, and tumorigenesis through the mTOR pathway. However, in recent years, multiple cases have been reported as solitary or not associated with TSC.[30] The occurrence of SEGA in non-TSC patients is very rare and may be a "forme fruste" of TSC, but also SEGA may be due to TSC1 and TSC2 somatic mutations in the tumor, or even due to mutations in other genes that share a common pathway.[12,31] There are many studies and reviews of SEGA associated with TSC, but no systematic review of solitary SEGA has been performed. It is important to define whether all reported SEGA cases are a homogeneous group or not, and to investigate the physio-pathogenesis of these tumors.

The International Tuberous Sclerosis Complex Consensus Conference of 2012 mentioned that 10–25% of TSC patients have no mutation identified by conventional genetic testing. Therefore, a normal result does not exclude TSC in patients with clinical criteria. In adult patients without TSC stigmata, somatic mutations gain greater value in the pathogenesis of these tumors.[32]

According to the analysis conducted in this review, SEGAs not associated with TSC are a morphologically heterogeneous group. There are tumors with glioneuronal expression and tumors that only express glial markers. Furthermore, although all authors used GFAP to demonstrate the glial component, the use of neuronal markers was not homogeneous. NSE, synaptophysin, NF, and MAP2 were used by different authors. According to Figure 2, 20 tumors (33.89%) expressed exclusively glial markers, 19 tumors (32.20%) were dual (glioneuronal),

Table 4: Summary of histological reports and immunohistochemistry (IHQ) of SEGA without TSC cases in the literature

Article	Consistent with SEGA	Histological report (H&E)	IHQ-positive stains	IHQ-negative stains
Non-dual expression				
Halmagyi *et al*. (1979)[15]	Yes	Composed of fibrillar astrocytes with pleomorphic and occasionally hyperchromatic nuclei. Processes of many of these cells contained thick glial fibers. In approximately half of the tissue examined, the astrocytes were arranged in well-formed perivascular pseudorosettes. The cells formed either a streaming pattern or had no architectural arrangement.	NA	Toluidine blue demonstrated no Nissl substance, and silver with a modified Bielschowsky technique showed no nerve fibers.
Bonnin *et al*. (1984)[13]	Yes	Biphasic pattern of long fibrillated and strap-like cells, adjacent to swollen, occasionally giant multipolar or pyramidal cells. Grouped into three morphological types: fibrillated or spindle-shaped cells, swollen, gemistocytic cells, and giant ganglion-like cells.	GFAP and NSE 68 Kd-NF (three cases)	NA
Kashiwagi *et al*. (2000)[16]	Yes	Composed of large gemistocytic cells with abundant cytoplasm and fibrillated spindle cell	GFAP	S100, NSE, NF, and SYN
Ichikawa *et al*. (2005)[18]	Yes	Composed mainly of large polygonal cells resembling gemistocytic astrocytes. Mitotic figures were rare, and no endothelial proliferation or necrosis was seen	NA	NA
Takei *et al*. (2009)[10]	Yes	Composed of sweeping bundles of fibrillary spindle cells with intimately admixed large tumor cells having eccentrically located nuclei, some of which appeared to resemble ganglion cells or gemistocytic astrocytes. Occasional multinucleated cells were seen. Scattered lymphocytic infiltration was observed primarily around the blood vessels. Focal nodular areas of what appeared to be gliosis with rosenthal fibers and microcalcifications were also noted.	GFAP, S100, NSE, and SYN (occasionally individual cells) MIB-1 (<1%)	Reticulin, NF, MAP2, and EMA
Elousrouti *et al*. (2016)[21]	Yes	Composed of fibrillated spindle cells and globular large cells, with abundant eosinophilic cytoplasm, and voluminous, eccentric nucleus, and large nucleoli, producing an aspect of ganglion cells; mitosis, necrosis, and microvascular proliferation were not rated. Calcifications and perivascular lymphocytes were observed.	GFAP and S100 MIB-1 (0%)	NF and SYN
Azam *et al*. (2017)[23]	Yes	Fibrillary background with large ganglion-like cells with abundant eosinophilic cytoplasm, eccentric nuclei, and large nucleoli with Virchow–Robin spaces.	GFAP	NS
Kim *et al*. (2017)[24]	Yes	Pleomorphic multinucleated eosinophilic tumor cells with abundant cytoplasm, associated with increased vascularity.	GFAP and S100 MIB-1 (<1%)	NS
Corlette *et al*. (2020)[26]	Yes	Large polygonal cells with plentiful cytoplasm, mixed with smaller cells with oval nuclei, and elongated cytoplasmic processes. Giant cells with ganglionic appearances were present, with eccentric, vesicular nuclei with distinct nucleoli and large amounts of glassy eosinophilic cytoplasm. Scattered calcifications were also seen.	GFAP and NF (occasionally individual cells)	NS
Fohlen *et al*. (2020)[12]	Yes	NA	NA	NA
Tompe *et al*. (2021)[27]	Yes	Markedly calcified glial tumor composed of the spindle to giant cells with abundant cytoplasm. There were no mitoses, necrosis, or vascular endothelial proliferation. The tumor contained many thin and thick hyalinized vessels.	GFAP, Olig-2, and CD34 (blood vessels) MIB-1 (1%)	IDH-1, NF, ERG, ATRX, H3K27me3, SYN, p53, and IDH
Dual expression				
Yamamoto *et al*. (2002)[17]	Yes	Composed of large gemistocytic cells with abundant cytoplasm and fibrillated spindle cells	GFAP, S100, vimentin, and NSE SYN (few polygonal cells) MIB-1 (<1%)	NF
Sharma *et al*. (2004)[14]	Yes	Sweeping bundles of spindle-shaped cells in a fibrillary background, ganglion-like cells with prominent nucleoli, and polygonal cells with moderate-to-abundant eosinophilic	GFAP, S100, NSE, SYN, LCA, and Rb	CgA, HMB-45, and p53

Contd...

Table 4: Contd...

Article	Consistent with SEGA	Histological report (H&E)	IHQ-positive stains	IHQ-negative stains
		Dual expression		
		cytoplasm. Marked pleomorphism. There was no endothelial proliferation, but hyalinization of vessel walls was seen in seven cases, and evidence of old hemorrhage in the form of hemosiderin-laden macrophages was seen in two cases.	MIB-1 (0-8%) NF (six cases)	
Stavrinou *et al*. (2008)[9]	Yes	Varied histological features, consisting mainly of neoplastic cells with astroglial differentiation or large cells with rounded nuclei intermingled with spindle cells and multinucleated giant cells. They were mainly diffuse, lacking explicit architecture. There was an abundance of mast cells and histiocytes.	GFAP and S100 Limited reaction vimentin, SYN, and CgA MIB-1 (<1%)	NA
Jung *et al*. (2015)[20]	Yes	Pleomorphic multinucleated eosinophilic tumor cells with abundant cytoplasm, and these elongated tumor cells formed streams. The tumor cells with abundant cytoplasm are clustered and arranged in perivascular pseudopalisading pattern.	GFAP, SYN, and MAP2	NS
Beaumont *et al*. (2015)[19]	Yes	Composed of glial cells with phenotypes varying from gemistocytic-like cells, ganglion-like cells, and spindle cells. The cells had moderate-to-abundant eosinophilic cytoplasm with vesicular nuclei and occasional prominent nucleoli.	GFAP, SYN, and NF MIB-1 (4.8%)	CgA
Konakondla *et al*. (2016)[22]	Yes	Cells had a spindle appearance with long processes running in fascicles. Focally, the long processes seemed to acquire a "vague perivascular," arrangement. Pleomorphic cells, with multinucleation and abundant eosinophilic cytoplasm. Only rare mitotic figures were seen. Extremely high vascularity was noted with thin-walled vessels and fibrin thrombi, which was suggestive of organizing hemorrhage.	GFAP and SYN CD34 (vascular walls) MIB-1 (4%)	BRAFV600E, NeuN, IDH1/IDH2, MGMT methylation, and p53
Palsgrove *et al*. (2018)[11]	Yes	Moderately cellular and characterized by cells with plump eosinophilic/glassy cytoplasm and large nuclei with macronuclei, arranged in nests or short fascicles. The architecture was mostly compact, but partially infiltrative in five cases.	GFAP, Olig2, S100, SYN (six cases), CgA (three cases), and ATRX (one case) MBI-1 (<1-20%)	CD34, IDH1, BRAF, and H3K27M
Barnes *et al*. (2020)[25]	Yes	Large tumor cells with abundant fine granular, eosinophilic cytoplasm, arranged in fascicles, sheets, and nets.	GFAP and SYN	NS
Calderón-Garcidueñas *et al*. (2023)[28]	Yes	Fibrillar background, composed of polygonal cells measuring 40–120 microns; with abundant eosinophilic cytoplasm; with fibrillar extensions and vesicular nuclei, frequently eccentric; and with a prominent nucleolus. Interspersed with elongated fibrillar spindle cells with vesicular nuclei that demarcated the nodules from giant cells. The vessels consisted of wide-lumen capillaries and arterioles. In some areas, neoplastic cells adopted a perivascular arrangement. Binucleated cells were observed, but mitosis was not detected.	GFAP, NF, AE1/AE3, nestin, hamartin, tuberin, and TTF-1 OCT4 (pericytes) INI-1 (cytoplasmic stain) STAT-6 (cytoplasmic stain)	NA

NA: not available; NS: not specified; GFAP: glial fibrillary acidic protein; NF: neurofilaments; CK-AE1/AE3: cytokeratins AE1/AE3; STAT-6: signal transducer and activator of transcription 6; OCT-4: octamer-binding transcription factor 4; INI-1: integrase interactor 1; TTF-1: thyroid transcription factor 1; NSE: neuron-specific enolase; SYN: synaptophysin; MAP2: microtubule-associated protein 2; Rb: retinoblastoma gene; ATRX: alpha thalassemia/mental retardation syndrome X-linked; EMA: epithelial membrane antigen; LCA: leukocyte common antigen; CgA: chromogranin; IDH: isocitrate dehydrogenase; MIB-1: cell proliferation marker

and in 20 tumors (33.89%), immunohistochemistry was not commented.

SEGA classically associated with TSC is a tumor with dual expression, which leaves no doubt with tumor cells strongly positive for the glioneuronal markers used, and not just few cells that could correspond to neurons trapped in the tumor. The patient commented by Corlette *et al*.,[26] a 26-year-old woman, with a deletion in the TSC1 gene in the tumor, presented glial expression with occasional NF-positive neuron, which did not rule out a trapped neuron. In the study by Fohlen *et al*.,[12] in which three patients had mutations in the TSC1 and TSC2 genes in the tumor, there were no comments about the immunohistochemical profile. However, there were SEGA-like tumors with only glial marker expression. After reviewing the images provided in the manuscripts, these only glial expression SEGAs had a more dispersed pattern and not the characteristic nodular arrangement of SEGA

associated with TSC. Furthermore, the tumors associated with NF1 were neuroglial in nine cases, with images of isolated cells with neuronal markers such as synaptophysin.[11] This suggests that tumors with SEGA-like morphology can be seen in different genetic and molecular profiles; thus, a minimal immunohistochemical diagnostic criteria are required. We suggest that in future case reports, besides the hematoxylin and eosin stain, immunohistochemistry should be included showing evidence of the dual or only glial nature of the tumor. A minimal panel to confirm the dual nature of the tumor should include GFAP, NF, and synaptophysin staining. Ideally, but not within the reach of most medical centers, screening of mutations in TSC1/2 genes and probably in NF1 gene should be performed, both in germinal and somatic lines. This will allow a better characterization of tumors that share the same morphology but do not necessarily have the same origin or the same biological behavior as seen in the low-grade IDH wild-type astrocytomas.[33]

Conclusion

Solitary SEGAs, not associated with TSC, as reported so far, are a heterogeneous group of tumors that include those with a neuroglial marker, and those that only express a glial nature. It has been proven that some of these dual nature tumors are associated with somatic mutations in the TSC1/2 genes. A minimal immunohistochemistry panel with GFAP, neurofilament, and synaptophysin should be included to confirm the dual nature of the tumor. Screening for mutations in the TSC1/2 genes, and probably in the NF1 gene, is recommended, both in germinal and somatic lines. Long-term clinical follow-up of these patients will make it possible to analyze the biological behavior and compare it with the genetic and molecular profile.

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Conflicts of interest

There are no conflicts of interest.

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