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Subependymal Giant Cell Astrocytomas (SEGAs): a Model of Targeting Tumor Growth and Epilepsy

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Abstract

Purpose of review Subependymal giant cell astrocytomas (SEGAs) are grade I astrocytic tumors according to WHO 2016, mainly associated to tuberous sclerosis complex. They are rare and achievements in their management are often the result of small series and case reports. The main purpose of this review was to summarize recent developments in diagnosis and treatment of SEGAs.
Recent findings The role of treatment with mTOR inhibitors has been confirmed through many studies in the last decade. New treatment options for patients with contraindication to surgery have been proposed, like Gamma Knife and laser interstitial thermal therapy (LITT). Furthermore, more recent preclinical studies, investigating MAPK/ERK pathways, CK2 protein (casein kinase), and metalloproteinases and their tissue inhibitors (TIMPs), have been published, suggesting new pharmacological treatments.
Summary This review is focused on natural history, pathogenesis, diagnosis, and treatment of SEGAs, with an update of the more recent developments. SEGAs are mainly associated to tuberous sclerosis complex, while in sporadic forms to mutations in genes TSC1 or TSC2 limited to the tumor. TSC2 mutation leads to higher incidence of SEGAs, earlier onset and more aggressive course. Diagnosis is made by MRI and by criteria defined in the EXIST-1 study. Treatment options are surgery and pharmacological treatment with mTOR inhibitors. LITT shows promising results. Besides tumor grade, SEGAs show a continuous tendency to growth after incomplete resection or withdrawal of mTOR

inhibitors. Preclinical studies have explored novel treatment options, but they need to be confirmed in clinical trials.

Introduction

Tuberous sclerosis is an autosomal-dominant inherited disorder, with an estimated incidence between 1:6000 and 1:10000, caused by inactivating mutations of either tuberous sclerosis complex (TSC) 1 or 2 genes encoding two proteins, hamartin and tuberin, respectively. They act as a heterodimer to suppress the mammalian target of rapamycin (mTOR), a serine/threonine protein kinase, which regulates cell growth and division. A mutation in one of these genes and a subsequent somatic second hit, which means loss of function of both alleles, results in mTOR pathway overactivation and development of hamartomas in multiple organs (skin, retina, kidney, heart, and brain).

Cerebral manifestations of TSC include subependymal nodules (SENs) in more than 80% of patients and subependymal giant cell astrocytomas (SEGAs) in 5–25% of patients.

Pathogenesis and natural history

SEGAs are slow-growing WHO grade I astrocytic tumors according to WHO 2016 [1] composed of large ganglionic astrocytes, originating from a neuroglial progenitor, typically located along the lateral ventricle wall, and in some cases adjacent to the foramen of Monroe. SEGAs account for 1–2% of all pediatric tumors. Serial neuroimaging studies have demonstrated that SEGAs arise from SENs. A study performed in 1989 by Fujiwara et al. [2], using sequential CT data, provided the first evidence that a subependymal nodule may transform into a SEGA, probably after the second TSC gene "hit." Risk factors for SENs to transform into SEGAs are size above 5 mm, incomplete calcifications, and gadolinium enhancement [3]. SEGAs in patients with TSC typically arise within the second decade of life (average age at presentation 11 years), although sporadic cases of onset in adulthood are described. According to the TuberOus SClerosis registry to increase disease Awareness (TOSCA) [4•], 2216 patients are affected by TSC (554 with SEGAs) with median age at SEGA diagnosis was 8 years (range 1–51 years), being diagnosed in 26.6% of patients before 2 years of age, in 81.9% before 18 years, and in 18.1% after 18 years [4•]. There is no clear prevalence of gender, and females have a milder phenotype. Among patients with TSC, the mutation of TSC2 is associated to an aggressive phenotype. In the EPISTOP study [5] including 94 patients (93 of whom with a confirmed mutation in TSC1 and TSC2 genes), a correlation genotype-phenotype was explored by comparing clinical manifestations in the two groups at 2 years of age. In the TSC2 group, cortical tubers, facial angiofibromas, hypomelanotic macules, two or more renal cysts, drug-resistant epilepsy, and developmental delay were seen more frequently than in TSC1 group with a > 20% difference [5].

According to another study [6], patients with a TSC2 mutation were 1.64 times more likely to develop SEGAs than those with TSC1 mutation, usually occurring at a younger age in the first group. Furthermore, surgery for SEGAs was performed at a younger age in patients with TSC2 mutation with respect to patients with TSC1 [7]. SEGAs may be also congenital (onset before 12 months of age). Chan et al. [8] reported, in a series of 109 pediatric patients affected by TSC, 10 children (9.2%) with congenital SEGAs and among them 4 patients with focal seizures and infantile spasms. All patients with congenital SEGAs had a mutation in TSC2 gene. Unfrequently, SEGAs may occur in patients without a diagnosis of TSC ("solitary SEGAs") and probably they result from somatic mutations in one of the TSC genes limited to the tumor, or are a part of mild forms of TSC with somatic mosaicism [9, 10]. In few cases of solitary SEGAs, a genetic analysis on the tumor was performed and the presence of mutation of TSC1 or TSC2 was confirmed, and was associated to absence of mutations in TSC genes on blood DNA. Next-generation sequencing (NGS) is the most powerful tool for detecting low levels of mosaicism in order to estimate the risk of transmission to offspring [11]. Moreover, in SEGA patients without a confirmed diagnosis of TSC, clinical features of TSC may present later in life, thus requiring a regular follow-up.

According to the TOSCA registry, many patients have multiple SEGAs at diagnosis (45.1%), often bilaterally (44.9%) [4•]. Different studies have estimated the SEGA pattern and speed of growth, with different results due to the different methods of measurement (maximal axial diameter, cross-sectional area, volume). According to a retrospective study [12], the median growth rate during a medium follow-up of 83 months before surgery was 3.4 mm/year in SEGA diameter. In subsequent studies, the median growth rate ranged from 2.53 [13] to 5.6 mm/year [14]. Epidemiological studies suggest that younger patients have a higher SEGA growth rate [15]. Torres et al. [16] observed SEGA growth to peak at puberty. Congenital SEGAs seem to have a higher growth rate: however, there is no concordance between studies. Chan et al. [8] reported a growth rate of 1.1 mm/year, similar to late-onset SEGAs (1–5 mm per year), and using volumetric estimation, a median growth rate of 150 mm^3/year. The velocity rate depended on the tumor volume at diagnosis, having patients with initial tumoral volume > 500 mm^3 a higher growth rate. In another series [7], the growth rate of congenital SEGAs was higher (33 mm per year) while SEGA with a contiguous TSC2/polycystin 1 (PKD1) deletion grew more rapidly than SEGAs with a TSC2 sequence mutation. It is still not clear whether SEGAs continue to grow beyond the second decade of life: Adriaensen et al. [17] described a continuous growth in 29% of patients over a period of 5 years (1 mm/year), and also a regrowth of SEGA after partial resection has been described [7].

According to the TOSCA registry, 50.3% of patients with SEGAs presented with one or more symptoms, while the remaining 49.7% were asymptomatic [4•]. The most frequent symptoms were increased seizure frequency (15.8%), mainly of generalized tonic-clonic or focal motor type, behavioral disturbances (11.9%), loss of cognitive skills (9.9%), and headache (8.4%). In most cases,

obstruction of CSF flow due to the location of SEGA close to the foramen of Monroe may lead to symptoms of intracranial hypertension (headache and vomiting), needing a ventricular derivation. In rare cases, acute symptoms are due to an intratumoral hemorrhage.

Diagnosis and follow-up

In 2013, an international panel of experts proposed to define SEGA as "a lesion at the caudothalamic groove with a size of > 1 cm in any direction or a subependymal lesion at any location that has shown serial growth on consecutive MRI images regardless of size" [18••]. The EXamining everolimus In a Study of Tuberous sclerosis complex (EXIST-1) trial [19••] accepted as inclusion criteria for SEGA "a lesion with the longest diameter of 1 cm or greater as assessed by multiphase MRI, along with evidence of lesional volume growth greater than 25%, worsening hydrocephalus or presence of new lesions when compared with previous scan."

Computed tomography (CT) is commonly used as first-line investigation for acute or unexpected symptoms. On CT scan, SEGA appears as a mass of uniform density, often with calcifications, while hemorrhage is a rare finding. Magnetic resonance imaging (MRI) is the recommended modality for screening and follow-up of SEGAs. On MRI, SEGAs appear as well-circumscribed tumors, with mixed T1/T2-weighted signal, i.e., iso- or hypointense on T1-weighted images and iso- or hyperintense on T2-weighted images. Also, they have an increased apparent diffusion coefficient (ADC) and inhomogeneous but intense contrast enhancement after gadolinium administration. Other findings may be ventricular dilatation (due to CSF circulation abnormalities) and transependymal edema (Fig. 1). Hydrocephalus can be unilateral or bilateral [20].

Differential diagnosis with SENs may be difficult: MR spectroscopy may be helpful, showing in SEGAs high choline/creatine and low N-acetylaspartate/creatine ratios. Overall, the presence of contrast enhancement and of a growing lesion are the two main clues in identifying SEGAs rather than SENs. The International Consensus Panel recommended performing brain imaging every 1–3 years until the age of 25 years; however, scans should be performed more frequently in younger patients with larger or growing SEGAs, or in patients who develop symptoms. Concerning TBC patients without SEGA by the age of 25 years, further MRI scans are probably not necessary because of the low probability of developing the tumor beyond this age. When performing follow-up scans, it is recommended to avoid contrast administration, which may be required only in case of a growing SEGA for adequate treatment planning [21]. In case of positive family history or features suggestive of TSC at fetal ultrasound, prenatal basal MRI (without gadolinium) may be indicated to detect brain abnormalities: a large mass filling the ventricle with associated ventriculomegaly is suggestive of SEGA.

Treatment

Surgery

According to the recommendations from the 2012 International Tuberous Sclerosis Complex Consensus Conference [18••], the indications for treatment

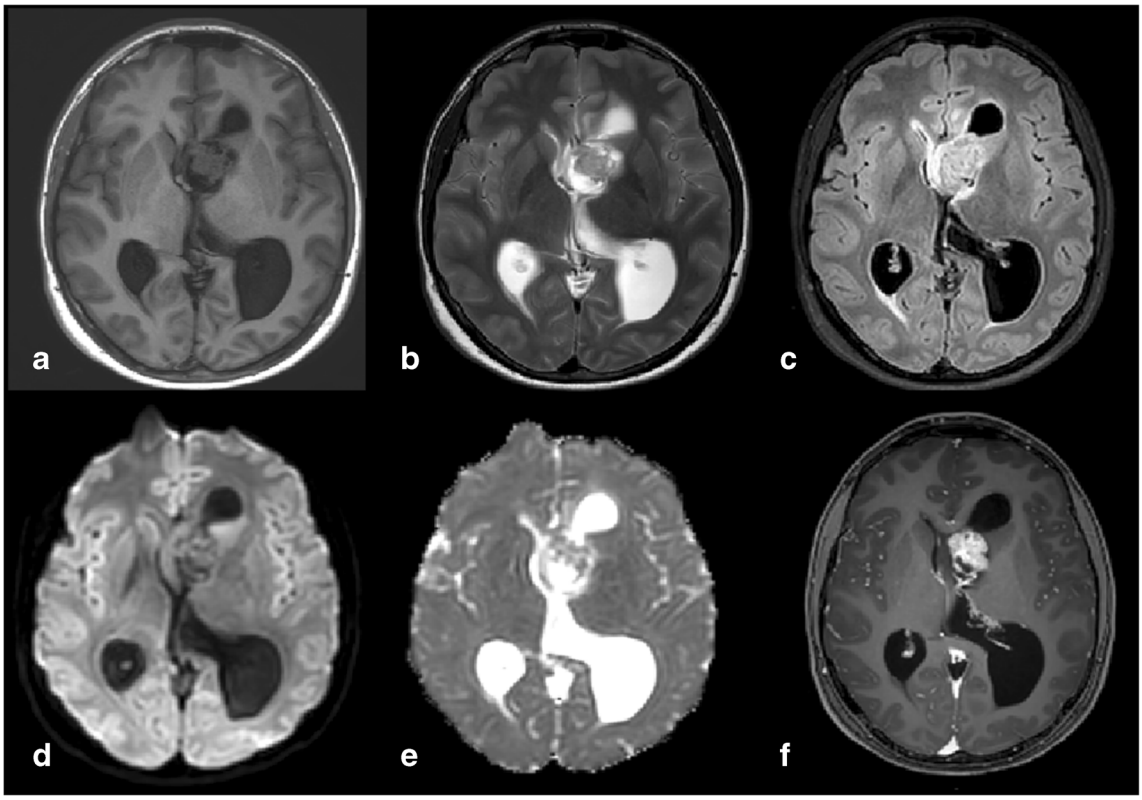

Fig. 1. MRI of a patient followed at our institution affected by tuberous sclerosis and a SEGA located in left subependymal region close to the Monroe foramen. Bilateral hydrocephalus coexists, involving mainly the left lateral ventricle. **a** T1-weighted axial scan. **b** T2-weighted axial scan. **c** FLAIR axial scan. **d** Diffusion-weighted imaging (DWI). **e** ADC map. **f** Contrast-enhanced T1-weighted axial imaging.

of SEGAs are a new onset of symptoms or radiological evidence of tumor growth. SEGAs do not respond to conventional chemotherapy, and radiotherapy may lead to an increased risk of secondary malignancies: as a consequence, surgery and therapy with mTOR inhibitors represent today the mainstay of treatment (see below). Due to the absence of clear guidelines and proven superiority of a treatment compared with the other one, each case should be discussed in a multidisciplinary team, to illustrate advantages and side effects of both options.

Surgery is the treatment of choice in SEGAs presenting with acute intracranial hypertension because of hydrocephalus and/or intralesional hemorrhage. In some cases, a CSF diversion may be necessary to relieve symptoms from intracranial hypertension. As any residual tumor probably will grow back, a gross total resection represents a major goal to achieve. Relative contraindications to surgery are bilateral SEGAs because of higher risk of morbidity, and absence of a feasibility of radical surgery. However, a resection of the largest side tumor in a staged procedure has been explored in recent studies [22]. The optimal surgical approach is transcortical or transcallosal like other ventricular tumors, and the choice depends on size, location, and laterality. Transcortical approach is preferred when tumors are located in the body of lateral ventricles

or when ventricles are enlarged, while the transcallosal one is preferred when tumors are smaller, in a central position or involve the anterior third ventricle, and the ventricular system is not enlarged. However, in more recent series [22], only transcortical route was used, also with normal ventricular size. To date, retrospective series on outcome, morbidity, and mortality of surgery do not provide univocal results, mainly due to the heterogeneity of patients. Post-surgical complications may be due to preoperative or acute postoperative hydrocephalus, major size of the tumor, and one-step bilateral resection. Location of SEGAs medial to the genu of internal capsule increases the risk of motor deficits of the face or upper extremities, while preservation of the fornix is important to prevent memory deficits. Other complications may be shunt dependence, intraoperative hemorrhage, and infections. According to Harter et al. [23], risk of permanent hydrocephalus requiring a ventriculoperitoneal shunt is higher in patients with overt hydrocephalus at time of surgery: thus, some authors suggest to resect SEGAs before the hydrocephalus development. In a study conducted by Sun et al. [24], a high percentage of incomplete resections after surgery was reported (34%), with a high complication rate (almost 50%) in the 12 months postoperatively. Kotulska et al. [7] related morbidity to tumor size: for tumors less than 2 cm, no complications were reported; for tumors between 2 and 3 cm, the complication rate was 46%; while for tumors larger than 3 cm, the complication rate increased to 80%. Conversely, in a more recent study [22], surgery in SEGAs had an acceptable morbidity with low mortality, due to modern surgical techniques and earlier diagnosis.

The location of SEGA and the growth pattern inside the ventricular system have led to consider an endoscopic approach since the late 1990s, especially after the development of neuronavigation techniques. This microsurgical approach may be considered for tumors with a diameter less than 2 cm, while for larger lesions endoscopic management becomes more invasive and the procedure requires longer time for surgery. However, some patients who underwent endoscopically resected tumors as large as 3 cm in maximum diameter have been successfully reported [25]. The main limits of an endoscopic treatment are a broad-based tumor attachment to the caudate nucleus, presence of calcifications and significant vascularization, and trajectory inside the ventricular system [26]. Recently, many techniques combining endoscopy and microsurgery have been described in order to improve the extent of resection and survival outcome.

Pharmacological treatment

Medical treatment of SEGAs consists in drugs targeting mTOR overexpression. The goal of pharmacological therapy is shrinkage or stabilization of SEGAs. The first drug, that was tested, is sirolimus (rapamycin), a macrolide compound isolated in 1975, which showed in TSC patients a significant reduction of SEGA volume (from 46 to 63%). Serum level monitoring is required, with a range of efficacy from 10 to 15 ng/ml. Clinical and radiological response may not be durable, as in most cases SEGAs tend to recur after withdrawal of rapamycin. Other drugs with similar activity like the prodrugs CCI-779 (temsirolimus) and RAD001 (everolimus) were developed. Everolimus has shown more favorable pharmacokinetic characteristics (oral bioavailability, shorter half-life, and faster achievement of steady-state). The chemical structure is similar to rapamycin,

with a 2-hydroxyethyl group introduced in position 40 [27]. Everolimus has been approved in 2010 by FDA for treatment of SEGAs when a surgical approach is not feasible, both in symptomatic and asymptomatic patients from birthdate to age 65. The EXIST-1 (Everolimus in the Treatment of SEGAs associated with Tuberous Sclerosis Complex) was a double-blind randomized trial, in which patients were randomly assigned to active treatment (117) or placebo (39) arms: 35% of patients treated with everolimus had at least 50% reduction in the volume of subependymal giant cell astrocytomas versus none in the placebo group [19••]. In another study of 28 patients aged ≥ 3 years, who were treated with everolimus, a reduction in SEGA size was reported in 75% of patients [28]. The starting dose is 4.5 mg/m^2/day, but for patients aged 1 to 3 years, a higher starting dose of 7 mg/m^2/day can be considered. The drug requires gradual titration (in order to prevent developing of side effects) until serum levels between 5 and 15 ng/ml are achieved, and a dose reduction after stabilization of SEGAs in long-term treatment is needed, to reduce side effects. Other studies displayed the safety of everolimus in patients < 2 years or with congenital SEGAs; however, side effects should be carefully monitored (infection, stomatitis, increased triglycerides, febrile status epilepticus) [29]. Concerning symptomatic patients, treatment is usually started in the presence of mild symptoms, like headache, worsening of seizures, cognitive disability, and mild ventriculomegaly, while in patients with severe hydrocephalus and intracranial hypertension, surgery is still today the treatment of choice.

MTOR inhibitors play a role in improving seizure burden and frequency. They do not act by modulating ion channels or neurotransmitter receptor like standard antiepileptic drugs but by regulating the expression of ion channels via effects on protein translation, thus reducing neuronal excitability. Other indications to medical treatment with mTOR inhibitors include incomplete resected SEGAs, which tend to recur; multiple and/or bilateral tumors not amenable to surgery; unfeasibility of a complete resection; presence of other systemic disorders that may respond to mTOR inhibitors, like angiomyolipomas, cardiac rhabdomyomas, and lymphangioleiomyomatosis. Also, systemic contraindication to surgical procedures may be an indication for medical treatment. In patients without symptoms, mTOR inhibitors are required in case of tumor growth, also as neoadjuvant treatment before surgery, in order to shrink the tumor, reduce the infiltration of deep structures, and reduce surgical morbidity, which is particularly high in patients under 3 years of age. Side effects are more frequent during the first year of treatment and are mild to moderate. The most common are aphthous ulcers, acneiform rash, nausea, anorexia, diarrhea, arthralgias, mucositis, pneumonia, impaired wound healing, altered renal and liver function, rising in serum lipids especially cholesterol levels, and lowering in red blood, white blood (mainly neutrophils), and platelet count [30•]. These adverse events typically disappear after short-term interruption of therapy: mTOR inhibitors bind to mTOR complex 1 and can be safety held in case of side effects without immediate loss of efficacy. Aphthous ulcers are the most frequent side effect with mTOR inhibitors, affecting as many as three-fourth of patients. They can be prevented by adequate oral hygiene, using sucralfate solutions, lysine supplementation, or dexamethasone solutions. Dexamethasone mouth rinses are used one or twice daily and, when aphthous ulcers occur, 4–5 times daily. Rising in lipid levels, especially in triglycerides, may lead to higher risk for pancreatitis. Because of impaired wound healing, it is

recommended to held mTOR inhibitors 1 week prior to elective surgery and as soon as possible for unexpected surgery. Minor procedures, like dental work, do not require withdrawal of therapy. Interruption of therapy is also required during systemic infections. Main contraindications to treatment are impaired liver function (elevated levels of bilirubin) and severe acute infections. During treatment, monitoring of red and white blood count, platelet levels, liver (AST, ALP) and renal (creatinine) function, and cholesterol levels is required. MTOR inhibitors are metabolized primarily by cytochrome CYP3A4 and glycoprotein P; consequently, they may interact with inhibitors of cytochrome p450 system, like sodium valproate, clarithromycin, erythromycin, ketoconazole (thus increasing their serum concentrations), or inducers like carbamazepine, phenytoin, and phenobarbital (thus reducing their serum concentrations and lowering the effect). Discontinuation of mTOR inhibitors is typically associated to regrowth of SEGAs. There are many questions about the duration and dose of the treatment over time: probably treatment may be continued until the patient achieved an age of 30 years if there is a stabilization of the lesion, while if therapy is well tolerated without significant side effects, lifelong treatment may be considered.

Other treatment options

When surgery is not feasible, Gamma Knife surgery (GKS) or laser interstitial thermal therapy may be alternative local treatment options. GKS has been employed both as primary or adjuvant treatment, with a variable efficacy and safety data are still lacking. According to available studies, GKS allows transient disease control, but ultimately tumor starts to regrow. In a study conducted by Park et al. [31], local tumor control was achieved in four of six patients (with a tumor reduction in volume of 0, 59, 63, and 86%, respectively); however, tumor progressed at 24, 42, 57, and 66 months of follow-up, respectively. Because of the slow volume reduction after treatment, this option is not recommended in case of hydrocephalus or progressive ventriculomegaly [32]. Moreover, a possible complication of radiation therapy may be malignant transformation into glioblastoma [33]. The real efficacy and tolerability of GKS should be established by larger studies.

Another emerging option may be laser interstitial thermal therapy (LITT), a stereotactic percutaneous procedure, consisting of thermal ablation of lesions by producing light energy via a fiberoptic catheter. Recently, magnetic resonance thermometry was introduced in real time to visualize the thermal energy delivered to tumor and surrounding tissue. Preliminary results of this procedure are promising: among the main case reports in literature, few side effects, and a tumor volume reduction in more than 50% of patients were reported (Table 1). The main post-treatment complication was hydrocephalus, caused by post-ablation peritumoral edema and to avoid the occurrence, preemptive septostomy was performed. In another retrospective study of three patients, a medium reduction in tumor volume of 70% was achieved on long-term postoperative MRI. Patients were dismissed from hospital on first or second postoperative day. All three patients had a septostomy performed in addition to ablation [38]. Because of these preliminary

Table 1. Patients treated with LITT: literature review

Study	Age at treatment (years)	Tumor volume before treatment (cm^3)	Percent decrease in tumor volume after treatment	Other adjuvant or neoadjuvant treatments	Clinical outcome and complications	Clinical follow-up (months after surgery)
Buckley et al. 2016 [34]	18.4	4.1	61%	Everolimus	No complication.	28.4
Buckley et al. 2016 [34]	7.5	4.1	–	Everolimus	No perioperative complication. Postoperative tumor progression requiring everolimus therapy.	29.5
Buckley et al. 2016 [34]	13	1.4	64%	None	No complication.	12.3
Dadey et al. 2016 [35]	13	2.62	74%	None	No complication. Improved behavior and quality of life, reduced seizure frequency, and stable neurologic exam.	9
Dadey et al. 2016 [35]	14	2.7	–	Concurrent	ventriculostomy	No
complication. Improved behavior and personality with no change in seizure frequency.	4					
Tovar-Spinoza et al. 2016 [36]	6	11.73	73%	Everolimus	No perioperative complication. Postoperative tumor progression requiring everolimus therapy starting 7 months after ablation.	27
Karsy M. et al. 2018 [37]	5	–	–		No perioperative complication	18 months after the

Table 1. (Continued)

Study	Age at treatment (years)	Tumor volume before treatment (cm^3)	Percent decrease in tumor volume after treatment	Other adjuvant or neoadjuvant treatments	Clinical outcome and complications	Clinical follow-up (months after surgery)
				Repeat ablation and delayed septostomy	during first ablation. After 18 months, tumor regrowth necessitated second ablation, during which time intraventricular gadolinium extravasation was noted. Delayed obstructive hydrocephalus developed 9 months after the second ablation, necessitating endoscopic septostomy for CSF diversion.	first ablation. 9 months after the second ablation.

results, LITT may be considered as primary or adjunctive treatment modality for SEGAs [39].

Prognosis and future perspectives

SEGAs, as other brain grade I tumors, have a good prognosis; however, they show a continuous tendency to grow and usually relapse after incomplete resection or after discontinuation of mTOR inhibitors. Furthermore, patients with TSC2 mutation develop SEGAs more frequently and at younger age, and the growth rate is faster. According to the Surveillance, Epidemiology and End Results (SEER) program [40] including 226 patients with newly diagnosed SEGAs from 2004 to 2013, OS at 3.5 and 9 years was 92.9%, 92.9%, and 87.5% respectively. During follow-up, 17 patients died, but only 6 deaths were attributed to SEGAs. Age younger than 18 years and surgical treatment were positive prognostic factors; however, gross total resection (GTR) did not show benefit in survival in multivariate analysis. In

addition, neither tumor size nor location demonstrated a significant relationship with OS in the SEER cohort.

The main challenge for the future is the development of other treatment strategies for SEGAs. One preclinical study [41•] investigated the role of mitogen-activated protein kinase (MAPK) and of extracellular signal-regulated kinase (ERK) pathways, which are overactivated in SEGAs. In this regard, the inhibition of ERK, regardless of mTOR blockade, decreased SEGA cell proliferation in cell cultures. This study showed that the MAPK/ERK pathway could be a target for treatment, alone or in combination with mTOR inhibitors for TSC patients. In another study [42••], the role of casein kinase 2 (CK2) protein, which has antiapoptotic properties in normal condition and plays a key role in glial tumor cell survival, was investigated by using specific inhibitors in vitro, and proliferation of SEGA cells was reduced. Further studies are needed to confirm the role of these compounds in clinical trials.

Lastly, a dysregulation in matrix metalloproteinases (MMPS) and their tissue inhibitors (TIMPs) system to enhance tumorigenesis was demonstrated in a preclinical study by Bongaarts et al. [43••]: thus, development of novel molecules targeting these pathways may constitute another therapeutic option.

Conclusions

SEGAs are grade I slow-growing gliomas with good prognosis. They are diagnosed in patients with TSC, being more frequent among those carrying a TSC2 mutation and a younger age. Main options are surgery and pharmacological treatments. However, despite being grade I tumors, they show a continuous tendency to grow after incomplete surgery and/or withdrawal of mTOR inhibitors: as a consequence, follow-up with MRI every 1–3 years is recommended. Some recent preclinical studies have suggested novel treatment options, to be confirmed in clinical trials.

Compliance with Ethical Standards

Conflict of Interest

Francesca Mo declares no competing interests. Alessia Pellerino declares no competing interests. Roberta Rudà declares no competing interests.

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