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Subependymal Giant Cell Astrocytoma: A Clinicopathological Analysis of 19 cases

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Abstract

Background Subependymal giant-cell astrocytoma (SEGA) is a rare WHO grade 1 ventricular neoplasm strongly associated with tuberous sclerosis complex (TSC). Misdiagnosis as a high-grade glioma may lead to overtreatment. This study aims to characterize the clinicopathological, immunophenotypic features, diagnostic pitfalls and molecular background of SEGA in a Chinese cohort.

Methods Nineteen surgically resected SEGA cases were retrospectively collected from two tertiary medical centers between 2011 and 2025. Clinical - radiological data, histomorphology, immunohistochemical profiles and follow-up outcomes were analyzed. All slides were re-reviewed by two experienced senior neuropathologists according to the 2021 WHO CNS tumor criteria.

Results Patients ranged in age from 3 to 30 years (mean 11.8 years; male-to-female ratio = 1.8:1). The majority of tumors (16 out of 19) developed in the lateral ventricles. The primary symptoms were signs of increased intracranial pressure and epilepsy. Under the microscope, the tumors displayed a mix of pleomorphic polygonal cells, spindle-shaped cells, and ganglion-like giant cells arranged in sheet - like or nested patterns, along with perivascular pseudopalisades, stromal calcification and thin-walled blood vessels. All cases showed widespread expression of GFAP, S100,

Nestin and TTF1. Partial expression of Synaptophysin (Syn) and Neuron-Specific Enolase (NSE) was noted, while IDH1 R132H, BRAF V600E, H3K27M, Olig2 and CD34 were universally negative. The Ki-67 proliferation index was always below 5%. Only one case that was subtotally-resected experienced recurrence during 8-78 months follow-up. Additionally, three cases exhibited weak to moderate PanTRK immunoreactivity, which has been rarely documented before. **Conclusions** SEGA should be diagnosed by combining clinical information (such as a history of tuberous sclerosis complex),radiology and distinctive morphological features. Consistent expression of TTF-1 and Nestin indicates that these tumors originate from medial ganglionic eminence-derived neural progenitors. Complete surgical removal leads to a very favorable outcome. The detection of PanTRK expression in some SEGA cases expands the range of their known immunophenotypic characteristics. Additionally, therapies targeting the mTOR pathway are effective for tumors that are partially removed or have recurred.

Keywords: Subependymal giant-cell astrocytoma; Tuberous sclerosis complex; TTF-1; PanTRK; Clinicopathology; Differential diagnosis; mTOR pathway

Abbreviations

SEGA: Subependymal giant-cell astrocytoma

TSC1/2: Tuberous sclerosis complex 1/2

CNS: Central Nervous system

mTOR: Mammalian target of rapamycin

MRI: Magnetic resonance imaging

MGE: Medial ganglionic eminence

HE: hematoxylin-eosin

Introduction

Subependymal giant cell astrocytoma (SEGA) is an uncommon, slow-growing benign tumor that predominantly arises near the interventricular foramen of the lateral ventricle [1]. It is classified as a WHO Grade 1 tumor according to the 5th edition of the WHO Classification of Tumors of the Central Nervous System published in 2021 [2, 3]. SEGA most frequently appears in patients with tuberous sclerosis complex (TSC), though it can sometimes be identified in individuals without

clinical manifestations of TSC [4]. TSC is an autosomal dominant genetic disorder caused by mutations in the TSC1 or TSC2 genes. The loss of heterodimer function of the hamartin and tuberin proteins encoded by these genes relieves the inhibitory effect on the mTOR signaling pathway, leading to uncontrolled cell growth and tumor formation [5]. Because SEGA growth can block cerebrospinal fluid circulation, resulting in increased intracranial pressure and potentially brain herniation, prompt and accurate diagnosis is critically important [6]. However, its morphological characteristics, such as abundant eosinophilic cytoplasm and pleomorphic giant cells, can be mistaken for high-grade gliomas and other tumors, which may lead to overtreatment. In this study, we conducted a retrospective analysis of the clinical and pathological features, immunophenotypes and molecular changes in 19 SEGA cases, along with a review of the literature, to identify the key points of diagnosis, differential diagnosis and molecular pathogenesis, aiming to enhance the understanding of this disease.

Materials and Methods

Case collection

A total of 19 surgically resected and pathologically verified SEGA specimens were obtained from the Department of Pathology of Tianjin Medical University Cancer Institute & Hospital and the Affiliated Hospitals of Xinjiang Medical University between 2011 and 2025. All cases were examined and validated by two experienced neuropathologists based on the diagnostic standards outlined in the 5th edition of WHO Classification of Tumors of the Central Nervous System. Clinical information, imaging results and follow-up data for all patients were gathered and analyzed.

Experimental Methods

All specimens were fixed in 4% neutral formalin, embedded in paraffin, and cut into serial sections with a thickness of 3-5μm for standard hematoxylin-eosin (HE) staining and immunohistochemical analysis. Immunohistochemistry was carried out using the EnVision two-step technique. The primary antibodies included GFAP, Olig-2, TTF-1, Pan-TRK, CKpan, IDH1 R132H, EMA, S-100, Vimentin, NeuN, Nestin, Syn, CD34, Ki-67, H3K27M, H3K27Me3, INI1 and BRAF V600E. All experimental procedures were strictly followed according to the manufacturer's guidelines.

Results

Clinical Characteristics

Among the 19 patients included in the study, 12were male and 7 were female, resulting in a male-to-female ratio of 1.8:1. The ages of the patients ranged from 3 to 30 years, with a median age of 11.8 years; 16 patients (84.2%) were younger than16 years old. Tumors were located in the lateral ventricle in 16 cases (84.2%), in the third ventricle in 1 case, in the fourth ventricle in 1 case and in the basal ganglia in 1 case. The primary clinical symptoms were related to increased intracranial pressure, such as intermittent headaches, nausea and vomiting; some patients also experienced epileptic seizures and blurred vision. Magnetic resonance imaging (MRI) showed that most tumors had both cystic and solid components. The solid portions appeared iso- or slightly hypointense compared to the cerebral cortex.

Pathological Features

Gross examination: The tumors ranged in size from 0.8 to 5.5cm in diameter, with an average maximum size of 2.6cm. The cut surfaces were mostly gray-white to gray-red in color and varied from soft to firm in texture. Six tumors showed a combination of cystic and solid structures, and one case exhibited focal calcification.

Microscopic examination: At low magnification, the lesions displayed varying levels of cellularity and were relatively well-circumscribed margins. Under high magnification, a diverse range of tumor types was observed: 1. Giant cells (Large polygonal or tapered cells) with abundant eosinophilic, ground cytoplasm, eccentric nuclei, and prominent nucleoli; some showed multinucleation (Fig. 1A and B); 2. Spindle-shaped cells arranged in fascicular or storiform patterns; 3. Plump cells resembling astrocytes. Tumor cells often formed perivascular pseudorosettes and palisading patterns (Fig. 1C). The stroma contained numerous thin-walled, dilated capillaries. Perivascular lymphocytic cuffs and calcifications were present in 3 out of 19 cases (Fig. 1D). Mitotic figures were rare, and there was no evidence of microvascular proliferation or necrosis.

Immunohistochemistry and Molecular Markers

In all 19 cases, tumor cells exhibited widespread strong positivity for GFAP (Fig. 2A) , TTF-1 (Fig. 2B), Vimentin (Fig. 2C), S-100 and Nestin. The neuronal marker Syn showed focal or variable positivity in 6 cases, while Neu-N was negative. NSE was variably expressed in 16 cases (Fig. 2D) . Pan-TRK demonstrated weak to moderate positive staining in 3 cases (Fig. 2E). All cases retained intact nuclear expression of INI1 and H3K27Me3, and tested negative for IDH1 R132H, BRAF V600E, H3K27M, Olig-2, EMA and CD34. The Ki-67 proliferation index ranged from 1% to 5%

(Fig. 2F).

Treatment and Follow-up

All 19 patients underwent surgery. Complete tumor removal was achieved in 16 cases and while 3 cases had partial removal. One patient received radiotherapy following partial resection. The follow-up duration varied between 8 and 78 months. One patient experienced tumor recurrence 5 years after partial resection and remained alive with residual tumor after a second surgery. The other 18 patients continued to be disease-free.

Discussion

Subependymal giant-cell astrocytoma (SEGA) is a rare WHO grade 1 tumor located within the brain ventricles, primarily affecting children and adolescents [1]. Since the publication of the 5th edition of the WHO Classification of Central Nervous System Tumors, there has been growing interest in the diagnostic criteria, cellular origin, and targeted treatment options for SEGA. Because of its marked cellular pleomorphism with abundant giant tumor cells, SEGA is at significant risk of being mistaken for a high-grade glioma, which could result in unnecessary aggressive therapy [7, 8]. While several Western studies have detailed its clinical and pathological characteristics [9, 10], large multi-institutional retrospective studies involving Chinese populations are still relatively scarce. Our cohort of 19 cases provides diagnostic and follow-up information for this rare ventricular tumor.

SEGA is one of the most characteristic central nervous system manifestations of tuberous sclerosis complex (TSC), an autosomal-dominant tumor-suppressor syndrome caused by heterozygous germline loss-of-function variants in TSC1 (9q34) or TSC2 (16p13.3), with second-hit biallelic inactivation in affected lesions [11, 12]. The hamartin-tuberin heterodimer encoded by these two genes, acts as an essential upstream inhibitor of the mTOR signaling pathway. Biallelic inactivation of the gene abolishes this inhibitory function, resulting in constitutive mTOR hyperactivation, increased protein synthesis, and uncontrolled cell proliferation, which ultimately promotes tumor development [5, 13].

In our study, only four patients were definitively diagnosed with TSC based on clinical criteria. The other cases represented sporadic SEGA without the typical systemic signs of TSC. According to previous research, sporadic SEGA may contain somatic or mosaic mutations in the TSC1 or TSC2 genes that are not identifiable through standard clinical testing for TSC [14]. This clinical-genetic

gap serves as a reminder to pathologists that a negative clinical evaluation for TSC does not exclude the possibility of SEGA. The well-known mTOR-driven disease mechanism also supports the use of mTOR inhibitors (such as everolimus) as treatment for unresectable or recurrent SEGA, a strategy that has been confirmed through multicenter clinical trials [15-18]. Unfortunately, genetic testing for TSC1/TSC2 was not conducted in our retrospective cohort, so we were unable to verify somatic mutations in our sporadic cases.

Histogenesis and Immunophenotypic Spectrum

In line with previous studies, all tumors examined in this research showed widespread expression of GFAP, S-100, Nestin and TTF-1. Notably, the sustained nuclear immunoreactivity of TTF-1 is particularly significant for diagnosis. TTF-1 plays a role in the development of the ventral forebrain during embryogenesis and is temporarily present in neural progenitor cells of the medial ganglionic eminence (MGE), but it is not found in the normal postnatal adult periventricular parenchyma [8]. When combined with the consistent positivity for Nestin, a marker for immature neural progenitors, this immune-profile strongly supports the theory that SEGA originates from neural progenitor cells derived from the MGE- that remain in the subependymal zone during embryonic development [8, 19-20]. Additionally, tumor cells expressed both glial markers (GFAP) and some partial neuronal markers (Syn, NSE), indicating the dual differentiation potential of these pluripotent progenitor cells [21].

Importantly, we observed weak-to-moderate Pan-TRK immunoreactivity in three out of our 19 SEGA cases. To our knowledge, Pan-TRK expression in SEGA has been rarely documented. Pan-TRK immunohistochemistry is commonly used to detect for NTRK gene fusions in various tumor types [15]. However, the biological and predictive relevance of Pan-TRK staining in SEGA is still unclear. This finding might reflect a non-specific up-regulation of TRK-family proteins driven by mTOR hyperactivation rather than genuine NTRK fusion events. Nevertheless, this observation raises a speculative question: could TRK-inhibitor therapy be beneficial for the rare cases of progressive, recurrent SEGA that do not respond to mTOR-targeted treatments? Additional molecular analyses, including NTRK fusion testing in Pan-TRK-positive SEGA cases, are necessary to investigate this possibility.

In all our cases, intact INI1 nuclear staining effectively rules out atypical teratoid/rhabdoid tumor, an aggressive pediatric posterior fossa/ventricular tumor, which is considered in the differential diagnosis of large-cell pediatric CNS neoplasms. The consistent absence of IDH1 R132H, BRAF V600E and H3K27M mutations provides strong immunohistochemical evidence to distinguish SEGA from IDH-mutant gliomas, pleomorphic xanthoastrocytoma and histone-mutant high-grade gliomas [22, 23]. Recent studies have suggested Glycoprotein Nonmetastatic Melanoma Protein B(GPNMB) as an additional supportive diagnostic marker for SEGA; however, GPNMB immunohistochemistry was not available in our retrospective study group [24]. Notably, rare cases of SEGA lacking TTF-1 expression have been reported in literature, which constitute a major diagnostic pitfall. In morphologically suspicious cases that are TTF-1-negative, DNA-methylation profiling may be required to establish the correct diagnosis [14].

Treatment and Prognostic Considerations

Complete surgical removal remains the primary treatment for SEGA and is linked to excellent long-term results. In our group, all patients who underwent total resection stayed free of disease during follow-up. For tumors located deep within the brain where complete removal poses significant surgical risks, partial resection is often necessary. In our study, one patient who had a partial resection experienced tumor recurrence five years after surgery. This case emphasizes the need for extended imaging monitoring when SEGA is not fully removed..

mTOR inhibitors, such everolimus, are now the standard treatment for SEGA that cannot be surgically removed, remains after surgery, or recurs, and they have been shown to effectively reduce tumor size in clinical settings [16, 17]. According to the WHO classification, malignant transformation of SEGA is extremely rare, ; however, there have been rare reports of atypical SEGA cases exhibiting aggressive behavior [2, 11]. Therefore, long-term close clinical and radiological imaging follow-up is recommended for these high-risk patients, particularly children with confirmed TSC-related germline mutations. The clinical role of radiotherapy for SEGA remains controversial, and due to the potential adverse effects of radiation in pediatric patients, its application should be approached with great caution [25].

Diagnosis and Differential Diagnosis: Practical Diagnostic Pitfalls

The diagnosis of SEGA depends on a multidisciplinary approach that combines its typical intraventricular location near the foramen of Monro, neuroimaging characteristics, histological features, and supportive immunohistochemistry findings. When classic features such as ganglion-like giant cells, perivascular pseudopalisades, stromal calcification, and a known history of TSC are present, the diagnosis is straightforward. However, pathologists may sometimes encounter morphologically atypical or sporadic cases of SEGA without clinical signs of TSC, requiring careful exclusion of other morphological mimics. Practical differential-diagnostic considerations for surgical neuropathologists are summarized below:

1. Diffuse astrocytoma, IDH-mutant: These tumors usually develop in the cerebral hemispheres instead of the lateral ventricle. The tumor cells tend to be fairly uniform and do not display the distinctive ganglion-like giant cells seen in SEGA. The presence of positive IDH1 R132H immunohistochemistry and common p53 overexpression supports this diagnosis; these markers are consistently absent in SEGA [22].

Practical note: IDH-mutant astrocytoma is very uncommon as a primary intraventricular tumor in young children.

2.Giant-cell glioblastoma: Although abundant giant cells can be seen, giant-cell glioblastoma clearly shows malignant characteristics such as significant nuclear pleomorphism, frequent mitotic figures, pseudopalisading necrosis and microvascular proliferation. Ki-67 proliferation index typically exceeds 20%, which is much higher than the low proliferation rate seen in SEGA [23].

Practical note: A high Ki-67 index and the presence of necrosis are important warning signs that suggest the diagnosis is not SEGA.

3.Rhabdoid meningioma: The cytoplasm of rhabdoid cells can resemble the giant cells found in SEGA. However, rhabdoid meningiomas typically retain areas of the usual meningothelial whorled pattern, test positive for EMA/SSTR2-positive, and do not show wide spread GFAP expression [26].

Practical note: Rhabdoid meningiomas are mostly seen in adults, whereas SEGA occurs predominantly in children and adolescents.

4.Gangliоglioma: Gangliоglioma consist of dysplastic ganglion cells that have centrally located nuclei and visible cytoplasmic Nissl bodies, unlike the eccentrically-located nuclei in SEGA

ganglion-like giant cells. The majority of gangliogliomas test positive for CD34 and often have BRAF V600E mutations, features that were not found in our group of SEGA cases [8].

5.Ependymoma: Intraventricular ependymoma needs to be distinguished from SEGA. Ependymoma consists of relatively uniform tumor cells that form true ependymal rosettes or perivascular pseudorosettes, and it does not contain prominent large ganglion-like giant cells. Additionally, EMA typically exhibits a distinctive paranuclear dot-like pattern of immunoreactivity in ependymoma [27].

6. General diagnostic pitfall reminder: Sporadic SEGA cases without a known history of TSC and rare TTF-1 negative SEGA pose significant challenges for diagnosis. In these complex situations, thorough comprehensive immunohistochemical panels and, when possible, DNA-methylation profiling are necessary to prevent incorrect diagnosis.

Limitations

This study has several inherent limitations of retrospective multi-institutional case-series research. First, we did not have TSC1/TSC2 sequencing or DNA-methylation data for our cohort, therefore we were unable to confirm underlying somatic or mosaic genetic changes in sporadic SEGA cases not associated with TSC. Second, only surgically removed specimens were included, which may introduce selection bias, and cases diagnosed solely by biopsy were not represented. Third, GPNMB immunohistochemistry, a recently identified supplementary marker for SEGA, could not be performed on the archived samples. Fourth, the clinical and predictive significance of Pan-TRK expression found in three cases remains uncertain, and larger independent cohorts are needed to confirm this observation. Despite these limitations, our study provides valuable real-world clinicopathological and follow-up data on SEGA from Chinese tertiary medical centers.

Conclusion

SEGA is an uncommon WHO grade 1 intraventricular tumor that occurs predominantly in children and adolescents. Accurate diagnosis depends on a multidisciplinary approach that combines clinical history-particularly signs related to tuberous sclerosis-neuroimaging results, distinctive histological features, and focused immunohistochemical analysis. The widespread expression of TTF-1 and Nestin in tumor cells supports the theory that SEGA originates from neural progenitor cells of the

medial ganglionic eminence that remain in the subependymal zone during embryonic development. We have observed varying levels of Pan-TRK immunoreactivity in some SEGA cases, broadening the known immunophenotypic profile of this tumor, although the biological and predictive importance this finding requires confirmation in larger studies. Complete surgical removal of the tumor generally leads to an excellent outcome. For tumors that are not fully resected or that recur, mTOR inhibitors offer an effective targeted treatment option. Pathologists should be cautions of diagnostic challenges, such as sporadic SEGA cases without clinical signs of TSC clues and rare TTF-1-negative variants, to prevent misdiagnosis and unnecessary aggressive treatment of these low-grade neoplasms.

Declarations

Ethics approval and consent to participate

This retrospective clinicopathological study received ethical exemption for retrospective analysis from the Institutional Review Boards of the involved hospitals. All experimental procedures complied with the principles outlined in the Declaration of Helsinki. Since all clinical and pathological data were completely anonymized, the requirement for individual written informed consent from patients was waived by the institutional review board.

Consent for publication

All images and patient data presented in this manuscript have been fully anonymized, containing no personally identifiable information; as a result, patient-specific consent for publication was not required.

Availability of data and materials

The datasets used in this study can be obtained from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Author contributions

Xuelian Cui and Junzhi Li conceived and designed the study. Wenxin Li, Shao Shuai collected clinical data and performed experiments. Junzhi Li, Leyi Feng and Na Miao completed data analysis and visualization. Xuelian Cui and Junzhi Li drafted the manuscript. All authors reviewed, critically

revised the manuscript, and approved the final submitted version. All authors agree to be accountable for all aspects of this work.

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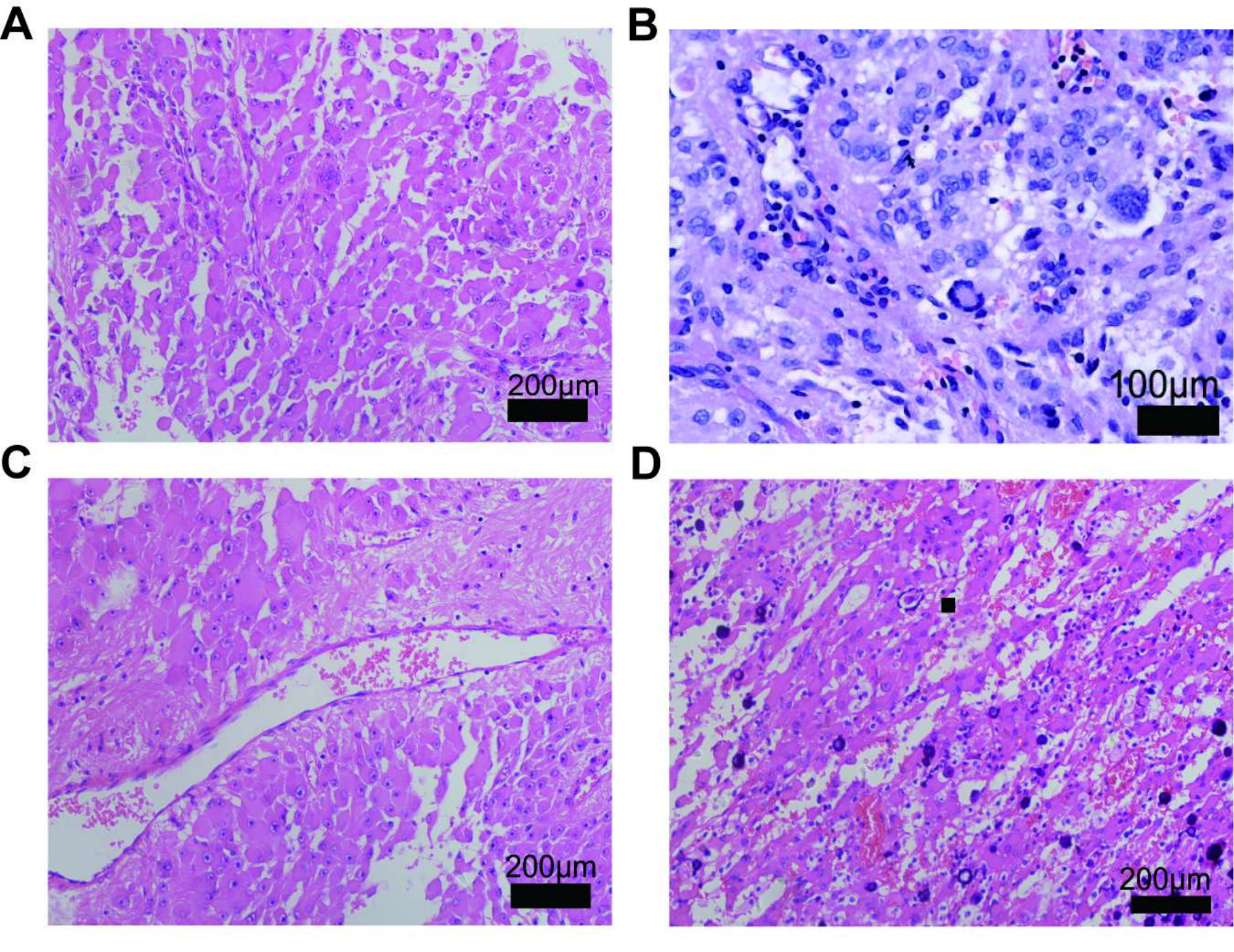
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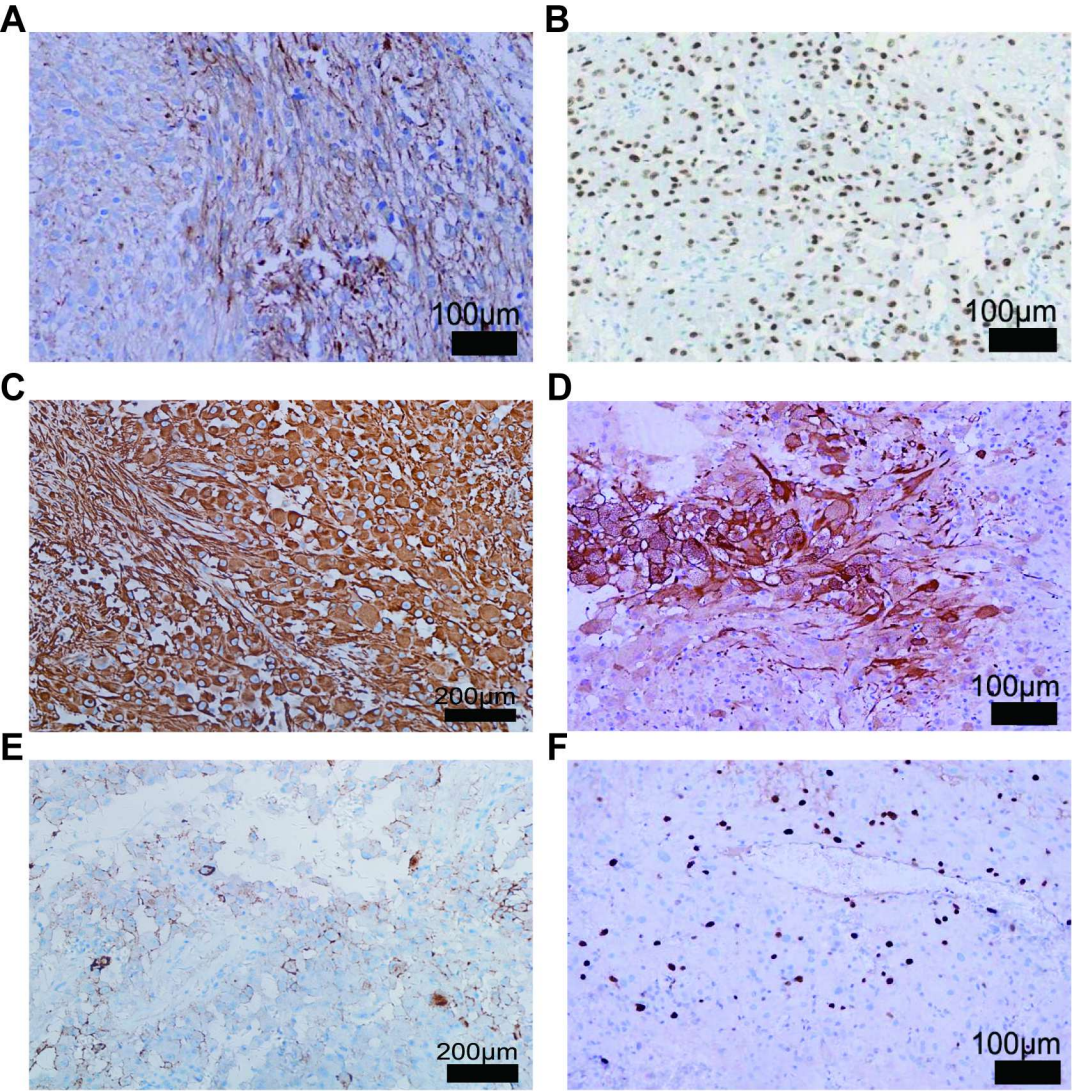
Figure legends

Fig.1 Representative histological images of the SEGA. **A** Tumor cells have a ground-glass appearance in their cytoplasm, with an off-center nucleus. **B** Giant cells are large and cone-shaped. Occasionally, binuclear or multinuclear cells can be observed. **C** Tumor cells frequently exhibited perivascular pseudorosette formations as well as palisading arrangements. **D** The stroma exhibited a substantial presence of thin-walled, dilated capillaries. Additionally, perivascular lymphocytic infiltrates and calcifications were observed.

Fig.2 Immunohistochemical characteristics of the SEGA. **A** The staining of GFAP is positive. **B** The staining of TTF-1 is positive. **C** The staining of Vimentin is positive. **D** The Vimentin staining

exhibited a moderate positive intensity. **E** The Pan-TRK staining exhibited a weak positive intensity. **F** The Ki-67 proliferation index was approximately 5%.


A
200μm
B
100μm
C
200μm
D
200μm


A
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E
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