Subependymal Giant Cell Astrocytomas in the Western Region of Saudi Arabia; A Clinicopathological Experience

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Abstract: Background: Subependymal giant cell astrocytomas (SEGAs) are rare slowly growing tumors that usually occur in the setting of tuberous sclerosis complex (TSC). Histologically they may simulate high-grade gliomas and such a misleading diagnosis might result in unnecessarily aggressive chemo-or radiotherapy. The aim of this study is to review the pathological pattern of SEGAs in two tertiary medical centres in the western region of Saudi Arabia. **Methods:** We retrospectively analyzed the pathological and clinical data of patients diagnosed with SEGAs in 2 tertiary medical centers (king Abdulaziz university hospital, [January 2000 to April 2012], and king Faisal specialist hospital and research center [January 2001 to April 2012]). **Results:** Ten cases were diagnosed as SEGAs. The age range was 5-35 years (mean 18.7 years). There were 5 Males and 5 female patients. Only three patients were diagnosed with TSC preoperatively and one patient diagnosed with TSC during the follow-up period. All the ten tumors developed in the lateral ventricles. All tumors showed similar histological features irrespective of their association with tuberous sclerosis. All the patients treated with complete microsurgical resection only. Clinical follow-up of the patients ranged from 2 to 144 months (mean 32 months), none of the patients had recurrence after surgery. **Conclusion:** SEGA should be considered in the differential diagnosis of intraventricular tumor even in the absence of TSC features. It is very important for pathologists to be aware with the morphological features of SEGA to avoid misdiagnosis and subsequent overtreatment. Surgical resection is usually sufficient treatment. Long term prognosis of patients with SEGA is excellent even in the presence of worrisome atypical histological features.
[Jaudah A. Al-Maghrabi and Saleh S. Baeesa. **Subependymal Giant Cell Astrocytomas in the Western Region of Saudi Arabia; A Clinicopathological Experience.** *Life Sci J* 2013;10(1):1837-1844]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 263

Keywords: Subependymal giant cell astrocytomas. Tuberous sclerosis. Misdiagnosis. Pathology. Pitfalls.

1. Introduction:

Subependymal giant cell astrocytoma (SEGA) is a rare and unique benign astrocytoma that usually arises in patients with tuberous sclerosis complex (TSC) and considered a major criterion for diagnosis of TSC **(1)**. Occasionally the histopathology of these tumors mimics malignant gliomas because of the presence of high cellularity, considerable nuclear pleomorphism and multinucleated and giant cells. The difficulty in the differential diagnosis becomes more evident in those SEGAs that show unusual atypical features such as necrosis, microvascular proliferation and mitotic figures. It is very important for pathologists to be aware with morphological features of these tumors to avoid unnecessarily excessive treatment of basically low-grade neoplasms. In this study the histopathological and immunohistochemical features of SEGAs diagnosed at two large medical centres in the western region of Saudi Arabia are reviewed.

2. Methods:

This is a retrospective study of patients diagnosed with SEGAs in 2 tertiary medical centers in Jeddah; King Abdulaziz University Hospital (KAUH) during the period January 2000 to April 2012, and King Faisal Specialized Hospital and Research Centre (KFSHRC) during the period January 2001 to April 2012. The study was in accordance with the Research Ethic Committee of KAUH and according to the ethical guidelines of the 1975 Declaration of Helsinki. Patients' histological materials were retrieved from the archive. Hematoxylin and eosin stained slides together with the immunohistochemistry material were reviewed. The immunohistochemistry panel was completed in those cases with slides available and not all the markers were done at the time of the diagnosis. The clinical and radiological data of the patients was reviewed. We used Chi square test to compare the distribution of variables. Data analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), Version 16. A p-value <0.05 was considered significant.

3. Results:

Of 1060 intracranial tumors sampled and/ or resected at both institutions during this period, 10 cases of SEGAs were diagnosed. The age range was 5-35 years (mean 18.7 years). The male to female

ratio was 1:1. The most common presenting symptom of our patients was seizure which identified in 5 patients, headache in 4 patients, visual disturbances in 3 patients and slurred speech in 1 patient. The clinical findings are summarized in **Table 1.** All patients had preoperative, immediate, and follow up MRI scans. The MRI scans demonstrated the tumor located in the lateral ventricle in all the patients with associated obstructive hydrocephalus in 4 patients **(Figure 1).** All cases showed similar histological features irrespective of their association with tuberous sclerosis. The pathological findings are summarized in **Table 2**. Microscopic examination showed sweeping bundles of elongated cells admixed with polygonal cells with abundant eosinophilic cytoplasm (resembling gemistocytic astrocytes) and ganglion- like giant cells with coarse chromatin and vesicular nuclei **(Figure 2)**. Tumor showed perivascular pseudorosettes (8/10), Infiltrating lymphocytes (10/10), nuclear pseudoinclusions (8/10), mast cells (10/10), microcalcification (6/10), necrosis (2/10), mitoses in the range of 1-2 per 10 HPF (2/10) and vascular proliferation (1/10). Infiltrating lymphocytes and presence of variable number of mast cells are constant features of SEGAs and are helpful pathological features to support the diagnosis. The immunohistochemical profiles are summarized in **Table 3** and illustrated in **Figure 3.** All tumors expressed GFAP. S100 expressed in all tested cases. Synaptophysin expressed in the large cells in 6 out of 9 cases. EMA was not expressed in any of the cases. Ki67 labelling index was low in all tested cases (<3%).

One of the patients referred from outside institution with the diagnosis of suggestive of glioblastoma and review of the slides confirmed the diagnosis of SEGA. Seven patients underwent frozen section evaluation, in one patient a diagnosis of high grade glioma was suggested; however, the case was finally diagnosed as SEGA on permanent sections evaluation. All the patients treated with image-guided frontal craniotomy through transcallosl transventricular approach and complete microsurgical resection only. None of them showed recurrence and all the patients are surviving at the time of reporting.

Only three patients were diagnosed with TSC preoperatively and one patient diagnosed with TSC during the follow-up period. No statistical difference in cases with or without associated tuberous sclerosis (p=0.527)

Clinical follow-up of the patients ranged from 2 to 144 months (mean 32 months), none of the patients had recurrence after surgery including the cases with mitosis and/or necrosis.

Table 1: Clinical features of the ten patients with subependymal giant cell astrocytomas.

Age (years)/Sex	Site	Clinical presentation	Assoc. TS	Tumor size on MRI	Treatment	Follow-up (months)
33 /F	Left lateral ventricle	Headache, vomiting	-	2	Surgical resection	9
5/M	Left lateral ventricle	Seizure	+	1.2	Surgical resection	25
32 /F	Left lateral ventricle	Headache	-	1.8	Surgical resection	35
8 /F	Left lateral ventricle	Seizure	-	2.4	Surgical resection	144
5 /F	Right lateral ventricle	Decreased visioin	-	5.2	Surgical resection	24
24/M	Left lateral ventricle	Seizure, headache	-	4.4	Surgical resection	4
13/M	Right lateral ventricle	Seizure	+	3.5	Surgical resection	22
21/F	Left lateral ventricle	Decreased visioin	+	2	Surgical resection	14
11/M	Right lateral ventricle	Seizure	-	3.8	Surgical resection	41
35/M	Left lateral ventricle	Decreased visioin, headache	+	3.2	Surgical resection	2

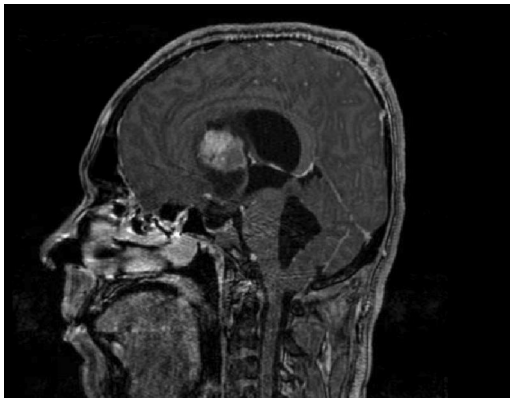
Table 2: Pathological features of subependymal giant cell astrocytomas.

Pathological features	Patients										p-value
	1	2	3	4	5	6	7	8	9	10	
Sweeping bundles of spindle cells and ganglion-like cells	+	+	+	+	+	+	+	+	+	+	0.011
Perivascular pseudorosettes	-	+	+	+	+	+	+	-	+	+	0.206
Infiltrating lymphocytes	+	+	+	+	+	+	+	+	+	+	0.011
Nuclear pseudoinclusions	+	+	-	+	+	+	+	+	-	+	0.05
calcification	+	+	+	-	+	+	-	+	-	-	0.527
Mast cells	+	+	+	+	+	+	+	+	+	+	0.011
Necrosis	-	-	+	-	-	-	-	-	+	-	0.05
mitosis	-	-	+	-	-	-	-	+	-	-	0.05
Vascular proliferation	-	-	-	-	-	-	-	+	-	-	0.011

Table 3: Immunohistochemical features of subependymal giant cell astrocytomas.

ient	GFAP	S100	Synaptophysin	EMA	ki-67
1	+	+	+	-	<1
2	+	+	+	-	<1
3	+	+	-	-	<1
4	+	+	+	-	3
5	+	+	-	-	<1
6	+	+	-	-	<1
7	+	+	+	-	2%
8	+	+	+	-	1
9	+	ND	ND	ND	ND
10	+	+	+	-	2

ND: Not done



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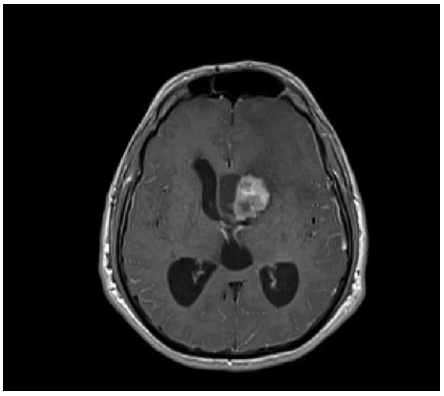

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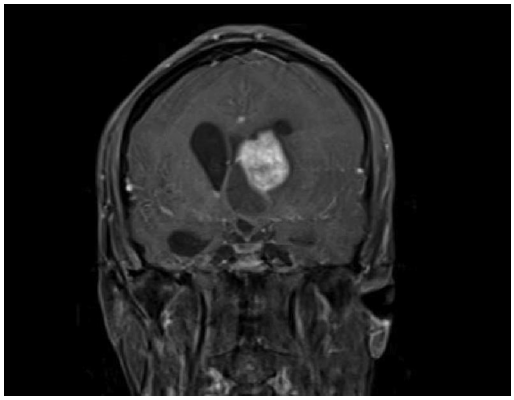

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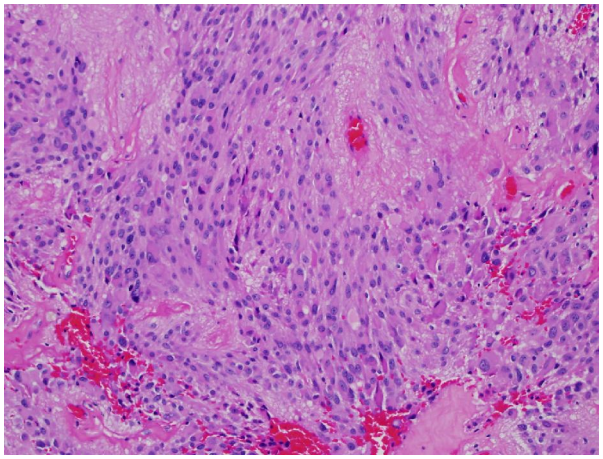
Figure 1: Radiology of SEGA:
Sagittal (A), Axial (B), and Coronal (C) T1 weighted MRI post-contrast administration, of 35-yr-old male presented with headache and decreased vision, demonstrating large left lateral ventricular solid and cystic SEGA with strong enhancement of the solid portion.



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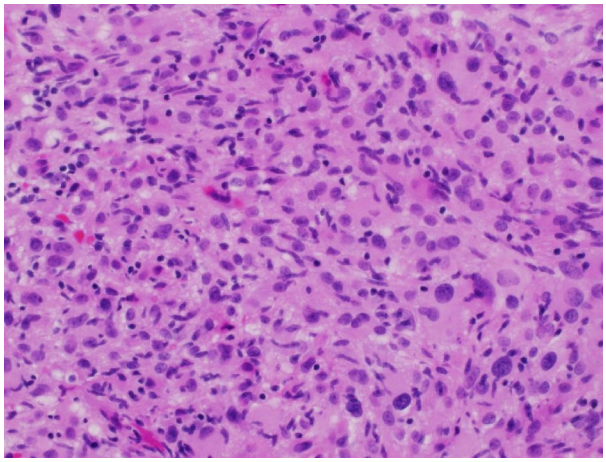

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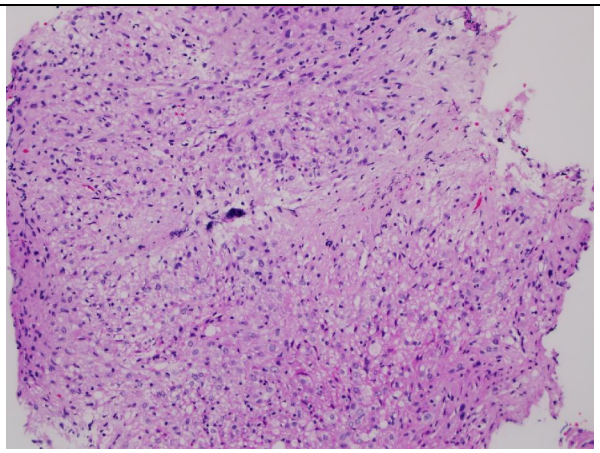

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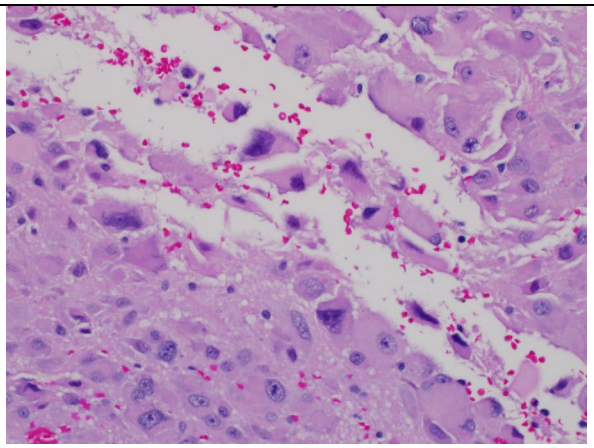

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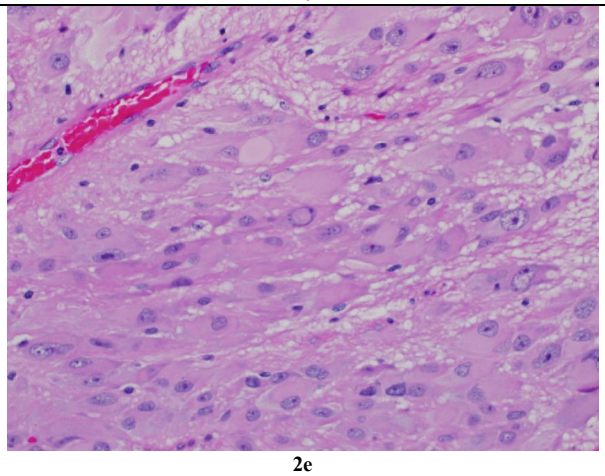

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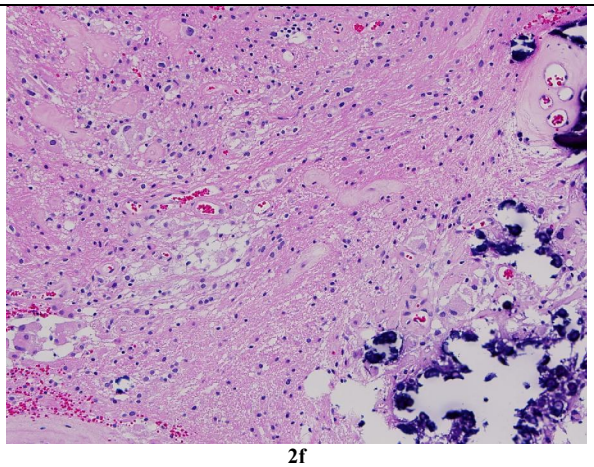

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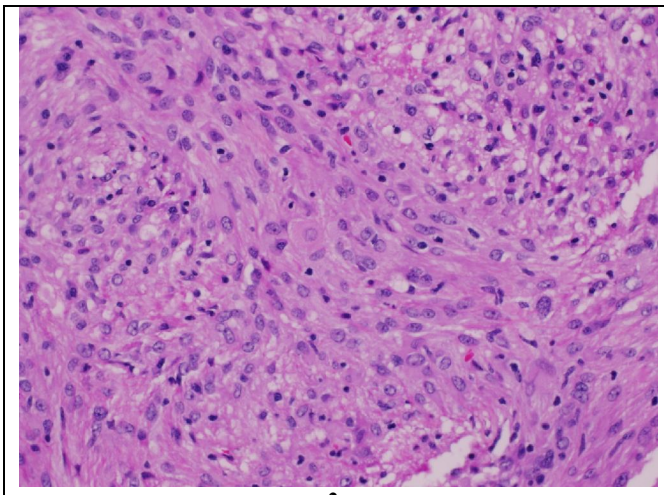
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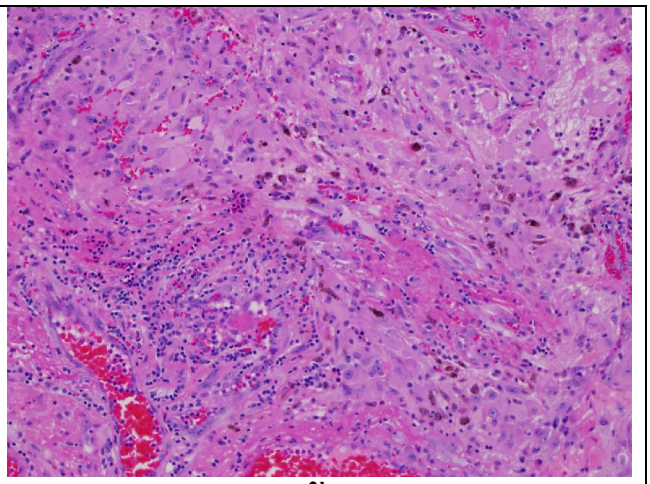
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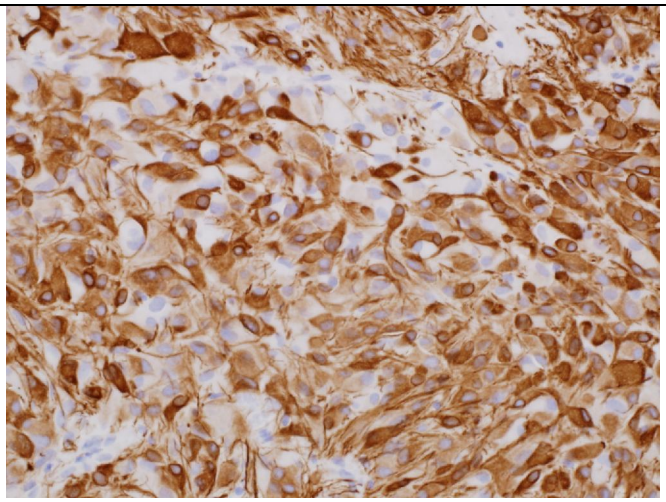
Figure 2:
Histopathology of SEGA:

A. Tumor composed of Sweeping bundles of spindle cells and ganglion-like cells with Perivascular pseudorosettes (H&E)
B. Tumor with small focus of necrosis identified in a frozen section in the center (H&E).
C. Tumor reveals cells with nuclear pseudo inclusion (arrow) (H&E).
D. Tumor composed predominantly of spindle ells (H&E).
E. Very cellular tumor with sprinkling of inflammatory cells (H&E).
F. Tumor with large cells revealing nuclear pleomorphism (H&E).
G. Tumor with areas of calcification and degenerative changes (H&E).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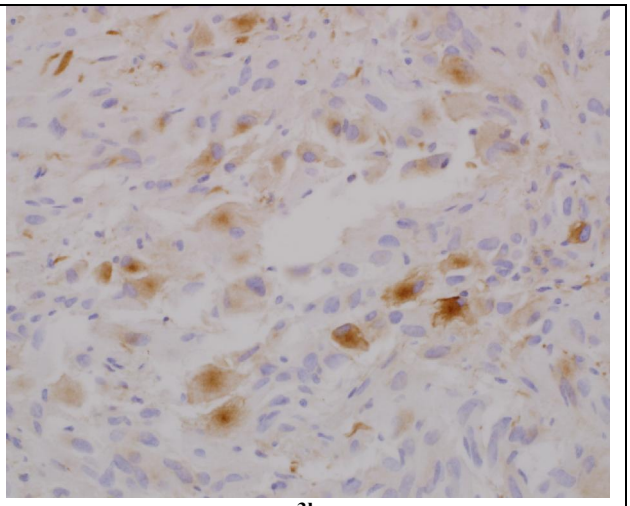
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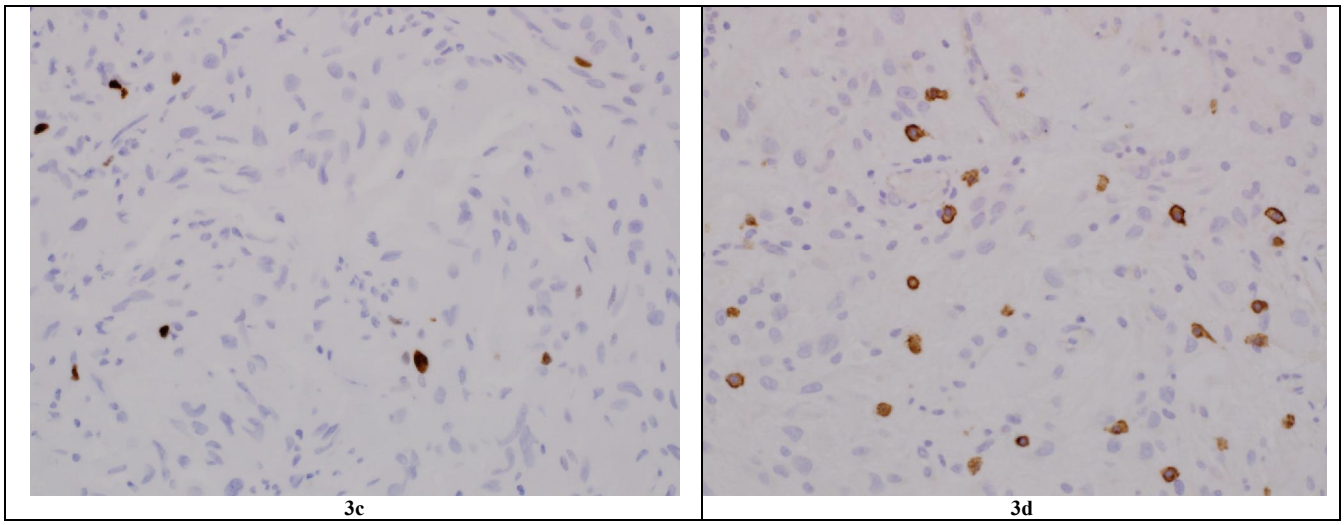

Figure 3: Immunohistochemistry of SEGA:

A) Diffuse GFAP immunoexpression
B) Some large tumor cells are immunoreactive for synaptophysin
C) Few cells are positive for Ki-67 (mib-1) consistent with low proliferative index.
D) CD117 highlight scattered mast cells

4. Discussion:

SEGA is a benign slowly growing tumor that is corresponding to WHO grades I. Although SEGAs accounts for 90% of intracranial tumors associated with TSC (2), generally they are considered a very rare tumor. In the current study they accounted for 0.94% of intracranial tumors.

In this study five patients presented in the first two decades which is consistent with the literature where most of the patients show clinical and pathological symptoms in the first two decades **(2-**4). There are published cases that took place in neonates **(5;6).** Furthermore, many cases diagnosed in the prenatal age and considered as congenital tumors **(7-9)**.

In the current study all the cases developed in the lateral ventricles which consistent with previous reports **(10)**. The tumor is most often located only on one side as in our cases, but it may also appear on both sides **(2).** The prevalence of SEGA in TSC ranges between 5% **(2;11)** and 20% (12). Prevalence of SEGA in TSC is higher in studies using radiological evidence to diagnose this tumor than in studies using histopathological evidence **(12)**.

In our study the most common presenting feature was seizure (5 patients) and headache (4 patients) followed by visual disturbances (3 patients). In the literature the majority of SEGA patients present with either worsening epilepsy or symptoms of increased intracranial pressure **(3;10;13).** SEGAs often result in obstructive hydrocephalus. Headache, vomiting, visual disturbances in the form of decreased vision and blindness are common presenting features **(3;10;13).** Some patients of SEGA develop manifestation of TSC in the follow – up period.

SEGA usually has a characteristic features on MRI. In the current study the diagnosis of SEGA was suggested in 3 out of the 10 cases based on the radiological findings. In those three patients the diagnosis of TSC was made preoperatively. In two other cases the radiological differential diagnosis included SEGA and central neurocytoma. In the rest of the cases no differential diagnosis was given radiologicaly. Central neurocytoma is a known radiological mimic of SEGA **(14).**

In this study all cases showed similar histological features irrespective of their association with TSC. Histologically, these tumors composed of three types of cells: spindle-shaped, large round eosinophilic gemistocytic cells and ganglion-like cells. The inflammatory cell component composed of an admixture of mast cells and T lymphocytes was evident in all the 10 cases of this study. By immunohistochemistry, these tumors are commonly positive for GFAP, neurofilament, neuron-specific enolase and synaptophysin **(13;15).** This immunoprofile indicates that these tumors are hybrid tumors with glial and neuronal differentiation. Because of the glioneuronal features of these tumors, the term “subependymal giant cell tumors” (SEGTs) has been suggested by some authors **(16;17)**. This may reflect their postnatal origin from neural progenitors in the subependymal zone **(16).**

In this study, mitosis and/or necrosis were seen in 3 cases and the prognosis of those patients was not different from the rest of the cases. It was also previously observed that occasional presence of mitosis and necrosis as well as endothelial proliferation is not indicative of malignancy progression in these tumors and do not suggest a worse prognosis and clinical follow-up in patients with tumors with these features revealed a lack of aggressive tumor behavior after surgery alone **(10;18-21)**. Even in the presence of these worrisome histological features, these tumors are still considered WHO grade 1 and have excellent prognosis. However, these tumors are more likely confused with high-grade gliomas. The discrepancy between the histological and clinical features should be emphasized. SEGAs that show predominantly spindle ell pattern may mimic gliosarcoma. Pathologists should be aware with these morphological features to avoid overdiagnosis and subsequent unnecessarily excessive treatment of basically low-grade tumors. SEGAs exhibiting distinct anaplastic features that might mimic malignant glioma have been described **(17)**. Grajkowska et al described tumors that show numerous foci of palisading necrosis, microvascular proliferation and high mitotic activity with atypical mitotic figures associated with high Ki67 labelling index (15-20%) and suggested using the term atypical SEGAs for such tumors **(17).** Very rare SEGAs with frank features of malignancy have been recorded in the literature **(22)**

The rare examples of SEGA that recur have not been reported to show malignant transformation **(23)**. Although SEGAs usually have benign nature, rare tumors show massive hemorrhage, rapid growth, and tumor recurrence **(21)**. Sporadic case reports of high-grade glioma in TSC patients are also reported **(5;22)**. The pathological differential diagnosis of SEGAs includes ependymomas, gemistocytic astrocytomas and giant cell glioblastomas

All the patients in this study underwent surgical resection without radiation or chemotherapy. Total surgical resection is the recommended treatment of SEGAs, and usually curative (24). In addition to surgical resection of SEGAs, other treatment options now include medical therapy. Positive results are being described with rapamycin (mTOR inhibitor) in the treatment of SEGA **(25-30).** The effect of rapamycin could be related to its ability to shrink tumor cells or to induce apoptosis **(2;25;26).** SEGAs have been reported to regrow if rapamycin is stopped, raising the possibility that long-term medication may be required to prevent tumor growth **(30)**

In conclusion SEGA should be considered in the differential diagnosis of intraventricular tumor irrespective of the age of the patients or the presence or absence of TSC features. Surgical resection is usually sufficient treatment. The Pathological recognition of these tumors is very important to avoid misdiagnosis and overtreatment. Long term prognosis of patients with SEGA is excellent even in the presence of some worrisome atypical histological features.

Acknowledgment

The authors would like to thank Dr. Wafaey Gomaa (Department of Pathology, KAUH), Dr. Hassan Sayadi and Dr. Hossam Al-Aradati (Department of Pathology, KFSHRC), and Dr. Mohammed Binmahfood (Department of Neuroscience, KFSHRC).

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