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Case Report

Subependymal Giant Cell Astrocytoma (SEGA) in the Absence of Tuberous Sclerosis: A Case Report and Review of Literature

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Abstract

Tuberous Sclerosis, an autosomal dominant disorder, occurs due to an inactivating mutation of TSC1 and TSC2 which blocks mTOR signaling pathway and inhibits cell proliferation. Failure of inhibition of this signal transduction gives rise to hamartomas of different organs of the body. Though SEGAs are usually seen in cases of tuberous sclerosis, few cases without any evidence of tuberous sclerosis are documented. We report a case of a 17- year old boy having subependymal giant cell astrocytoma (SEGA) without any clinical or radiological stigmata of tuberous sclerosis. This patient presented with headache and diminution of vision. MRI brain showed a 32.3 x 30.3 x 38.9 mm tumor in the body of left lateral ventricle obstructing the foramen of Monro causing hydrocephalus. Gross total resection of the tumor was done via middle frontal gyrus approach. Post operatively, the patient's symptom improved. Follow up scan done after 3 months showed no residual tumor.

Keywords: *Central Nervous System (CNS); Subependymal Giant Cell Astrocytoma (SEGA); Tuberous Sclerosis*

Introduction

In the 2016 molecular classification of central nervous system (CNS) tumors, Subependymal Giant Cell Astrocytoma (SEGA) has been placed under the category of pediatric low grade glioma (grade 1 tumor) [1]. These tumors have mixed glial and neuronal components and hence are best classified under mixed glial-neuronal neoplasm. SEGAs are usually associated with an autosomal dominant disease; Tuberous Sclerosis and are invariably found in the walls of the lateral ventricle [2]. The loci for tuberous sclerosis disease are identified on two chromosomes; 9q34 (TSC1) and 16p13 (TSC2) [3]. An 8.6 kilobase transcript of TSC1 encodes a 130 kilodalton protein; hamartin, which heterodimerize with 5.5 kilobase transcript of TSC2- a protein tuberin and acts as a chief negative regulator of mammalian target for rapamycin (mTOR) and inhibits cell growth [4]. Mutation in any of these 2 genes leads to overexpressed signal transduction of mTOR resulting in hamartomas of various organs seen in tuberous sclerosis. Almost all SEGAs are seen in patients of tuberous sclerosis and they invariably have biallelic inactivation of TSC1 or TSC2 genes; consistent with the Knudson's two-hit hypothesis [5]. The first hit is genetically acquired while the second hit is acquired during the lifetime resulting in biallelic loss of tumor suppressor gene and tumorigenesis. However, there are few cases of SEGAs which are found in patients having no clinical or radiological signs of tuberous sclerosis [6].

Case Description

17 yr old boy presented with a dull aching, on and off holocranial headache for 1 yr which was relieved with vomiting. The headache was associated with painless, progressive vision loss of both eyes (R > L) for 6 months and imbalance while walking for 20 days. The patient had no significant personal history of any disease. There was no familial history of any syndromic association in the patient.

The GCS score of the patient on admission was 15/15 with an MMSE score of 30. Cranial nerve examination revealed visual acuity of PL+ with pale optic disc in the right eye and 6/18 with blurred lateral margins of the disc in the left eye. The direct light reflex and smooth pursuit movements were absent on the right side while consensual light reflex was absent on the left. The ocular motility of the right eye of the patient was impaired. Clinical examinations were negative for the hallmark signs of tuberous sclerosis like adenoma sebaceum, shagreen patch, ash-leaf macules, axillary freckling, café-au-lait spots, etc.

Patient underwent MRI brain which revealed a 32.3 * 30.3 * 38.9 mm lesion in the body and frontal horn of left lateral ventricle which was iso to hyperintense on T2 and hypointense on T1 (Figure 1). The lesion showed heterogenous contrast enhancement with slight extension into the 3rd ventricle and frontal horn of right lateral ventricle (Figure 2). The lesion had perilesional edema along with ventriculomegaly. A tentative diagnosis of left intraventricular tumor was made.

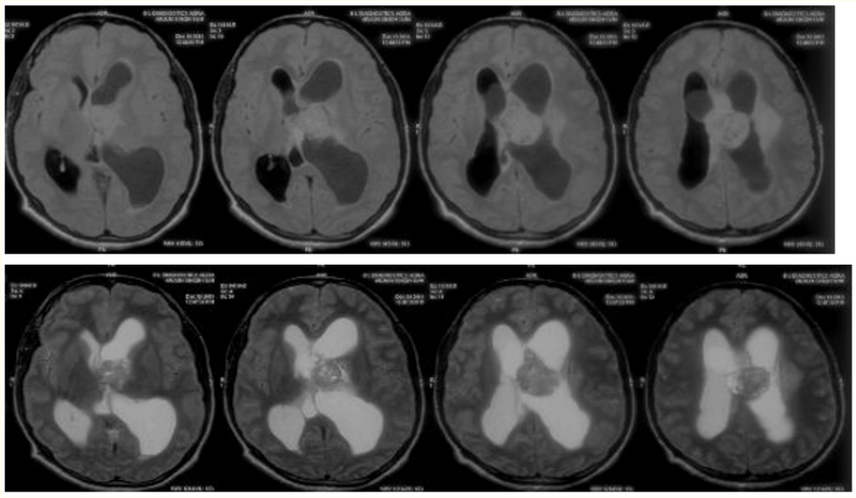

Figure 1: *(a) FLAIR (b) T2 WI showing 32.3*30.3*38.9 mm tumor intraventricular lesion.*

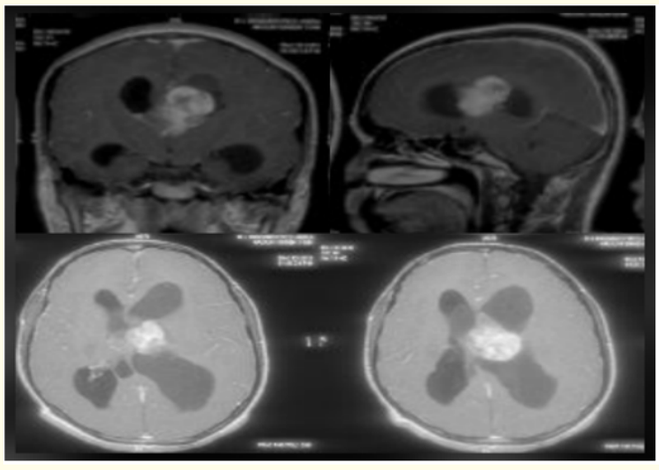

Figure 2: *MRI brain with contrast showing heterogenous uptake of contrast by the tumor.*

The case was operated by the senior author (SB). The tumor was approached via the middle frontal gyrus. The tumor was soft to firm, moderately vascular and variegated in appearance. Intraoperative frozen section was performed which showed the tumor to be astrocytoma. Gross total excision of the tumor was done, preserving the deep cerebral veins. Patient had an uneventful post-operative course. The patient was discharged in a stable condition on the 8th post-operative day.

Histopathological examination

The tumor comprised of sheets of cells having moderately pleomorphic nuclei, conspicuous nucleoli and moderate to abundant eosinophilic cytoplasm in a fibrillary background which confirmed it to be astrocytoma. Many binucleated and multinucleated forms were noted with Rosenthal fibers in the background. No mitosis, necrosis or endothelial proliferation was seen. The tumor was negative for IDH, p53, CD34, NeuN, chromogranin, synaptophysin and positive for GFAP and ATRX. MIB-1 labelling index was 2%.

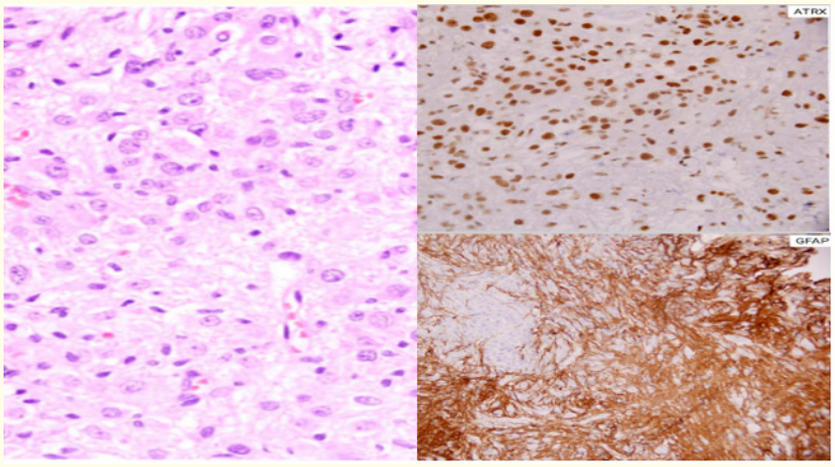

Figure 3: *Histopathological section showing pleomorphic nuclei with eosinophilic cytoplasm of the tumor which is GFAP and ATRX positive.*

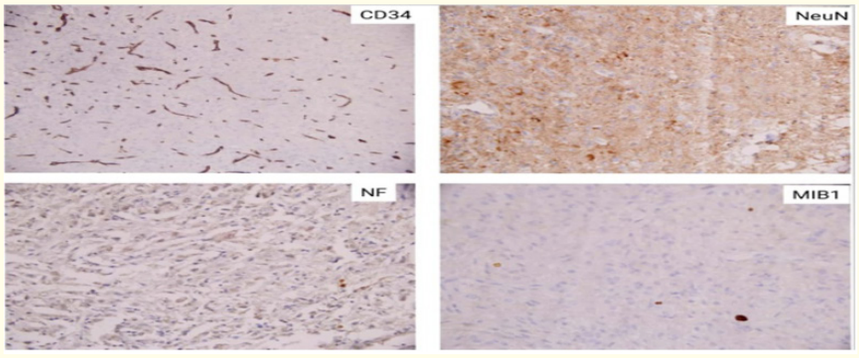

Figure 4: *Tumor tissue showing negative staining for CD34, NeuN and NF with slight positivity for MIB-1.*

Follow up

The patient was doing well at last follow up 3 months after surgery. He was symptomatically better. CEMRI brain was performed which showed no residual/recurrent tumor (Figure 5).

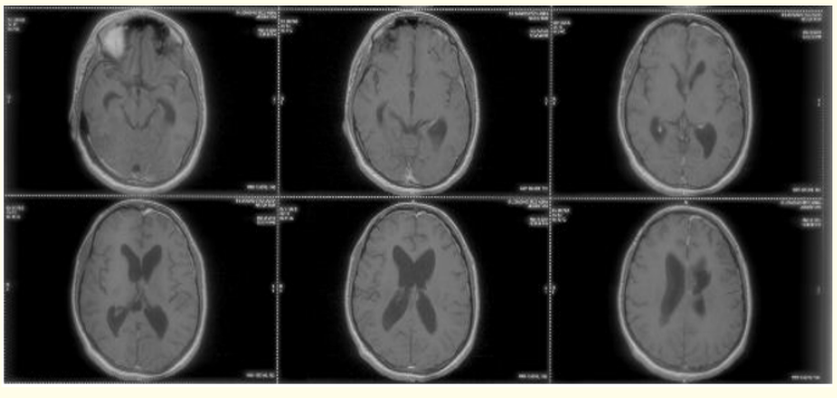

Figure 5: *MRI brain after 2 months showing no recurrence of tumor and resolving hydrocephalus.*

Discussion

Tuberous Sclerosis or Bournville-Pringle disease is a neurocutaneous, multisystem disorder characterized by hamartomas of various organs of the body; namely; brain, heart and kidney [7]. Recent studies by the 2012 International Tuberous Sclerosis Complex Consensus Conference estimates the incidence of this disease to be around 1/6000 to 1/10000 and a prevalence of 1 in 20000 [8]. The disease is characterized by Vogt's triad comprising of seizures, mental retardation and adenoma sebaceum. The hallmark lesion seen in brain in this disease is Subependymal Giant Cell Astrocytoma (SEGA). Approximately 5 - 14% patients of tuberous sclerosis presents with SEGA [9]. Though SEGA is considered to be invariably associated with Tuberous Sclerosis; there are very few cases where isolated SEGA without tuberous sclerosis is reported (Table 1). There are 2 theories explaining the isolated development of SEGA without any features of Tuberous Sclerosis:

Authors	Publication (Years)	Total cases of SEGA	Isolated SEGA without TSC	Treatment	Follow Up
Halmagyi [12]	1979	1	1	Total Surgical Resection	Relapse after 12 and 45 yrs
Taraszewska [14]	1997	3	2	Total Surgical Resection in 1 case and Partial Resection in other2 cases	Data Not Available
Kashiwagi [11]	2000	1	1	Total Surgical Resection	No recurrence after 28 months of surgery
Yamamoto [15]	2002	1	1	Partial Surgical Resection	Relapse after 1 yr
Sharma [16]	2004	23	14	Total Surgical Resection in 5 and Partial in 9	2 recurrence- in one patient after 2 yr and in other after 22 yr of surgery
Kim [17]	2004	6	1	Total Surgical Excision	No recurrence even after 18 months
Ichikawa [18]	2005	1	1	Total Surgical Excision	No Data
Stavrinou [19]	2008	1	1	Total Surgical Excision	No Data
Takei [20]	2009	1	1	Post-mortem finding	-
Beaumont [21]	2015	1	1	Total Surgical Resection	No Data
Konakondla [22]	2016	1	1	Total Surgical Resection	No recurrence after 9 months of surgery
Elousrouti [23]	2016	1	1	Total Surgical Resection	No Data
Apalla [24]	2016	1	1	mTOR inhibitor- Everolimus	No recurrence after 3 yrs
Kim [25]	2016	1	1	Total Surgical Resection	No recurrence after 2 yrs
Azam [26]	2017	1	1	Definitive Radiotherapy	No recurrence after 1 yr
Present Study	2019	1	1	Near Total Surgical Resection	No recurrence after 2 months

Table 1: *Isolated cases of SEGA documented without evidence of tuberous sclerosis.*

1. Isolated SEGA could develop due to somatic mosaicism of tissues resulting in cell growth and proliferation [10].
2. Others believe it to be due to both loss of heterozygosity and biallelic mutation of TSC2 gene [11].

Most cases of SEGAs present clinically with features of raised ICP, headache, altered sensorium, seizures [23]. The ICP is raised in most cases due to obstruction of foramen of Monroe as the tumor lies in close relation to it in the body of the ventricle. Radiologically, the lesion can be well delineated as a well circumscribed mass in the body of ventricle near the foramen of Monroe which is hypo to isointense on T1 and iso to hyperintense on T2; sometimes also presenting with calcifications and cysts [26]. The lesion shows strong but heterogenous uptake of contrast [27].

Histologically, SEGA appear as large elongated to polygonal cells which resemble like astrocytes composed of finely granular, eosinophilic cytoplasm with large round nucleus and prominent nucleoli. Perivascular pseudorosette formation are commonly seen in this tumor along with infiltration of lymphocytes and mast cell in the tumor tissue [28]. Immunohistochemically, these tumors are usually positive for GFAP and S100 and negative for HMB45 unlike other lesions associated with tuberous sclerosis.

Surgical excision is the treatment of choice along with radiotherapy. In cases where complete surgical excision is possible, the prognosis is good. With the advent of new molecular pharmacology, targeted therapy against mammalian target for rapamycin (mTOR) has developed. Everolimus, an mTOR inhibitor, has shown a significant reduction in tumor size of 75% of patients treated with it when used in concentrations between 5 - 10 ng/ml [29]. The major drawback of targeted therapy is its side-effects and relapse of tumor following its discontinuation. In our case, the patient was managed by surgical excision of the tumor and followed in OPD to see any recurrence of tumor. An MRI brain following 2 months of surgery showed no recurrence of tumor.

Conclusion

Subependymal Giant Cell Astrocytoma (SEGA) is rare tumor of CNS but it should be considered in the differential diagnosis of any mass around the foramen of Monro even in the absence of other clinico-radiological features of tuberous sclerosis. Early surgical intervention with complete tumor excision improve the patient's prognosis significantly.

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Volume 8 Issue 7 July 2019