Case Report

A solitary extraventricular subependymal giant cell astrocytoma in the absence of tuberous sclerosis ☆

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ABSTRACT

Subependymal giant cell astrocytomas (SEGAs) are the most common intracranial tumors in Tuberous Sclerosis Complex (TSC). Very few cases of solitary SEGA without a diagnosis of TSC have been described. Most of these previously reported solitary SEGAs were located near the caudothalamic groove or in close proximity to the lateral ventricles. Here, we describe a unique case of solitary extraventricular SEGA in a 17-year-old boy who presented with new-onset seizures in the absence of the clinical and genetic diagnosis of TSC. This extraventricular SEGA was involving white matter and cortex of the occipital lobe and was predominantly hypointense on T1 and T2-weighted images with a markedly hypointense signal on susceptibility-weighted images likely secondary to dense internal calcifications. Solitary SEGA can occur in the extraventricular location in patients without TSC and should be included in the differential diagnosis of a densely calcified supratentorial intra-axial tumor in children, especially during the second decade of life.

Introduction

Subependymal giant cell astrocytomas (SEGAs) are the World Health Organization grade I tumors, which are the most common intracranial tumors in Tuberous Sclerosis Complex (TSC). They are seen in 10%-20 % of patients with TSC and are a major cause of morbidity and mortality in TSC patients during pediatric age [1]. SEGAs are slow growing tumors that are most commonly located at the caudothalamic groove adjacent to the foramen of Monro [1–3]. They are most commonly seen between 8 and 18 years of age [2]. Although SEGAs are most commonly seen in patients with TSC and is one of the major criteria for the diagnosis of TSC, very few cases of solitary SEGA without a clinical and genetic diagnosis of TSC have been described in the literature [4]. Most of the previously reported cases of solitary SEGA were located near the foramen of Monro or in close proximity to the subependymal region of
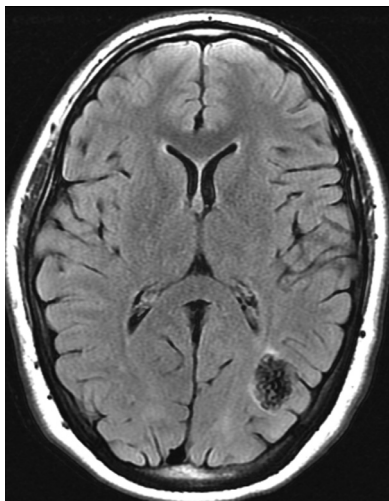

Fig. 1 – Axial T2-FLAIR weighted images shows a 1.8 x 2.4 x 2.2 cm predominantly hypointense mass involving the subcortical and deep white matter and adjacent cortex of the left occipital lobe with mild surrounding T2/FLAIR signal, likely representing perilesional edema.
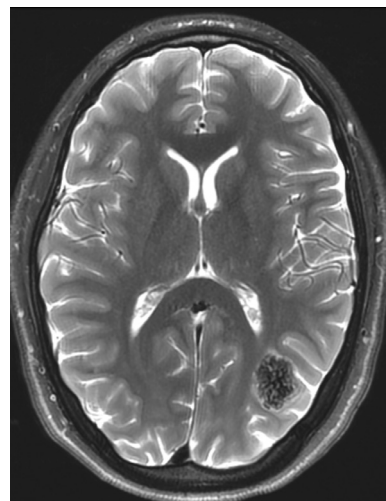

Fig. 2 – Axial T2-weighted image reveals a heterogeneous, predominantly hypointense lesion in the left occipital lobe with internal linear T2 hyperintensities.

the lateral ventricles. We describe this unique case of extra-ventricular solitary SEGA in the absence of genetic and clinical features of TSC. The tumor was involving subcortical and deep white matter and the adjacent cerebral cortex of the occipital lobe in our case.

Case report

A 17-year-old boy presented with new-onset seizures. The seizure semiology was a combination of focal motor seizures involving the right upper and lower extremities and partial complex seizures with secondary generalization. The patient was otherwise healthy, had no other symptoms or comorbidities. Laboratories including a CBC, TSH, and complete metabolic panel were normal. There was no family history of seizures. The clinical examination was normal without focal neurological deficits. EEG was normal in the awake and drowsy state and during photic stimulation and hyperventilation. Magnetic resonance imaging showed a 1.8 × 2.4 × 2.2 cm mass involving the subcortical and deep white matter and adjacent cortex of the left occipital lobe with mild surrounding T2/FLAIR signal, likely representing perilesional edema (Fig. 1). The lesion was heterogeneous, predominantly hypointense on T2-weighted images with internal linear T2 hyperintensities (Fig. 2). It showed peripheral mild hyperintense signal and central hypointense signal on T1-weighted images (Fig. 3). It was markedly hypointense on susceptibility-weighted images (Fig. 4). It showed a few small central areas of enhancement on T1-weighted contrast-enhanced images (Figs. 5 and 6). The remainder of the tumor did not show significant enhancement. No enlarged feeding arteries or draining veins were seen, to suggest an AVM. Hence, the differential diagnosis on MRI in-
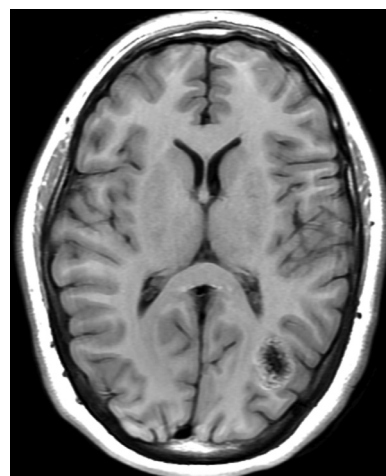

Fig. 3 – Axial T1-weighted image shows a heterogeneous left occipital lesion with peripheral mild hyperintense signal and central hypointense signal.

cluded cavernous malformation, calcified low-grade tumor, and dystrophic cerebral calcification.

The patient was placed on Keppra 750 mg twice daily. He underwent left parieto-occipital craniotomy aiming for the complete resection of the lesion and to increase the chance for resolving the newly diagnosed epilepsy. Pathology slides (Fig. 7) of the resected tumor demonstrated a 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. Immunostains showed tumor cells positive for Olig-2, most of them were positive for GFAP and CD34, and negative for synaptophysin, p53, IDH-1, neurofilament protein, and Erg. There was an intact expression of ATRX and H3K27me3. The Mib-1 was very low (0%-1%). Immunostains for CD34 and Erg highlighted blood
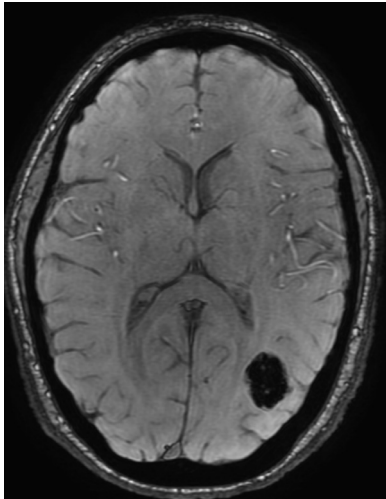
Fig. 4 – Axial susceptibility-weighted image demonstrates markedly hypointense signal within the lesion.
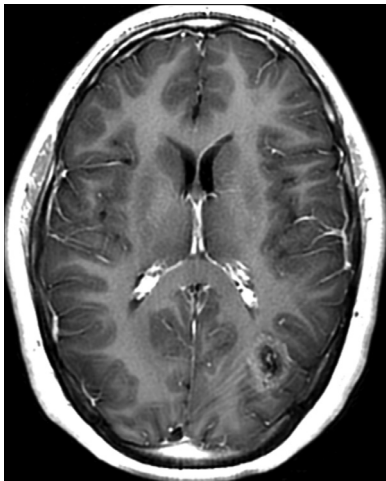

Fig. 5 – Axial T1-weighted contrast-enhanced image shows predominantly non-enhancing left occipital tumor with a few small central areas of enhancement.
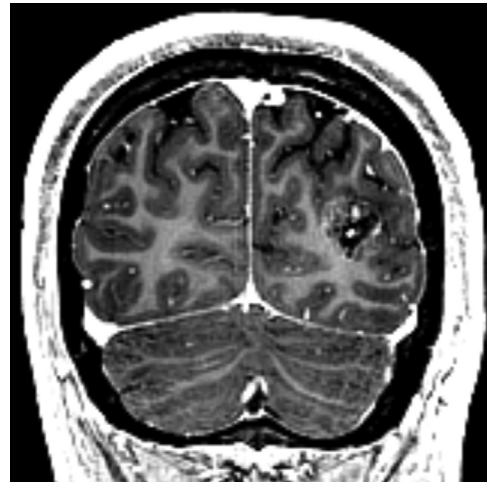

Fig. 6 – Coronal T1-weighted contrast-enhanced image shows predominantly non-enhancing left occipital tumor with a few small central areas of enhancement.

vessels. These findings were consistent with the diagnosis of subependymal giant cells astrocytoma.

A detailed imaging and clinical evaluation including renal ultrasonography, echocardiography, and ophthalmological and dermatological examination did not show other features of TSC. DNA sequencing of the TSC1 and TSC2 genes using peripheral blood did not show any mutations of TSC. There was no family history of TSC. The patient did well after surgery and has been seizure free for 6 months after surgery without any medications. MRI brain done 6 months after surgery did not show the residual or recurrent tumor.

Discussion

Subependymal giant cell astrocytoma (SEGA) is a World Health Organization grade I tumor of glioneuronal origin, which is

most commonly located at the caudothalamic groove adjacent to the foramen of Monro.[1] As SEGAs are distinct from astrocytomas, several authors have suggested using the term "subependymal giant cell tumor" instead.[1,3] SEGAs can present with increased intracranial pressure due to obstruction of the foramen of Monro. Other potential presenting symptoms include seizures and focal neurologic deficits. SEGAs are one of the major diagnostic criteria for tuberous sclerosis (TSC) and their incidence in TSC varies from 10% to 20%. [1] SEGA is the primary cause of morbidity and mortality in pediatric TSC patients.[1] They are most commonly seen between 8 and 18 years of age [2]. The new SEGA very rarely arises after 20-25 years of age.[1]

TSC is an autosomal dominant neurocutaneous syndrome characterized by the development of hamartomatous lesions in multiple organs including the brain, kidney, liver, skin, heart, and lung and neuronal migration abnormalities. The most common genetic mutations in TSC involve the two tumor suppressor genes: TSC1 (located on 9q34) or TSC2 (located on 16p13). SEGAs results from inactivation of the tumor suppressor genes TSC1 and/or TSC2 gene, which encode the proteins tuberin and hamartin, respectively.[1,4]

Very rarely SEGAs can occur outside the typical location of the caudothalamic groove in TSC patients including fornix, hypothalamus, basal ganglia, and genu of the internal capsule.[1] Most of these cases are still located in the vicinity of the lateral ventricles. Although SEGA is the major criterion for the diagnosis of TSC, very few cases of solitary SEGA have been reported in the absence of clinical and genetic features of TSC.[4] Most of these cases of previously reported solitary SEGA were seen at the caudothalamic groove or in close proximity to the subependymal region of the lateral ventricles.[4–8] Also, genetic analysis for TSC was performed in only a few of these reported cases.[4,8] Beaumont et al. reported a case of SEGA in the absence of TSC in a 14-year-old boy, which was located in the region of the foramen of Monro.[4] Konakondla et al. reported a case of SEGA in a 25-year-old female with genetically
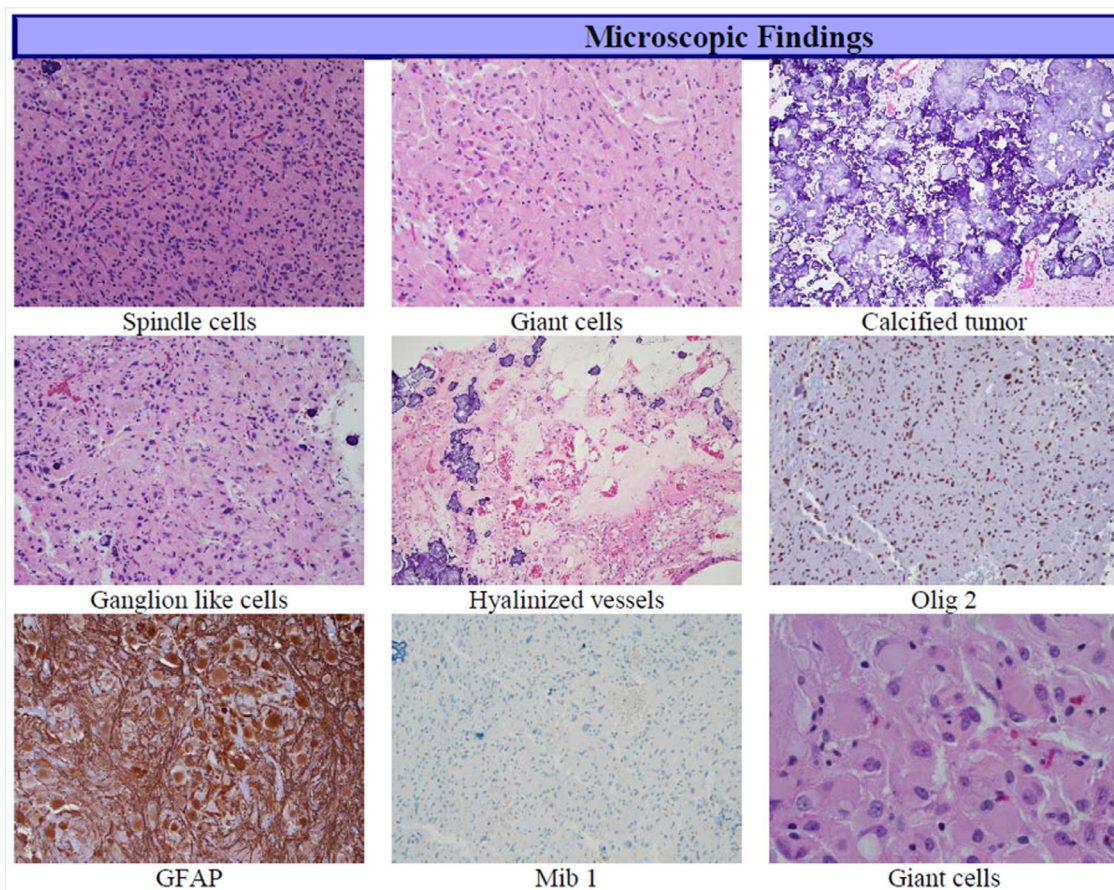
Fig. 7 – Photomicrographs show tumor composed of spindle cells (picture labeled – spindle cells, hematoxylin and eosin, original magnification 200 x), ganglion-like cells with basophilic cytoplasmic Nissl substance (picture labeled – ganglion like cells, hematoxylin and eosin, original magnification 200 x) and large giant cells like gemistocyte with moderate eosinophilic cytoplasm and peripherally displaced nuclei (picture labeled giant cells low and high power, hematoxylin and eosin, original magnification 200 x and 400 x, respectively); (picture labeled calcified tumor, hematoxylin and eosin, original magnification 200 x) and (picture labeled hyalinized vessels, hematoxylin and eosin, original magnification 200 x) show calcified area and hyalinized vessels, respectively. The immunostains show tumor is positive for glial fibrillary acidic protein (picture labeled GFAP, anti-GFAP, original magnification 200 x) and Olig-2 (picture labeled olig 2, anti-olig 2, original magnification 200 x) and show low Mib-1 labeling (picture labeled Mib-1, anti-Mib-1, original magnification 200 x). These imaging findings are consistent with SEGA.

negative TSC, in which the tumor was located in the left lateral ventricle causing obstructive hydrocephalus.[8] Our unique case of solitary SEGA was extraventricular in location and was involving the subcortical and deep white matter and cortex of the occipital lobe. Our patient did not have clinical features and genetic evidence of TSC. It should be noted that genetic testing is expected to detect at least 85% of pathogenic TSC 1/2 mutations.[2–4] It is possible that genetic analysis failed to detect novel single-base variants for TSC in our case. Our clinical team will continue to do clinical and imaging follow-up to exclude this rare possibility.

At the 2012 Washington Consensus Conference, SEGA in the setting of TSC is defined as the lesion at the caudothalamic groove with either size of more than 1 cm in any direction or a subependymal lesion at any location that has shown serial growth on consecutive imaging regardless of size.[1] On noncontrast CT images, SEGAs are usually isodense to hyperdense and often show calcifications.[3] On MRI, SEGAs are usually hypointense to isointense on T1-weighted images and hyperintense to hypointense on T2-weighted images.[3] Avid contrast enhancement is seen, particularly in noncalcified lesions.[1,3] In our case, SEGA was predominantly hypointense on T1 and T2-weighted images and did not show any significant contrast enhancement, probably related to dense internal calcification. The SEGA reported by Beaumont et al. was avidly enhancing mixed cystic and solid mass at the foramen of Monro, which showed an isointense signal to the brain on T1-weighted and heterogeneous signal on T2-weighted images with moderate perilesional edema.[4] Konakondla et al. reported a case of SEGA located at the foramen of Monro, which was homogeneously enhancing mass with eccentric calcification and resultant obstructive hydrocephalus.[8] On MR spectroscopy, SEGAs show high choline/creatine and low N-acetylaspartate /creatine ratios.[2] SEGAs typically show slow growth with a

growth rate of less than 0.5 cm/year in the longest dimension.[3] Differential considerations for calcified intra-axial supratentorial pediatric lesions include cavernous malformation, ganglioglioma/gangliocytoma, ependymoma, oligodendroglioma, and primitive neuroectodermal tumor.

For SEGAs with interval growth or if associated with obstructive hydrocephalus, surgical resection is the standard of care.[3] Medical treatment with mTOR inhibitors have a role in cases where surgery is contraindicated, or in recurrent lesions where scarring and distorted anatomy may increase complications from surgical intervention.[3] For the best management, SEGA patients should be discussed with a multidisciplinary team of pediatric neurologists/oncologists and neurosurgeons to consider the pros and cons of the respective treatment modality before finalizing an individualized treatment.[1]

In conclusion, solitary SEGA can occur in an extraventricular location in the absence of clinical and genetic diagnosis of TSC. Solitary SEGA should be included in the differential diagnosis of densely calcified supratentorial intra-axial tumor involving white matter and adjacent cortex and showing a predominantly hypointense signal on T2-weighted images in the pediatric patients, especially during the second decade of life.

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