Complete Excision of a Rare Case of Subependymal Giant Cell Astrocytoma (SEGA) in Tuberous Sclerosis Complex

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Case Summary

Subependymal giant cell astrocytoma is a rare tumor that occurs in the walls of the lateral ventricles, foramen of Monro, and less frequently, in the third ventricle. It is one of the intracranial lesions found in tuberous sclerosis complex (TSC) — a rare multisystem genetic disease. We present a rare case of an adult Filipino with cutaneous signs of TSC, who initially presented with signs of increased intracranial pressure. The patient underwent right frontal craniotomy, endoport-assisted excision of the tumor with insertion of a ventriculoperitoneal (VP) shunt. Histopathology was consistent with a subependymal giant-cell astrocytoma WHO grade 1. The general status of the patient improved thereafter – there was the relief of headache and improvement in vision and gross hearing. Subependymal giant cell astrocytoma is a rare tumor of the central nervous system especially in adults, whose diagnosis is based on clinical, radiological, and histological, and immunohistochemical stains. It should be included in the differential diagnosis of a mass near the foramen of Monro. Given the hereditary nature of the disease, genetic counseling is essential when encountering patients with this condition.

Keywords: subependymal giant cell astrocytoma, tuberous sclerosis complex, Filipino, adult, case report, endoport-assisted excision

INTRODUCTION

Tuberous sclerosis complex (TSC) is a rare autosomal dominant inherited neurocutaneous syndrome affecting multiple organs of the body. Globally, the incidence is approximately 1 in 6,000-10,000 live births. In the Asia-Pacific, there are few epidemiological data.[1] Subependymal giant cell astrocytoma (SEGA) is an even more rare clinically benign tumor usually associated with tuberous sclerosis complex (TSC) occurring in about 5-15% of people with TSC. This lesion is included in the 2012 International Tuberous Sclerosis Complex Consensus Group as a major feature (which includes subependymal nodules, cortical tubers, retinal astrocytoma, and SEGA).[2]

SEGA usually arises in the walls of the lateral ventricles, foramen of Monro, and occasionally in the third ventricle. The prevalence rate of TSC in patients with SEGA ranges from 5% to 20%. Solitary SEGAs in the absence of TSC-related lesions have also been reported.[3-6] Most commonly, SEGA occurs in the first two decades of life. Therefore, it is quite uncommon for patients to present in adult life. It may present with neurological symptoms secondary to obstructive hydrocephalus and increased intracranial pressure. We present a rare case of SEGA in an adult Filipino male who presented primarily with symptoms of increased intracranial pressure but with syndromic neurocutaneous features. We also describe the radiological, histological, and post-operative outcomes for SEGA.

CASE REPORT

R.P., a 29-year-old male, single, right-handed, working as an automobile technician overseas with an unremarkable medical and familial history presented with a chronic progressive holocranial headache in the last quarter of 2017. It was described as throbbing, non-radiating intermittently becoming moderate to severe headache which was worse in the morning upon awakening. Exertion and lifting of heavy objects also aggravated the symptom. As a result, the patient preferred to stay mostly in bed. During that time, there were no other accompanying symptoms such as dizziness, vomiting, or loss of consciousness. In the following months, he began to experience decreased hearing on both ears, more on the right associated with tinnitus and fullness. In the interim, there was a progressive hearing loss on both ears which led to him communicate by writing. He did not complain of fever, ear pain, or ear discharge. He then sought consult with an otorhinolaryngologist. Pure tone audiometry was done and he was found to have severe hearing loss bilaterally. He was advised to use a hearing aid.

In the following year, there was worsening of headache and hearing loss resulting in the patient's inability to communicate effectively. This prompted him to resign from work and go back to the Philippines. Upon return,

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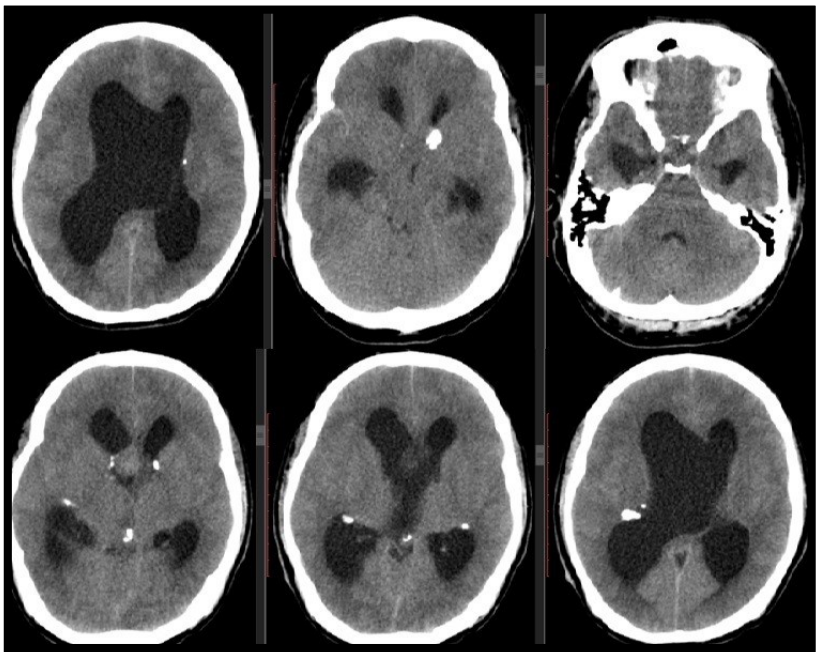

Figure 1. *Plain and contrast-enhanced cranial CT scan in axial view*. There is a homogenously enhancing intraventricular mass measuring 1.3 x 1.5 x 1.4 cm (CC x W x AP) noted just above the third ventricle, more on the right. The lateral ventricles were dilated. There is no dilatation of the third and fourth ventricles. Multiple calcific (hyperintense) subependymal nodules are evident.

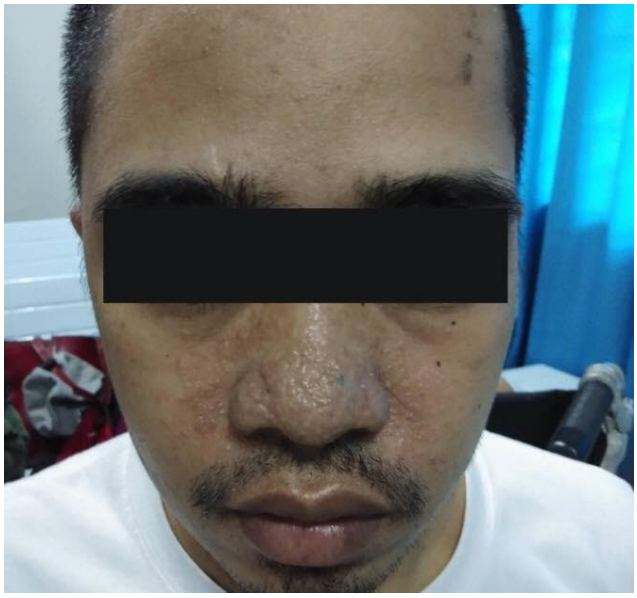

Figure 2. *Photograph of the patients's skin on the face*. There are multiple ill to well-defined erythematous papules coalescing to plaques over the nose and bilateral malar area and multiple well-defined flesh-colored nodules with slightly hyperkeratotic surface on the forehead.

he started to experience blurring of vision on the right eye which progressed bilaterally in four months. He visited an optometrist who assessed him as having astigmatism. He consulted an ophthalmologist later on. During this time, there was a total loss of vision on the right eye while visual acuity on the left was found to be 20/100. During the consultation, he had an episode of vomiting. There was a stiffening of all extremities with upward rolling of eyes lasting for approximately two minutes with a loss of consciousness. A cranial computed tomography (CT) scan was immediately done (*Figure 1*). There is a homogenously enhancing intraventricular mass seen just above the third ventricle, more on the right. The lateral ventricles were dilated and multiple calcific subependymal nodules are found. The seizure episodes recurred with similar semiology. There was also progressive worsening of the headache prompting a consult at the emergency room. On general examination, he was conscious, coherent, oriented but could barely hear spoken voice hence questions asked had to be written. On examination of the skin, there are multiple ill to well-defined erythematous papules coalescing to plaques over the nose and bilateral malar area. On the forehead, multiple well-defined flesh-colored nodules with a slightly hyperkeratotic surface are also seen (*Figure 2*). On neurologic examination, there was no light perception on the right eye with blurred vision (20/100) on the left. Fundoscopy revealed optic atrophy of both eyes. He also had impaired gross hearing bilaterally (no lateralization on Weber test; Rinne test revealed air conduction (AC) is greater than bone conduction (BC) on both ears implying a sensorineural hearing loss which was confirmed on pure tone audiometry. There were no other cranial nerve, sensory, motor, and cerebellar signs elicited. Pathologic reflexes and meningeal signs were likewise absent.

Later, a cranial MRI with contrast was done showing the contrast-enhancing mass at the Foramen of Monro, obstructing cerebrospinal fluid (CSF) flow. Subependymal hamartomas, radial band signs, and cortical tuber, specifically seen in tuberous sclerosis,

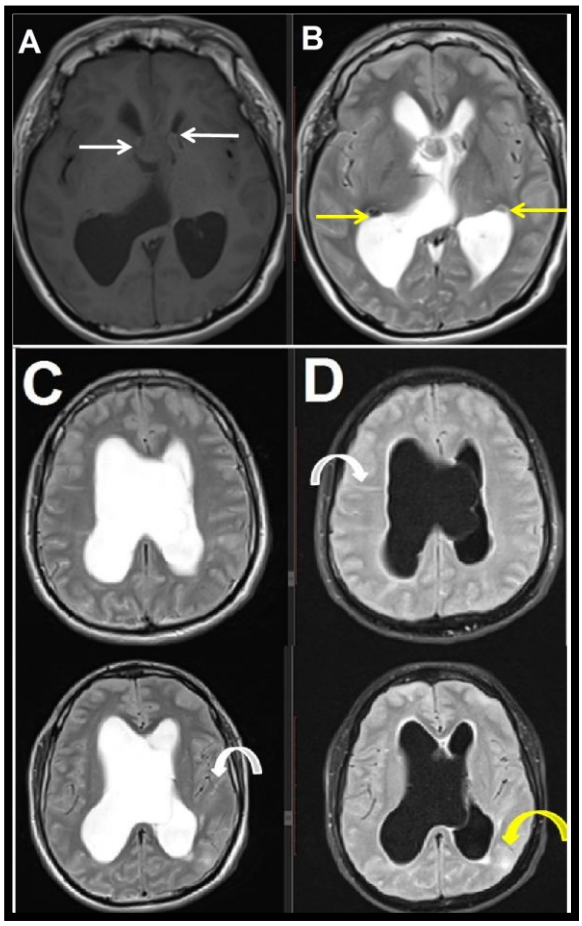

Figure 3. *Cranial MRI, T1 (A) and T2 (B).* There are two isointense intraventricular masses (*white arrows*) noted in the Foramen of Monro, largest of which is noted in the right side measuring 1.3 x 1.5 x 1.4 cm (CC x W x AP) and the other measuring 1.1 cm in widest dimension. The bilateral ventricles are dilated. There are small (approximately < 1 cm), irregular nodules (*yellow arrows*) along the ventricles. These nodules demonstrate variable signal likely representing subependymal hamartomas (nodules) seen in TSC. On T2 (C) and FLAIR (D) sequences, there are linear bands radiating from the periventricular white matter to the subcortical region (*an example is shown by the white curved arrows*) likely representing radial migration bands which are thought to be specific for tuberous sclerosis. On the left posterior parietal region, there is a wedge-shaped high-signal focus on FLAIR likely representing a cortical tuber (*yellow curved arrow*).

were also observed.[7-9] These findings are discussed in detail in *Figure 3*, A-D.

On a background of an intraventricular mass in association with syndromic neurocutaneous findings and particular radiological features, the approach that we took in the diagnosis and management of this case was to investigate the personal and family history of the patient, perform thorough physical and clinical examination, and identify radiological and histological findings helpful in coming up with the diagnosis. Molecular diagnosis utilizing DNA-based testing to identify mutations in the *TSC1* and *TSC2* genes could have been the definite diagnostic examination however it is not routinely available yet. A multidisciplinary team in a tertiary public hospital consisting of specialists from Neurology, Neurosurgery, Ophthalmology, Otorhinolaryngology, Dermatology, Internal Medicine, Radiology, and Pathology were on board in the management and follow-up of this case. Among other clinical findings are secondary bilateral optic atrophy and bilateral sensorineural hearing loss as a result of the long-standing increased intracranial pressure. Skin findings were multiple flesh-colored papules with a slightly hyperkeratotic surface on the nose, malar area, and forehead likely representing facial angiofibromas. Electrocardiogram (ECG) was also done as a baseline study and revealed no cardiac arrhythmia. To address the more immediate symptoms, he was started on Valproic acid 500 mg twice daily to control the seizure. For symptomatic SEGA, total surgical resection can be curative hence it should be offered without debate.[10] To decompress the increased intracranial pressure, decrease disease burden and obtain tissue diagnosis, he underwent right frontal craniotomy, endoport-assisted excision of the tumor, and right ventriculoperitoneal shunt insertion. Intraoperatively, there was a subependymal tumor which is pink-gray, moderately vascular, obstructing the Foramen of Monro. Histopathology was consistent with a subependymal giant-cell astrocytoma WHO grade 1 (*Figure 4*). The general status of the patient improved after the surgery. Follow-up neuroimaging revealed no residual tumor and a significant decrease in the size of the ventricles (*Figure 5*). The patient followed up at the outpatient department with relief of headache, improved vision (now able to read from his cellphone 12 inches apart). Prior to excision and VP shunting, the patient had severe hearing loss. On follow-up after three months, he claimed that he is already able to hear loud voice. His general well-being improved after the intervention. Ideally, patients diagnosed with tuberous sclerosis undergo genetic testing for mutation and polymorphism of TSC1 and TSC2 genes.[11]

DISCUSSION

SEGA is a rare tumor of the central nervous system with mixed glioneuronal features, most frequently seen in the setting of TSC. TSC results from mutations in one of two genes, TSC1 on chromosome 9 and TSC2 on chromosome 16, that encode distinct proteins, hamartin, and tuberin, respectively.[12] From the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference, it was emphasized that the diagnosis of TSC is highly variable in clinical presentation and that disease manifestations continue to develop and emerge over the lifetime of an affected individual.

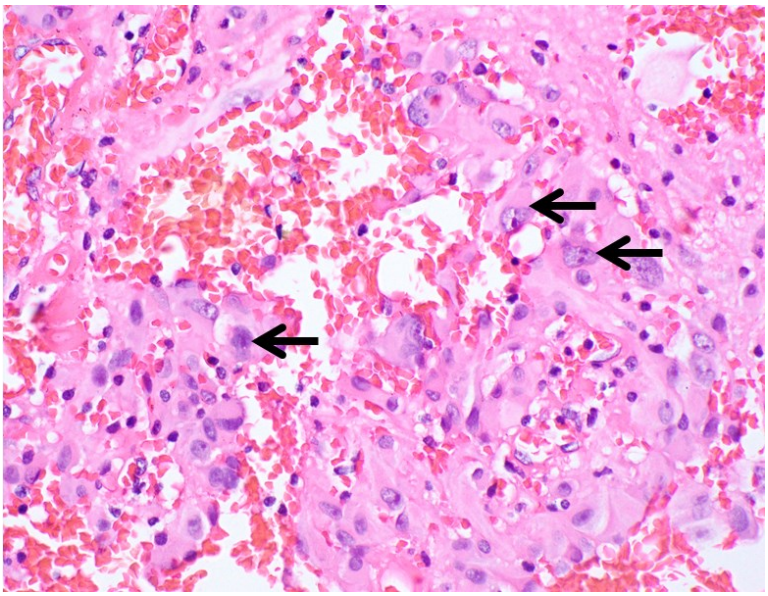

Figure 4. *Histopathology of the intraventricular tumor* excised from R.P. illustrating dysmorphic "giant" glioneuronal cells (black arrows) with abundant eosinophilic cytoplasm resting on a fibrillary background. Lymphocytic infiltrates are also common. (H&E)

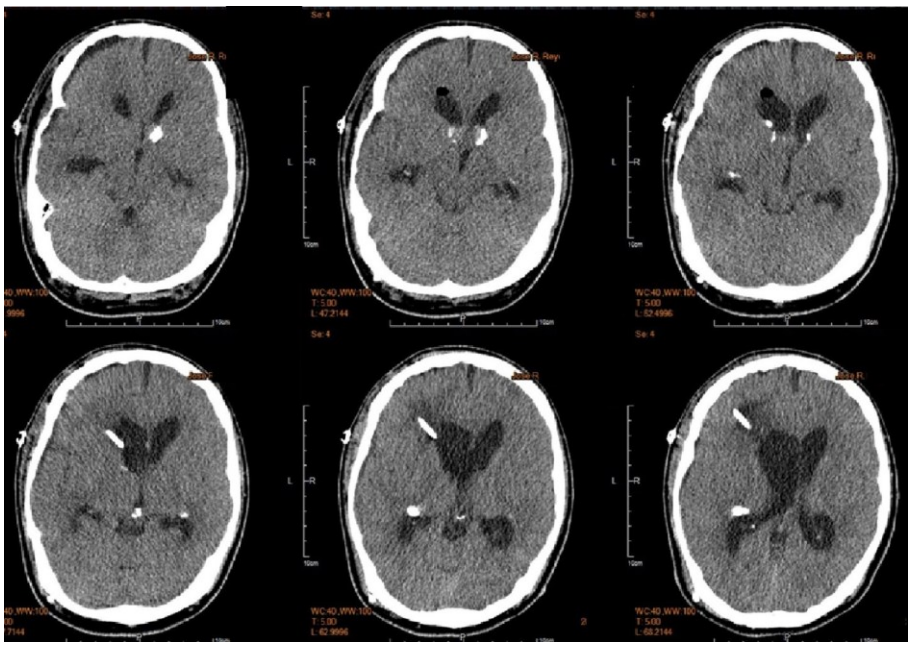

Figure 5. *Post-operative cranial CT Scan, axial;*. There is no residual mass as previously identified with marked decrease in the size of the ventricles. A shunt is in place with tip at the right lateral ventricle.

Genetic, clinical, radiological, and histological aspects of the disease are highly valuable in the diagnosis. These features are classified into major and minor features. Reference to the diagnostic criteria may be found in the consensus of the congress published in 2013.13 "Definite TSC" consists of at least two major features or one major feature plus two minor features satisfied. "Possible TSC" requires at least either one major feature or >2 minor features. Present in this patient are three major central nervous system findings consisting of (1) cortical dysplasia in the form of tubers (2) subependymal nodules (3) SEGA. Cutaneously, the patient's numerous facial angiofibroma fulfills the fourth major criteria in this case making it a definite diagnosis of TSC.

The incidence of Subependymal Giant Cell Astrocytoma in Tuberous Sclerosis (TS) which causes increased intracranial pressure (ICP) is even relatively rare varying from 5% to 14%, and may also be detected prenatally or at birth, although they are much more likely to arise during childhood or adolescence, and it would be unusual for one to occur after the age of 20 years if not previously present. In the Philippines, published reports on the prevalence of TSC are limited. TSC usually manifests during childhood and adolescence; neonatal cases have also been reported.[5,13] This patient only presented with signs of increased ICP at 29 years. He also experienced blindness which is an unusual reason for a consult. In a study by Pascual-Castroviejo et al. three patients presented with blindness and increased intracranial pressure. These children were slowly losing vision without their families being aware. They had not complained of a lack of vision until a headache appeared and papillary edema was found already. In addition, sensorineural hearing loss as a result of increased ICP is rare. This patient had sensorineural hearing loss. A prospective study of 138 patients with elevated ICP from a variety of etiologies and found that 81.5% had some degree of

hearing impairment. They hypothesize that increased ICP is transmitted to the perilymph by the cochlear aqueduct, resulting in relative perilymphatic hydrops.[14]

Subependymal nodules may undergo transformation into SEGAs, which are found in 10% of patients and may lead to progressive hydrocephalus and death. Radical and early surgery is the treatment of choice; it is associated with a better prognosis [15] On the other hand, skin manifestations of TSC, particularly angiofibromas, may be psychologically distressing for some patients. Laser treatment or electrosurgery can be used to remove angiofibromas.

It is important to note that a patient with SEGA and who underwent VP shunt should be followed closely for hydrocephalus before and after surgical treatment is performed. Sudden death may be due to cardiac arrhythmia, epilepsy, and intratumoral hemorrhage with additional complications including cardiac outflow obstruction, obstructive hydrocephalus, aneurysm rupture, and spontaneous pneumothorax. In this patient, surgical resection was successful and there was no complication post-operatively. There was also relief of headache and improvement of vision and hearing.

CONCLUSION

Subependymal giant cell astrocytoma is a rare tumor of the central nervous system whose diagnosis is based on genetic, clinical, radiological, histological and immunohistochemical features. It should be included in the differential diagnosis of a mass near the foramen of Monro. Early recognition of the manifestations of TSC is necessary so a diagnosis may be established and prompt surveillance be done to prevent debilitating consequences such as hydrocephalus and seizure. Given the hereditary nature of the disease, it is prudent to perform genetic testing and counseling in these patients, which is a limitation of this study in the local setting.

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