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CASE REPORT Open Access

Subependymal giant cell astrocytoma as presentation of tuberous sclerosis: a case report

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Abstract

Background A case of tuberous sclerosis patient on long-term follow-up is reported here.

Case presentation A 22-year-old female patient with epilepsy was diagnosed with tuberous sclerosis at the age of 12 years. At that time, a small subependymal giant cell astrocytoma has been detected along with the other signs of the disease. But the patient was not symptomatic of the intracranial lesion at that time. So, she was kept under follow-up with treatment for the epilepsy. Within 10 years, the lesion gradually enlarged and caused symptoms and the tumour had to be resected at the age of 22 years of age.

Conclusions Subependymal giant cell astrocytoma is very slow-growing low-grade tumour. If small and asymptomatic at the time of the initial diagnosis, resection is not advised. The patient should be kept under close follow-up.

Keywords Ash leaf spot, Cortical tubers, Confetti lesions, Subependymal giant cell astrocytoma, Shagreen patch, Tuberous sclerosis

Background

Subependymal giant cell astrocytoma (SEGA) is a low-grade, slow-growing tumour usually arising in the wall of lateral ventricle. Majority are sporadic due to somatic mutation. The incidence rate of SEGA among patients with confirmed tuberous sclerosis is 5–15% [1] and is one of the major diagnostic criteria of the condition. It is the most common CNS neoplasm in patients with tuberous sclerosis (TS/TSC). Hereditary TS is transmitted as an autosomal dominant condition, due to germline mutation, with variable penetrance and expressivity. Mutation occurs in either TSC1 gene located on chromosome 9q34 which encodes for the protein hamartin or TSC2 gene located on chromosome 16p13.3 which encodes for tuberin or in both genes. The role of these genes consists in the regulation of cellular growth through the phosphatidylinositol 3-kinase signalling pathway, inhibiting the mammalian target of rapamycin (mTOR) [2]. Hamartin and tuberin forms a heterodimer and suppresses the cell cycle. In tuberous sclerosis patients, changes in these proteins lead to a permanent activation of the mTOR pathway and therefore to the formation of hamartomas in multiple organs [3].

Early diagnosis of TS is important to prevent serious complications due to organ dysfunction. Here, we are presenting a case of SEGA in a patient with clinicopathological criteria fulfilling a definitive diagnosis of TS.

Case report

A 22-year-old female patient was presented with gradually progressive blurring of vision for 1 year and headache, vomiting and giddiness in the past 4 months that were aggravated since last 1 month. At the age of 12 years, patient had recurrent episodes of seizures and was diagnosed with tuberous sclerosis. She had a small

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focus of subependymal nodule at the time of diagnosis. There was no detectable mass lesion in the brain at that time. She was put on antiepileptics and was on close follow-up with intermittent computed tomography (CT)/magnetic resonance imaging (MRI). An MRI done at the age of 16 years showed a mass of 2.3×2×1.8cms projecting into the frontal horn of left lateral ventricle adjacent to the foramen of Monro and diagnosed radiologically as subependymal giant cell astrocytoma (SEGA). There was no evidence of ventricular obstruction. On clinical examination, the patient had ash leaf spots in face and body, confetti skin lesions, multiple angiofibroma (adenoma sebaceum) on the face (Fig. 1a) and shagreen patch on the back (Fig. 1b). Patient was advised to continue antiepileptics and follow-up of the tumour.

An MRI done during this time, at the age of 22 years, showed well defined relatively hyperdense lesion measuring 5×4×3.7cms in the frontal horn and body of left lateral ventricle, reaching up to the foramen of Monro. Multiple calcified nodules in subependymal location along the lateral wall of the body of bilateral lateral ventricles were also seen. Left lateral ventricle and fourth ventricle were dilated. The present radiology shows significant increase in the size of lesion compared to previous study, with ventricular obstruction at the level of foramen of Monro (Fig. 1C). MRI with contrast study also confirmed the diagnosis of SEGA. In MRI, calcified subependymal nodule, and cortical and subcortical tubers (Fig. 1D) were also noted. Fundoscopy showed bilateral papilledema.

Surgical excision of the tumour was done. Post-operative period was uneventful. She was put on antiepileptic therapy, is on close follow-up and is symptom-free till date.

The surgical specimen was received in our pathology department as multiple pale brown tissue aggregate measuring 3×2.5×1 cm. Histopathological examination showed the neoplasm arranged in sheets and nests separated by delicate fibrovascular septa (Fig. 2a). Focally sweeping fascicles of tumour cells were noted. High vascularity with thin- and thick-walled vessels was noted within the tumour (Fig. 2b). The cells are

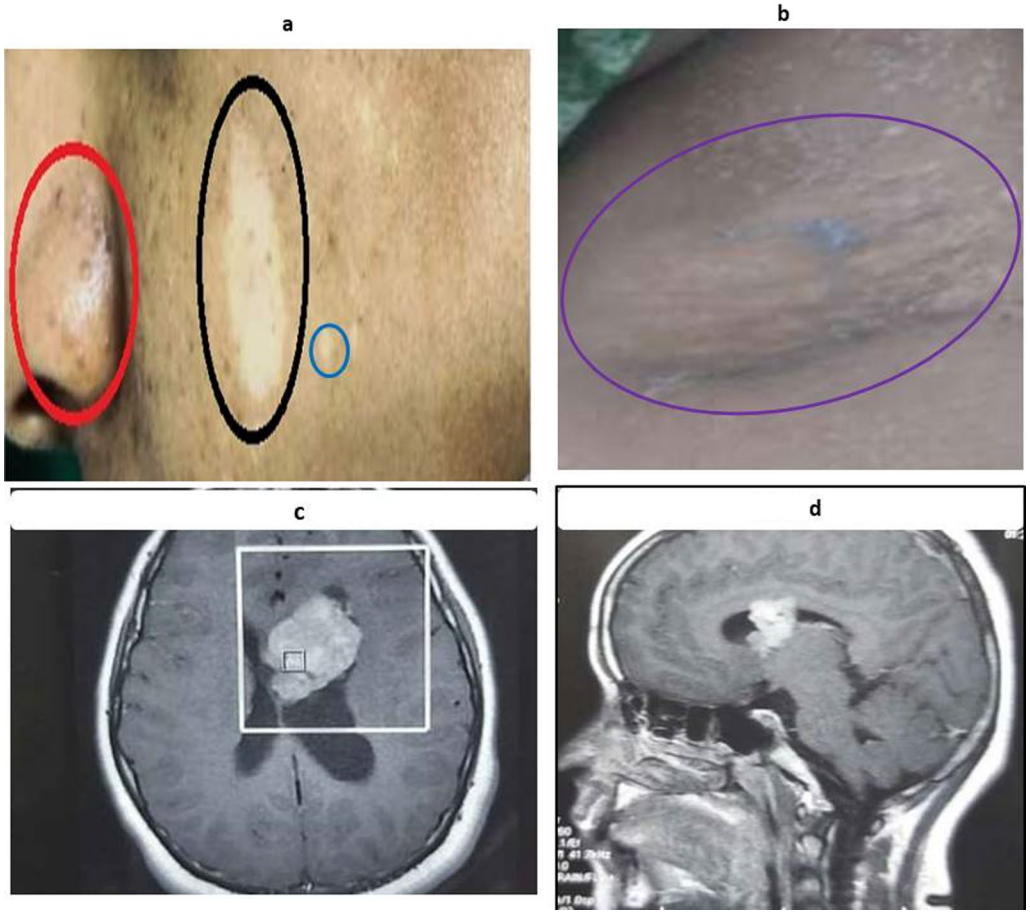

Fig. 1 **a** Angiofibroma (red circle), ash leaf patch (black circle), confetti lesions (blue circle) on the face of the patient. **b** Shagreen patch on the back (violet circle). **c** MRI plain and **d** MRI with contrast showing location of the tumour

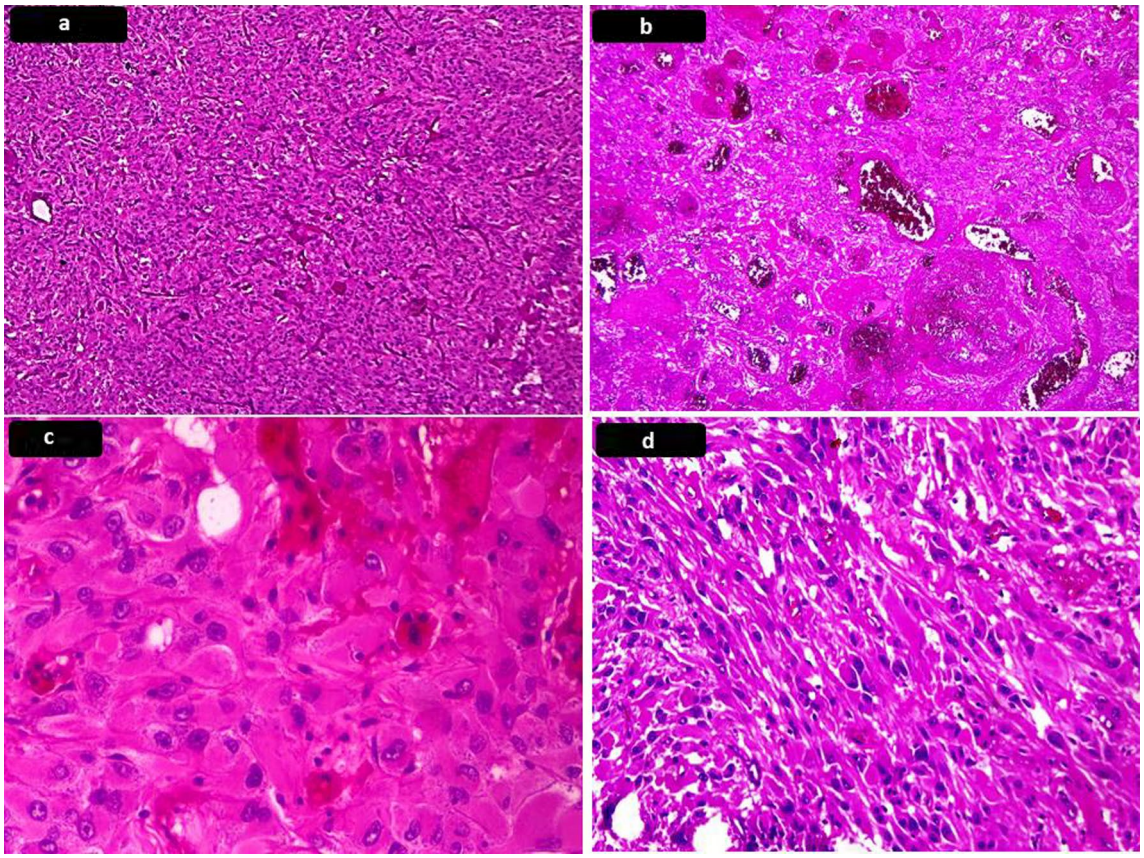

Fig. 2 **a** Low-power microscopic view of the tumour (H&E × 100). **b** Areas of thin- and thick-walled vessels (H&E × 100). **c** Ganglion cell-like and gemistocytic cells (H&E × 400). **d** Spindle cell area (H&E × 400)

medium to large with abundant glassy cytoplasm and eccentrically placed vesicular nuclei. Some of the cells showed distinct nucleoli. Many cells were gemistocyte-like and ganglion cell-like (Fig. 2c). Moderate nuclear pleomorphism and intranuclear inclusions were noted. Many bi-/multinucleated cells were also seen. Focally spindle cells with elongated fibrillary cytoplasm and vesicular nuclei were noted (Fig. 2d). Intervening cystic spaces also were present. Mitosis was scanty. Necrosis was absent.

For confirmation, immunomarker study was done with antibodies to S100, synaptophysin and glial fibrillary acidic protein (GFAP). Immunomarker for S100 showed strong diffuse positivity in tumour cells. Antisynaptophysin highlighted scattered ganglion cell-like cells. A few scattered cells showed GFAP positivity. Proliferation index was assessed with Ki67 immunomarker and was found to be low (8%) (Fig. 3a–d).

Thus, a histological diagnosis of subependymal giant cell astrocytoma (SEGA) was made. Genetic testing of the patient or tumour tissue was not performed since the patient could not afford the cost.

Discussion

SEGA is a periventricular tumour composed partly of large ganglion cell-like astrocytes and strongly associated with tuberous sclerosis [4]. It has been assigned WHO Grade 1. SEGA and subependymal nodules are considered a continuum of a single entity. In the present case, patient was already diagnosed with tuberous sclerosis at the age of 12 years. She had a small focus of subependymal nodule at the time of diagnosis, which gradually enlarged in size over 10 years, causing symptoms related to it, like headache, vomiting and blurring of vision. Hence, the surgeon opted for surgical removal.

The patient had features of tuberous sclerosis satisfying the definitive criteria. The tuberous sclerosis diagnosis revised criteria were formulated at the International Tuberous Sclerosis Complex Consensus Conference and published by Northrup H et al. [5]. The criteria describe a genetic one and a clinical one. The identification of either a TSC1 or a TSC2 pathogenic mutation in the DNA from normal tissue is sufficient to make a definitive diagnosis. But these costly tests cannot be done by patients in resource poor countries. Hence, a clinical criterion with

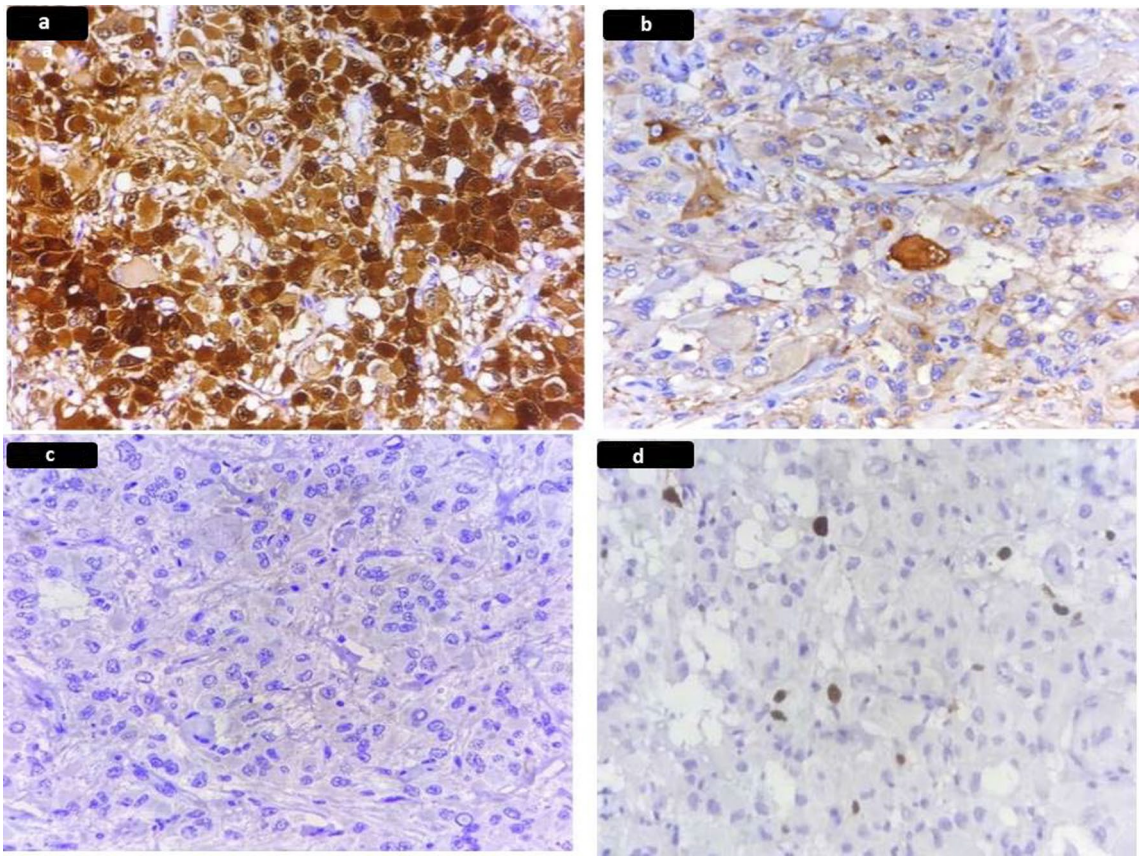

Fig. 3 Immunomarkers for: **a** S100—strong diffuse positivity in tumour cells. **b** Synaptophysin-highlighted ganglion cell-like cells. **c** Glial fibrillary acidic protein (GFAP)—scattered cell positivity. **d** Ki67 proliferation index—low

a group of major and minor features was put forward. Definitive diagnosis requires 2 major features or 1 major with at least 2 minor features. With 1 major or at least 2 minor features, the diagnosis is to be put as possible. Of the major criteria, this patient had SEGA, subependymal nodules, cortical and subcortical tubers, shagreen patch on the back, ash leaf spots on the face and cutaneous angiofibroma. Of the minor criteria, this patient had confetti skin lesions.

The disorder affects 1–2 million individuals worldwide, with an estimated prevalence of 1 case per 6000–10,000 live births [5]. Skin lesions are detected in all ages and affect more than 90% of TSC patients [6]. In the present case, almost all skin manifestations of TSC were present. The main neurological manifestation of TSC is epilepsy, which occurs in 70–90% of the individuals with the condition, and this is the sign that most frequently leads to the diagnosis of the syndrome [3]. Our case presented first with epilepsy at the age of 12 years, was investigated and diagnosed as TSC. Since TSC is a multiorgan systemic disease, a multidisciplinary diagnostic and therapeutic approach is needed for proper diagnosis and management. Rapamycin mTOR inhibitors and their derivative everolimus have been studied in TSC patients since 2006 and are promising for the treatment of multiple tumours including renal angiomyolipoma, giant cell subependymal astrocytoma and lymphangio-leiomyomatosis, with secondary benefits on the cutaneous manifestations [7]. Everolimus has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with renal angiomyolipoma associated with TSC. Treatment with mTOR inhibitors should be life long, because withdrawal of the medication results in a rebound growth of the tumour (SEGA, renal angiomyolipoma, cardiac rhabdomyoma and cutaneous lesions) in the majority of the patients [8]. Adriaensen et al. [9] had done a retrospective longitudinal study by following up of 214 TSC patients who were included in a previous single-centre cross-sectional study in 2007. Of the 43 patients with radiological signs of SEGA in 2007, follow-up CT scan was available for 34 patients. Out of this, only in ten patients (29%), the initial SEGA lesion was found to be increased in size. They also found that 2% of 138 other cases in whom there was no SEGA lesions in 2007

developed new lesion of SEGA later in life and detected in follow-up CT scan. If the tumour associated with tuberous sclerosis is small and of low grade, the patient can be put in close follow-up, till the patient becomes symptomatic of the tumour.

Conclusions

Herewith, the authors are reporting a case of a young female with a definitive diagnosis of tuberous sclerosis made at the age of 12 years, who developed a small asymptomatic SEGA detected during the follow-up period, became symptomatic at the age of 22 years and needed surgical intervention. If the tumour is small and of low grade and do not produce any symptoms, the patient can be put in close follow-up before early surgical intervention, as in our patient. We could depict the natural progression of the intracranial mass lesion in this case by long-term close follow-up of the patient. Our patient is symptom-free till date.

Abbreviations

SEGA	Subependymal giant cell astrocytoma
TS/TSC	Tuberous sclerosis
mTOR	Mammalian target of rapamycin
MRI	Magnetic resonance imaging
CT	Computed tomography
GFAP	Glial fibrillary acidic protein

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Author contributions

PSJ performed the histological examination and diagnosis of the case and was a major contributor in writing the manuscript. AM collected the patient data and contributed to the writing and editing. RR did the follow up of the patient and contributed to the writeup and editing. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Consent was taken from the patient.

Competing interests

We, the authors, hereby declare that there are no financial or nonfinancial competing interests.

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