

Seizure Management in Tuberous Sclerosis Complex with Suspected Phenytoin Toxicity: A Case Report Highlighting Therapeutic Challenges and the Role of Emerging mTOR Inhibitor Therapy

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Abstract: *Tuberous sclerosis complex (TSC) is a rare genetic disorder with autosomal dominant inheritance. Pathogenic variants in either TSC1 or TSC2 can result in hamartomatous lesions affecting multiple organs, including the brain, heart, kidneys, skin, lungs, and liver. We report the case of a 19-year-old woman who presented with seizures, facial angiofibromas, and hypopigmented skin lesions on her lower back. Brain magnetic resonance imaging (MRI) revealed a subependymal giant cell astrocytoma (SEGA), subependymal nodules, and cortical tubers. Abdominal ultrasonography demonstrated multiple renal angiomyolipomas and simple cysts in both kidneys. Because of financial constraints, the patient had been receiving phenytoin, a less expensive antiseizure medication, and serum phenytoin levels had not been monitored regularly. An elevated serum phenytoin concentration raised concern for phenytoin toxicity in the setting of ongoing seizures. This case highlights the diagnostic imaging features of TSC, the challenges of long-term antiseizure treatment and therapeutic drug monitoring in a resource-limited setting, and the potential role of emerging targeted therapies, including the mTOR inhibitor everolimus. It also underscores the value of multidisciplinary care, patient and family education, and access to support services.*

Keywords: Tuberous sclerosis complex; facial angiofibromas; subependymal giant cell astrocytoma; renal angiomyolipomas; seizures; phenytoin toxicity; mTOR inhibitor therapy

1. Introduction

Tuberous sclerosis complex (TSC), historically also known as epiloia, is a rare genetic disorder with autosomal dominant inheritance. It affects individuals of all sexes and ethnic backgrounds and is a multisystem condition involving the brain, skin, heart, kidneys, eyes, lungs, and liver. The condition is caused by pathogenic variants in TSC1 and TSC2, which encode the proteins hamartin and tuberlin, respectively. These proteins help regulate cell growth through the mechanistic target of rapamycin (mTOR) pathway.

The classic clinical triad historically associated with TSC comprises seizures, intellectual disability, and facial angiofibromas; however, this triad is not present in all affected individuals. Cutaneous manifestations may provide an important clue to the diagnosis. Early recognition is essential because TSC can affect multiple organ systems and requires ongoing surveillance and individualized management.

2. Case Presentation

A 19-year-old woman weighing 35 kg was admitted to the Department of General Medicine at Pravara Institute of Medical Sciences, Loni, with a provisional diagnosis of

seizure disorder. Physical examination revealed multiple facial angiofibromas over the lower face (Figure 1). According to her mother, these lesions had gradually appeared when the patient was approximately four years old and had increased in number over time. A hypopigmented skin lesion, described as an ash-leaf macule, was also observed on her lower back (Figure 2).

Her mother reported that the patient had experienced multiple generalized tonic-clonic seizures during childhood, each lasting a few minutes and occurring approximately three times daily over a period of four months. She had been prescribed phenytoin 100 mg three times daily and phenobarbital (Gardenal) 60 mg twice daily. Because seizures continued at presentation, levetiracetam 500 mg twice daily was added. Gingival hypertrophy was also noted (Figure 3). The patient had intellectual disability and had not attended school beyond the first grade because of her seizure episodes and associated difficulties.

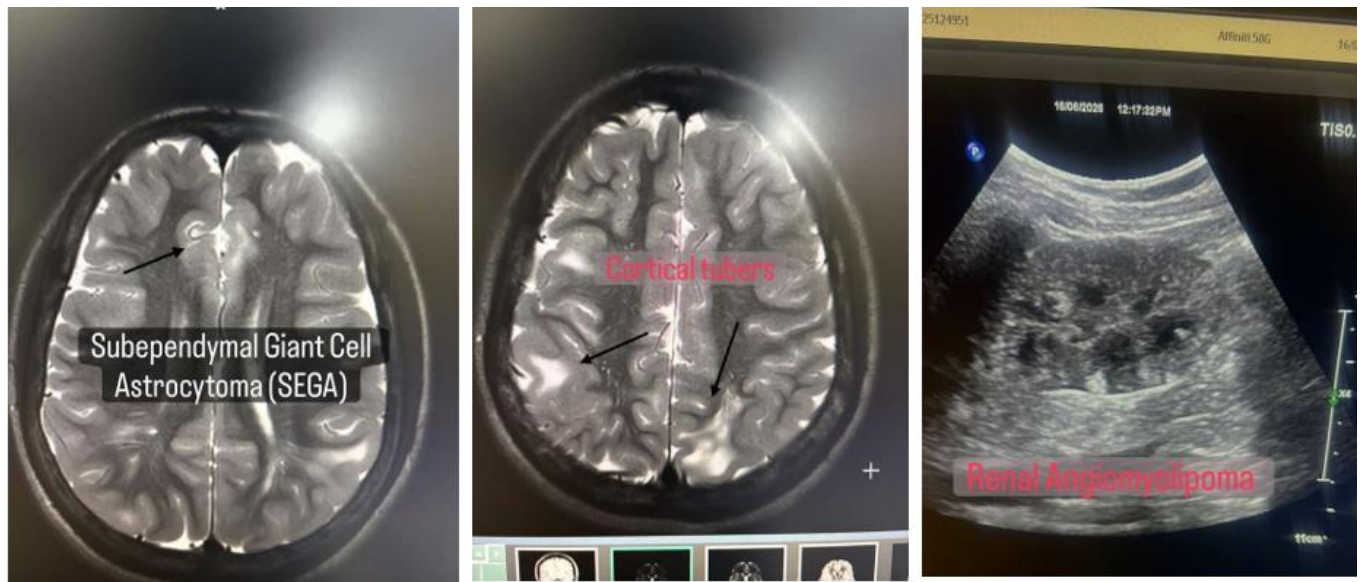
A family history of similar cutaneous findings was reported: her mother, sister, and brother were said to have facial angiofibromas (Figure 4). Renal function was assessed, and the initial laboratory work-up included liver function tests, routine urine examination, a complete blood count, and haemoglobin measurement. Unenhanced brain MRI was subsequently performed.



Brain MRI demonstrated a relatively well-defined subependymal mass suggestive of a subependymal giant cell astrocytoma (Figure 5). Asymmetric areas of hyperintensity involving the cortex and subcortical white matter in the bilateral parieto-occipital regions were suggestive of cortical and subcortical tubers (Figure 6). Radially oriented linear T2-weighted hyperintensities extending from the periventricular to the subcortical white matter in both parietal regions were suggestive of radial migration lines. T1- and T2-hypointense nodules showing susceptibility-related blooming were seen

along the lateral walls of the atria of both lateral ventricles, consistent with subependymal nodules (Figure 6).

Given the clinical history, cutaneous findings, and brain MRI features, TSC was strongly suspected. Abdominal ultrasonography showed mildly enlarged kidneys for age, measuring $9.3 \times 4.6 \times 2.8$ cm on the right and $9.7 \times 5.8 \times 5.0$ cm on the left. Both kidneys had heterogeneous echotexture due to well-defined, rounded, hyperechoic masses in the renal parenchyma, suggestive of angiomyolipomas. No hydronephrosis was observed (Figure 7).



The complete blood count showed a low haemoglobin level (Figure 8). Serum phenytoin concentration was found to be elevated, raising concern for phenytoin toxicity in the context of ongoing seizures and gingival hypertrophy (Figure 9). The patient's family reported financial constraints that limited access to some recommended therapeutic options. Phenytoin had been used because it was more affordable, while regular therapeutic drug monitoring had not been performed.

The mTOR inhibitor everolimus is an established adjunctive treatment option for selected patients with TSC-associated treatment-resistant seizures and may also be indicated for certain TSC-associated lesions. TSC1/TSC2 dysfunction can lead to loss of inhibition of mTORC1 signalling, contributing to abnormal cellular growth and TSC-associated lesions. Everolimus inhibits mTORC1 and can reduce seizure frequency in appropriately selected patients. Suitability for treatment requires individualized specialist assessment, consideration of other TSC manifestations, safety monitoring, and attention to affordability.

3. Discussion

Tuberous sclerosis complex is an autosomal dominant multisystem disorder caused by pathogenic variants in TSC1 or TSC2, resulting in dysregulation of the mTOR pathway. Neurological involvement, particularly epilepsy, is a major cause of morbidity. In this patient, the combination of facial angiofibromas, a hypomelanotic macule, cortical tubers, radial migration lines, subependymal nodules, a suspected SEGA, and bilateral renal angiomyolipomas strongly supported the clinical diagnosis of TSC. These findings should be assessed against established clinical diagnostic criteria and interpreted in conjunction with the complete clinical and imaging record.[1]

Epilepsy is common in TSC and is frequently associated with cortical tubers and other abnormalities of cortical development. [1,2] In this patient, recurrent seizures beginning in childhood, cortical tubers on MRI, and intellectual disability suggest longstanding TSC-associated epilepsy. Persistent seizures and neurodevelopmental impairment can substantially affect education, independence, and quality of life, as illustrated by the patient's inability to continue schooling.

UMR NO / IP No : PMT25124951 / IP260611138		Bill Date : 12-Jun-2026 01:43 AM	
Name : Miss .		Sample Collected Date : 12-Jun-2026 01:43 AM	
Age / Gender : 16Y(s) / Female		Reporting Date : 12-Jun-2026 10:25 AM	
Type / Bed No : CASH / 36 FMW		Sample No : 2606120062	
Doctor Name : DR.GENERAL MEDICINE UNIT 4			

CCL PATHOLOGY			
LAB NO : LAB2243714			
HE-CBC(HEMOGRAM)			
Performed On Sysmex XN 1000 Fully Automated Analyser			
NATURE OF THE SPECIMEN : Whole Blood			
RED BLOOD CELLS			
RBC COUNT (XN 1000-Fluorescence Flowcytometry / DxH 900-Coulter Principle)	4.63	10 ⁶ /μL	
Haemoglobin	7.4	g/dL	11.5 - 15.5
Packed cell Volume(Hematocrit)	28.4	%	36 - 46
MCV	61.3	fL	76 - 96
MCH (Calculated)	16.0	pg	27 - 32
MCHC (Calculated)	26.1	g/dL	31.5 - 34.5
RDW-CV (Calculated)	20.3	%	11.5 - 12.5
WHITE BLOOD CELLS			
WBC Total Count (XN 1000-Fluorescence Flowcytometry / DxH 900-Coulter Principle)	8.08	10 ³ /μL	4 - 10
DIFFERENTIAL COUNT(FLOWCYTO-VCS360)			
Neutrophils	62.0	%	40 - 75
Lymphocytes	26.0	%	20 - 40
Monocytes	10.0	%	2 - 10
Eosinophils	2.0	%	1 - 6
Basophils	0	%	0 - 1
PLATELETS(Impedence method)			
Platelet Count	535	10 ³ /μL	150 - 450
*** End Of Report ***			

  		
Patient Name : MISS .		
Age / Sex : 16 YEAR / FEMALE		
Ref By : DR. DR SOMANI		
Barcode : FN117555		
Reg No : HL6300654775 / HP001/MH6687/AG2233		Registered On : 15-06-2026 10:41 PM
Collected At : SOMANI LAB		Received On : 16-06-2026 06:12 AM
		Reported On : 16-06-2026 01:17 PM
		Sample : SERUM
		INV : PHENYTOIN/DILANTIN/EPTOIN

PHENYTOIN/DILANTIN/EPTOIN			
TEST DESCRIPTION	RESULT	UNITS	BIOLOGICAL REFERENCE RANGE
Phenytoin (Eptoin)	29.63	μ g/mL	10.0 - 20.0
Clinical significance : Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective.			
Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent.			
Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin.			
Some drug side-effects occur in the therapeutic range; these include gingival hyperplasia, hyperglycemia, and skin rash.			
Phenytoin pharmacokinetics are significantly affected by a number of other drugs. As noted above, phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels.			
Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized.			
The free phenytoin level is the best indicator of adequate therapy in renal failure.			
In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure.			

The patient's long-term antiseizure treatment highlights an important therapeutic challenge. She had received phenytoin and phenobarbital for several years, and levetiracetam was subsequently added because of continuing seizures. The elevated serum phenytoin concentration, together with gingival hypertrophy, raised concern for phenytoin toxicity and chronic drug-related adverse effects. Gingival

overgrowth is a recognised adverse effect of long-term phenytoin therapy.[3] Because phenytoin has a narrow therapeutic range and nonlinear pharmacokinetics, therapeutic drug monitoring and individualized dosing are important, particularly during prolonged treatment.

However, seizures occurring alongside an elevated phenytoin concentration should not automatically be attributed to phenytoin toxicity. Breakthrough seizures may also reflect persistent drug-resistant epilepsy, inadequate seizure control, missed doses, or other contributing factors. The clinical context, timing of the drug level, dose history, adherence, and relevant laboratory findings should be considered when interpreting the result.

The patient's socioeconomic circumstances further complicated management. Her family reported relying on phenytoin because of its affordability, while regular serum drug-level monitoring and access to other therapeutic options were limited. This illustrates that effective epilepsy management depends not only on drug efficacy but also on affordability, availability, adherence, monitoring, and continuity of care. Multidisciplinary follow-up and patient-support services may be particularly valuable in resource-limited settings.

The identification of a suspected SEGA and renal angiomyolipomas is clinically important because management of TSC now includes targeted therapies in addition to symptomatic treatment. Loss of TSC1/TSC2-mediated inhibition can lead to abnormal mTORC1 activation, contributing to TSC-associated lesions. Everolimus, an mTOR inhibitor, targets this pathway and has an established role in selected TSC manifestations.[1]

The phase III EXIST-3 trial demonstrated that adjunctive everolimus reduced seizure frequency in patients with TSC-associated treatment-resistant seizures compared with placebo. The magnitude of benefit and tolerability vary between individuals, and treatment requires appropriate monitoring. In patients with inadequately controlled TSC-associated epilepsy, everolimus may be an option after specialist assessment. Treatment decisions should account for seizure characteristics, associated TSC manifestations, potential adverse effects, monitoring requirements, and affordability.

This case highlights the complexity of managing TSC-associated epilepsy when longstanding conventional antiseizure treatment, suspected phenytoin toxicity, limited therapeutic monitoring, socioeconomic constraints, and multiple TSC-associated lesions coexist. Early diagnosis, regular multisystem surveillance, appropriate antiseizure treatment, therapeutic drug monitoring, and consideration of targeted therapy are important components of comprehensive care.

4. Conclusions

Tuberous sclerosis complex is a multisystem disorder in which epilepsy can cause substantial long-term neurological and functional disability. This case illustrates the therapeutic challenges encountered in a young patient with longstanding seizures, intellectual disability, characteristic cutaneous manifestations, cortical tubers, subependymal lesions, a suspected SEGA, and bilateral renal angiomyolipomas.

The combination of ongoing seizures, an elevated serum phenytoin concentration, gingival hypertrophy, and

prolonged phenytoin exposure highlights the importance of therapeutic drug monitoring, individualized dosing, and recognition of adverse drug effects. Socioeconomic limitations may also influence treatment choice, monitoring, and continuity of care.

Management of TSC should extend beyond seizure suppression and include regular surveillance for multisystem complications, genetic counselling where appropriate, and assessment for drug-resistant epilepsy. Everolimus provides a targeted therapeutic option for appropriately selected patients, particularly when seizures remain inadequately controlled or other TSC-associated lesions meet treatment criteria. A multidisciplinary, patient-centred approach that integrates antiseizure medications, targeted therapy, monitoring, and social support is essential to optimize long-term outcomes.

Acknowledgments

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Human Ethics

Written informed consent for publication of this case report and the accompanying clinical images was obtained from the patient's legal guardian.

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