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Case Report

Clinical and Radiological Evaluation of Tuberous Sclerosis Complex with Valproic Acid–Induced Pancytopenia: A Case Report

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ABSTRACT

Tuberous sclerosis Complex (TSC) is a rare autosomal-dominant genetic disorder caused by pathogenic variants in TSC1 or TSC2 genes, resulting in multisystem hamartomatous lesions. The classic triad of TSC consisting of seizures, cognitive impairment, and facial angiofibromas is only present in29% patients. Valproic acid, commonly used for seizure management in TSC, can rarely cause severe hematologic complications including pancytopenia. A 16-year-old male with a 10-year history of generalized tonic-clonic seizures and mild intellectual disability, managed with valproic acid, presented with per-rectal bleeding and fever secondary to lower respiratory tract infection. Physical examination revealed facial angiofibromas, gingival fibromas, dental enamel pits and Hypomelanotic "ash leaf" macule on the right hand dorsum. Laboratory investigations demonstrated severe pancytopenia and mildly deranged LFTs. Brain computed tomography showed subependymal calcified nodules along lateral ventricles and multiple cortical tubers. Abdominal ultrasound and echocardiography were unremarkable. TSC diagnosis was confirmed using the Updated Diagnostic Criteria for Tuberous sclerosis Complex (2012). The patient's current peripheral smear revealed severe pancytopenia. Past FBCs revealed chronic pancytopenia. Valproic acid discontinuation resulted in hematologic improvement, establishing valproic acid-induced pancytopenia as the cause of bleeding and increased infection susceptibility. He was discharged from the hospital on Levetiracetam and attendants counseled about the condition. The purpose of this case is to highlight this rare condition and to emphasize the need for increased awareness about Tuberous Sclerosis. This case also highlights valproic acid-induced pancytopenia as a serious complication in epileptic patients requiring long-term antiepileptic therapy.

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Introduction

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder with an estimated prevalence of 1 in 6,000 to 1 in 12,000 individuals, affecting both sexes and all ethnic groups equally [1]. This multisystem disorder typically manifests in childhood and involves the central nervous system, skin, kidneys, heart, eyes, lungs, and liver [2]. Although the classic triad of seizures, intellectual disability, and facial angiofibromas is traditionally associated with TSC, it occurs in only approximately 29% of affected individuals [3].

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TSC results from pathogenic variants in either the TSC1 or TSC2 genes, which encode the proteins hamartin and tuberin, respectively. These proteins function as a tumor suppressor complex, regulating cellular growth and differentiation. Mutations in TSC1 or TSC2 geneslead to abnormal cell growth and the development of benign tumors in various organs [4-5]. Diagnosis is established according to the updated 2012 diagnostic criteria for tuberous sclerosis complex (TSC), which include genetic diagnostic criteria based on the identification of a pathogenic mutation in either the TSC1 or TSC2 gene; however, a normal DNA result does not exclude TSC. The clinical diagnostic criteria comprise major and minor features. The presence of two major features or one major feature with ≥2 minor features establish a definite diagnosis of TSC, whereas the presence of either one major feature or ≥2 minor features indicate a possible diagnosis [6].

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Valproic acid is a widely used broad-spectrum antiepileptic drug for seizure management in TSC patients. Its mechanism involves enhancing γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission through increased GABA synthesis and decreased degradation [7].

While hematologic complications such as thrombocytopenia and macrocytosis are relatively common, pancytopenia is rare but potentially life-threatening [7]. Valproic acid-induced cytopenia occurs through two mechanisms: direct bone marrow suppression, demonstrated by in vitro inhibition of bone marrow progenitor cells [8], and immune-mediated destruction [9]. Long-term valproate therapy may also cause hepatotoxicity [10].

We present a case of TSC and severe valproic acid-induced pancytopenia in a 16-year-old male with TSC, manifesting as per-rectal bleeding and recurrent infection, which resolved following discontinuation and transition to levetiracetam.

CASE REPORT

History

A 16-year-old male from Madian, Swat, presented to the Medical C Ward, Saidu Group of Teaching Hospitals, Swat, with a 12-day of cough, 10-day history of feverand 6-day of per-rectal bleeding. The cough was productive, yielding approximately half a teaspoon of non-bloody sputum per episode, and was associated with chest congestion. The fever was sudden onset, high-grade, intermittent, with no diurnal pattern, and responsive to oral antipyretics. Per-rectal bleeding was scanty, mixed with stool, with no bleeding from other sites.

The patient had a 10-year history of generalized tonic-clonic seizures beginning at age five. He had been maintained on sodium valproate for 10 years with good compliance. For the past three years, he has been on oral sodium valproate at a dose of 500 mg twice daily. Despite treatment, he experienced at least one seizure weekly. With the current febrile illness and associated chest congestion, generalized tonic-clonic seizure frequency increased to 2-3 episodes daily but with no status epileptics.

The patient has mild intellectual disability with independent performance of basic activities of daily living and simple household chores. He has limitations in academic performance (attended school for three years), abstract reasoning, decision-making, and exhibits poor anger control (intermittent aggressive behavior). He can hear and communicate verbally.

Birth history revealed normal vaginal home delivery with immediate cry, no neonatal seizures, and no neonatal intensive care unit admission. Developmental milestones were delayed by approximately two months. Family history was non-contributory with non-consanguineous parents and no similar conditions in family members. The economic history was satisfactory.

Examination

On examination, the patient appeared pale with icteric sclerae. Multiple cutaneous manifestations were present: facial angiofibromas including a prominent lesion on the left forehead, single average-sized mid-forehead lesion with multiple small lesions over whole face (Fig.1 and Fig.2),a hypopigmented "ash-leaf" macule on the left hand dorsum (Fig.3) and multiple ecchymosis on the trunk and back (Fig.4). No ungual fibromas were noted. Gingival fibromas and enamel pits were observed (Fig.1 and Fig.2).

Respiratory examination revealed bilateral chest crepitations, more pronounced on the right side with normal vesicular breath sounds. Abdominal examination showed a soft, non-tender, non-distended abdomen without organomegaly. Cardiovascular examination demonstrated normal S1 and S2 heart sounds without murmurs. Neurological examination was unremarkable.



Figure 1



Figure 2

One prominent angiofibroma on left forehead, one average size on mid-forehead, multiple small on cheeks, nose, and chin. Dental enamel pits seen.



Figure 3
hypomelanotic "ash-leaf" macule on left hand dorsum.

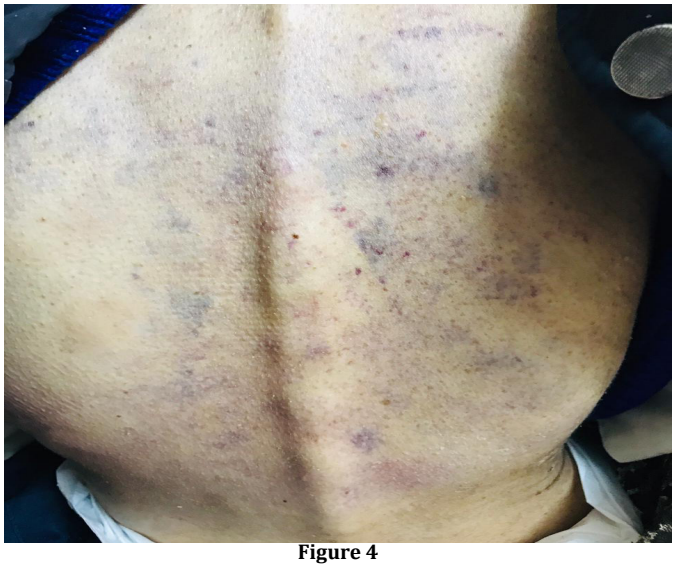


Figure 4
Dorsum of Patient shows Ecchymosis secondary to low platelets.

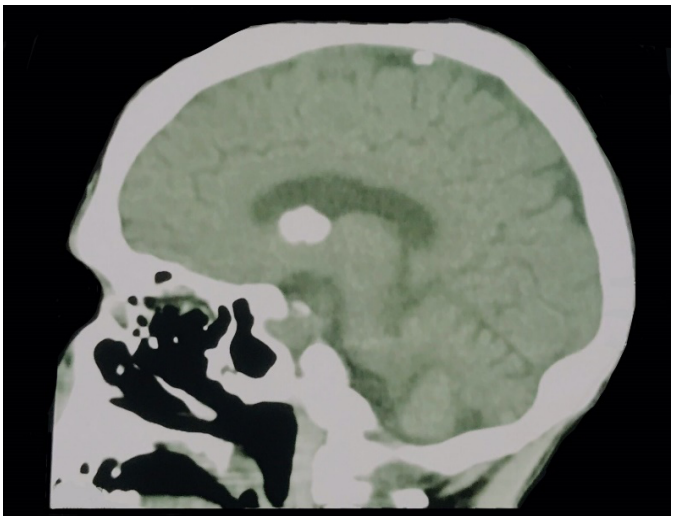


Figure 5
Sagittal view of Brain CT showing subependymal Nodule

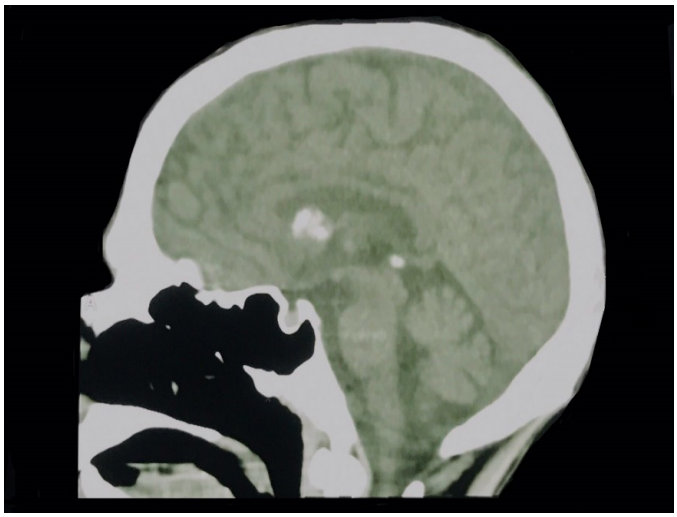


Figure 6
Sagittal view of Brain CT showing subependymal Nodule

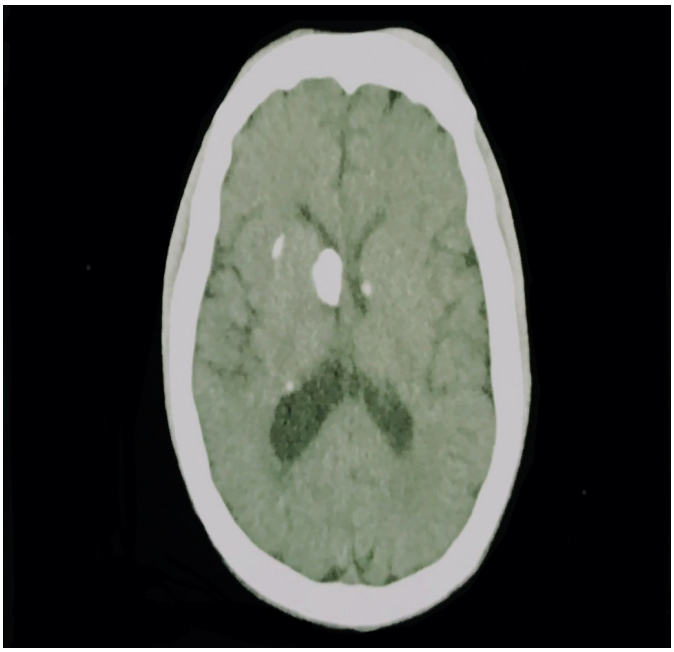


Figure 7
Axial view of Brain CT showing subependymal Nodule.

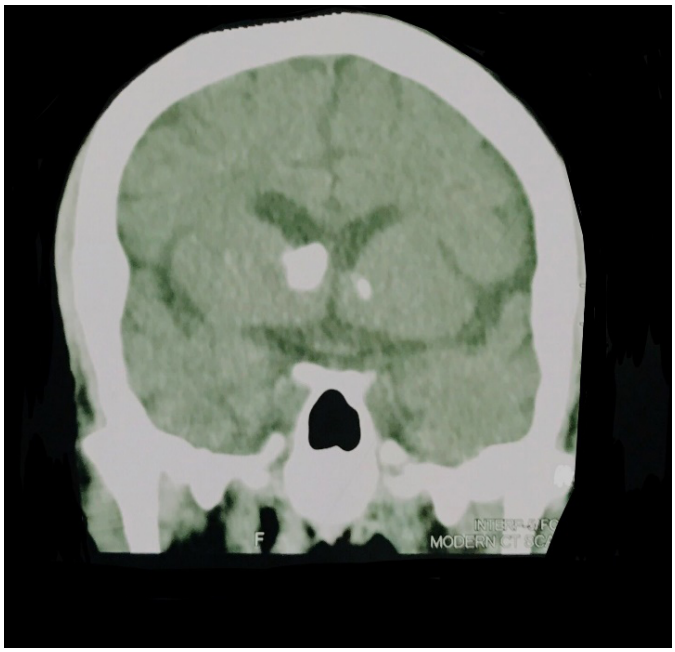


Figure 8
Coronal view of Brain CT showing subependymal Nodule.

DISCUSSION

A 16-year-old male with a 10-year history of generalized tonic-clonic seizures and mild intellectual disability, managed with valproic acid, presented with per-rectal bleeding and fever secondary to LRTI. Brain CT showed subependymal calcified nodules along lateral ventricles and multiple cortical tubers. These brain findings contribute to epileptogenesis, explaining the patient's recurrent seizures. [1].

The patient also presented with cutaneous manifestations such as facial angiofibromas and Hypomelanotic "ash-leaf" macules, which are characteristic features of TSC and aid in clinical diagnosis. This patient exhibited the classic TSC triad of seizures, intellectual disability, and facial angiofibromas, which is observed in only about 29% of cases. [3].

Following the 2012 Updated Diagnostic Criteria for TSC, genetic testing was not performed due to lack of available facilities, so only the clinical criteria are considered. According to the 2012 Updated Diagnostic Criteria for TSC, a definite diagnosis is made with either two major features or one major plus two or more minor features, while a possible diagnosis requires one major or two or more minor features.

This patient exhibited three major features i.e. hypomelanotic "ash-leaf" macules, angiofibromas, and subependymal nodules and two minor features i.e. gingival fibromas and dental enamel pits, fulfilling criteria for a definite diagnosis of TSC. [6].

The patient's current peripheral smear revealed severe pancytopenia (Table. 1), while previous full blood counts demonstrated chronic pancytopenia (Table. 2).

Table.1: Laboratory and Radiological Investigations

No	Investigation	Results	Interpretation
1	Peripheral Smear with Reticulocyte Count	Anisocytosis, Normocytic Normochromic Picture, Few Microcytic and Macrocytic RBCs, Rare Nucleated RBCs, Roulex Formation Positive, Blasts Negative, MP Negative. RC-0.6%. WBC-1.18× 103/mm3, HBG-4.78×g/dL, MCV-87.7×fL, PLT-4.13 ×103/mm3	Low Reticulocyte Count
2	LFTs	ALT-64 IU/L, ALK P-176 IU/L, SBR-1.8 mg/dL	Mildly Deranged
3	Serum Electrolytes	Sodium-140.5 mmol/L, Potassium-5.18 mmol/L, Cloride-108.6 mmol/L.	Normal
4	RBS	95 mg/dL	Normal
5	RFTs	Serum Creatinine-1.0mg/dL, Blood Urea-34mg/dL.	Normal
6	Non-Contrast CT brain	Multiple subependymal calcified nodules along the walls of the lateral ventricles, most prominently located near the foramen of Monro. The cortical mantle demonstrates multiple cortical tubers, appearing as patchy areas of cortical and subcortical hypodensity, most prominent in the frontal, parietal, and temporal lobes. These tubers are associated with subtle cortical thickening and blurring of the gray-white matter junction, consistent with hamartomatous cortical malformations. Findings are suggestive of TSC.	subependymal calcified nodules, multiple cortical tubers
7	Ultrasound Abdomen	Normal Liver, Normal Gallbladder, CBD is of normal caliber, Normal Pancreas, Normal Spleen, Normal Kidneys, Normal urinary bladder.	Normal Study
8	Echocardiography	No signs of rhabdomyoma in heart. Normal size chambers, preserved LV systolic function, no RWMA, Normal valves, EF of 60%.	Normal Study
* RBCs (Red Blood Cells), MP (Malarial Parasite), WBCs (White Blood Cells), HBG (Hemoglobin), MCV (Mean Corpuscular Volume), PLT (Platelets), LFTs (Liver Function Tests), ALT (Alanine Aminotransferase), ALK-P (Alkaline Phosphatase), SBR (Serum Bilirubin), RBS (Random Blood Sugar), RFTs (Renal Function Tests), CT (Computed Tomography). CBD (Common Bile Duct), LV (Left Ventricle), RWMA (Regional Wall Motion Abnormality), EJ (Ejection Fraction).			

Table.2: Trend of Hematological Parameters before and After Valproic Acid Withdrawal

No	FBC	Date						
		7-8-25	16-9-25	9-11-25	10-11-25	1-11-25	12-11-25	14-1-26
1	WBC (103/mm3)	6.2	5.1	1.18	1.7	2.58	3.0	6.0
2	RBC (106/mm3)	3.0	2.9	3.1	3.26	3.36	3.6	4.4
3	HGB(g/dL)	8.7	7.5	4.78	4.9	5.3	7	10
4	MCV(fL)	88	90	87.7	94	88.1	92.3	84
5	PLT (103/mm3)	140	100	4.13	18	40	50	150
* Look for abbreviations in Table.1, * Date/Month/Year.								

As the PR bleeding was limited to two minor episodes, endoscopic evaluation was not considered. The patient had been on long-term antiepileptic therapy with sodium valproate. Valproic acid–induced pancytopenia was supported by hematologic improvement following drug discontinuation. A reduced reticulocyte count further suggested bone marrow suppression as the underlying mechanism, establishing valproic

acid–induced pancytopenia as the cause of bleeding and recurrent LRTIs. Bone marrow examination was not performed due to refusal by the patient's attendants. Valproic acid–induced cytopenia occurs primarily through direct bone marrow suppression [9]. Long-term valproate therapy may also cause hepatotoxicity, as evidenced in this patient by abnormal liver function tests, which normalized after drug withdrawal [10].

Along with withdrawal of valproate, the patient was managed with platelet and packed red blood cell transfusions and received replacement therapy for pancytopenia. He was initiated on levetiracetam 500 mg twice daily. His hematological parameters improved progressively, and he was discharged on levetiracetam and replacement therapy. The patient's attendants were counseled regarding the condition.

CONCLUSION

The purpose of this case is to highlight this rare clinical presentation and to emphasize the importance of increased awareness and early recognition of Tuberous Sclerosis Complex. Additionally, this case underscores valproic acid–induced pancytopenia as a serious complication in patients receiving long-term antiepileptic therapy. It reinforces the need for regular hematological and hepatic monitoring, timely identification of adverse drug effects, and prompt modification of treatment to prevent significant morbidity while ensuring effective seizure control.

Conflict of interest

No conflict of interest associated with this work.

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Disclosures Human subjects

Verbally informed consent was obtained from the patient's father and brother for publication of this study.

Authors' Contribution

Prof. Dr. Abdul Jabbar diagnosed the case, supervised the work, and critically revised the manuscript. Dr. Naeem Ullah drafted and critically revised the manuscript. Dr. Ryhan Uddin wrote and drafted the manuscript. All authors reviewed and approved the final manuscript.

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