Diagnosis and Management of Tuberous Sclerosis Complex in a Resource-Limited Setting—A Case Report of a 14-Year-Old Female Zambian Adolescent

Clinical Medicine Insights: Case Reports
Volume 18: 1–6

DOI: 10.1177/11795476251321268

Mwamba Lienda[1], Meek Mwila[2], Chilala Sichula[3], Chishiba Kabengele[4], Moses Akombwa[5], Christina Zulu[3], Chihena Hansini Banda[6] and Hellen M'hango[3]

[1]Lusaka Apex Medical University, Lusaka, Zambia. [2]University of Zambia School of Medicine, Lusaka, Zambia. [3]Department of Paediatrics and Child Health, University of Zambia School of Medicine, Lusaka, Zambia. [4]Rwanda Zambia Health Research Group, Lusaka, Zambia. [5]Department of Radiology, University Teaching Hospital—Adult Hospital, Lusaka, Zambia. [6]Plastic and Reconstructive Surgery Unit, Department of Surgery, University Teaching Hospital, Lusaka, Zambia.

ABSTRACT: Tuberous sclerosis complex (TSC) is a rare multisystemic neurocutaneous syndrome with a wide spectrum of clinical manifestations. We present a case of a 14-year-old adolescent female who presented with a history of facial angiofibromas since the age of 8 months. Physical examination was remarkable for multiple angiofibromas on the face, and other multiple cutaneous manifestations of TSC. MRI of the head, and abdomen revealed cortical tubers, multiple bilateral periventricular and subependymal nodular lesions, calcifications, and bilateral kidney enlargement with multiple bilateral renal angiomyolipomas of varying sizes in a background of bilateral polycystic kidneys, MRI of the chest was unremarkable. A diagnosis of TSC was made using the clinical diagnostic criteria which consist of major and minor features. A diagnosis using genetic studies could not be made due to a lack of resources. Management was multidisciplinary and regular monitoring every 6 months will be required to monitor disease progression and manage complications as they arise. This case illustrates the multidisciplinary approach needed to address the diverse clinical manifestations of TSC and the diagnostic challenges, treatment limitations, and psychological impact of TSC in low-resource settings like Zambia where access to advanced therapies is limited.

KEYWORDS: Tuberous sclerosis complex (TSC), multisystemic, subependymal nodules, cortical tubers, Zambia

RECEIVED: October 4, 2024. **ACCEPTED:** January 31, 2025.

TYPE: Case Report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Hellen M'hango, University Teaching Hospitals—Children's Hospital, P/Bag RW IX Lusaka, Zambia. Email: hellenmhango26@gmail.com

Introduction

Tuberous sclerosis complex (TSC), a neurocutaneous disease, is a rare multisystemic, autosomal dominant disorder affecting children and adults, with a wide spectrum of clinical manifestations.[1,3] It is characterized by the growth of benign tumors, or hamartomas, in several areas of the body including the brain, spinal cord, nerves, eyes, lungs, bone, heart, kidney, and skin.[4] TSC has an incidence of 1 in 10 000 births,[5] and, it has been estimated that 60% to 70% of TSC mutations are de novo while the remaining 30% to 40% are due to autosomal dominant inheritance.[3] Germline mosaicism is uncommon but explains how parents who do not carry the mutation can have multiple children with tuberous sclerosis.[5] TSC occurs as a result of mutations in the TSC1 (located on chromosome band 9q34) or TSC2 (located on chromosome 16p13) genes which code for the tumor suppressor proteins hamartin and tuberin, respectively.[2] Hamartin and tuberin both function as tumor suppressor proteins.[6] Mutations in the hamartin and tuberin suppressor complex results in constitutive mammalian target of rapamycin (mTOR) pathway signaling, which is a regulator of cell growth, leading to cell overgrowth, as in TSC.[6]

The clinical manifestations of TSC include those of neurological origin such as epilepsy, cortical dysplasia (ie, in the form of cortical tubers), subependymal nodules (SENs), subependymal giant cell astrocytomas (SEGAs), SEGAs associated with hydrocephalus, and autism spectrum disorder.[6,10,18] Facial angiofibromas have been reported in up to 74.5% of pediatric TSC patients.[8] They are the most visible and unsightly of all the cutaneous manifestations of TSC.[9] This facial dermatological condition has negative psychosocial impacts, that is, anxiety, depression, low self-esteem, and self-isolation, especially in patients of school-going and adolescent age, a time when peer relationships gain importance and self-concept matures.[8] The other cutaneous manifestations include ungual fibromas, confetti skin lesions, ash leaf spots, shagreen patches, and angiofibromas. Respiratory manifestations include lymphangioleiomyomatosis; cardiovascular manifestations include cardiac rhabdomyoma; gastrointestinal manifestations include dental enamel pits and intraoral fibromas, and renal manifestations include angiomyolipoma, multiple renal cysts, and renal failure.[18] These manifestations often result in absenteeism from school, subsequent unemployment, and a generally low quality of life.[10]

TSC is diagnosed based on genetic or clinical diagnostic criteria as per the second International Tuberous Sclerosis Complex Consensus Conference 2012.[7] The management of

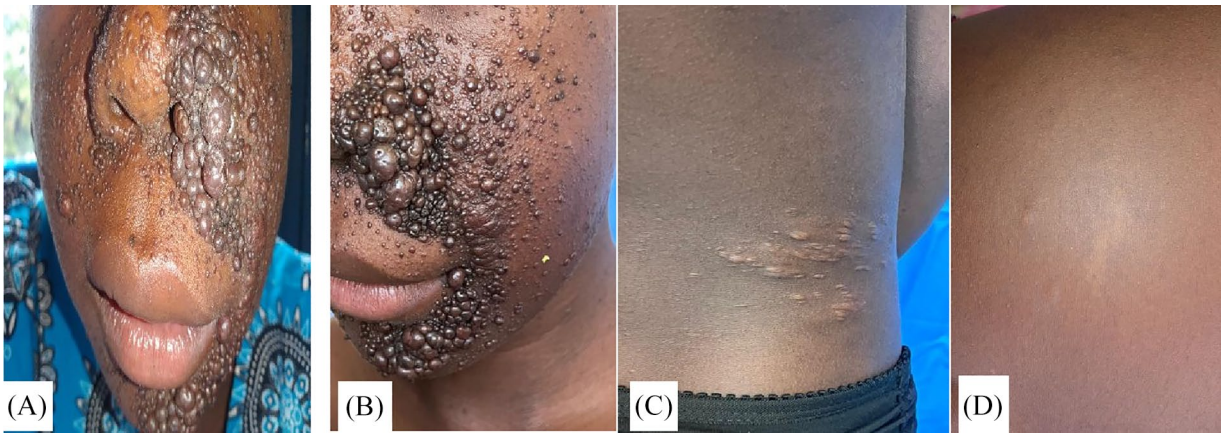

Figure 1. Pictures showing skin manifestations of TSC. (A, B) The characteristic adenoma sebaceum (angiofibromas) in a butterfly pattern across the face, partially occluding left nostril; (C) Shagreen patches on the left lumbar region; (D) Hypopigmented macule (ash leaf spot).

TSC is multidisciplinary. It generally involves preventing or reversing the development of the various hamartomatous lesions and their effects in virtually every body organ system.[6] We report a case of a 14-year-old female adolescent diagnosed with TSC using a clinical diagnostic criterion and managed by a multidisciplinary team at the University Teaching Hospital in Lusaka, Zambia.

Case Report

A 14-year-old female adolescent was referred to our facility from a tertiary hospital 300 km away for further management of a neurocutaneous syndrome. She presented with a progressive history of hyperpigmented, painless, papular growths on her face which would bleed when scratched—they began to develop when she was 8 months old. Her mother had been taking her to local clinics where different therapies were tried with no improvement in symptoms and she noticed they progressively worsened with time. The facial growths greatly affected her self-esteem such that she had not attended school since she was in grade 2 at the age of 8 years, due to social stigma. There was no history of seizures, she had normal neurodevelopment, attained all developmental milestones on time and interacts well with her family and friends in the neighborhood. On review of other systems; the care giver gave no history of cough, shortness of breath, no flank pain, and reddish discoloration of urine. No family member has had a similar presentation

On physical examination, all vitals were within normal ranges except for raised blood pressure which was above the 99th percentile for age and height. Her systolic BP ranged between 141-160 mmHg and diastolic BP 87-106 mmHg. She had multiple angiofibromas on her face appearing as the characteristic adenoma sebaceum in a butterfly pattern which was more concentrated on the left side and, partially occluding the left nostril; fibromas on the scalp and left lumbar region; 2 teeth with enamel pitting in the oral cavity; shagreen patches on the left lumbar region and the anterior and posterior aspect of the right thigh; and a hypopigmented macule (ash leaf spot) on the upper chest (Figure 1A-D). Abdominal examination revealed a mildly distended abdomen which was non-tender on palpation; neurological examination, including fundoscopy, was unremarkable, and bedside dipstick urinalysis was normal.

Laboratory investigations done at first presentation were all normal as shown in Table 1. Histopathology report of the biopsied facial lesions showed a benign neoplasm favoring cutaneous angiofibromas with moderate chronic inflammatory cell presence. This was essential in ruling out differential diagnoses such as Neurofibromatosis. Imaging done, no pathologies noted on the echocardiogram, electrocardiogram, and chest X-ray, which were taken within the first week of admission. An MRI scan of the brain revealed cortical tubers, multiple bilateral periventricular and subependymal nodular lesions, and calcifications (Figure 2A-E). An MRI scan of the abdomen showed bilateral kidney enlargement with multiple bilateral renal angiomyolipomas of varying sizes with the largest measuring 5 cm × 4 cm in a background of bilateral polycystic kidneys with left hydroureter (Figure 3A and B). MRI of the chest was unremarkable. Based on the clinical and radiological findings, a diagnosis of TSC was made using the clinical diagnostic criteria. Genetic studies were not done due to limited resources.

The management of our patient was multidisciplinary. The team included Pediatricians, Pediatric Neurologists, Nephrologists, Ophthalmologists, and Plastic Surgeons. The pediatric neurologists prescribed the antiepileptic drug Sodium Valproate 200 mg once daily due to the high likelihood of developing epilepsy in TSC. The pediatric nephrologists prescribed antihypertensives Atenolol 25 mg and Amlodipine 7.5 mg once daily to manage her hypertension. An ophthalmology consult revealed a refractive error and as such, corrective lenses have been acquired. The plastic surgeons performed debulking of the facial angiofibromas by electrocauterization. This was achieved over 2 stages, 3 months apart. After each electrocautery session, the wounds were dressed with non-adherent vaseline gauze with topical antibiotic gel for 2 to 3 weeks. Successful reduction in angiofibromas was attained without any complications and the patient was pleased with

Table 1. Laboratory investigations.

PARAMETER	FIRST ADMISSION	REFERENCE RANGE
White cell count ($\times 10^9$/L)	4.35	4.00-10.00
Red cell count ($\times 10^{12}$/L)	4.38	3.80-4.80
HB (g/dL)	13.2	12.1-16.3
HCT (%)	39.8	36.0-46.0
MCV (fL)	90.9	79.1-98.9
MCH (pg/cell)	30.1	27.0-32.0
MCHC (g/dL)	33.2	32.6-36.0
Platelets ($\times 10^9$/L)	203	150-400
AST (U/L)	22.86	0.0-37.0
ALT (U/L)	15.73	3.0-42
ALP (U/L)	303.50	0-645
DirectBilirubin (mg/dL)	0.21	0.0-4.0
Indirect Bilirubin (mg/dL)	0.46	0.0-0.6
Total Bilirubin (mg/dL)	0.67	0.2-1.2
Albumin (g/dL)	3.64	3.5-5.0
Creatinine (umol/L)	60.0	26.52-61.88
eGFR (mL/min/1.73 m^2)	98.1	104.4-19.9
BUN (mmol/L)	4.20	1.66-8.32

Abbreviation: eGFR, estimated glomerular filtration rate.

the result (Figure 4A-D). The management plan also included psychosocial support for the patient and family.

The long-term follow-up plan involves reviewing the patient every 6 months to monitor for complications in each system involved. A routine brain MRI will be done every 3 years to monitor for the development of SEGAs and an EEG for seizures. Renal monitoring will involve performing an abdominal MRI scan every 3 years to monitor the progression of angiomyolipoma and renal cysts throughout the patient's life. Skin and dermatological care will include 6 monthly reviews by plastic surgeons to monitor cosmetic deformity. Ophthalmological assessment to check for retinal hamartomas. Coordination of care across the different healthcare providers is essential to ensure comprehensive management of our patient.

Discussion

The case highlights the multifaceted and complex nature of TSC, especially in the context of a low-resource setting like Zambia. Our patient presented with a severe form of the disease involving multiple organ systems, including dermatological, neurological, and renal manifestations. This case illustrates the diagnostic challenges, treatment limitations, and psychological impact of TSC in low-resource settings where access to advanced therapies is limited.

TSC has a wide spectrum of clinical manifestations from severe cases to cases so mild that the carriers of the faulty gene do not realize they have it.[15,17] Our patient presented with the severe form of this disease with multisystemic involvement. The central nervous system manifestations that were present in our patient included SENs and cortical tubers seen on the MRI scan, while renal manifestations included multiple bilateral renal angiomyolipomas of varying sizes in a background of bilateral polycystic kidneys with left hydroureter, as shown by MRI scan. Concerning the cutaneous manifestations, the patient exhibited angiofibromas, fibromas on the scalp, an ash leaf spot, and shagreen patches. There were no cardiac or respiratory manifestations in our patient.

The diagnosis of TSC is made using 2 sets of diagnostic criteria; one is the Genetic diagnostic criteria, where the identification of either TSC1 or TSC2 gene mutations is sufficient to make a diagnosis of TSC, and the other is the Clinical diagnostic criteria which favors resource-limited settings such as Zambia where genetic studies are not performed. The Clinical

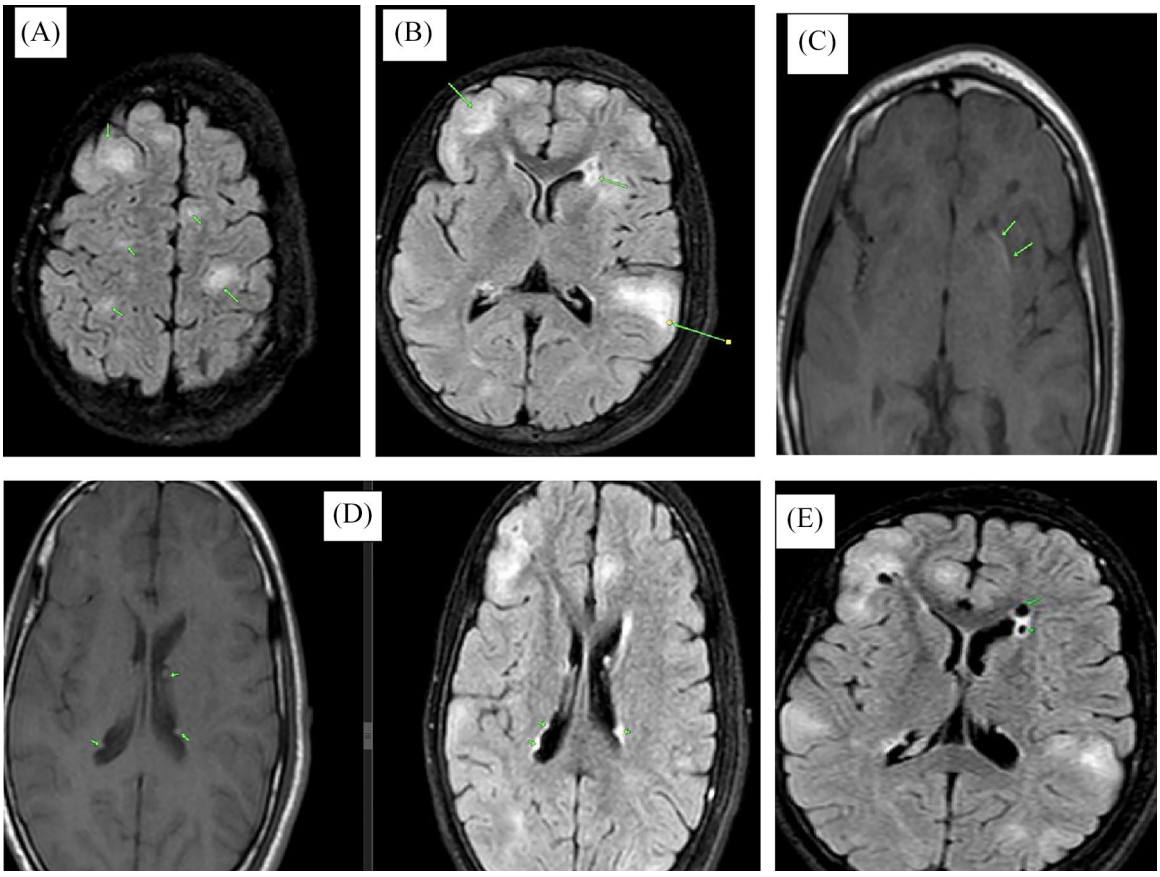

Figure 2. Radiological findings: (A, B) Bilateral cortical/subcortical patchy areas of variable T1 and high T2/FLAIR signal intensity with no restricted diffusion or enhancement compatible with cortical tubers; (C) Radial bands are orientated perpendicular to the ventricular wall; (D, E) Multiple bilateral periventricular and subependymal nodular lesions with predominantly high T1 and low to intermediate T2/FLAIR signal intensity—some of which are calcified (blooming on SWI).

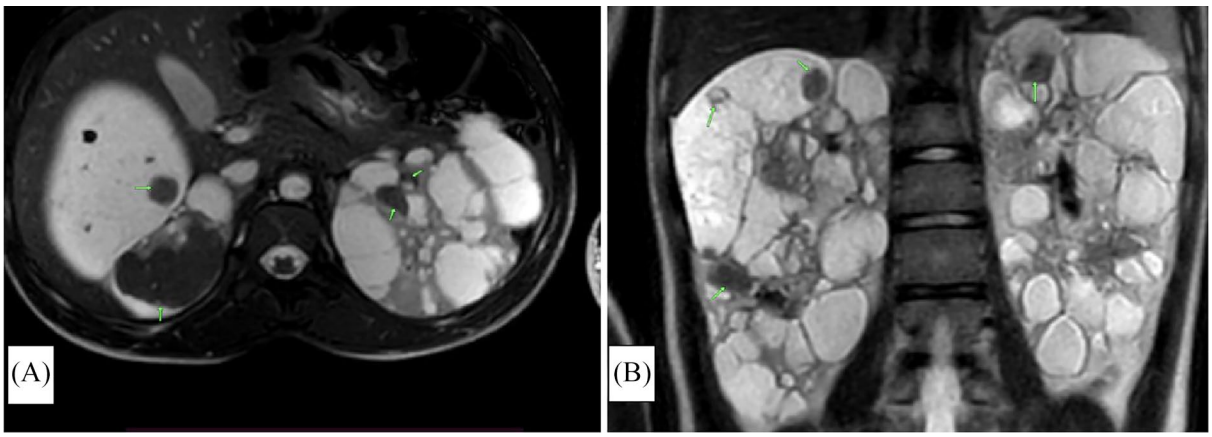

Figure 3. (A, B) Multiple bilateral renal angiomyolipomas of varying sizes—largest measuring 5 cm × 4 cm in a background of bilateral polycystic kidneys with hydroureter on the left.

diagnostic criteria have major and minor features as shown in Supplemental Table 1.[17] A definite diagnosis is made in the presence of 2 major features or 1 major feature plus ⩾ 2 minor features. A possible diagnosis is made with either 1 major feature or ⩾ 2 minor features.[17] A definite diagnosis was made in this case because the patient had more than 2 major features, that is, hypomelanotic macules, angiofibromas, shagreen patch, subependymal nodules, cortical tubers, and angiomyolipomas as well as 2 minor features, that is, dental enamel pits and multiple renal cysts.

In resource-limited settings, a thorough physical examination is pivotal for the clinical diagnosis of TSC. Physicians should be vigilant for hallmark signs such as facial angiofibromas, particularly in a butterfly distribution, shagreen patches,

Figure 4. (A) and (B) shows face with Angiofibromas before electrocauterization; (C) and (D) shows face after 2 sessions of electrocauterization.

hypopigmented macules (ash leaf spots), and renal manifestations like angiomyolipomas and polycystic kidneys, which may present as abdominal distention, with or without hematuria. In our case, the diagnosis of TSC was delayed until the patient was 14 years old when she was referred to the University Teaching Hospital (UTH) Children's Hospital. The condition had been missed in peripheral healthcare settings, largely due to its rarity and the clinicians' unfamiliarity with the disease. This led to delayed diagnosis and suboptimal management, highlighting the need for improved awareness and training among healthcare professionals in these regions.

The most challenging TSC symptoms for patients and their families to deal with are those that influence behavior, learning, and mental health.[11] It is imperative for parents, caregivers, and educators to have an extensive understanding of TSC Associated Neuropsychiatric Disorders (TAND).[11] Evidence of this is shown in this patient who, by the end of Grade 2, could no longer attend school due to the stigma associated with TSC and the ill-treatment she received from other students due to the facial angiofibromas. Epilepsy will affect between 75% and 90% of people with TSC at some stage. In persons with TSC, epileptic seizures are thought to be caused by the abnormal cells that make up cortical tubers.[13] The tubers are believed to disrupt the highly organized neurological connections of the cerebral cortex, resulting in the misfiring of neuronal electrical activity, that is, seizures. There has been no history of seizures or infantile spasms in our patient.

Approximately 5% of individuals with TSC have a condition called autosomal dominant polycystic kidney disease (ADPKD).[11] The polycystic kidney disease gene, PKD1, is adjacent to the TSC2 gene on chromosome 16p13.[12] Other renal manifestations include angiomyolipomas and renal cancer. Two major manifestations of polycystic kidney disease are renal failure and hypertension.[12] Our patient presented with both polycystic kidneys and angiomyolipomas with preserved renal function. She, however, has hypertension which is being managed medically.

Treatment for TSC was considered to be purely symptomatic because it has no cure, however, growing information from randomized clinical trials, observational studies, and real-world evidence have largely demonstrated the safety and efficacy of mTOR inhibitors in changing the natural history of TSC. mTOR inhibitors may improve clinical manifestations, ameliorate seizures, reduce angiomyolipoma size, and its risk of bleeding, resulting in greater quality of life and survival.[19] Unfortunately, this therapy is not available in limited resource setting like ours. Evidence-based management and coordination of care across medical specialties are crucial throughout the patient's lifespan to reduce morbidity and mortality associated with TSC.[7,14] A multidisciplinary team was involved in managing the patient, including Pediatricians, Pediatric Neurologists, Nephrologists, Ophthalmologists, and Plastic Surgeons. Because of the psychological impact that the angiofibromas had on the patient, such as low self-esteem, leading to self-isolation, psychosocial support was provided for the patient and the family, providing counseling and fostering a supportive environment are essential to improve the quality of life for these patients.

In settings of adequate resources, angiofibromas are treated both non-surgically and surgically. Non-surgical treatment involves the use of mTOR inhibitors such as topical Everolimus and oral Sirolimus, the latter of which has also been used in the treatment of the neurological and renal manifestations of TSC.[9,17] Surgical treatment includes electrodessiccation and curettage, shave or elliptical excision, laser treatment with pulsed dye laser, carbon dioxide laser, and potassium-titanyl-phosphate (KTP) laser.[6,9] However, the outcomes are often less than satisfactory and it should be explained emphatically to the patient, before the procedures, that extensive scar formation follows.[9] In a resource-limited setting like Zambia, the treatment of choice, as in this patient, is electrocauterization which involves the application of direct or alternating current via a resistant metal wire electrode that generates heat to safely remove unwanted tissue. Non-surgical treatment with the use of mTOR inhibitors such as topical Everolimus and oral Sirolimus could not be done in our patient due to the unavailability of these drugs in our setting.[16]

The prognosis of patients with TSC is typically dependent on the severity of each presentation. It also depends on how early treatment for the different manifestations is started.[18] In our case, the diagnosis of TSC was delayed due to the condition

not being recognized in peripheral health centers. This led to suboptimal management, highlighting the need for improved awareness and training among healthcare professionals in these regions. Follow-up for this patient is complicated by her living 300 km away from the tertiary care facility. Long distances and limited transportation are significant barriers to continuous care in low-resource settings. To help improve the above limitations telemedicine/e-health can be used as a useful strategy to overcome the barriers of distance for patients living in remote areas, it can be cost saving for both patients and health systems, and may be used as a channel to improve education and knowledge on rare disorders, such as TSC, reaching health care professionals, patients, and their families.

Conclusion

TSC is a rare multisystemic neurocutaneous disease that is almost always diagnosed clinically. It is therefore important for healthcare professionals, especially those in low- and middle-income countries like Zambia who don't have access to genetic studies to be vigilant for hallmark signs of TSC such as facial angiofibromas, particularly in a butterfly distribution, shagreen patches, hypopigmented macules (ash leaf spots), etc. Diagnosis in our patient was delayed because the condition was missed in the peripheral healthcare centers due to the unfamiliarity of the healthcare professionals with this rare condition. The implementation of telemedicine and/or eHealth would become handy in such cases as it can help improve the knowledge of healthcare professionals in remote areas on rare disorders such as TSC. The management was multidisciplinary and it is important for disease progression to be monitored throughout the patient's life via scheduled reviews to control or prevent further complications. In addition, raising awareness and building communities that support individuals living with TSC would help reduce the stigma associated with TSC which would in turn improve their general outlook on life.

Acknowledgements

We are grateful to UTH-Children's Hospital management for the support given to conduct various tests, the nurses and doctors who have been attending to the patient, and Young Emerging Scientists Zambia (YES Zambia) for the mentorship and support.

Author Contributions

ML and MM wrote the first draft of the manuscript which was revised several times by HM, and the rest of the Authors.

Consent

The patient's mother provided written informed consent for the publication of the case.

ORCID iDs

Mwamba Lienda https://orcid.org/0009-0007-5662-5930
Chishiba Kabengele https://orcid.org/0000-0003-0087-8596
Christina Zulu https://orcid.org/0009-0006-0015-8301
Chihena Hansini Banda https://orcid.org/0000-0002-2743-4218
Hellen M'hango https://orcid.org/0000-0002-4917-9481

Supplemental Material

Supplemental material for this article is available online.

REFERENCES

1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med*. 2006;355:1345-1356.
2. Krymskaya VP. Tumour suppressors hamartin and tuberin: intracellular signalling. *Cell Signal*. 2003;15:729-739.
3. Alsowat D, Whitney R, Hewson S, et al. The phenotypic spectrum of tuberous sclerosis complex: a Canadian cohort. *Child Neurol Open*. 2021;8:2329048x211012817.
4. Rosser T, Panigrahy A, McClintock W. The diverse clinical manifestations of tuberous sclerosis complex: a review. In: *Seminars in Pediatric Neurology*. WB Saunders; 2006:27-36.
5. Marcdante KJ, Kliegman R, Nelson WE. Neurocutaneous disorders. In: *Nelson Essentials of Paediatrics*. 7th ed. Saunders WB-Elsevier; 2015:645-646.
6. Franz DN. Diagnosis and management of tuberous sclerosis complex. In: *Seminars in Pediatric Neurology*. WB Saunders; 1998:253-268.
7. Krueger DA, Northrup H, Roberds S, et al. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. 2013;49:255-265.
8. Monaghan M, Takhar P, Langlands L, Knuf M, Amin S. Impact of facial angiofibromas in tuberous sclerosis complex and reported efficacy of available treatments. *Front Med*. 2022;9:967971.
9. Vasani RJ. Facial angiofibromas of tuberous sclerosis treated with topical sirolimus in an Indian patient. *Indian J Dermatol*. 2015;60:165-169.
10. Zöllner JP, Conradi N, Sauter M, Knuf M, Knake S, Kurlemann G, Mayer T, Hertzberg C, Bertsche A, Immisch I, Klein KM. Quality of life and its predictors in adults with tuberous sclerosis complex (TSC): a multicentre cohort study from Germany. *Neurological Research and Practice*. 2021 Dec;3:1-8.
11. De Vries PJ, Wilde L, De Vries MC, Moavero R, Pearson DA, Curatolo P. A clinical update on tuberous sclerosis complex-associated neuropsychiatric disorders (TAND). *Am J Med Genet C Semin Med Genet* 2018;178:309-320.
12. Cai S, Everitt JI, Kugo H, Cook J, Kleymenova E, Walker CL. Polycystic kidney disease as a result of loss of the tuberous sclerosis 2 tumor suppressor gene during development. *Am J Pathol*. 2003;162:457-468.
13. Curatolo P, Verdecchia M, Bombardieri R. Tuberous sclerosis complex: a review of neurological aspects. *Eur J Paediatr Neurol*. 2002;6:15-23.
14. Curatolo P, Maovero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. *Lancet Neurol*. 2015;14:733-745.
15. Northrup H. Tuberous sclerosis complex: genetic aspects. *J Dermatol*. 1992;19:914-919.
16. Jiying DO, Shen WA, Min YA, et al. Combined treatment with electrocauterization, carbon dioxide laser, and microneedle fractional radiofrequency for facial angiofibromas in tuberous sclerosis complex: a case report and literature review. *Chin J Plast Reconstr Surg*. 2021;3:41-45.
17. De Vries PJ, Leclezio L, Wilmshurts JM, et al. Diagnosis, monitoring and treatment of tuberous sclerosis complex: a South African consensus response to international guidelines. *S Afr Med J*. 2017;107:368-378.
18. Mahadevappa M, Patil V, Poornima KS, Velamala S, Guruprasad BV. Two cases of tuberous sclerosis with multiple rhabdomyoma succumbing to sudden cardiac death. *Indian J Clin Cardiol*. 2021;2:151-157.
19. Monich AG, Bissler JJ, Barreto FC. Tuberous sclerosis complex and the kidneys: what nephrologists need to know. *Braz J Nephrol*. 2024;46:e20240013.