Tuberous Sclerosis Complex and Acute Kidney Injury in an Adult Female Nigerian: A rare Presentation and Review of the Literature

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ABSTRACT

Tuberous sclerosis complex (TSC) is a rare condition classically characterized by mental retardation, facial angiofibroma (adenoma sebaceum) and epilepsy. It is an autosomal dominant disorder with formation of harmatomas involving multiple organs such as the skin, central nervous system, kidneys, lungs, and heart. The renal manifestations of TSC include formation of angiolipoma, cyst formation and renal malignancies. The occurrence of renal failure is very rare in patients with tuberous sclerosis, though it is projected that more cases with renal impairment will be seen as a result of improved life expectancy arising from improving standard of neurology care services received by these patients. We report a case of 25 year old female Nigerian with tuberous sclerosis complex and acute kidney injury precipitated by sepsis.

INTRODUCTION

Associations between tuberous sclerosis complex (TSC) and renal harmatomas and cysts have been well established by several studies [1-3], occurrence of renal failure is rarer probably due to the fact that most patients with tuberous sclerosis were not living beyond the third decade of life because of the complications of epilepsy and mental retardation [3]. It is projected that with improved standard of care, patients with TSC will live longer and manifestations such as renal failure will be observed more frequently [3].

CASE REPORT

A 25 year old female who was referred from a private facility to the haematology unit of the University College Hospital, Ibadan on account of unexplained anaemia. About 6 months earlier, she has observed progressive weight loss, easy fatigability, reduced appetite and recurrent fever. The symptoms worsened over 2 weeks before admission and it was accompanied with bilateral leg swelling, reduction in urine volume, recurrent vomiting and cough productive of scanty whitish sputum. She had difficulty with breathing, but there was no history of orthopnea or paroxysmal nocturnal dyspnea.

She reported a history of rash over the face and trunk since birth, but observed that the rash have been increasing in sizes and numbers. Had no history of seizure, or hearing impairment while her performance at both primary and secondary schools was reported to be below average by the mother. She had no family member with similar rash and her father is hypertensive.

Examination revealed a young female that was dypneic, markedly pale and had bilateral pitting pedal oedema up to the knees. On central nervous

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examination, she was conscious, alert, oriented in time place and person. She was able to perform simple arithmetic sum, and there was no evidence of cranial nerve palsies or that of speech, sensory or motor abnormalities. Her pulse was 100beats/minute, blood pressure was 150/94mmHg while only the first and second heart sounds were heard. She had a respiratory rate of 28cycles/minute with coarse crepitations over left middle and lower lung zones anteriorly. The abdomen was distended with bilateral renal angle tenderness and bilaterally palpable kidneys, there was no ascites and bowel sound was normoactive. Examination of the skin showed multiple hyperpigmented papules and nodules on the face (sebaceous adenoma), leavy scaly patches overlying the back (Shagreen patches), hypopigmented macules on the trunk and dystrophic nails and nail beds (periungual fibroma). See figures 1-3.

The results of her laboratory investigations on admission are shown in table I. Abdomino-pelvic

Table 1: Results of Laboratory investigations at Presentation

Investigations	On admission	2 Weeks after admission	4 Weeks after discharge hospital
Urinalysis			
Blood	2+		Nil
Protein	+		Nil
Nitrite	Nil		Nil
Urine Microscopy	Numerous WBC and 5RBC/HPF		No RBC, 2WBC/HPF
Urine Culture	Escherichia coli sensitive . to Levofloxacin, Ofloxacin and Ceftriaxone		No growth
Full Blood Count			
Haemoglobin concentration	4.5g/dl	7.9g/dl	10.2g/dl
PCV	18%	25%	31%
WBC	12,900/mm^3	9,300/mm^3	5,800/mm^3
Neutrophils	83%	79%	64%
Lymphocytes	17%	21%	37%
Monocytes	Nil	Nil	3%
Platelet	345,000/mm^3	389,000/mm^3	287,000/mm^3
Electrolytes,urea and creatinine			
Serum Potassium	4.8mmol/L	4.2mmo/L	4.1mmol/L
Serum Sodium	134mmol/L	139mmol/L	138mmol/L
Serum Bicarbonate	10mmol/L	17mmol/l	22mmol/L
Serum Chloride	102mmol/L	99mmol/L	104mmol/L
Serum Creatinine	450.48µmol/L	298 µmol/L	93µmol/L
Serum Urea	36.83mmol/L	13.80mmo/L	8.43mmo/L
Serum Calcium	2.05mmol/L		
Serum Phosphate	2.26mmol/L		
Serum Uric Acid	529mmol/L		
Serum Albumin	41g/L		
eGFR(MDRD)	13.3mL/min/1.73m^2	21.4mL/min/1.73m^2	81.944mL/min/1.73m^2

eGRF – Estimated Glomerular Filtration Rate, HPF – High Power Field, MDRD – Modification of Diet in Renal Disease, RBC – Red Blood Cell, WBC – White Blood Cell.

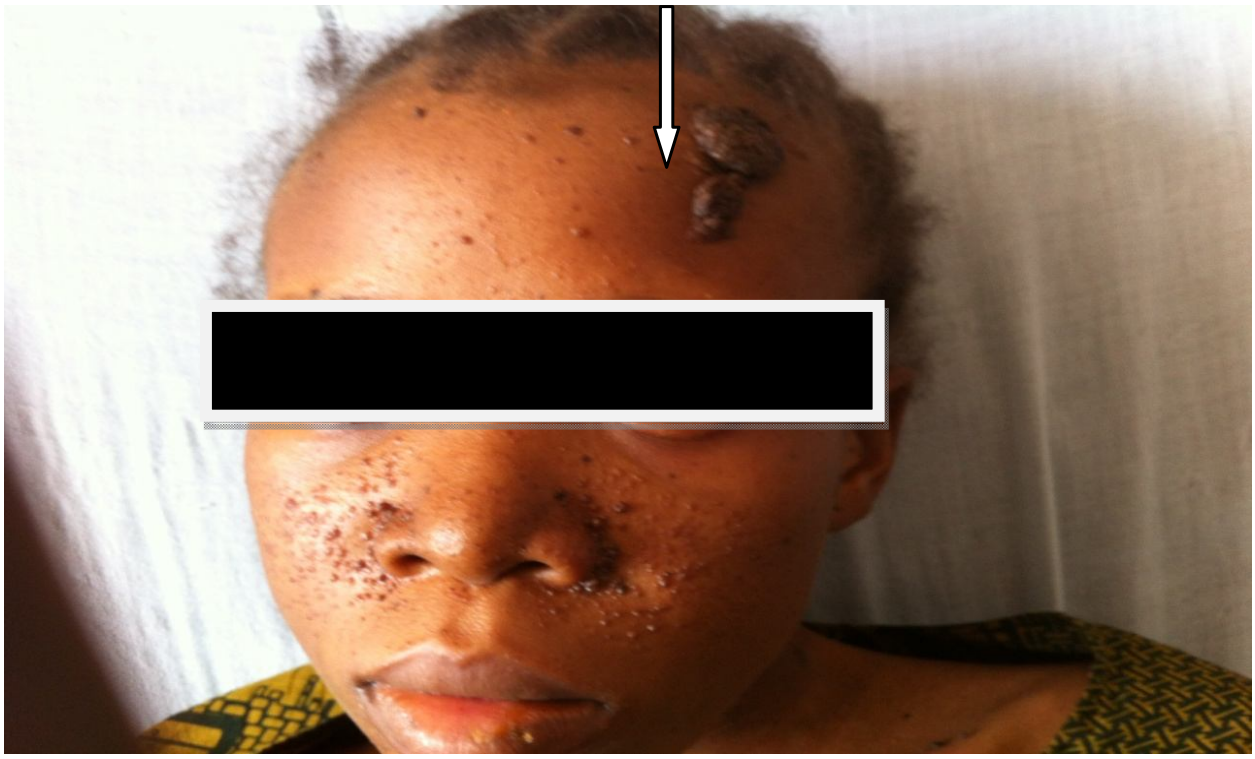

Fig. 1: Showing facial angiofibroma (Adenoma sebaceum) in the patient

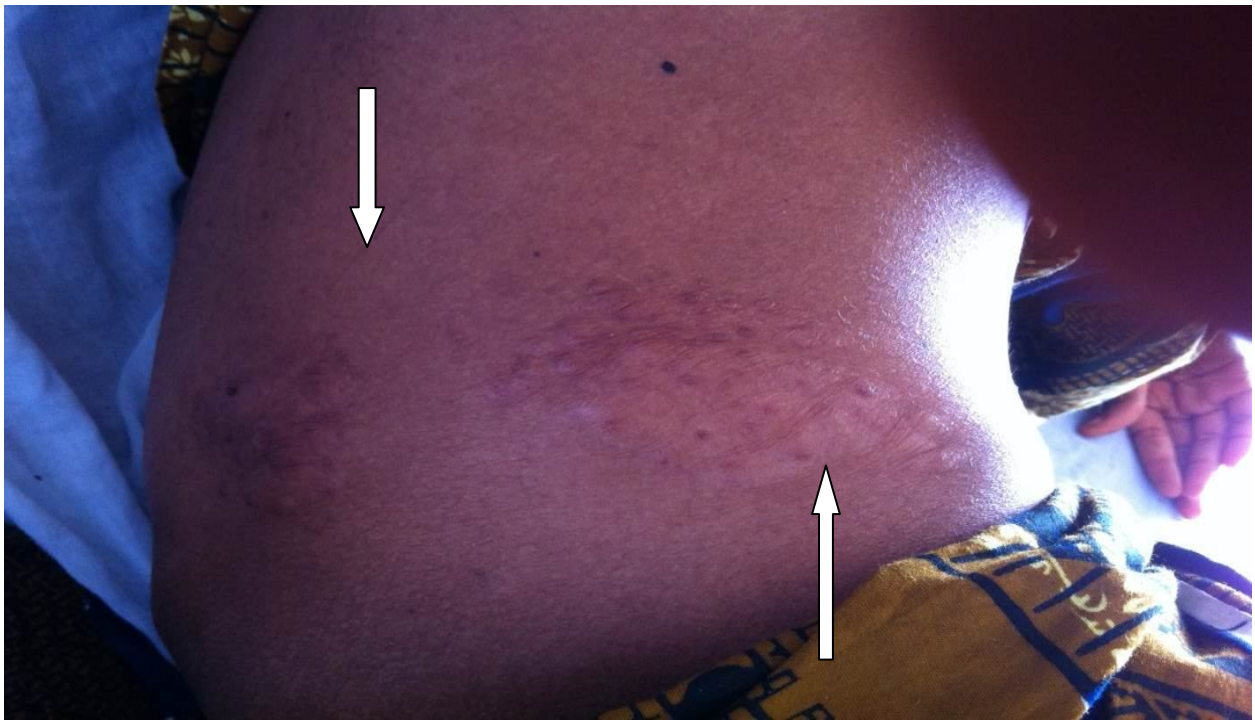

Fig. 2: Showing Shagreen patches in the patients

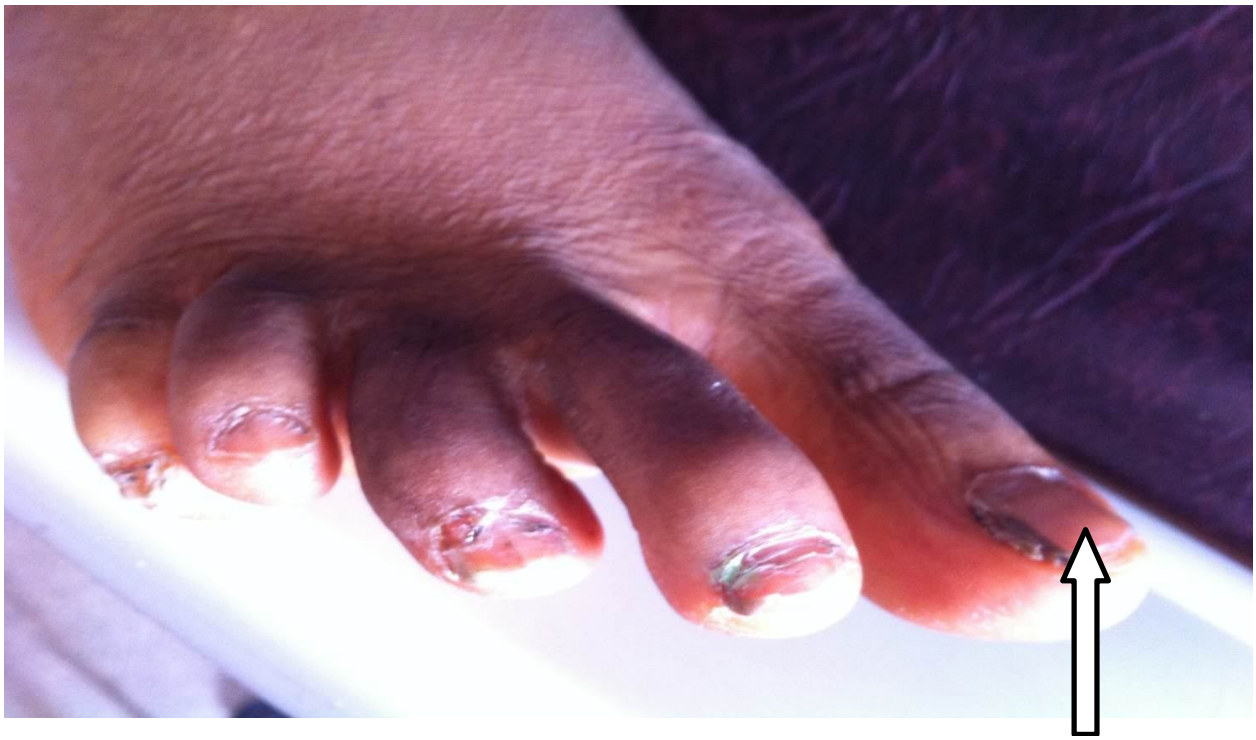

Fig. 3: Showing periungual fibroma

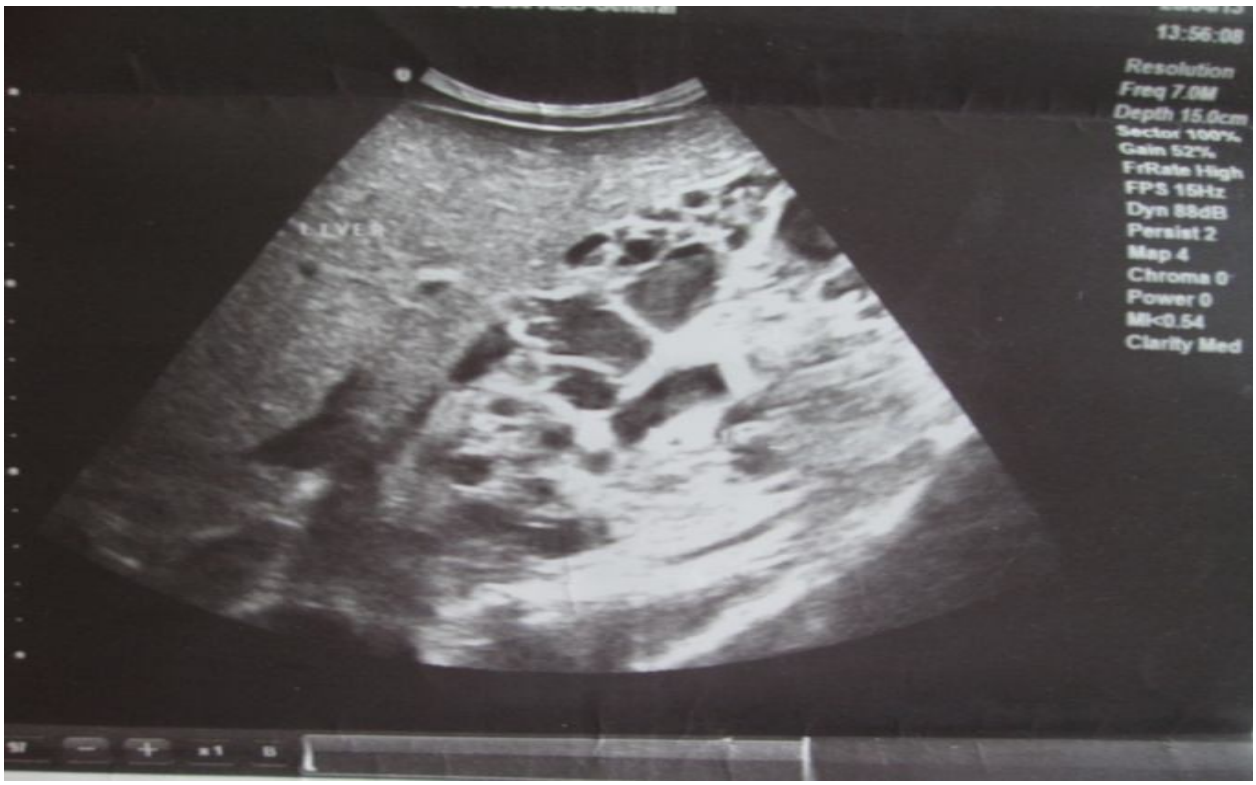

Fig. 4: Shows abdominal ultrasonographic scans of the right kidney with multiple cysts

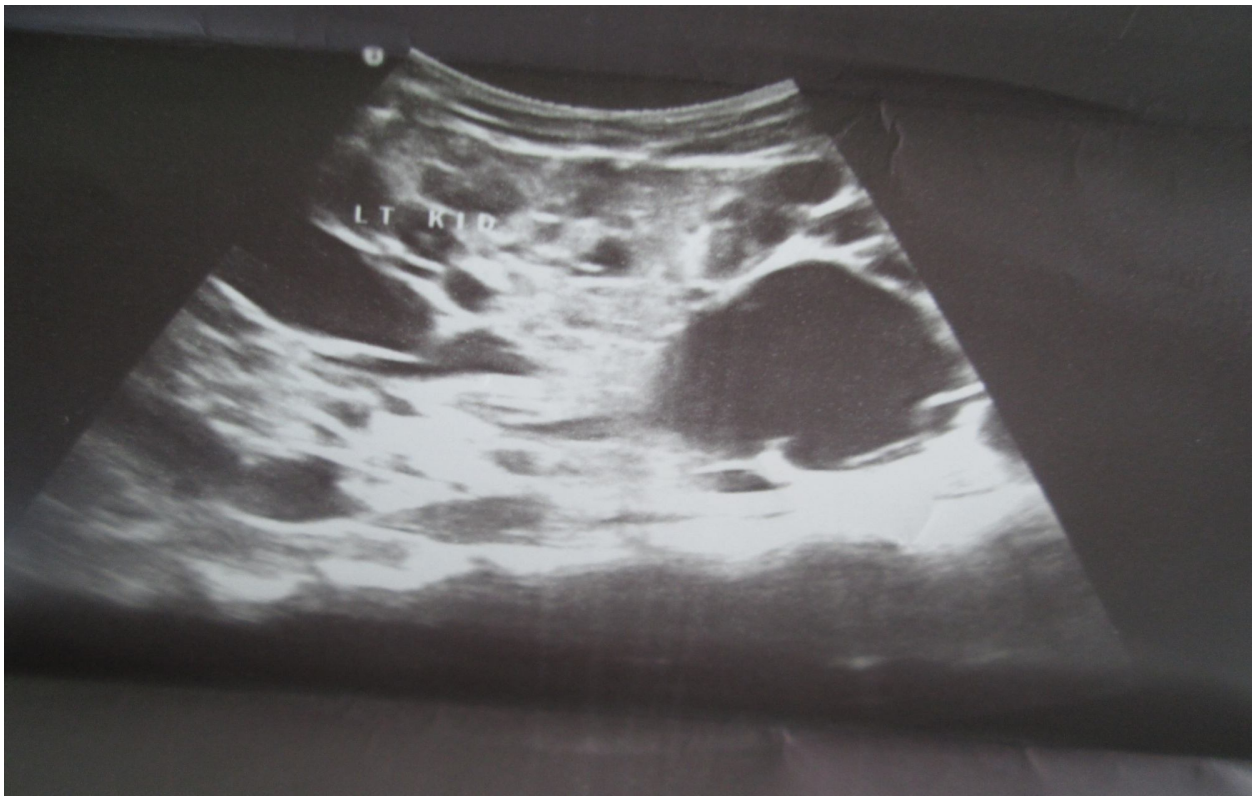

Fig. 5: Shows abdominal ultrasonographic scan with multiple cysts in the left kidney

ultrasound scan showed multiple renal cysts and renomegally bilaterally (Figures 4 and 5). Chest radiograph showed left lower lobe homogeneous opacity with air bronchogram. Echocardiography and cranial computer tomographic scan could not be done because of financial constraint. A diagnosis of Tuberous sclerosis complex with acute kidney injury precipitated by urosepsis and lower respiratory tract infection was made.

She had a 10 day course of intravenous levofloxacin, 2units of red blood cells transfusion and one session of haemodialysis. She was also placed on lisinopril 5mg daily and twice weekly subcute recombinant erythropoetin 4,000 IU and intravenous iron sucrose 200mgweekly. Her clinical condition improved and she was discharged home after 2 weeks of admission. Follow up review of the patient a month after discharge showed sustained improvement with rise in haemoglobin concentration and improved biochemical parameters (see table I). Recombinant erythropoetin was subsequently stopped and she is being followed up in the renal clinic of the hospital.

DISCUSSION

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder characterized by the growth of dysgenic lesions in multiple organs, including the brain, skin, kidneys, heart, lungs, and the eyes. TSC arises from the mutations of either TSC1 gene (chromosome locus 9q34.3) or TSC2 gene (16p13.3), which encode hamartin and tuberin, respectively, these proteins function as tumor suppressors by forming a complex that regulates cellular proliferation [4]. TSC2 is contiguous with type 1 polycystic kidney disease gene (PKD1), the gene involved in one form of polycystic kidney disease (PKD) [5]. TSC is classically characterized by seizure, mental retardation, variety of cutaneous lesions and visceral harmatoma, this classical features are seen in about 60% of cases, the prevalence of TSC is estimated to be 10 – 16 cases per 100,000 live birth [6]. The manifestations of TSC are classified into major and minor, the major features include facial angiofibroma, forehead plaque, hypomelanotic macules, shagreen patches, multiple retinal harmatomas, cortical tubera, subependyma nodules or astrocytoma, renal angiolipomas, cardiac rhabdomyoma,

lymphangioleomyomatosis while the minor features include gingival fibromas, hartomatous rectal polyps, lung cysts, bone cysts, pit in dental enamel, retinal achromic patches. Definite diagnosis requires the presence of 2 major or 1 major and 2 minor features. Probable diagnosis of tuberous sclerosis requires the presence of 1 major and 1 minor features while for possible diagnosis, it requires the presence of 1 major or 2 minor features [7]. Our patient had 4 major features (angiofibromas, coloured plaque on the forehead, shagreen patch, periungual fibroma and hypomelanotic macules) thus the case fit into definite tuberous sclerosis complex.

Renal manifestations is a common finding in patients with TSC, it's estimated rates of involvement range from 48 to 80%, though severe forms of renal impairment are very rare [8]. Only few cases of Tuberous Sclerosis have been reported in Nigeria and the common presentations observed were neurological and dermatological [9-11]. Renal involvement of TSC include angiolmyolipoma (AML), renal cysts, renal cell carcinoma and rarely renal failure. AML is a benign renal tumour and it consists of vascular, smooth muscle and fat tissues, that are usually located in the cortex, it is the commonest renal manifestation in TSC and it is observed in 34-80% of TSC, however the index patient did not have renal angiomyolipoma [3], [12]. One of the severe complications of AML is haemorhage. This patient had multiple bilateral renal cysts of various sizes that were mostly located within the cortices, renal cyst is the second most common renal manifestation of TSC, observed in 14-32% of TSC cases [12]. The presence of multiple bilateral cysts makes TSC a close mimic of autosomal dominant polycystic kidney disease (ADPKD), in fact it may actually co-exist with ADPKD. The association between TSC and ADPKD is demonstrated by the close proximity of TSC2 and PKD1 genes [5]. The occurrence of both diseases together is characterized with severe form of the disease. Renal cell carcinoma occurs in only about 4.2% of patients with TSC and tends to develop at an earlier age compared to the general population [12]. Our patient presented with features of acute kidney injury (AKI) which included reduction in urine volume, bilateral leg swelling, elevated urea and creatinine with improvement in both clinical and bichomical parameters following the treatment of the precipitants. Occurrence of AKI is extremely rare among patients with TSC and the rarity with TSC has been previously documented. Crotchley *et al* [13] and Golji *et al* [14] reported no case of renal failure among 29 and 38 cases of TSC studied respectively. Schillinger et al in France reported that 1 in 100 cases of TSC developed renal failure [15]. The reason for the rarity of renal failure among patients with TSC has been attributed to the fact that most patients rarely live beyond the age of 20 years due to complications arising from seizure disorder and mental retardation.(4) With improved standard of care particular neurological services, most patients with TSC are now living longer and thus the incidence of renal failure is projected to be on the rise among them. Renal failure among TSC is commoner among females just like in the index case, however the reason for female preponderance is not quite clear [15]. The disease is associated with increase severity among females, TSC type 2 and cases coexisting with ADPKD [15]. This case like previous ones have demonstrated that renal impairment will be a common presentation among patients with TSC especially with improving life expectancy resulting from improved neurological cares received by this group of patients.

CONCLUSIONS AND RECOMMENDATIONS

With improvement in standard of neurological care received by the patients with TSC and the improving life expectancy, Nephrologists will be faced with more patients with TSC developing renal failure, it is therefore imperative that preventive strategies be adopted to prevent and delay the development of renal failure through education and regular screening for kidney disease among patients with TSC.

REFERENCES

1. Anderson D and Tannen RL. Tuberous sclerosis and chronic renal failure. Am J Med 1969, 47: 163-168.
2. Okada RD, Platt M and Fleishman J. Chronic renal failure in patients with tuberous sclerosis: association with renal cysts. Nephron 1982, 30: 85-88.

3. Rakowski SK, Winterkorn E, Paul E, Steele DJR, Halpern EF and Thiele EA. Renal manifestations of tuberous sclerosis complex: incidence, prognosis, and predictive factors. Kidney Int. 2006, 70: 1777 – 1782.

4. The European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell 1993; 75: 1305-1315

5. Durham DS. Tuberous sclerosis mimicking adult polycystic kidney disease. Aust NZ J Med 1987; 17: 71-73

6. O'Callaghan FJ, Shiell A.W, Osborne JP and Martyn CN. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. Lancet 1998; 351: 1490.

7. Roach ES, DiMario FJ and Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. J Child Neurol. Jun 1999; 14(6): 401-407.

8. Ewalt DH, Sheffield E, Sparagana SP *et al*. Renal lesion growth in children with tuberous sclerosis complex. J Urol 1998; 160: 141–145.

9. Lagunju IA, Okolo CA, Ebruke GE, Emejulu K, Malomo OA, Akang E *et al*. Severe Neurological involvement in Tuberous Sclerosis. A Review of two cases and Review of African Literature. Afr. J Neuro Sci. 2007; 26: 103-109

10. Ogunrin AO, Adeyekun AA, Akhigbe A and Ofovwe C. Tuberous Sclerosis in a Nigerian Male: Case report and review of the Literature. Discovery and Innovation 2005; 17: 122-128

11. Ogunrin AO. Misdiagnosis of Tuberous Sclerosis in a Nigerian Girl. A case Report and Review of the Literature. Ann Afri Med. 2005; 9(2): 95-101

12. Cook JA, Oliver K, Mueller RF *et al*. Across sectional study of renal involvement in tuberous sclerosis. J Med Genet 1996; 33: 480–484.

13. Critchley M and Earl CJC. Tuberous sclerosis and allied conditions. Brain 1952; 55: 311-346.

14. Golji H. Tuberous sclerosis and renal neoplasms. J Urol 1961, 85: 919-923.

15. Schillinger F and Montagnac R. Chronic renal failure and its treatment in tuberous sclerosis.Nephrol Dial Transplant 1996; 11: 481-485