Incidental finding of Tuberous Sclerosis Complex in a woman with Hematuria: A Case Report of Renal Angiomyolipoma and Review of the Literature

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Abstract

Tuberous sclerosis complex (TSC) is a rare genetic multisystem disorder that was first described by Von Recklinghausen. We report a case of a female who initially presented with hematuria and was later found to have multiple manifestations of the disease. The report emphasizes the value of investigations on suspected cases.

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Abstract

Tuberous sclerosis complex (TSC) is a rare genetic multisystem disorder that was first described by Von Recklinghausen. We report a case of a female who initially presented with hematuria and was later found to have multiple manifestations of the disease. The report emphasizes the value of investigations on suspected cases.

Keywords: Angiofibroma, Angiomyolipoma, Hematuria, Radial migration lines, Subependymal nodules, Tuberous sclerosis complex.

Introduction

Tuberous sclerosis (TS) is a rare autosomal dominant multisystem disorder which was described firstly by Von Recklinghausen and later by Desiree-Magloire Bourneville. The condition has a prevalence ranging from 1:6000 to 1:10000 live births and with a population prevalence of 1: 20,000. With the use of most recent diagnostic criteria a study in Germany estimated the incidence rate of the disease from 1:6760 to 1:13,520 live births. People of any age group, sex or ethnic group can be affected with the condition.

Tuberous Sclerosis Complex 1 (TSC 1) or Tuberous Sclerosis Complex 2 (TSC 2) are two genes linked to the formation of hamartomas in various organs of the body including brain, kidneys, skin, lungs and liver. Seizures, angiofibromas and mental retardation are a part of classic triad of TS that is seen in only 29% of the patients. We describe the case of a 26 years old female who presented with a complain of hematuria in the emergency department of tertiary care center in Nepal.

Case presentation

A, 26 years old female, presented to emergency department with complains of bleeding during micturition for one week and lower abdominal pain of five days. Bleeding was sudden on onset and persistent for about a

week followed with abdominal pain on the lower region. There were no associated gastrointestinal symptoms. There was no prior history of loss of consciousness, seizure, shortness of breath, hemoptysis, chest pain, flank pain, renal stones or other genitourinary disease. There was no history of hypertension, diabetes mellitus, bleeding disorder or tuberculosis. There was no history of similar illness or any lung disease in the family. She is a non-smoker and non-alcoholic.

On examination, she had multiple facial angiofibroma and multiple fibrous plaque on forehead as in Figure 1, 2. Her organ system examination was found to be normal except for mild suprapubic fullness which was non tender on palpation and dull on percussion.

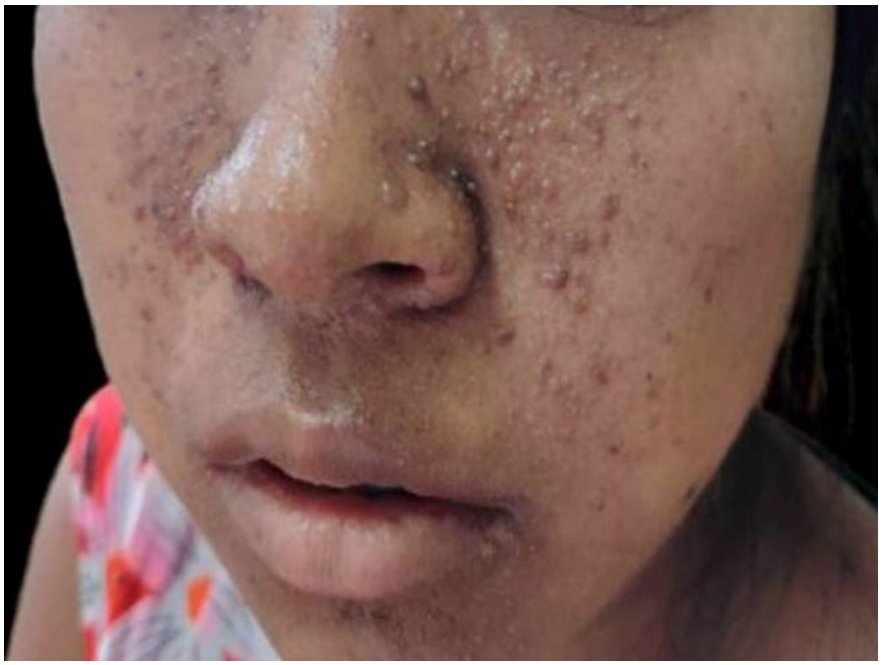

Figure 1: Facial angiofibromas.

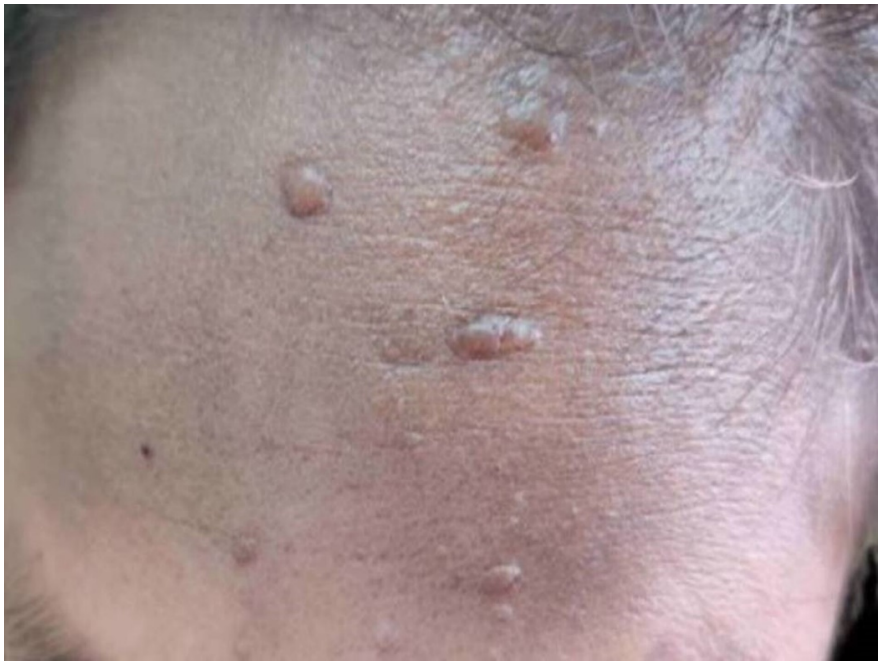

Figure 2: Multiple fibrous plaque on forehead.

Her initial hemoglobin was 7.7 gm/dl and total count was slightly raised to 12400/mm^3. Her other laboratory investigation including electrocardiography, kidney function tests and liver function tests were essentially normal.

She was initially managed with III units of whole blood transfusion and her hemoglobin raised to 9.9 gm/dl. She persistently had hematuria and developed urinary obstruction following which intravenous urogram with computed tomography was done which showed a large hyperdense structure in urinary bladder measuring 12.4x12.2x11.2 cm almost filling the lumen as shown in Figure 3.

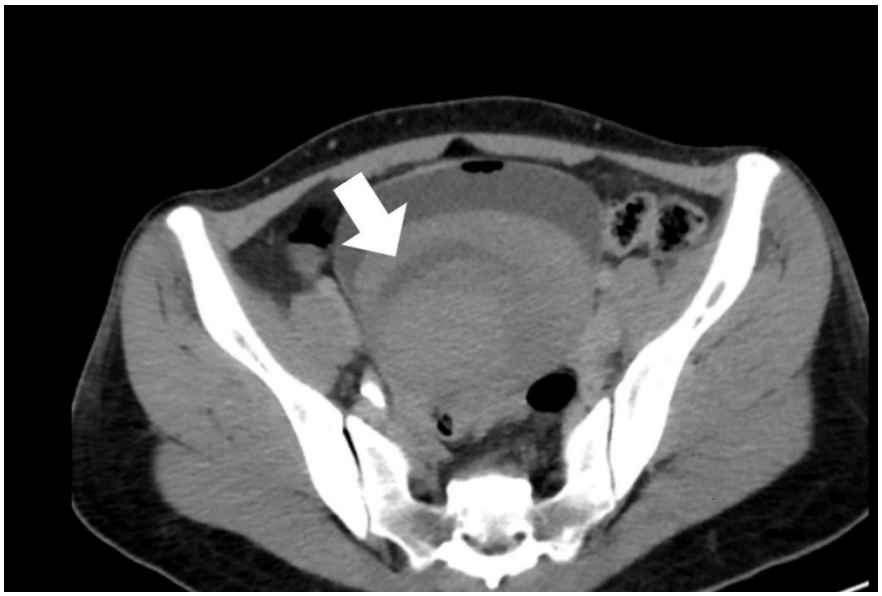

Figure 3: Axial pelvic computed tomography, illustrating urinary bladder with hematoma (white arrow) which was later evacuated with cystoscopy.

Additionally, multiple fat attenuating lesions with soft tissue components were noted to be randomly distributed in bilateral kidneys as shown in Figure 4. The lesion on the left kidney also demonstrated the presence of aneurysmal vessel as shown in Figure 5. Furthermore, multiple well defined fat attenuating lesions with enhancing solid component were noted in liver as shown in Figure 6.

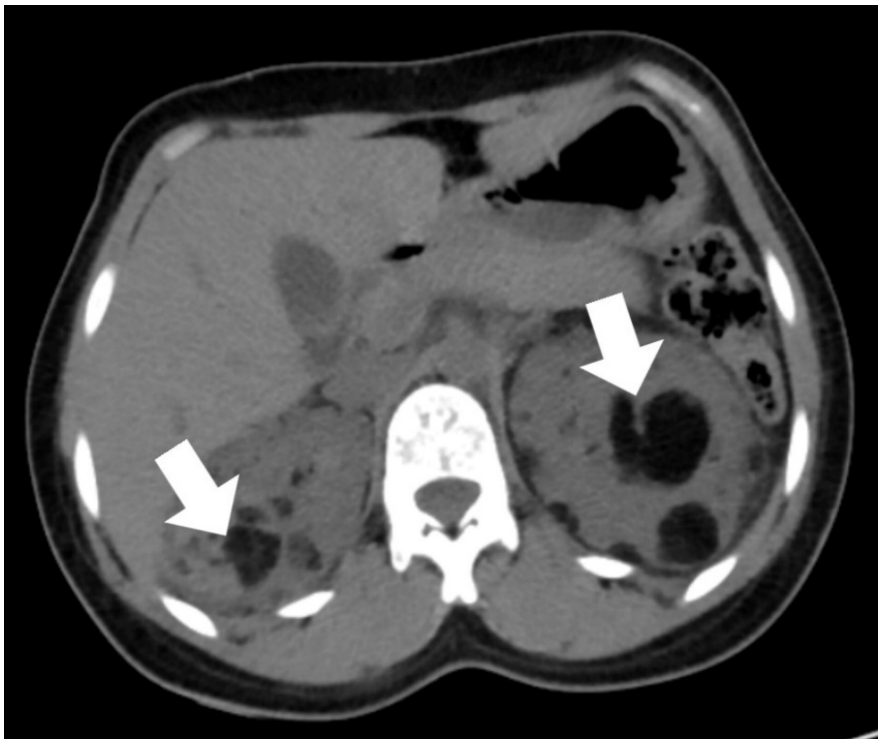

Figure 4: Axial abdominal computed tomography, illustrating multiple bilateral renal angiomyolipoma. White arrow shows darker fat attenuation seen in the lesion.

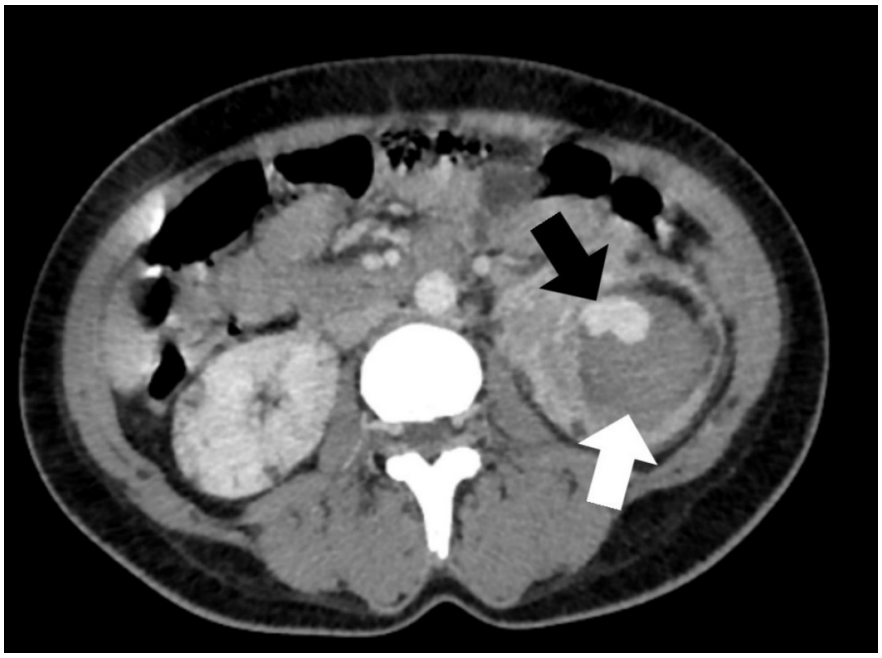

Figure 5: Axial abdominal computed tomography, illustrating aneurysm (black arrow) with adjacent hematoma (white arrow) in the left kidney.

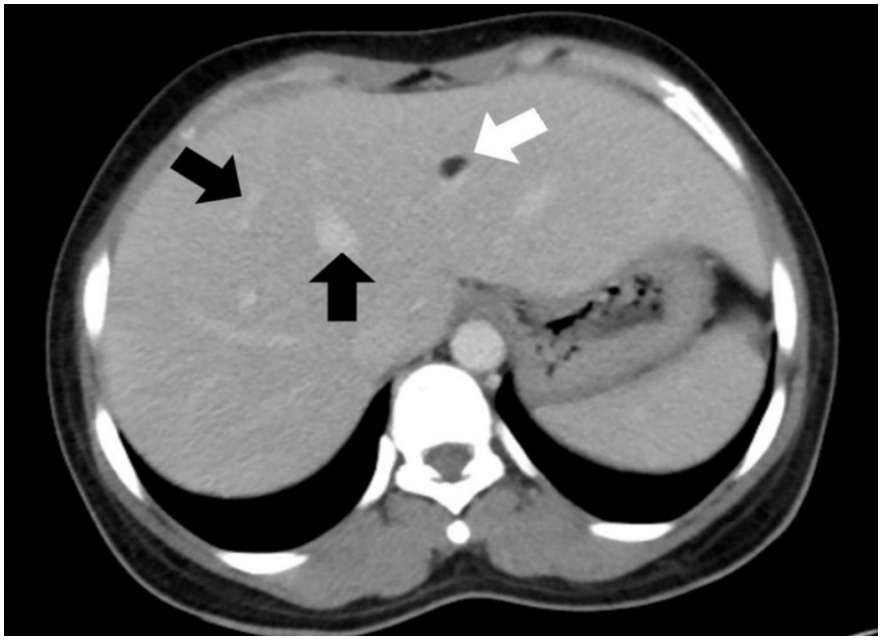

Figure 6: Axial abdominal computed tomography, illustrating fat attenuating lesion (white arrow) with enhancing solid component (black arrow) in the liver.

Cystoscopy was done to relieve urinary obstruction and about 500 ml of organized clot was removed from the urinary bladder. During the procedure gross blood was visualized at the ureteral meatus.

Considering her findings, differential diagnosis of TS, smooth muscle hamartomas, neurofibromas and multiple endocrine neoplasia was made. She underwent further investigations including computed tomography (CT) of head (patient denied MRI). Her brain scan showed multiple calcified nodules along the margin of the ventricles largest one measuring 9 x 6 mm (subependymal hamartomas) and also in subcortical regions (subcortical tubers) as shown in Figure 7, 8 respectively. In addition, her CT image also showed cerebral white matter radial migration lines which is shown in Figure 9.

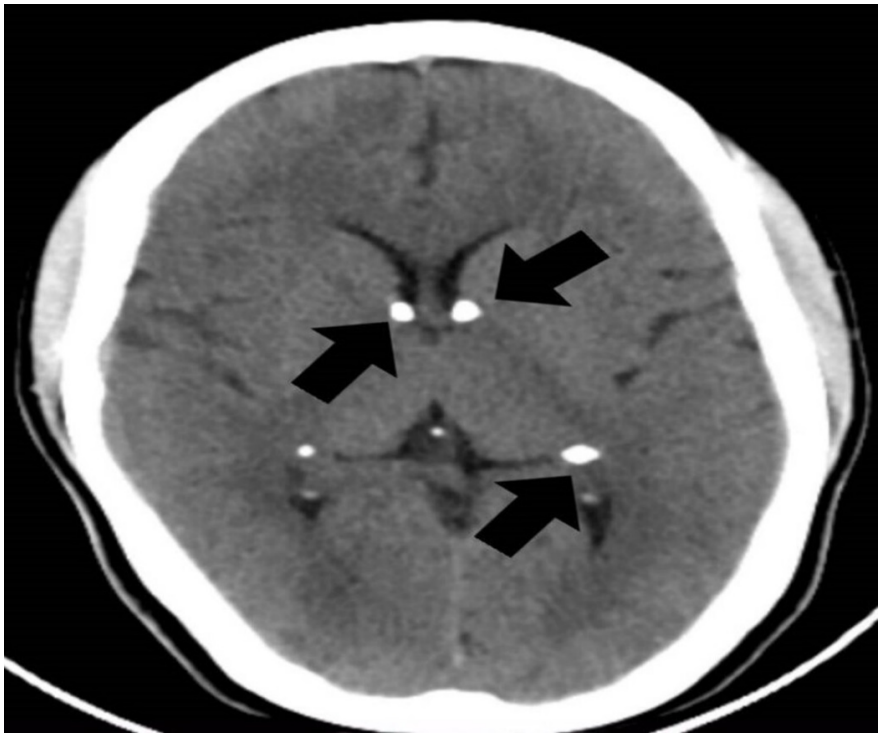

Figure 7: Axial computed tomography of the brain, calcified subependymal nodules along the margin of the ventricles (black arrows).

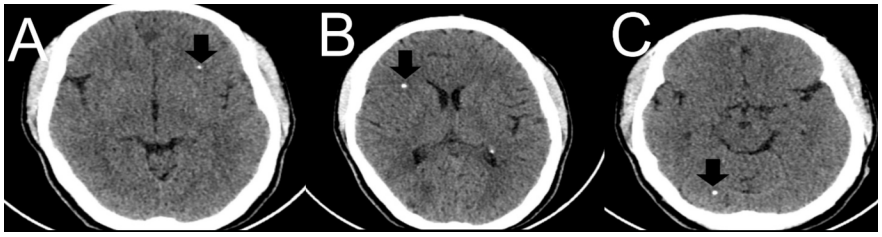

Figure 8: Axial computed tomography of the brain, illustrating calcified cortical dysplasia (black arrows) in the left frontal region (A), right frontal region (B) and right occipital region (C).

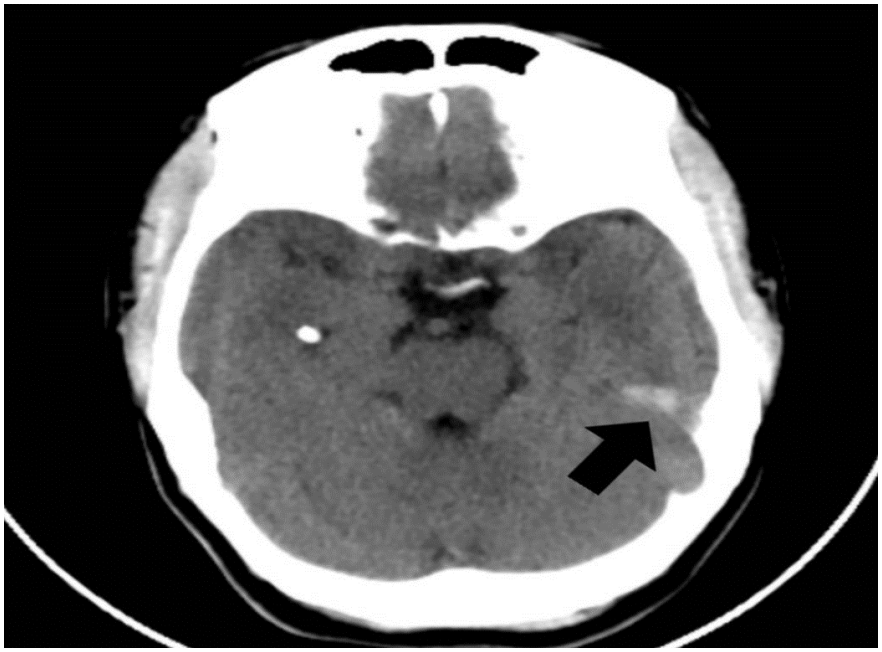

Figure 9: Axial computed tomography of the brain, illustrating cerebral white matter radial migration lines (black arrow).

Interdepartmental discussion was made and she was diagnosed as a case of TSC as she met the diagnostic criteria of definite TS. Patient along with her family were counselled regarding the condition, possibility of another bleeding per urethra which might be fatal and probable need for nephrectomy. Despite the counselling, she opted for medicinal care with regular screening and follow-up for her ailment. During discharge her vitals were stable and her hemoglobin was 12.2mg/dl.

Discussion

Tuberous sclerosis is a rare inherited neurocutaneous syndrome affecting multiple organ system that can have many manifestations associated with severe morbidity and potential mortality. TS is due to the mutation of genes encoding hamartin and tuberin which leads to the uncontrolled growth of hamartomas or tubers in multiple organs of the body. Clinical manifestations of the condition have varied age predilection and extent to which one or the other organ systems are involved and severity are also diverse.

Diagnostic criteria given by International TSC Clinical Consensus Group in 2012 clearly mentioned the importance of independent genetic diagnostic criteria and clinical diagnostic criteria. It is to be noted that in about 10% to 15% of the patient meeting the clinical diagnostic criteria have no mutation identified by conventional genetic testing. This shows the importance of other clinical criteria in resource poor setting where genetic testing is difficult to attain for most of the patients. Also, about two-thirds of the cases are sporadic which might explain absence of family history or features suggestive of TS in any member of family in this patient.

Findings in TS which are a part of the clinical diagnostic criteria are represented on the Table 1.

Table 1: Findings of Tuberous Sclerosis in different organ system of the body classified as a part of clinical diagnostic criteria

Major Criteria	Minor Criteria
Hypomelanotic macules	Confetti skin lesion

Major Criteria	Minor Criteria
Angiofibroma	Dental enamel pits
Ungual fibroma	Intraoral fibromas
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/ or radial migration lines	Non renal hamartomas
Subependymal nodules	Sclerotic bone lesion
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangiomyomatosis	
Angiomyolipomas	

Among the cutaneous lesion in TS hypomelanotic macule occurs in about 90%, angiofibroma in 75%, shagreen patch is seen in about 50%, %, ungual fibroma in 20% and confetti skin lesion in 3% to 58%. Forehead plaque is seen in 25% of TSC patient and is paired with angiofibroma in diagnostic criteria.This patient had both multiple facial angiofibroma and multiple forehead plaque.

Approximately half of the patient with TS have normal intelligence, seizure accounts in about 63% to 78% of infants with TSC and facial angiofibroma occur in about 75% of patients with onset typically occurring between ages 2 to 5 years. In a study on epilepsy in adult patient with TSC, authors found 71.2% of the patient had epilepsy. The classic triad of mental retardation, epilepsy, and facial angiofibroma, also known as Vogt triad occurs only in 29% of the cases with 6% lacking all three of them. Hence, it can be corelated to our patient who has no history of epilepsy and has normal intelligence.

Brain findings in TSC comprises of multiple cortical tubers observed in 90% which is commonly seen together with radial migration lines, subependymal nodules (SEN) and subependymal giant cell astrocytoma (SEGA) which are observed in 80% and 5% to 15% respectively. SEN is often detected prenatally or at birth and SEGA are likely to arise during childhood or adolescence but unlikely after 20 years of age. Calcified multiple subcortical tubers with radial migration lines and subependymal nodules were seen in our patient as well.

In regards to renal findings, three major renal manifestations of TSC are: angiomyolipoma, cysts and renal cell carcinoma. Out of these three, only angiomyolipoma has been considered a part of major diagnostic criteria. Angiomyolipomas are benign tumors composed of varying proportion of vascular, smooth muscle and adipose tissue. It is to be noted that a patient who has lymphangiomatosis (LAM) and renal angiomyolipoma but no other features of TSC, does not meet criteria for a definite diagnosis.

Angiomyolipomas are relatively specific for TSC with incidence of 50 to 75% however it does occur in general population as well with an incidence of 1-2% and a female predominance of 6:1. Classic angiomyolipoma occurs mostly in female in fifth decade sporadically while angiomyolipoma in TSC presents earlier in third decade with no sex predominance. Angiomyolipoma in TSC is more likely to be multiple (97% vs. 13%), bilateral (80% vs 12%), grows with time (67% vs 21%) and bleeding tendency (44 vs 14%). Number and size of angiomyolipoma are known to increase with age which has been corelated with the second-hit hypothesis, marked more in adolescence with a higher frequency in girls. Since, patient in this report had her first presentation at the age of 27 years, increase in size and number could not be estimated. However, she had multiple such lesions of variable size which could have been increasing since long.

Symptoms of angiomyolipoma are absent or minimal with most complains being painless hematuria as in our patient, flank pain or a gross retroperitoneal bleed. There are some other complications that have been reported which include Wunderlich syndrome and end stage renal disease (ESRD). Wunderlich syndrome is a spontaneous bleeding that is confined to the subcapsular and perirenal space which can arise when enlarging vessel becomes aneurysmal and ruptures within angiomyolipoma. Our patient did not have classical Lenk's triad of the syndrome which consists of acute flank pain, palpable flank mass, and hypovolemic shock.

However, the imaging findings does demonstrate aneurysmal vessel and hematoma. The incidence of ESRD in TSC is low and that can be ascertained in our patient with no signs of renal failure despite the presence of multiple angiolipoma in bilateral kidney.

In relation to the imaging finding for diagnosis presence of focal or diffuse fat containing masses is the characteristics feature of an angiomyolipoma which can be visualized with all ultrasonography, CT and MRI with latter being the best alternative in case of limitations or equivocal findings with other modality. It is needless to say biopsy should not be the mode of diagnosis due to the vascularity of the tumor and increased morbidity. In our case, CT was done and it was able to delineate the lesion accurately for us to be able to diagnose the condition.

Regarding treatment of renal angiomyolipoma, recommendations are to use both tumor size and symptomatology to assess the course of tumor progression and intervention to be used. One study found that lesion less than 4 cm were less likely to be symptomatic than lesions that are [?]4 cm (24% vs 52%) and is also less likely to grow (27% vs 46%). Surgical interventions in angiomyolipoma are reserved for patients with symptomatic lesions or lesions with rapid growth. Our patient had symptom of hematuria for which she underwent cystoscopy with the evacuation of hematoma from the bladder, however surgical management of the condition was declined.

Renal manifestations of TSC were the second leading cause of premature death after severe intellectual disability thus it is recommended to have a closer observation and prompt treatment as needed.

Angiomyolipoma has been found not only in kidney but also in other organs including liver as seen in this patient.. Incidence of hepatic angiolipoma is increasing in part due to routine monitoring of patients of TS with renal angiomyolipoma. Hepatic angiomyolipoma are usually asymptomatic though one study mentioned about spontaneous hemorrhage of hepatic angiolipoma in a patient with TS. The clinical significance of recognition of hepatic angiomyolipoma lies in the fact, that misdiagnosis of these usually benign lesion may result in unnecessary and invasive diagnostic procedure.

Other findings associated with TS such as LAM, cardiac rhabdomyoma, dental and ophthalmologic findings, other skin findings along with associated clinical manifestations were not evident in our patient. However, counselling regarding the conditions, possible manifestations in future and treatment was given to the patient.

Conclusions

TS is a rare neurocutaneous disorder. Sometimes a patient may appear with life-threatening symptoms or may not have any symptoms at all for an extended period of time. It is advised that any patient who is suspected to have the condition should undergo further assessment. Additionally, as it can be passed down the generation, information dissemination in the family with this condition needs to be done accordingly.

In conclusion, even though studies have pointed to different aspects and manifestations of the illness, further research and reporting has to be continued to fully comprehend its varied expressions.

References

Figure legend

Figure 1: Facial angiofibromas.

Figure 2: Multiple fibrous plaque on forehead.

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