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Case Report

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Tuberous Sclerosis Complex Unveiled: Presentation of Bilateral Enlarged Diffuse Fatty Kidneys

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ABSTRACT

Tuberous Sclerosis (TS), which is also known as Tuberous sclerosis complex or Bourneville disease, is a rare genetic autosomal dominant disorder with multiorgan involvement. It is a neurocutaneous syndrome or phakomatosis spectrum, characterized by the presence of multiple hamartomas and benign or malignant neoplasms throughout the body, typically in the brain, skin, retina, kidneys, heart and lung. Mutations in Tuberous Sclerosis Complex1 (TSC1) or Tuberous Sclerosis Complex2 (TSC2) genes contribute to the development of these lesions. Despite advancements in treatment, the prognosis for TS remains poor, with approximately 40% of patients succumbing by the age of 35. This abstract is about a young woman presented with bilateral enlarged and abnormally hyperechoic kidneys with loss of normal renal architecture and appeared as retroperitoneal masses on ultrasonography (USG). Subsequent Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) confirmed the presence of fatty parenchyma secondary to multiple bilateral angiomyolipoma's, along with subependymal hamartomas on MRI of the brain, thus aiding in the definitive diagnosis of tuberous sclerosis complex.

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Introduction

Tuberous Sclerosis (TS) is a rare genetic disorder characterized by autosomal-dominant inheritance, with a prevalence ranging from one in 6,000 to one in 12,000. It transcends gender and ethnic boundaries, affecting both sexes and all ethnic groups. First described by Von Recklinghausen and later expanded upon by Desiree-Magloire Bourneville in the 19th century, the disorder is also referred to as Bourneville syndrome, owing to key pathological findings identified in affected individuals. This multisystem disorder involves various organs like brain, skin, heart, kidneys, eyes, lungs, and liver, typically presenting in late childhood [1].

Mutations in either of the two genes, TSC1 and TSC2, encoding for the proteins hamartin and tuberin, respectively, are causative factors for TS. These proteins act as tumour growth suppressors, regulating cell proliferation and differentiation [1]. TS typically presents in childhood with the Vogt triad, consisting of seizures, adenoma sebaceum (facial angiofibromas), and intellectual disorders. Seizures and facial angiofibromas are observed in three-quarters of patients, while intellectual disorders occur in half of patients. However, the complete triad is only present in a minority of patients, approximately 29% [1,2].

The presence of common manifestations aids in confirming the diagnosis of TS, particularly when associated with skin lesions. These include
(i)Cortical tubers or subependymal nodules, White Matter (WM) abnormalities,
(ii)Retinal abnormalities,
(iii)Cardiac rhabdomyoma,
(iv)Lymphangioleiomyomatosis (LAM),
(v)Renal angiomyolipoma (AML),
(vi)Hepatic AML's,
(vii)Splenic hamartomas,
(viii)Renal cysts,
(ix)Bone lesions [2,3].

Skin features such as angiofibromas, ungual fibromas, and shagreen patches rank as the second most common major features documented in the literature for TSC. However, it's notable that skin manifestations often do not prompt investigation and diagnosis of TSC. Renal features, AMLs, were reported as the third most common major feature [1].

Imaging plays a crucial role in the evaluation of TSC, not only aiding in presumptive diagnosis but also in defining the full extent of involvement. Additionally, imaging contributes significantly to treatment planning. The consensus conference in 2012 recommended surveillance guidelines for TSC patients, which include

- Brain and abdominal MRI every 1–3 years until the age of 25 in symptom-free TSC patients, with more frequent monitoring for patients with SEGA or AMLs showing progressive growth.
- Echocardiography every 1–3 years for pediatric TSC patients

to monitor cardiac rhabdomyomas.

- Chest MDCT every 5–10 years for women at risk of LAM.
- Annual detailed dermatologic, ophthalmologic, and pulmonary function testing examination.

Here we present a case of a 19-year-old girl presented at the radiology department for USG abdomen and pelvis examination with a history of menstrual irregularities which revealed diffusely echogenic bilateral kidneys. Further imaging investigation confirmed the diagnosis of Tuberous Sclerosis Complex (TSC)

Case Report

A 19-year-old female with complaints of irregular menstrual history came to the department of radiology for a routine USG to rule out polycystic ovarian disease. She had no other complaints / symptoms. On examination, multiple small lesions appearing reddish-pink or skin-colored bumps on the face, predominantly around the check and nose (Figure 1).

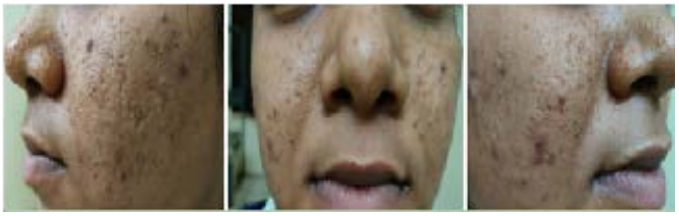

Figure 1: Showing Multiple Small Sized Pink to Red Lesions involving the Cheek and the Nose, Suggestive of Multiple Facial Angiofibroma's

Renal Findings

On USG, both kidneys appeared mildly enlarged [measuring 12.5/5.6 cm on right side and on left side13.5/5.4 cm]. In addition to that the renal parenchyma was completely replaced by echogenic tissue with complete obliteration of corticomedullary differentiation. There was an anechoic area in the midpole region which was in consistent with dilated pelvicalyceal system. CT was done to evaluate further (Figure 2).

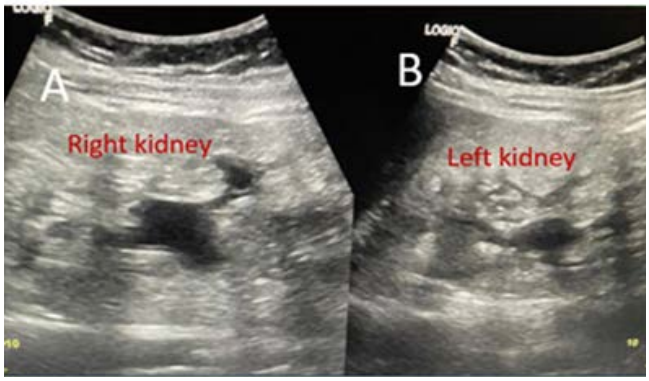

Figure 2: Image A (Right Kidney) and B (Left Kidney) are USG Images Showing Echogenic Kidneys with Loss of Normal Renal Parenchyma

Non contrast CT of abdomen and pelvis revealed bilateral renal enlargement. Multiple low-density areas predominantly of fat attenuation (~56 Hounsfield Units), were observed, replacing the normal renal parenchyma. Based on these findings, a diagnosis of bilateral multiple renal angiomyolipomas with secondary fatty infiltration of the renal parenchyma was considered (Figure 3). Mild prominence of the collecting system was noted bilaterally, without evidence of ureteric dilatation.

Following this non contrast MRI abdomen and pelvis was performed which showed multiple fat intensity lesions involving the bilateral kidneys which are supressed on fat saturation images

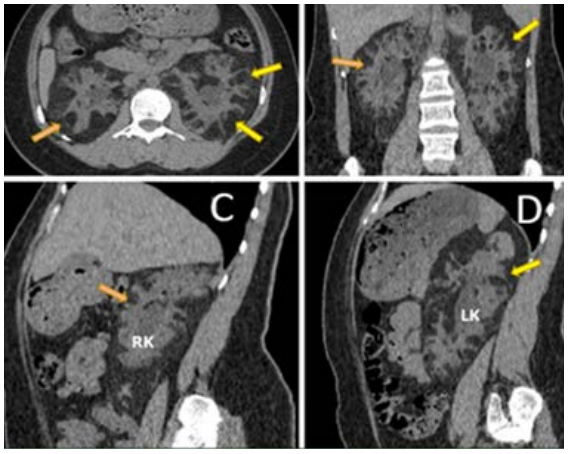

Figure 3: A(Axial), B(Coronal), C and D (Sagittal) Multiple Fat Attenuation Areas, Replacing the Normal Renal Parenchyma of the Right (Orange Arrow) and Left (Yellow Arrow) Suggestive of Bilateral Multiple Renal Angiomyolipoma's with Secondary Fatty Infiltration of Renal Parenchyma. (RK-Right Kidney, LK-Left Kidney).

To further evaluate MRI brain was performed to look for features of TS.

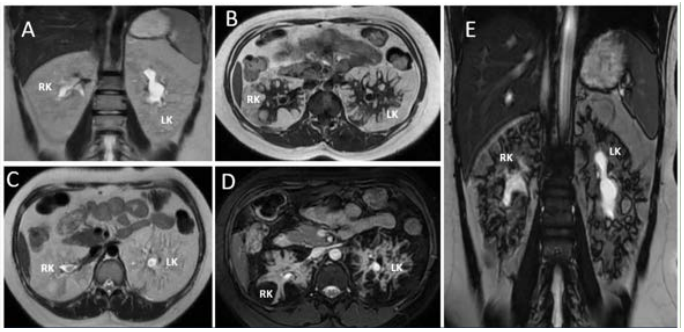

Figure 4: MR Images A (Coronal Single Short Spin Fast Echo), B (Axial T1 out phase), C (Axial T1 in phase), D (Axial T2 FIESTA), D (Axial T2 Fat Suppression) and E(Coronal T2 FIESTA) shows multiple angiomyolipoma's causing secondary Fatty Infiltration of Bilateral Kidneys and showing Fat Suppression of FAT SAT images, Decrease Signal Intensity between in and out phase Images. RK (Right Kidney, LK- Left Kidney).

CNS Finding

On Non contrast brain MRI there were multiple small rounded nodules in the periventricular region, largest measuring 3.9 mm appearing hyperintense to grey matter on T1w and iso to hyperintense to grey matter on T2w weighted images. These finding are in consistent with subependymal hamartomas (Figure 5).

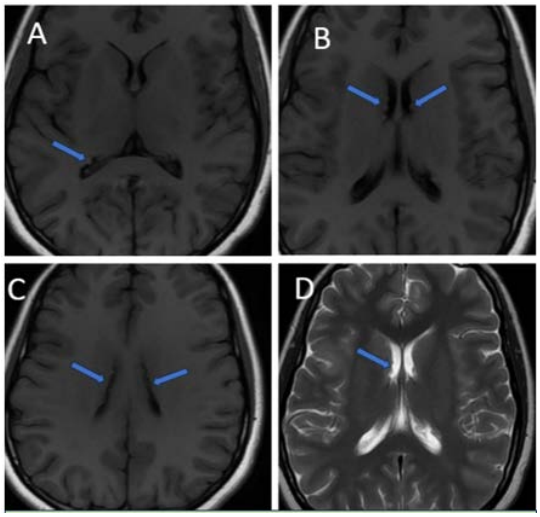

Figure 5: MR Images Axial A to C (T1W1) and D (T2W1) shows multiple rounded nodules were in the Periventricular region of bilateral lateral ventricles, appearing hyperintense to grey matter on T1 and iso to Hyperintense to grey matter on T2 weighted Images, Suggestive of subependymal hamartomas

Few subcortical lesions appearing hyperintense on T2w and FLAIR images were seen in frontal, parietal and occipital region. These features were more in favor of subcortical tubers (Figure 6).

On Coronal images, there were linear areas of signal intensities, hyperintense to white matter on T2 and FLAIR images extending from left periventricular white matter to subcortical white matter of the parietal region. These were inconsistent with the radial migration bands (Figure 6).

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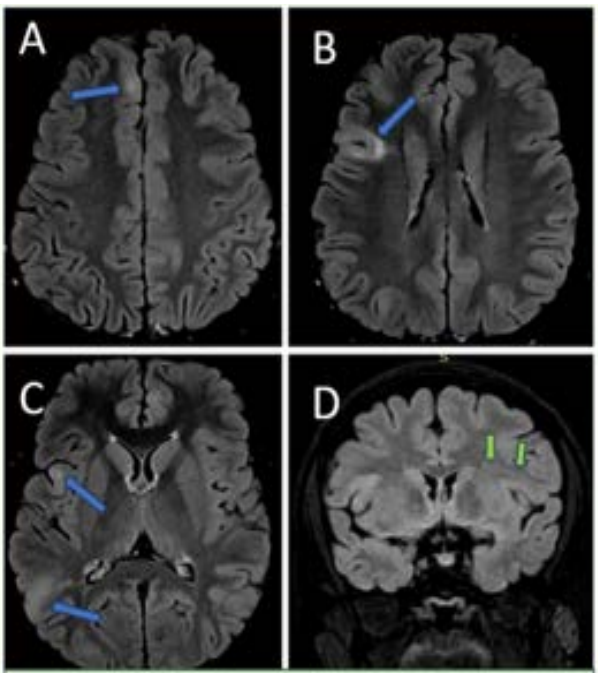

Figure 6: MR Images Axial A to C(T2W1) shows T2 and FLAIR hyperintensities in subcortical white matter in frontal, parietal and occipital, suggestive of Cortical Tubers (Blue Arrows). D Coronal T2W1 shows Linear Hyperintense Signal intensity, Suggestive of Radial Bands (Green Arrows).

Thorax Findings

CT thorax showed no cystic lesions, however multiple randomly distributed nodular lesions measuring < 10 mm were seen in the right middle and bilateral lower lobes (Right > Left) , largest nodule was measuring 5.8 mm. These nodules were of both semi solid and solid type lesions. Based on this possibility of multifocal micronodular pneumocyte hyperplasia was thought which was a part of TSC (Figure 7).

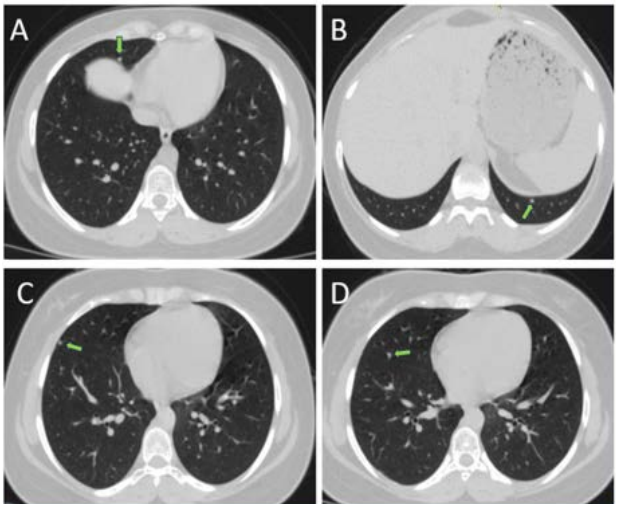

Figure 7: Axial CT image in Lung Window Shows Multiple Randomly Distributed Nodular Lesions in Bilateral Lung Fields. A Possibility of Multifocal Micronodular Pneumocyte Hyperplasia was Considered

Discussion

TSC is defined by the emergence of atypical tumor-like growths, known as hamartomas, in different parts of the body including the brain, skin, retina, and internal organs. The term "tuberous sclerosis" specifically denotes the occurrence of multiple sclerotic masses dispersed across the cerebrum. Diagnosis of TSC based on the detection of hamartomas in more than one organ system [4]

In our case, the initial imaging finding that provided a clue for the diagnosis of TSC was the presence of multiple facial angiofibroma's and bilateral enlarged kidneys with fatty changes of renal parenchyma which could be renal angiomyolipomas with secondary fatty infiltration of the kidneys. Subsequent radiological investigations revealed additional features such as subcortical tubers, radial bands, subependymal hamartomas, and multifocal multinodular pulmonary pneumocyte hyperplasia, further supporting the diagnosis of TSC. These findings are very specific for the diagnosis of TS and hence the diagnosis of TS was established in this patient.

Angiomyolipomas occur in a significant percentage of tuberous sclerosis cases, ranging from 40% to 80%. Typically, these angiomyolipomas associated with tuberous sclerosis are small, multiple, and often bilateral, exerting pressure on the renal parenchyma and collecting system without invasive tendencies. CT imaging serves to confirm the diagnosis by revealing the characteristic low density of the fatty component. The combination of typical ultrasound and CT findings is considered pathognomonic for angiomyolipoma [5]. However, the interesting aspect of this

patient lies in that complete replacement of the renal parenchyma by echogenic fat, which is an unusual presentation. The differential diagnosis for abnormally echogenic kidneys includes conditions such as acute and chronic glomerulonephritis, ethylene glycol poisoning, amyloidosis, and leukemia. However, these disorders typically exhibit diffusely increased parenchymal echogenicity with preserved corticomedullary differentiation, unlike the findings observed in our case. Jackson et al. also reported a similar case of bilateral renal angiomyolipomas with secondary fatty infiltration [6].

Brain lesions in TSC often manifest as cortical tubers, which are developmental abnormalities characterized by the disruption of the normal six-layer structure of the cerebral cortex, alongside the presence of dysmorphic neurons and large astrocytes. These tubers are the underlying cause of neurological symptoms in TSC patients and are typically best detected through MRI imaging. However, in our study, all brain lesions were incidentally discovered during MRI scans. It's important to note that cortical tubers differ from cortical dysplasia, which is a congenital abnormality resulting from a failure of a group of neurons to migrate to their proper location in the brain during development. Subependymal hamartomas are benign growths often characterized by calcifications. Radial bands are distinctive linear structures extending from the periventricular white matter to the subcortical region and are highly specific for tuberous sclerosis [7].

MMPH, or multifocal micronodular pneumocyte hyperplasia, is a lung feature in TSC characterized by multiple small pulmonary nodules. High-resolution CT scans typically reveal nodules ranging from 1 to 8 mm in diameter, scattered diffusely throughout the lungs in a random distribution with respect to the secondary lobule. The presence of these tiny nodules in a random pattern in a TSC patient should raise suspicion for MMPH. However, it's important to consider other potential diagnoses such as miliary granulomatous infections, Langerhans' cell histiocytosis (LCH), or hematogenous metastases. While MMPH is more commonly associated with TSC compared to LAM, it rarely occurs in patients without TSC or LAM. The presentation of MMPH as a manifestation of TSC, which, to our knowledge, has only been reported once before in the radiologic literature [8].

Drug therapy for certain manifestations of TSC is currently under development. Recent trials have demonstrated promising results with the use of topical 0.1% rapamycin for treating facial angiofibromas. Additionally, the utilization of mTOR inhibitors in inducing regression of various hamartomatous growths represents a novel approach in the management of TSC [4].

The prognosis of TSC varies depending on the severity and extent of organ involvement. Approximately a quarter of severely affected infants are believed to pass away before the age of 10 years, with 75% succumbing before reaching 25 years. However, in cases where individuals are diagnosed later in life with few cutaneous signs, the prognosis depends on the presence of associated internal tumours and cerebral calcifications [9].

Conclusion

Tuberous sclerosis is a rare autosomal dominant neurocutaneous syndrome characterized by benign congenital tumours in multiple organs. The classical triad of epilepsy, mental retardation, and adenoma sebaceum is infrequently observed at clinical examination. Radiologic examinations play a vital role in both the diagnosis and treatment of tuberous sclerosis. Common radiologic findings include cardiac rhabdomyoma, renal angiomyolipoma, and neurologic involvement such as cortical or subependymal tubers and white matter abnormalities. The detection of these entities can strongly suggest tuberous sclerosis. Furthermore, the presence of LAM, MMPH, or multiple renal cysts can also raise suspicion of tuberous sclerosis.

The clinical course and prognosis of patients depend on the sites of manifestations. Diagnosis is typically established based on diagnostic criteria applied to physical or radiologic findings, hence imaging plays a crucial role in the diagnosis of TS. Therefore, familiarity with both the clinical and radiologic findings across various organs is crucial for accurate diagnosis and effective treatment

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