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A Classic Case of Tuberous Sclerosis with Multisystem Involvement Including Giant Bilateral Renal Angiomyolipomas Presenting as Massive Hematuria

Kewal A. Mistry^{1ABCDEF}, Dinesh Sood^{1AEF}, Rohit Bhoil^{2EF}, Veenal Chadha^{3EF},
Ajay K. Ahluwalia^{1EF}, Saurabh Sood^{1EF}, Pokhraj P. Suthar^{4EF}

¹ Department of Radiology, Dr. Rajendra Prasad Government Medical College, Kangra, India

² Department of Radiology, Indira Gandhi Medical College, Shimla, India

³ Department of Community Medicine, Dr. Rajendra Prasad Government Medical College, Kangra, India

⁴ Department of Radiology, Baroda Medical College, Vadodara, India

Author's address: Dinesh Sood, Department of Radiology, Dr. Rajendra Prasad Government Medical College, Kangra, India, e-mail: drpgmc12@gmail.com

Summary

Background:

Tuberous Sclerosis (TSC) also known as Bourneville disease is a neurocutaneous syndrome having an autosomal dominant inheritance pattern, though the condition has a high rate of spontaneous mutation. It is the second most common neurocutaneous syndrome after neurofibromatosis. This disease demonstrates a widespread potential for hamartomatous growths in multiple organ systems.

Case Report:

We report a case of a 36-year-old female with TSC presenting as massive hematuria with underlying giant bilateral renal angiomyolipomas (AML) with estimated total tumor burden of more than 8 kg which is to the best of our knowledge the highest ever reported. The patient also had lymphangiomyomatosis and lesions in the brain, skin, teeth and bones.

Conclusions:

TSC has a wide variety of clinical and radiologic manifestations. It should be suspected when some of the common radiological manifestations are found, including CNS involvement, renal and hepatic AMLs and LAM, even if clinical signs are not obvious. Renal AMLs in setting of TSC may reach giant proportions and may present with massive hematuria.

MeSH Keywords:

Angiomyolipoma • Congenital Abnormalities • Lymphangiomyomatosis • Tuberous Sclerosis

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Background

Tuberous Sclerosis (TSC) also known as Bourneville disease is a neurocutaneous syndrome which has an autosomal dominant inheritance pattern [1], though the condition has a high rate of spontaneous mutation. It is the second most common neurocutaneous syndrome after neurofibromatosis. This disease demonstrates a widespread potential for hamartomatous growths in multiple organ systems [2]. The incidence is estimated to be one in 6000 to one in 12000 [3]. An increasing number of cases of TSC are being diagnosed which may in part be due to better imaging modalities, revision of the diagnostic criteria and screening of the family members of a known case resulting in recognition

of the condition in people with a less severe phenotype. It affects all races and though a congenital disorder, it may manifest at any age ranging from birth to adulthood [4]. No sex predilection is noted; however it has higher morbidity in females which is due to increased incidence of lung involvement. Overall, the most common cause of death is lymphangiomyomatosis (LAM), if present, and in its absence, renal failure, status epilepticus, bronchopneumonia and heart failure (in that order) are responsible for the death of the patient [2]. At the molecular level, mutations in TSC1 (Tuberous sclerosis complex) or TSC2 resulting in overproduction of vascular endothelial growth factor are responsible for this condition; however, its diagnosis remains largely clinical. Molecular analysis may be helpful

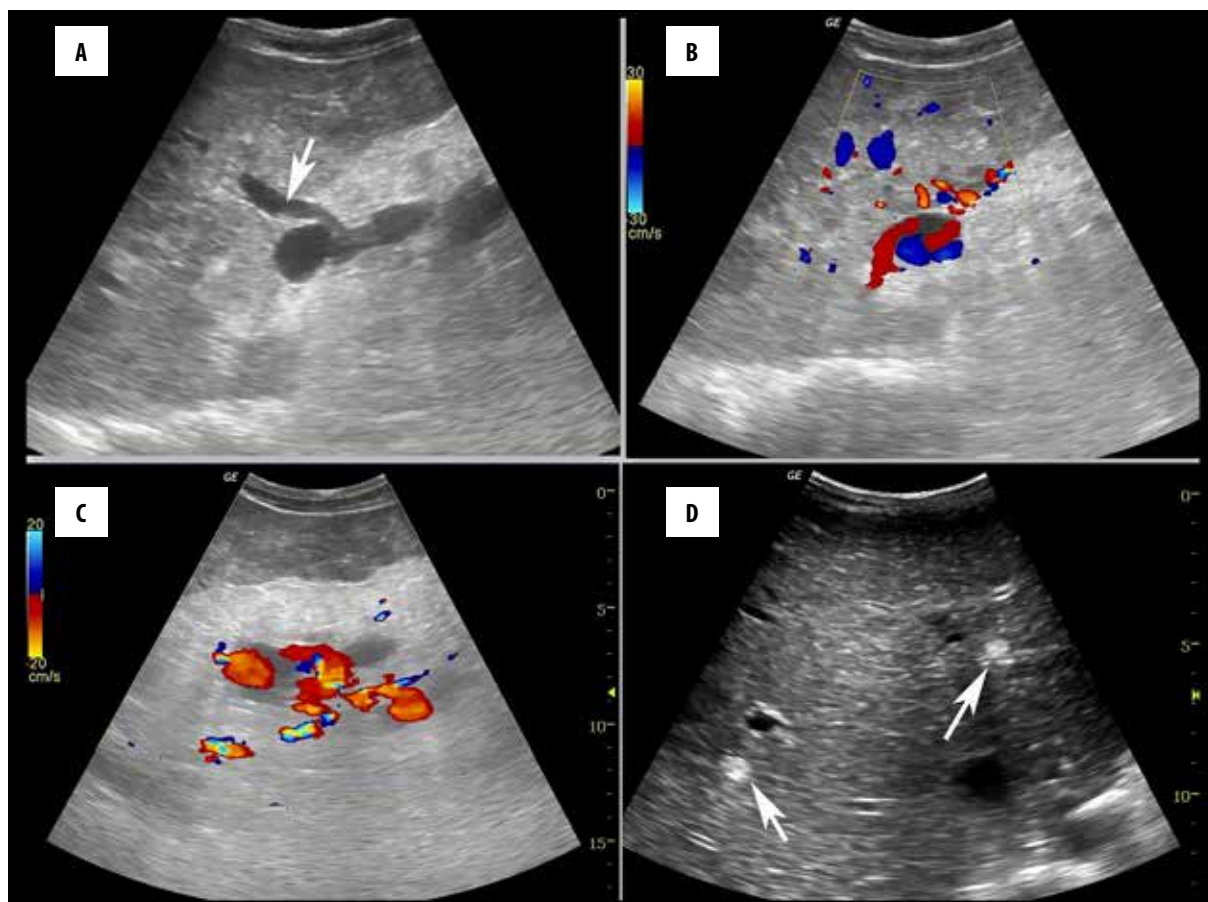


Figure 1. (A) Oblique coronal US image of the right renal region showing a heterogenous mass with a large echogenic fatty component and a less echogenic soft-tissue component with prominent vessels within it (arrow). (B, C) Oblique coronal color Doppler US image in the right and left renal region respectively, showing highly vascular fatty masses. (D) Subcostal US scan of the liver showing presence of small echogenic lesions in both lobes consistent with small angiomyolipomas.

in confirming the diagnosis and for genetic counseling [3]. Failure in regulation of the mTOR pathway also appears to be critical to the pathogenesis of TSC and mTOR inhibitors such as rapamycin have been used in treatment of this condition [5].

Case Report

A 36-year-old female presented with a sudden onset of massive hematuria with a longstanding history of gradually progressing abdominal distension. She had a similar but milder episode two months back. Her hemogram revealed anemia with hemoglobin of 6.4 g/dL. Erythrocyte sedimentation rate was 30 mm in the 1st hour. Her renal function tests (RFTs) were deranged with serum creatinine level of 1.8 mg/dL. Serum electrolytes and liver functions were normal. The patient had not undergone any previous imaging or medical treatment.

Emergency ultrasound (US) of the abdomen revealed multiple heterogeneously hyperechoic masses occupying the whole abdomen, showing internal tortuous vessels with aneurysmal dilations at places which were seen on color Doppler scans (Figure 1A–1C). The mass on the right side showed a large non-fatty soft tissue component along its superior aspect (Figure 1A). Kidneys were not visualized

separately from the mass. The liver revealed a few small well-defined hyperechoic lesions (Figure 1D). That sonographic appearance was suggestive of giant bilateral renal angiomyolipomas (AML) and small hepatic AMLs. Non-contrast-enhanced computed tomography (CT) of the brain, thorax, and abdomen was carried out which confirmed the sonographic diagnosis of giant bilateral renal AMLs with prominent fatty components and internal prominent vessels showing aneurysmal dilations at places (due to her deranged RFTs, contrast-enhanced CT could not be carried out.) Those lesions measured 29×27.5×15.5 cm on the right side and 30×19×13 cm on the left side (Figure 2A, 2B). The urinary bladder showed hyperdense fluid with attenuation of 30–40 Hounsfield units suggestive of hemorrhagic contents. Small well-defined lesions having fat density were seen in the liver, consistent with AMLs. Volumes of both kidneys were calculated using CT volumetry software. The right kidney measured 4546.7 cc and the left one 3758.3 cc, with a total tumor volume of 8305 cc and estimated tumor burden of more than 8 kg.

Multiple calcified subependymal nodules were noted in the brain on CT (Figure 2C, 2D), and thorax CT revealed variable-sized air-filled cysts throughout the parenchyma in both lungs (Figure 3) consistent with lymphangioliomyomatosis (LAM). Multiple small ill-defined sclerotic lesions

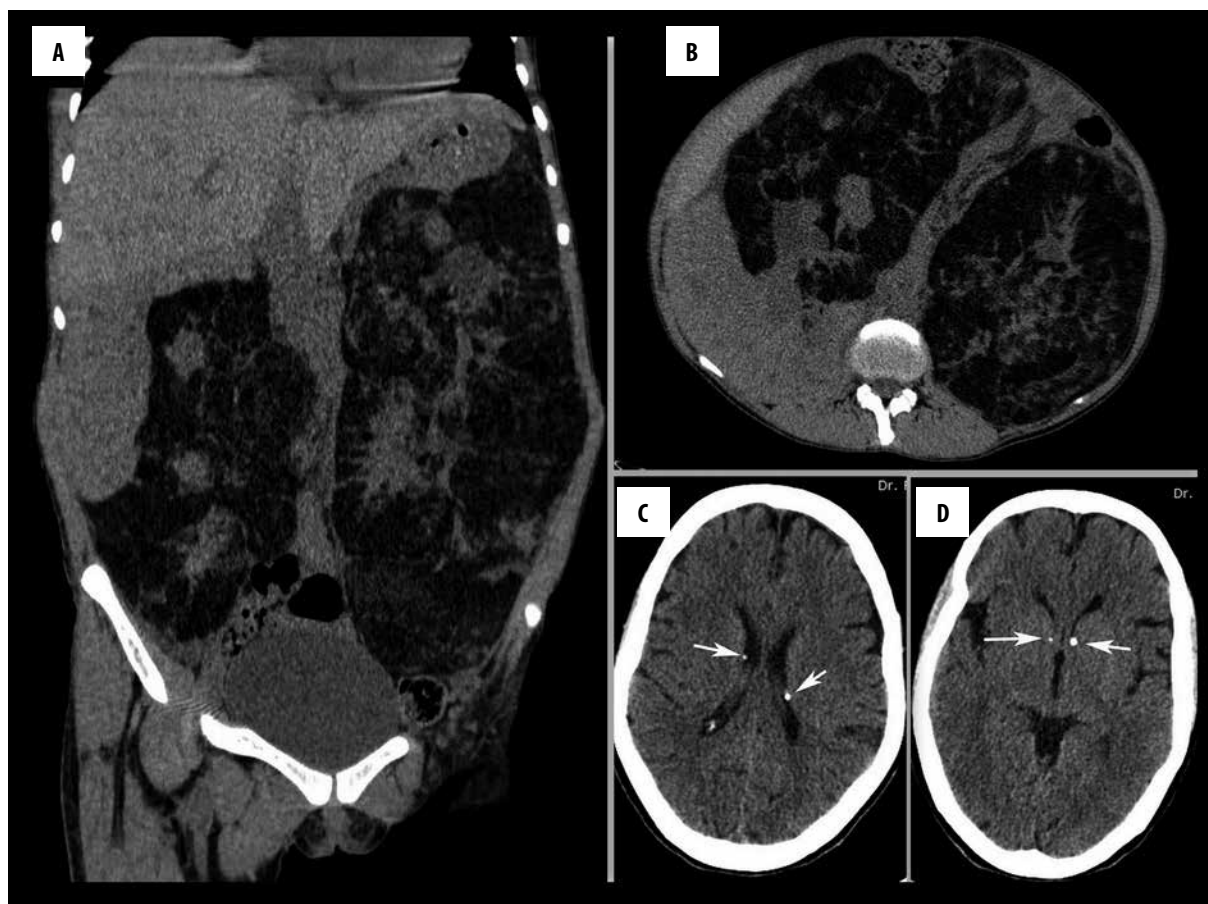


Figure 2. (A, B) Coronal and axial non-contrast-enhanced CT scans showing massive bilateral predominantly fatty renal masses consistent with angiomyolipomas. (C, D) Axial non-contrast-enhanced CT of the brain showing calcified subependymal nodules (arrows).

were seen throughout scanned axial skeleton including the skull, vertebrae and ribs (Figure 4).

There was no history of seizures and the patient did not have mental retardation; though there was a history of intermittent headaches for which she took over-the-counter analgesics but never sought medical advice. She also complained of generalized body aches for the last 5–6 years. On examination typical facial angiofibromas (adenoma sebaceum) (Figure 5A) were present over the face along with a few hypopigmented macules and patches over the trunk. There was presence of dental pitting over a few teeth in the upper jaw (Figure 5B) along with multiple periungual and gingival fibromas (Figure 5B–5D). Echocardiography was normal. There was no family history of similar complaints.

The patient was considered for bilateral nephrectomy; however, she declined surgery and did not come back for a follow-up.

Discussion

Historically, TSC has been characterized by Vogt's triad, comprising mental retardation, adenoma sebaceum and seizures; however, all of these are seen together in fewer than 50% of patients [3,6,7]. However, seizures are seen in 60–90% of patients with TSC [1]. Tuberous sclerosis has a

broad clinical spectrum affecting almost every organ system in the body.

Clinical presentations of TSC may range from clinically asymptomatic to a wide range of symptoms like headache, seizures, chest pain, cough, flank pain, hematuria etc. Whenever a characteristic feature of TSC like brain tubers, SEN, SGCA, lymphangiomatosis or renal angiomyolipoma etc. is encountered, a thorough evaluation of other organ systems should be made. Besides ultrasound of the abdomen and CT and MRI of the brain, abdomen, as well as CT of the thorax, other investigations include CT angiography, echocardiography, pulmonary function testing, fundoscopic examination, electroencephalography, renal and liver function tests [4,8,9]. For confirmation of the findings and for genetic counseling, molecular tests may be used. However, these are expensive and not routinely available [9].

Hamartomas in different body organs, mainly in the brain, skin, eye, kidney, liver, lung, and heart are characteristic of TSC. Renal involvement in tuberous sclerosis complex consists of angiomyolipomas and renal cysts and rarely renal cell carcinoma. Angiomyolipomas, found in 70–80% of patients with tuberous sclerosis complex, are benign but progressive lesions composed of blood vessels, smooth muscle, adipose tissue, and connective tissue [4]. The gene for polycystic kidney disease (PKD), PKD1, is contiguous

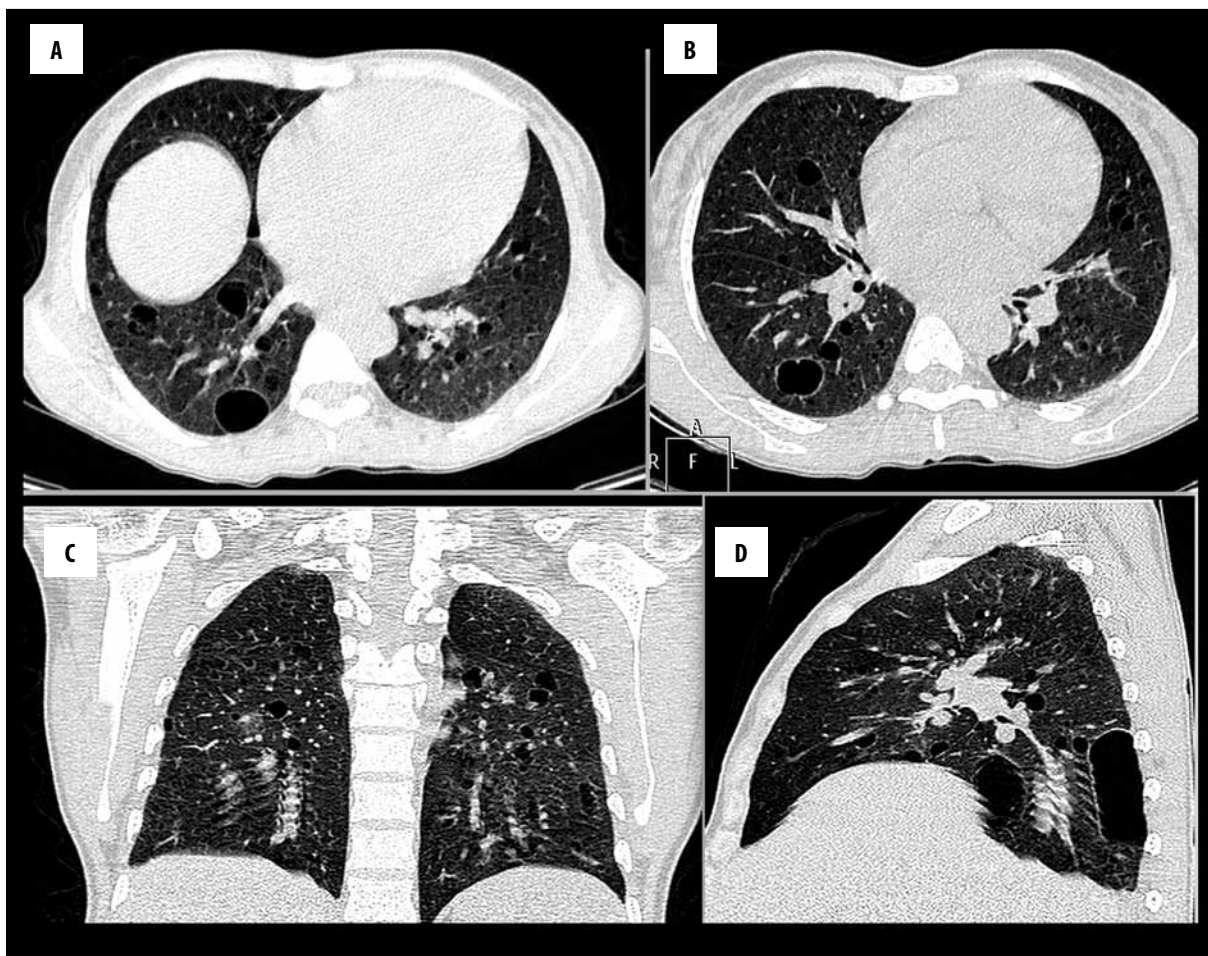


Figure 3. Axial (A, B), coronal (C) and sagittal (D) CT images of thorax in lung window showing presence of multiple variable sized air filled cysts consistent with LAM.

with the TSC2 gene on chromosome 16, and patients with tuberous sclerosis complex occasionally have symptoms of PKD [8]. It has been suggested that concomitant presence of renal cysts rather than angiomyolipomas is the cause of renal failure seen in these patients [2]. There seems to be no consensus on when to term an AML as 'giant'; however, these are often bilateral and lesions larger than 4 cm may present with hemorrhage either spontaneously or after a minor trauma [3]. It is important to differentiate large benign AMLs from renal malignancies and moreover patients with TSC are at a risk of malignant transformation of these lesions [10].

To the best of our knowledge, the largest reported case of unilateral renal angiomyolipoma measured 39×29×9 cm with tumor burden of 7500 g [11] and the largest bilateral renal angiomyolipomas measured 30×21×13 and 30×18×10 cm with total tumor burden of 7843 g [12]. Our case is likely to exceed both of those cases in terms of total tumor burden with an estimated total weight of more than 8 kg.

Pulmonary involvement in TSC is in a form of lymphangiomyomatosis (LAM) and pulmonary cysts. These lesions are composed of blood vessels, smooth muscle and adipose tissue in abnormal arrangements. LAM is a common disease of young women with TSC, which affects the lungs

and lymphatics [3]. Clinically patients present with shortness of breath on exertion, pneumothorax, and fatigue, leading to debilitating respiratory impairment in many cases. Since LAM is predominantly seen in females and may be exacerbated by exogenous estrogens, it has been suggested that the increased estrogen levels seen during pregnancy may be related to disease progression or deterioration [2,13].

Cortical tubers, the hamartomas in the brain, are composed of abnormal glial and neural cells, and their size, number, and location varies among patients [4]. Based on diffusion properties of the white matter, these lesions are associated with disorganized and structurally compromised axons with poor myelination [3,13]. The severity of seizures correlates with the number of tubers; however, these do not have any malignant potential [6,9]. Besides tubers, other CNS lesions include sub-ependymal nodules (SEN) and sub-ependymal giant cell astrocytomas (SGCA) [4,14]. SEN are typically located on the surface of the lateral ventricles, giving a candle-dripping appearance and usually calcify early in childhood [7]. SGCA are typically seen at or near the foramen of Monro and are frequently calcified. These may enlarge in due course but are histologically benign. They may cause obstructive hydrocephalus which is the most common cause of symptoms in patients with SGCA. In

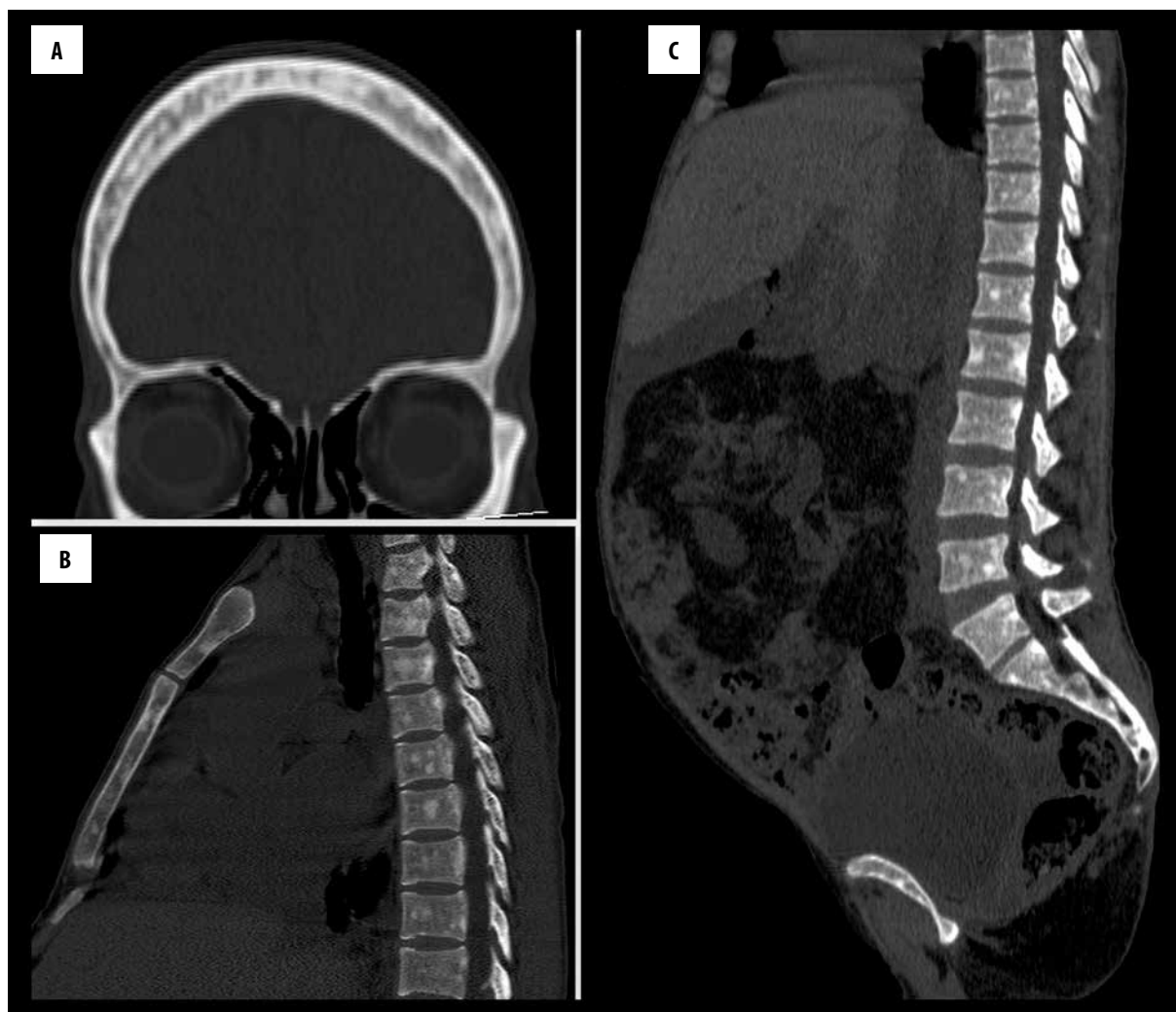


Figure 4. (A) Coronal CT image of the skull, (B, C) sagittal CT images of spine showing multiple patchy sclerotic lesions throughout all bones.

addition, white matter abnormalities in patients with TSC include superficial white matter abnormalities associated with cortical tubers, radial white matter bands, and cyst-like white matter lesions [9].

Cutaneous manifestations include ash-leaf spots, shagreen patches, confetti lesions, facial angiofibromas, fibrous plaques, and periungual fibromas. The hypopigmentation of ash-leaf spots is because of smaller melanosomes and defective transfer of melanin to keratinocytes. Hypomelanotic macules are the most common earliest finding in TSC. Fibromas, plaques, and patches are due to fibrosis with defective collagen and blood vessel accumulation [15].

Other manifestations of TSC include rhabdomyomas in the heart, retinal hamartomas which are seen in over a half of the patients with TSC and may calcify but usually do not lead to visual impairment unless they involve the macula or cause vitreous hemorrhage [9]. Progressive degenerative changes in large elastic arteries, especially the thoracic and abdominal aorta, may lead to aneurysm formation. A 'moyamoya' pattern of collateral circulation may be seen due to vascular dysplasia with progressive occlusion in cranio-cervical vessels. Adenomas may be seen in the liver, spleen

or pancreas [6]. Musculoskeletal involvement is seen in more than half of cases in the form of multiple sclerotic lesions in the diploic space, pelvis and spine. Periosteal new bone may be seen in metatarsals, metacarpals and phalanges [8]. A rectal hamartoma or polyp may be detected using a digital rectal examination. Children with tuberous sclerosis complex may rarely develop a chordoma, a malignancy that arises from notochordal remnants [15]. Oral manifestations of TSC include gingival fibromas and pitting of the dental enamel involving permanent teeth. Dental pitting is seen in almost all patients with TSC.

Due to the broad spectrum of clinical features seen in TSC, all of which may not be simultaneously present, certain criteria have been proposed for the diagnosis of TSC. These consist of both major and minor diagnostic features (Table 1) [16]. As no single clinical manifestation is diagnostic for TSC, all clinical features should be evaluated. Radiological assessment is useful not only in diagnostics but also in determining the course of treatment. Treatment is primarily medical and depends on the clinical presentation of the patient [14]. Low-dose rapamycin has been used to treat LAM and to reduce the size of AML in TSC [17]. Surgery is reserved for cases of giant renal



Figure 5. Clinical photographs of the patients showing. (A) adenoma sebaceum, (B) dental pitting (arrowhead) and gingival fibromas (arrows), (C, D) subungual fibromas (arrows).

Table 1. Diagnostic criteria for tuberous sclerosis complex.

Major clinical features of TSC	Minor clinical features of TSC
<ul style="list-style-type: none"> • Facial angiofibromas or forehead plaques • Shagreen patch (connective tissue nevus) • Three or more hypomelanotic macules • Nontraumatic unguual or periungual fibromas • Lymphangi leiomyomatosis • Renal angiomyolipoma • Cardiac rhabdomyoma • Multiple retinal nodular hamartomas • Cortical tuber • Subependymal nodules • Subependymal giant cell astrocytoma 	<ul style="list-style-type: none"> • Confetti skin lesions (multiple 1 to 2 mm hypomelanotic macules) • Gingival fibromas • Pits in dental enamel • Hamartomatous rectal polyps • Multiple renal cysts • Nonrenal hamartomas • Bone cysts • Retinal achromic patch • Cerebral white matter radial migration lines

angiomyolipomas and aims at preserving the normal renal parenchyma [8,13]. Embolization of the vessels supplying the angiomyolipoma may also be helpful [6,14].

Conclusions

TSC has a wide variety of clinical and radiological manifestations. It should be suspected when some of the common

radiological manifestations are found, including CNS involvement, renal and hepatic AMLs and LAM, even if clinical signs are not obvious. Renal AMLs in the setting of TSC may reach giant proportions and may present with massive hematuria.

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