

## Case Report

# Radiological appearance of tuberous sclerosis complex: a case report and review of literature

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**Abstract:** Tuberous sclerosis complex (TSC) is a rare, auto-somal dominant, hereditary neurocutaneous syndrome, in which hamartomas develop in various organs. Cutaneous features and computed tomography (CT) findings are of great value in the diagnosis of TSC. The present study reported an unusual case of multiple organ abnormalities in a patient with TSC. Radiological findings indicated the presence of cerebral tuberous sclerosis, pulmonary lymphangioleiomyomatosis, renal angiomyolipomas, hepatic hemangioma and hamartomas, vertebral osteosclerosis, and phalangeal cysts of the fingers. TSC is a complex multisystem disorder and radiological analysis is pivotal in its diagnosis. The present study determined that, upon the development of characteristic cutaneous lesions, patients with TSC require radiological examinations, particularly CT scans, to diagnose multiple organ involvement. Furthermore, radiological examinations are useful for the early identification of TSC-associated lesions and for monitoring disease progression.

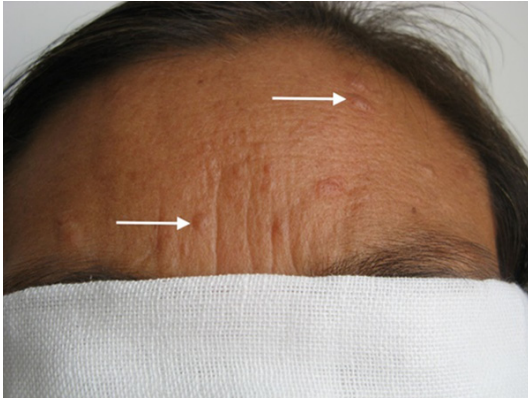
**Keywords:** Tuberous sclerosis complex, computed tomography, appearance

## Introduction

Tuberous sclerosis complex (TSC) is a genetic, variably expressed, multisystem disorder that can cause circumscribed, benign, non-invasive lesions in any organ [1]. The wide range of organs affected by the disease was associated with two genes located at chromosomes 9q34 (TSC1) and 16p13.3 (TSC2) in the regulation of cell proliferation, and differentiation. TSC1 and TSC2 encode the proteins hamartin and tuberlin, respectively [2]. TSC is a protean disease that is characterized by the formation of hamartomas in multiple organs. The incidence rates for TSC were estimated to be 1/6000 to 1/10000 live births and a population prevalence of around 1 in 20000 [3, 4]. There is no cure for TSC, although treatment is available for a number of the symptoms. Because TSC is a lifelong condition, individuals need to be regularly monitored by a doctor to make sure they are receiving the best possible treatments. To the best of knowledge, the current study is the first to present a case of TSC involving the skin, brain, kidney, liver, lung and skeleton, as well as one large renal angiomyolipoma and renal function loss.

## Case report

A 37-year-old female presented to the Emergency Department of Zhongnan Hospital (Wuhan, China) with acute of abdominal distension and a left inferior abdominal mass that had been apparent for 5 months. At five years old, the patient had developed facial angiofibromas and fibrous cephalic plaques that increased in number and size with age; however, the patient experienced no seizures or mental retardation, and no family history of TSC. Upon physical examination, angiofibromas and fibrous cephalic plaques were observed on the forehead and neck, and particularly on the face (**Figures 1 and 2**). The patient's vital signs were within the normal ranges, as follows: Resting heart rate, 90 beats per min; blood pressure, 118/86 mmHg; temperature, 37.5°C; and respiratory rate, 20 breaths/min. The lungs were clear on percussion and auscultation, and no abnormal neurological findings were noted. Furthermore, ophthalmological and cardiac examinations were normal, and the results of laboratory tests and tumor markers were within the normal ranges.



**Figure 1.** Angiofibromas scattered on forehead (arrows).



**Figure 2.** Angiofibromas scattered on face, and neck, obviously on face (white arrows), and fibrous cephalic plaque (black arrow).

The patient underwent X-ray examinations of the chest and hand, intravenous pyelography, and a computed tomography (CT) scan of the brain, lungs and abdomen. The brain CT revealed multiple calcifications along the wall of the lateral ventricle (**Figure 3**). The abnormal pulmonary lesions were inconspicuous on the chest X-ray, however, high-resolution CT (HRCT) revealed small cystic lung lesions that indicated lymphangioleiomyomatosis (LAM; **Figure 4**). Intravenous pyelography demonstrated left renal pelvic and calices deformities, and right renal non-visualization (**Figure 5**). Contrast-enhanced abdominal CT revealed nine hemangiomas and two hamartomas scattered throughout the two lobes of the liver (**Figure 6**). Furthermore, the large left renal angiomyolipoma (AML; diameter, 15 cm) appeared to be pre-



**Figure 3.** CT scan of brain shows multiple calcifications along the wall of the lateral ventricle (white arrows).

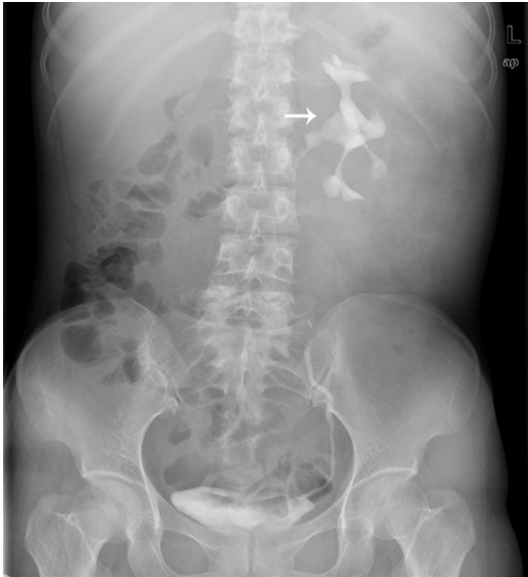


**Figure 4.** Chest HRCT shows thin-walled cysts (arrows) throughout both lungs surrounded by normal lung parenchyma.

dominantly composed of fatty tissue surrounded by abundant vascularities, and the right kidney exhibited atrophic and cystic presentation (**Figures 7 and 8**). Osteosclerosis could be observed in the vertebral verge and vertebral adjacent pedicles (**Figure 9**). In addition, X-ray examination of the hands revealed phalangeal cysts (**Figure 10**).

In consideration of the aforementioned findings and according to the diagnostic criteria of the 2012 International Tuberous Sclerosis Complex Consensus Conference, a diagnosis of TSC was

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**Figure 5.** Intravenous pyelography showed left renal pelvic and calices deformity (arrow), and the right renal nonvisualization.

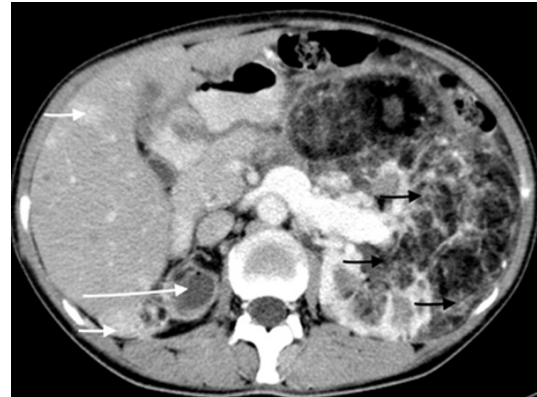


**Figure 6.** Contrast-enhanced CT scan of abdomen shows hepatic hemangiomas (white long arrows) and hamartomas (black short arrows) scattered both lobes of liver, the left renal mass accompanied with predominantly fatty tissue (black long arrows).

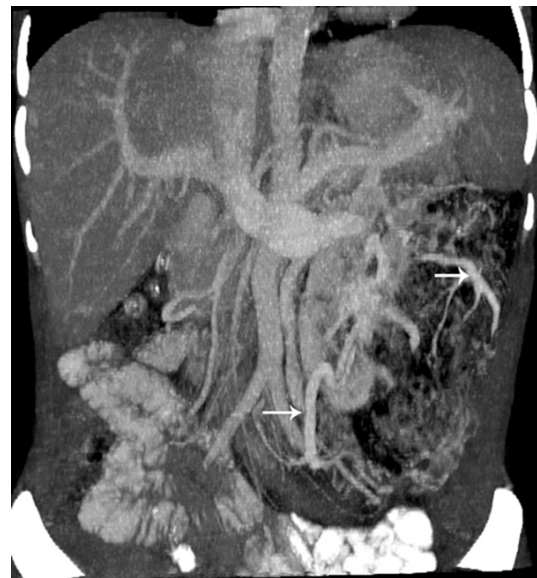
proposed [5, 6]. Due to the loss of right renal function, surgical intervention and embolization therapy were contraindicated. As an alternative, it was proposed that the patient undergo annual radiological follow-up and renal transplantation if required.

### Discussion

It is estimated that TSC affects 1/6,000-10,000 live births and has an incidence rate of about 1/20,000 [3, 4]. The age of onset ranges



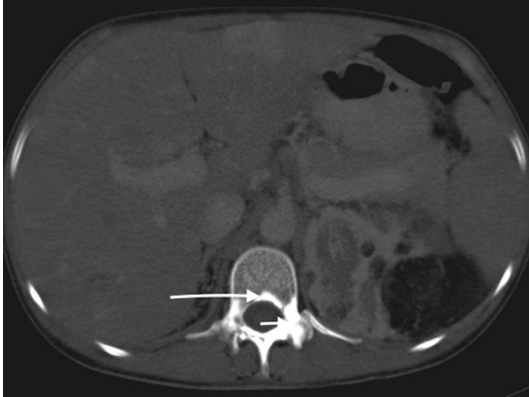
**Figure 7.** Contrast-enhanced CT scan of abdomen shows hepatic hemangiomas (white short arrows), the left renal huge mass accompanied with predominantly fatty tissue (black arrows) and the right kidney appeared atrophy and cystic presentation (white long arrows).



**Figure 8.** Coronal volumetric reconstruction shows the left huge mass was surrounded by abundant vascularity (arrows).

between 2 months and 58 years, with 88.5% of patients surviving for  $\geq 3$  years [7]. Even between closely related individuals, marked variation has been observed in the manifestation of TSC in different organ systems. Furthermore, the clinical diagnosis of TSC can be difficult due to its status as a protean disease. Although analysis of DNA obtained from healthy tissues can be used to identify pathogenic mutations in TSC1 or TSC2 and thus make a definite diagnosis of TSC, conventional





**Figure 9.** Vertebral CT shows osteosclerosis in vertebral body (long arrow), vertebral plate and lateral mass of vertebrae (short arrow).



**Figure 10.** X-ray of hand showed multiple phalanges of toes cysts (arrows).

genetic analyses cannot identify the mutation in 10-25% of patients with TSC. Therefore, the identification of a normal result upon genetic analysis does not exclude a diagnosis of TSC [5]. Instead, TSC is defined by 11 major and 6 minor criteria, with a diagnosis determined by the presence of two major features, or one major and two minor features [5].

TSC is characterized by the presence of hamartomas in various organs. Cutaneous involvement is the most common, including facial angiofibromas, fibrous cephalic plaques, ungual fibromas, shagreen patches and confetti skin

lesions. The aforementioned conditions have distinct appearances and their presence strongly supports a diagnosis of TSC. Hypomelanotic macules are the most common or earliest cutaneous lesions to occur and hypomelanotic macules with a diameter of  $\geq 5$  mm are observed in 90% of patients [5]. In the current case, angiofibromas and fibrous cephalic plaques were scattered on the forehead and neck, as well as clearly on the face.

Epilepsy and mental retardation, which occur in 85-96 and 50% of TSC patients, respectively, are common neurological features of TSC [8]. However, the intracranial pathology of TSC can be complex, and may involve cortical, subcortical, subependymal and cerebellar tissues, as well as calcification and hamartomas. Additionally, CT findings are typically highly positive among patients exhibiting no neurological symptoms [9]. For example, numerous calcified subependymal nodules protruding into the ventricle, rarely occurring giant cell astrocytomas, and cortical and subcortical tubers, which are observed as areas of decreased attenuation, have been identified by performing CT scans [10]. Furthermore, certain patients with no childhood history of seizures may develop brain tumors.

Renal involvement occurs in  $\leq 60\%$  of patients with TSC [11]. Renal AMLs, which are the most common type of lesion, are almost pathognomonic of TSC when multiple and bilateral, and AMLs typically increase in size and number with patient age [12]. Patients are more likely to exhibit clinical symptoms and spontaneous hemorrhage when renal AMLs measure  $> 4$  cm in diameter, thus, resulting in a higher rate of nephrectomy. The majority of renal tumors that occur in patients with TSC are benign, however, malignant tumors have been reported. For example, using a growth threshold rate of  $> 0.5$  cm/year, one study identified the only reported case of renal cell carcinoma in TSC. Therefore, it is recommended that patients with TSC undergo annual radiological follow-up examinations of undiagnosed renal masses [13]. Due to their benign nature, the principles of renal AML management are the relief of symptoms and the preservation of renal function. The preservation of renal function is essential, as renal failure, a long-term complication of TSC, is the second leading cause of premature death after

severe intellectual disability. With advances in medical care, death in TSC from renal disease is much less likely, however, it continues to represent a significant medical burden to TSC patients [5]. In the current case, the large left renal AMLs and the loss of function of the right kidney indicated a poor prognosis. However, for the majority of cases of renal AML, conservative management with annual imaging is sufficient. Therefore, early detection and lifelong or periodic follow-up are required to improve the prognosis of patients with TSC.

Multiple organ involvement, which manifests as hepatic hemangiomas and hamartomas, occurs in the liver in a small percentage of TSC cases [7]. Hepatic hemangiomas can be distinguished from other tumors by performing enhanced CT or magnetic resonance imaging scans [14]. Furthermore, hepatic hamartomas are characterized by a fatty composition.

Pulmonary involvement occurs in 0.1-2.3% of TSC cases and is associated with LAM in the majority of patients [15]. In a retrospective analysis, the incidence of LAM in women with TSC was identified as 26-34% [16]. By contrast, LAM in men with TSC is rare [17]. Upon CT examination, TSC consists of thin-walled cysts throughout the lungs, surrounded by healthy lung parenchyma. The majority of cysts are round in shape, measuring 0.2-2.0 cm in diameter, and are distributed diffusely throughout the lung, with no zonal predominance. Characteristic clinical features of LAM in women include progressive obstructive dysfunction and pneumothoraces. Other forms of pulmonary involvement, such as multifocal micronodular pneumocyte hyperplasia, angiomyolipoma and clear cell tumors, may also occur [18, 19]. Furthermore, HRCT examinations may facilitate the early identification of lesions.

Skeletal manifestations are not included in the 2012 International Tuberous Sclerosis Complex Consensus Conference diagnostic criteria of TSC [5, 6], however, osteosclerosis is the most common skeletal manifestation of the disease [7, 20]. The radiographic appearance of sclerosis is due to thickening of the calvarium, and periosteal thickening of the long bones, metacarpals, metatarsals and phalanges. The neural arches and pelvic brim are other common sites of involvement [20], and osseous cysts have also previously been identified in a patient

with TSC [7]. Osseous stigmata in TSC patients are typically asymptomatic and their benign nature means they do not require targeted treatment [21].

In conclusion, TSC is a complex multisystem disorder, and radiology is pivotal in its diagnosis. When characteristic cutaneous lesions appear, radiological examinations, particularly CT scans, are required for the diagnosis of multiple organ involvement, as determined in the present case. Thus, radiological examinations are useful for identifying lesions early and for monitoring disease progression.

### Disclosure of conflict of interest

None.

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