A Misdiagnosed Case of Tuberous Sclerosis and Literature Review

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ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disease that affects multiple organs. TSC is caused by inactivating mutations in TSC subunit 1 (*TSC1*) or *TSC2* genes. The main symptoms of TSC are skin abnormalities, intellectual disability, and hamartomas. The clinical manifestations of TSC are complex and varied, and the disease is frequently misdiagnosed. In this case report, we describe a patient who experienced symptoms from the age of 10 to 54 years, during which multiple treatments were attempted at different hospitals without a definitive diagnosis. After a thorough examination, compound heterozygous mutations in *TSC2* were identified in the patient at the age of 56 years, leading to the diagnosis of TSC. Palliative treatment was subsequently initiated.

Key Words: *Tuberous sclerosis, Dermatosis, Hamartomas, Leiomyomatosis of the lung.*

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INTRODUCTION

Tuberous sclerosis complex (TSC) is a type of neurocutaneous syndrome with an incidence of approximately 1 per 6,000 – 10,000 live births. Because of the rare occurrence of this disease, it is frequently underdiagnosed.[1] The typical clinical triad of symptoms is epilepsy, intellectual impairment, and facial angiofibroma. The diagnostic criteria for TSC were updated in 2012,[2] and the main criteria include brain, kidney, heart and lung lesions, and skin manifestations. Multiple systems can be involved. The severity of the disease varies greatly, and the misdiagnosis rate is high.[3]

Here, we present a patient who was misdiagnosed for many years with conditions such as simple skin disease and kidney tumour by a regional hospital. She received various treatments, such as skin dermabrasion, nephrectomy, and pneumothorax drainage. After the comprehensive examination and genetic testing, TSC was confirmed. This case underscores the need for patients with atypical clinical symptoms to be closely examined to reduce misdiagnosis and ensure appropriate treatment.

CASE REPORT

A 56-year female patient was admitted to our hospital because of the presence of a rash for approximately 50 years and shortness of breath for 23 years that was aggravated in the previous week.

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Physical examination showed an emaciated body type and a finger pulse oxygen of 80–85%; the patient had an anaemic appearance and pale lips and nail beds, accompanied by facial pigment loss. Multiple light red, bean-sized, raised masses were observed on both sides of the nasal alar, fingertips and toes (Figure 1). The computerised tomography imaging results are shown in Figure 2.

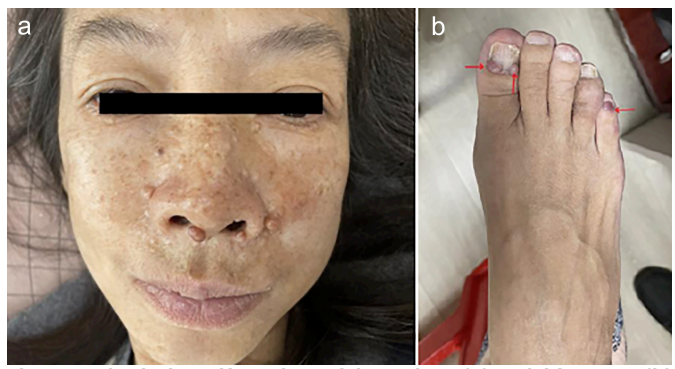

Figure 1: Physical manifestations of the patient. (a) Facial features. (b) Foot lesions. The patient exhibited pale lips and nail beds, accompanied by facial pigment loss; multiple light red, small, raised masses were observed on both sides of the nasal alar, fingertips and toes (arrows).

From the patient's history, signs, and imaging results, we initially suspected a kidney tumour with multiple metastases, and the initial diagnosis was as follows: 1. renal tumours with multiple metastases (liver, brain, bone, lymph nodes); 2. pulmonary nodules with emphysema and bullae; and 3. skin fibromas.

To determine the cause of the multiple systemic lesions in the patient, we conducted a multidisciplinary consultation and reviewed the patient's medical history in detail. The patient developed skin lesions at the age of approximately 3 years and visited other hospitals multiple times from the age of 6 to 54 years.

Table I: Results of genetic analysis of the patient.

Gene Name	Genotype	Chromosome location and HGVS annotation	Variation type	Variation pathogenicity	Genetic model	Name of disease
TSC2	Compound heterozygote	chr16:2100472 NM_000548:exon3:c.211_220del:(p.K72Sfs*31)	Frameshift mutation	Possibly pathogenic	Autosomal dominant	Tuberous sclerosis Type 2
		chr16:2106645 NM_000548:exon8:c.G649A:(p.V217I)	Missense mutation	Unclear meaning	Autosomal dominant	Taylor type focal cortical dysplasia Type II Lymphangioleiomyomatosis

HGVS, Human Genome Variation Society.

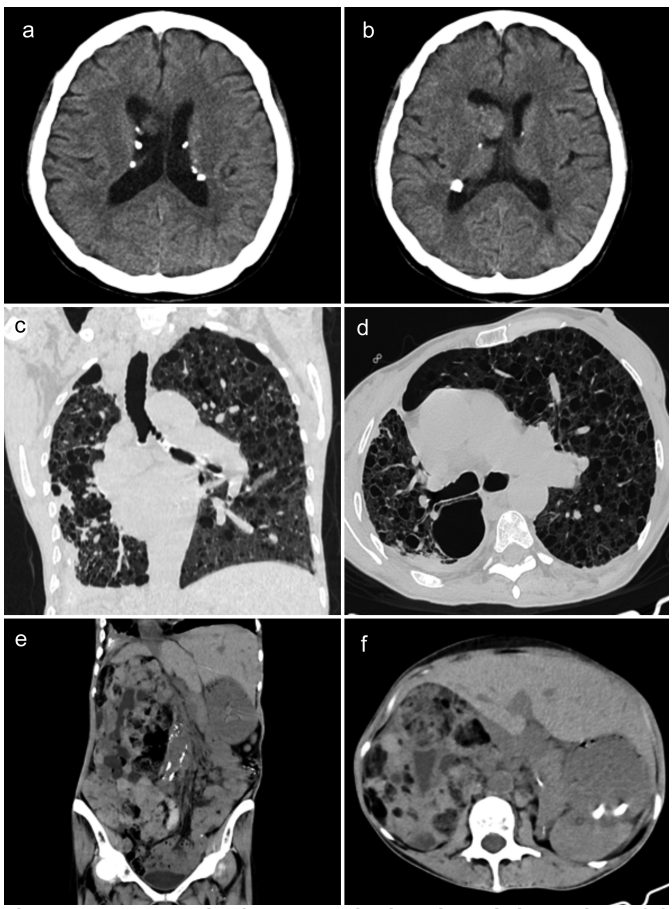

Figure 2: Computerised tomography imaging of the patient. (a) Multiple calcified nodules were found in the subependymal space of the bilateral lateral ventricles, with a diameter of 2–8 mm and a clear boundary; the modules were symmetrically distributed. (b) Mencius foramen in the right lateral ventricle, with a size of approximately 17 mm × 21.3 mm, considered as nodular sclerosis with subependymal giant cell astrocytoma. (c,d) Multiple small, round, thin-walled cystic cavities with a diameter of approximately 2–40 mm were observed in both lungs. (e,f) Multiple hamartomas in the right kidney and left renal insufficiency were observed.

For these complaints, she underwent skin abrasion surgery, thoracotomy, and drainage surgery because of pneumothorax, and left nephrectomy because of left kidney rupture and bleeding. These findings indicated the possibility of TSC. High-throughput genetic testing and bioinformatics analysis identified compound heterozygous mutations in *TSC2* (Table I), which led to a diagnosis of TSC, Type 2.

Many organs of the patient were damaged, especially the lungs and kidneys, and no curative treatment was available. Treatments to ameliorate her symptoms included a ketogenic diet, respiratory training, kidney protection, blood pressure control, uric acid reduction, anaemia correction, phosphorus reduction, and calcium supplementation. To alleviate symptoms and delay progression, we administered immunosuppressants such as everolimus.[4] However, the patient's renal function was poor. After using everolimus for one month, the patient's renal functions decreased and she experienced a decrease in appetite. Therefore, everolimus was discontinued. After discontinuation of the drug, her appetite improved, but renal function did not markedly improve. The patient was then stable and now undergoes regular monthly follow-ups, which indicate gradual improvement.

DISCUSSION

TSC is a multisystem, autosomal dominant genetic disorder characterised by the formation of tumours in multiple organs, such as the skin, central nervous system, kidneys and lungs.[5] Because of the large population in China, TSC is not uncommon in clinics; however, it is frequently misdiagnosed as acne, cardiac rhabdomyosarcoma, neurofibroma, or vitiligo, resulting in delayed diagnosis and treatment.

The characteristic symptoms of skin involvement in TSC are cutaneous angiofibroma in the trigone area of the mouth and nose, with a symmetrical butterfly distribution, and hard waxy papules that are light red or reddish brown, with sizes ranging from the tip of a needle to bean size that fuse into patches after puberty. Most of these skin manifestations associated with TSC occur in infants and are commonly misdiagnosed as a skin disease because they are usually the first symptoms.[6] In the current case, skin lesions occurred in early childhood and were misdiagnosed as a simple skin disease. The patient was treated with skin dermabrasion with little effect. In early childhood, papules appeared on her face and the tips of her fingers and toes. The secondary manifestations that meet the diagnostic criteria of TSC include different skin lesions at different ages.[7] Recognition of these lesions as associated with TSC requires dermatologists to be vigilant.

Kidney involvement is very common in TSC and is characterised by the development of angiomyolipomas (AMLs) and cysts,[8] which can lead to the misdiagnosis of sporadic renal AML. Sporadic renal AML is mostly unilateral and single, with a small size. However, AMLs in TSC are mostly bilateral and their size gradually increases over time. The complications caused by kidney abnormalities are the main cause of death

in TSC patients.[9] However, early identification and intervention can reduce the risk of complications and improve patient prognosis.[10]

Another misdiagnosis of TSC is sporadic pulmonary lymphangioleiomyomatosis (LAM). LAM can be divided into TSC-LAM and sporadic (S-LAM). TSC-LAM is present in both men and women and often accompanied by other TSC symptoms, such as skin angiofibromas, kidney AMLs and other major features.[11] S-LAM occurs almost exclusively in women, and the incidence is much lower than that of TSC-LAM, at 1 in 100,000–400,000.[12]

In summary, the clinical manifestations of TSC are varied and may change with age. To reduce the rate of missed and misdiagnosis of TSC, clinicians should pay close attention to the patient's medical history and conduct a careful physical examination to avoid overlooking lesions in other systems.

COMPETING INTEREST:
The authors declared no competing interest.

PATIENT CONSENT:
Written informed consent was obtained from the patient to publish this case.

AUTHORS' CONTRIBUTIONS:
XZ: Designed the study, collated documents and participated in writing the manuscript.
JB: Collated documents and participated in writing the manuscript.
TW: Managed the patients and collected data.
CZ: Revised the manuscript for intellectual content.

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