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Case Report

Late diagnosis of tuberous sclerosis: a case report

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Abstract

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder characterized by the formation of hamartomas in organ systems such as the brain, skin, kidneys and lungs. Patients with TSC are usually diagnosed early in life. However, in some cases, the diagnosis is delayed until adulthood because various manifestations occur at various times throughout an individual's life. In this regard, we present the case of a female patient diagnosed at the beginning of the seventh decade of life. The patient had a history of seizures and showed clinical findings on the skin (facial angiofibromas, ungual fibromas, 'Confetti-like' skin lesions, shagreen patch), brain (cortical tubers), heart (cardiac rhabdomyomas), kidneys (angiomyolipomas) and a positive genetic test for mutations in TSC2, fulfilling the diagnostic criteria. We compared the differences between manifestations in patients diagnosed during childhood and adulthood. Knowledge of the clinical spectrum of TSC allows early identification.

INTRODUCTION

Tuberous sclerosis complex (TSC), also called Pringle Bourneville disease, is a rare autosomal dominant neurocutaneous syndrome characterized by hamartomatous growth in multiple organ systems, such as the brain, retina, kidney, skin, heart and lung, because of hyperactivation of the mechanistic target of rapamycin pathway as a result of a mutation in the tumor-suppressor gene TS1 (encoding hamartin) or, more commonly, TSC2 (encoding tuberin) [1, 2]. The name of the disorder is derived from the Latin word tuber (root-shaped growths) and the Greek word skleros (hard), which refers to thick, firm and pale gyri called 'tubers' that Desire-Magloire Bourneville first described in 1880 [1]. Its estimated population incidence rate is from 1:6760 to 1:13 520 [3]. The TSC diagnostic criteria include genetic testing to improve the identification of cases, although clinical features continue to be the principal means of diagnosis [3]. The diagnosis is established in early life in more than 80% of cases, often secondary to the presence of seizures or hypomelanotic macules [4]. Nevertheless, there remains a subset of patients in whom the diagnosis is delayed until adulthood, usually performed because of dermatological, renal or pulmonary alterations [4, 5]. Here, we present the case of a patient diagnosed with TSC in the seventh decade of life.

CASE REPORT

A 60-year-old female was admitted to the emergency department because of blisters on the right arm that began 72 h before admission after exposure to grass. In her family history, she reported a daughter with a genetic diagnosis of tuberous sclerosis; other family members were not reported. Her medical history included a diagnosis of seizures during childhood, receiving unspecified treatment for a short time with spontaneous remission, and a 2-year history of arterial hypertension treated with losartan 50 mg/-day. Physical examination revealed the presence of blisters on an erythematous base on the anterior right forearm. In addition, other skin lesions characterized by multiple shiny dome-shaped papules on the nose and cheeks (Fig. 1a), multiple fibromas growing in the periungual area of the left foot (Fig. 1b), slightly hypopigmented plaques on the lumbar region suggestive of shagreen patch (Fig. 1c) and multiple hypomelanotic macules on the anterior chest compatible with guttate leukoderma ('Confetti-like' skin lesions, Fig. 1d) were observed; she referred that these lesions appeared since childhood. The rest of the exploration was normal, including intellectual status and ophthalmologic review.

A diagnosis of contact dermatitis was established for the lesions on the right arm. However, the patient was hospitalized for further study because of other skin findings. Initial laboratory

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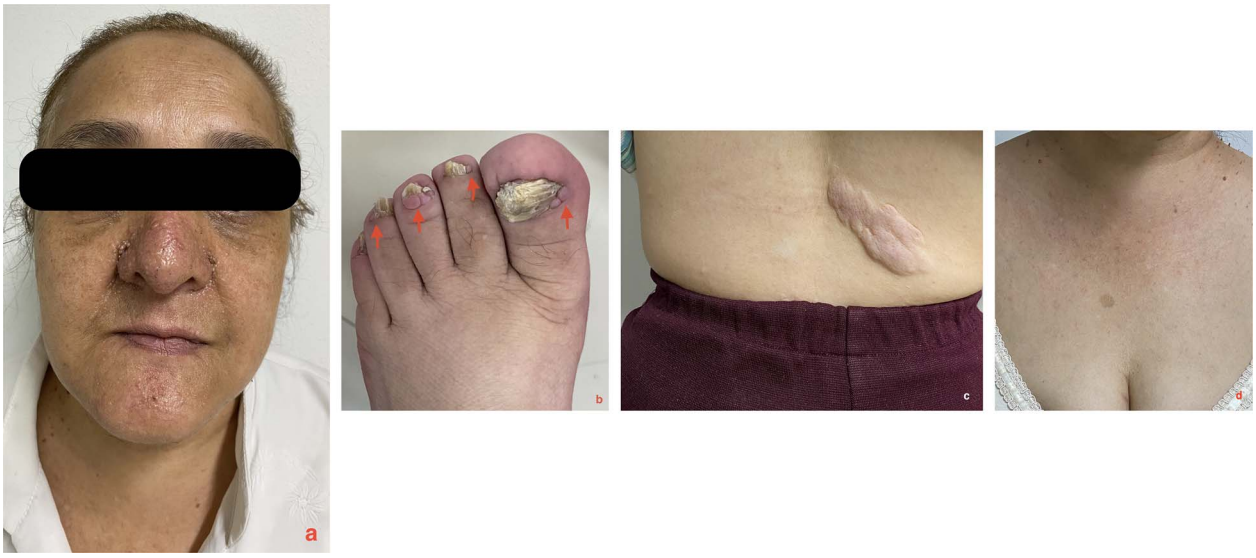

Figure 1. Cutaneous manifestations of TSC: (**a**) facial angiofibromas: multiple shiny dome-shaped papules on the nose and cheeks. (**b**) Periungual fibromas: multiple fibromas growing in the periungual area of the first, second and third toes of the left foot (red arrows). (**c**) Shagreen patch: slightly hypopigmented plaques on the lumbar region. (**d**) Leukoderma guttata 'confetti' macules: multiple hypomelanotic macules on the anterior chest.

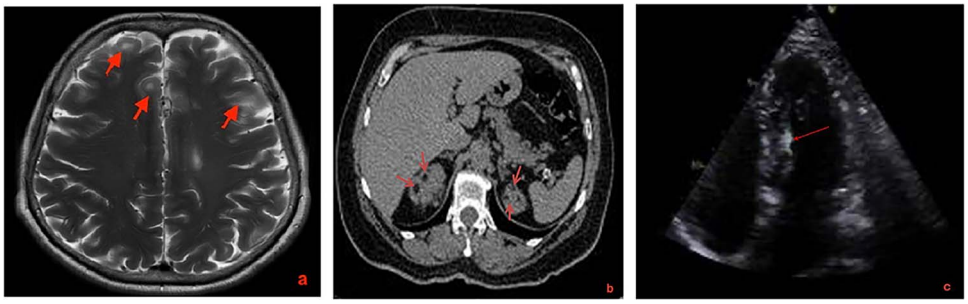

Figure 2. T2-weighted brain magnetic resonance imaging (PROPELLER): (**a**) hyperintense lesions with diffuse limits in the subcortical region of the bilateral frontal lobes suggestive of tubercles (red arrows). At the level of the periventricular white matter, hyperintense lines were observed bilaterally, extending toward the cortex and corresponding to the radial migration lines. (**b**) Simple transverse abdominal tomography image showing multiple hypodense renal lesions compatible with renal AMLs (red arrows). (**c**) Echocardiogram in the apical four-chamber projection: cardiac rhabdomyoma: a homogeneous hyperechoic nodular mass with well-defined contours of 6 × 9 mm (red arrow) is observed in the interventricular septum, which protrudes intracavitarily without generating an obstruction gradient.

tests (complete blood count, and renal and hepatic function tests) did not reveal any alterations. Cranial magnetic resonance imaging revealed the presence of cortical tubers (Fig. 2a). Thoracic and abdominal computed tomography (CT) revealed more than two angiomyolipomas (AMLs) in the kidneys, with no lymphangioleiomyomatosis (LAM) at the pulmonary level (Fig. 2b). Transthoracic echocardiography showed a cardiac rhabdomyoma in the interventricular septum (Fig. 2c). A genetic test was performed for suspected tuberous sclerosis, which reported a mutation in the tumor suppressor gene TSC2. Tuberculous sclerosis was diagnosed according to the 2021 International TSC Consensus Group [3] (Fig. 3). The patient was discharged to follow up in the outpatient clinic of the Internal Medicine Department.

DISCUSSION

The diagnosis of TSC may be difficult because its symptoms are not pathognomonic. The 'classic triad' of symptoms in TSC (seizures, mental retardation and angiofibromas) occurs in only 29% of patients [6]. Many features can be considered as isolated findings or because of other conditions. The differential diagnosis of hypopigmented macules includes vitiligo, nevus depigmentus and piebaldism. Single facial angiofibromas or renal AMLs may be seen as isolated findings, whereas ungual fibromas may result from trauma. Therefore, the presence of multiple findings may help distinguish isolated conditions from TSC [7]. In addition, the clinical presentation of TSC differs between patients diagnosed in childhood or adulthood. Skin lesions are among adults' most common manifestations of TSC [4, 5]. In a case series of 30 adult women with delayed diagnosis of TSC (performed at age ≥ 18 years), angiofibromas and ungual fibromas were the most frequently observed cutaneous findings in 100 and 83% of the cases, respectively [5]. In contrast, hypomelanotic macules are often the first and most frequently reported cutaneous finding in children and are detected less frequently in older patients [4, 8]. In this regard, our patient showed cutaneous tubers and hypopigmented skin lesions.

Neurological involvement is present in almost all individuals with TSC and is one of the leading causes of morbidity [1, 2]. Nearly 100% of patients develop epilepsy, which usually begins within the first year of life; however, in some cases, it is not present until adolescence or early adulthood [2]. This can be explained by

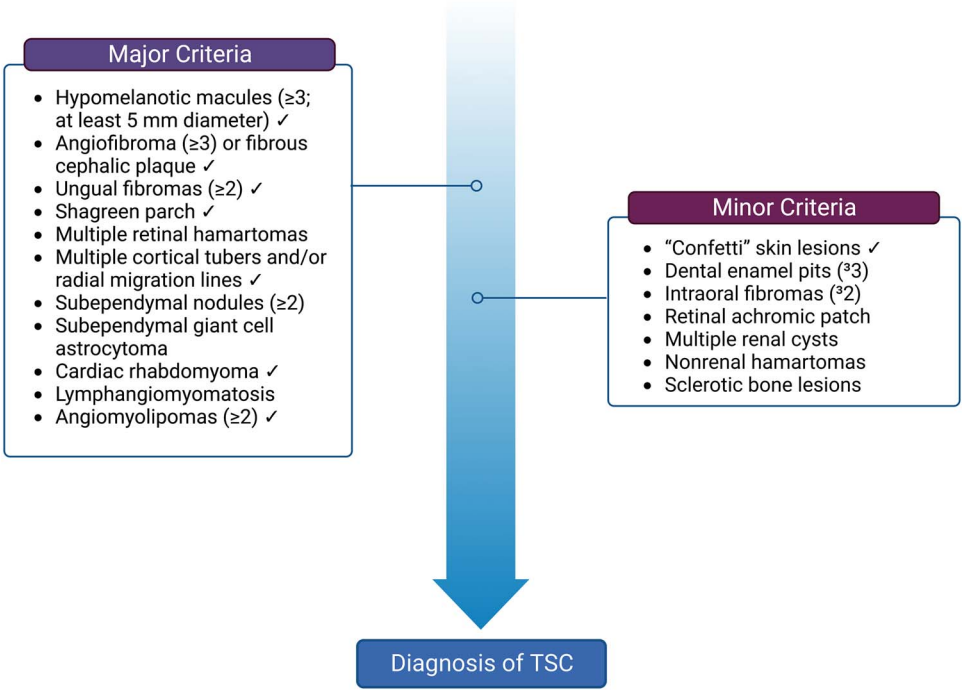

Figure 3. 2021 International Tuberous Sclerosis Complex Diagnostic Criteria. Definite TSC: two major features or one major feature with two minor features. Possible TSC: either one major feature or ≥2 minor features. Genetic diagnosis: a pathogenic variant of TSC1 or TSC2 is diagnostic of TSC. *The patient met the criteria marked with a ✓.

the high prevalence of intracranial abnormalities, such as cortical tubers and/or subependymal nodules, which can be seen in 95–100% of cases [9]. However, adults with TSC are less likely to have seizures or present seizures later in life [5, 6]. Furthermore, many adult patients diagnosed with TSC do not have profound intellectual deficits [4]. In the present case, the patient reported seizures in childhood but not during her adult life, despite the presence of cortical tubers, and did not present with intellectual deficits.

Cardiac rhabdomyomas are found in 40–60% of patients with TSC, usually in patients < 2 years of age, and their presence in adults is infrequent. In addition, almost all patients are asymptomatic [10]. In this regard, we identified a cardiac rhabdomyoma in the interventricular septum of the patient. This could be explained by the *de novo* appearance or growth of the previous mass [10].

AMLs are the most common renal manifestation. In adult patients with TSC, more than 67% had AMLs, in contrast to what was observed in children (17%). It is believed that AMLs grow during childhood and early adulthood [1]. Searching for renal involvement even without symptoms is essential, because renal disease is the leading cause of death in patients with TSC [11]. Therefore, we performed abdominal CT searching for renal lesions even though the patient did not show symptoms or abnormalities in renal function.

In patients with TSC diagnosed in adulthood, identification of the illness is usually delayed for prolonged periods. In a study that included 30 patients diagnosed at ≥21 years of age, 77% had symptoms or signs years before diagnosis, such as seizures, skin lesions and renal AMLs [6]. In this respect, we classified our patient with a late diagnosis because she showed early neurological and cutaneous manifestations. Earlier missed manifestations may be because some features remain entirely absent, whereas others appear, grow and regress over time. The manifestations of TSC may be incorrectly classified, leading to a diagnosis of other diseases. Seibert *et al.* [5] proposed that TSC should be considered in adults with any one of the following: bilateral or multiple renal AMLs, LAM- or TSC-associated skin lesions, even in the absence of seizures, intellectual disability or an affected family member.

In conclusion, the clinical spectrum of TSC varies with age. Therefore, physicians should be aware of the myriad potential of presenting symptoms and signs of TSC. Furthermore, when a child is identified as having TSC, their parents should be screened to rule out the disease. Early diagnosis is essential to reduce the morbidity and mortality associated with this disease.

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CONFLICT OF INTEREST STATEMENT

None declared.

AUTHORS' CONTRIBUTIONS

All authors listed in this manuscript made substantial contributions to data acquisition, analysis or interpretation and were involved in critically drafting or revising this article for important intellectual content. All authors approved the final version of the manuscript.

ETHICAL APPROVAL

Ethical approval was not required for this study.

CONSENT

Written informed consent was obtained from the patient.

GUARANTOR

Luis Fernando Dominguez-Valdez is the guarantor of this article.

DATA AVAILABILITY

The data underlying this article are available in the article.

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