Case Report

Tuberous Sclerosis Complex in a 20-year-old Female: Delayed Recognition and Life-threatening Outcomes

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Abstract

Tuberous sclerosis complex (TSC) is a rare, autosomal dominant multisystem disorder affecting the brain, heart, kidneys, lungs, and skin leading to significant morbidity and mortality. We report a case of TSC and highlight the need for prompt diagnosis and proper surveillance to minimize life-threatening complications. A 20-year-old female presented with facial and ungual papulonodular lesions 4 years after being diagnosed with epilepsy at the age of eight. No family history of genetic diseases was reported. Eight years later, the patient developed recurrent cough, shortness of breath, and blurring of vision. Biopsy of facial and digital nodule showed angiofibroma and ungual fibroma (Koenen tumor), respectively. Chest computed tomography scan revealed extensive cystic lesions diffusely scattered throughout the entire lung parenchyma suggestive of lymphangioleiomyomatosis. Cranial MRI revealed cortical and subependymal tubers, compatible with TSC. The patient had multidisciplinary management. However, her symptoms progressed, and she eventually succumbed to death. Cutaneous lesions such as facial angiofibromas and ungual fibromas along with multisystemic manifestations should alarm the clinician to TSC. Given its highly variable expressivity, awareness of different TSC-associated signs and symptoms is essential for prompt diagnosis, proper treatment, disease monitoring, and early recognition of TSC complications.

Keywords: Angiofibroma, lymphangioleiomyomatosis, tuberous sclerosis complex

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Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder characterized by the formation of benign hamartomatous lesions in multiple organs. It is an autosomal dominant disease resulting from loss-of-function mutation in a tumor suppressor gene, either TSC1 or TSC2 encoding hamartin and tuberin, respectively.[1] In two-thirds of patients, TSC is caused by a *de novo* mutation while it is hereditary in the rest of the cases. Disease severity is highly variable and can range from mild symptoms to severe disabilities in different organ systems.[1] The diagnosis of TSC is based on clinical manifestations, imaging findings, and genetic tests in accordance with the International Consensus Conference for the diagnosis of TSC.[2] Clinical diagnostic criteria consist of 11 major features and 6 minor features. The 11 major features include hypomelonatic macules (>3, at least 5 mm in diameter), angiofibromas (>3) or fibrous cephalic plaque, ungual fibromas (>2), shagreen patches, multiple retinal hamartomas (>2), cortical dysplasias (includes tubercles and cortical migration lines), subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis (LAM), and

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angiomyolipomas (AML) (>2). Meanwhile, minor features are "confetti" skin lesions, dental enamel pits (>3), intraoral fibromas, retinal achromic patch, multiple renal cysts, and nonrenal hamartomas. One major criterion and two minor criteria are required for a definitive diagnosis.[2] Identification of the pathogenic mutation in TSC1 or TSC2 is adequate to make a confirmatory diagnosis, however, in 10%–25% of TSC patients, mutations are not detected.[3] Common complications include refractory seizures, cognitive impairment, AML resulting to hemorrhage, and LAM leading to spontaneous pneumothorax.[4] The prognosis among TSC patients is highly individualized, determined by the variable clinical manifestations of the disease.[5] Deaths occurring during infancy are commonly caused by brain and heart tumors, whereas lung and kidney tumors cause premature death in adult TSC patients.[6] This report underscores the importance of recognition of TSC-associated manifestations and monitoring of possible outcomes.

Case Report

A 20-year-old Filipino female came into our hospital with a chief complaint of centrofacial nodules. The patient was diagnosed with epilepsy since 8 years old with noted cognitive difficulties and aggressive behavior. There was poor treatment compliance and follow-up care. She developed centrofacial and ungual papulonodular lesions, which gradually progressed 4 years after the onset of seizures. No family history of similar lesions or genetic diseases was reported. No further diagnostic investigations were done. During the consult, it was reported that the patient experienced recurrent cough, shortness of breath, and blurring of vision.

On physical examination, multiple confluent and reddish-brown papules and nodules were noted on the forehead, nose, cheeks, and chin sparing the upper lip and lateral face, having a characteristic "butterfly pattern" [Figure 1a]. Several firm, flesh-colored, and pink nodules on the nail beds of the hands and feet were also observed, suggestive of periungual fibromas or Koenen tumors [Figure 1b]. Dental pits were noted on the central incisors. A clinical impression of TSC was made.

Laboratory tests such as complete blood count and renal and hepatic function tests were satisfactory. Biopsy of the facial nodule revealed a dome-shaped lesion with elevation of epidermis, zone of fibroplasia, vertically oriented collagen fibers, fibrosis around adnexal structures and blood vessels in a concentric or onion-skin arrangement, increased blood vessels with some dilation, increase in

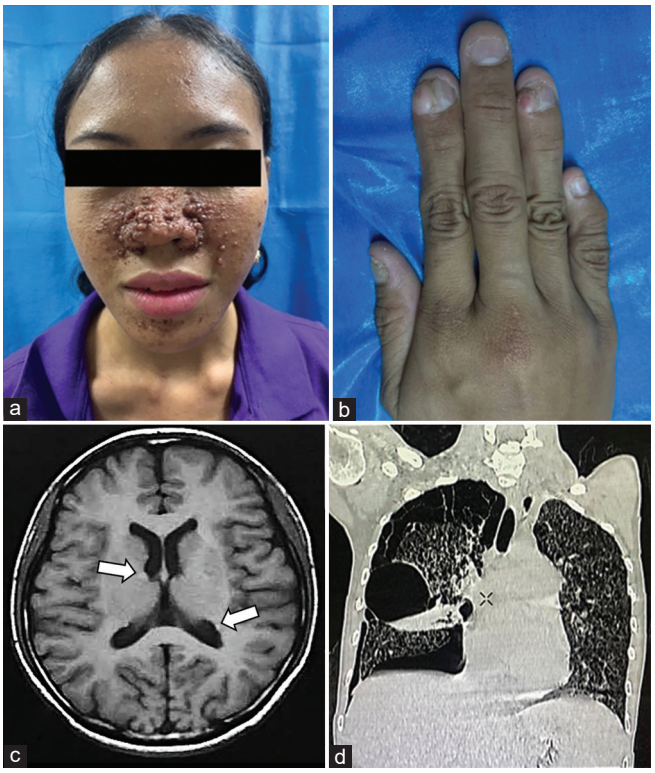

Figure 1: (a) Facial angiofibromas, (b) Ungual fibromas or Koenen tumors, (c) Subependymal tubers (white arrows), (d) Extensive cystic lesions diffusely scattered throughout the entire lung parenchyma

fibroblasts and sparse superficial perivascular infiltrate of lymphohistiocytes, while histopathology results of the nailbed nodule showed compact orthokeratosis, acanthotic epidermis, hypergranulosis, prominent dermal fibrosis, scattered stellate fibroblasts, and sparse superficial perivascular infiltrates of lymphohistiocytes. Both were consistent with angiofibroma and ungual fibromas, respectively. Ultrasound of the whole abdomen showed bilateral polycystic kidney disease. T2-weighted cranial MRI revealed cortical and subependymal tubers [Figure 1c]. Chest computed tomography (CT) scan showed extensive cystic lesions diffusely scattered throughout the entire lung parenchyma suggestive of LAM [Figure 1d]. Clinical findings and diagnostic results were consistent of TSC.

Multidisciplinary management was provided. Oral mammalian target of rapamycin (mTOR) inhibitor was strongly recommended but was unavailable in our setting. Dermatology service offered carbon dioxide laser for facial papules, while plastic surgery service advised for excision with full-thickness skin grafting for large facial nodules to address the patient's cosmetic concern. However, neurologic and pulmonary manifestations worsened. Neurology service maintained the patient on anticonvulsants. Cranial CT scan with contrast revealed

optic nerve thickening and was started on systemic steroid therapy by ophthalmology service. Pulmonology service informed the family of possible lung transplantation for progressive cystic disease. Shortly after, the patient was admitted for pneumothorax later succumbing to death.

Discussion

TSC is a genetic multisystem disease with an incidence of 1 in 6000–10,000 live births.[2] Based on the Philippine Dermatological Society Health Information System census, there have been 109 cases of TSC from 2011 to 2022. It is an autosomal dominant disorder resulting in an overactivation of the mTOR pathway.[1] However, two-thirds of cases present sporadically, which can explain the absence of family history in our case.[4] In sporadic cases, TSC2 gene mutations are more frequent and are usually associated with more severe clinical outcomes. Given that our case had sporadic nature, having TSC2 mutation can explain our patient's severe manifestations.[1] In general, the clinical presentation of TSC is extremely variable affecting multiple organs including the skin, central nervous system, heart, kidneys, lungs, or eyes, and the manifestations continue to develop over the patient's lifetime.[4] There is no single symptom that is present in all patients or a pathognomonic sign for TSC.[7] This entails challenges to clinicians in making prompt diagnoses and in detecting the extent of disease severity. In a longitudinal study involving 125 patients, the median age of presentation was 7 months.[4] However, some patients are only diagnosed during adulthood[7] which was similar to our case.

It is estimated that about 80% of TSC individuals have seizures and subependymal nodules. Half of patients with TSC develop cognitive impairment.[3] Our patient initially presented with seizures and developed intellectual disability. On brain imaging, it revealed that the patient had subependymal tubers. Four years after the onset of seizures, she started to grow facial angiofibroma and ungual fibromas. Facial angiofibromas affect up to 90% of patients occurring on the central face. Ungual fibromas, also known as Koenen tumors, are also common dermatologic findings in TSC affecting up to 85% of patients.[6] Other TSC cutaneous findings such as hypomelanotic macules, fibrous cephalic plaques, and shagreen patches were not present in our case. No further investigations were done despite neurocutaneous manifestations until she developed blurring of vision and pulmonary symptoms. Lung involvement in individuals with TSC includes LAM, multifocal pneumocyte hyperplasia, and clear cell tumors of the lung.[6] In our case, LAM was noted on chest CT scan. LAM presents with cystic lung destruction due to smooth muscle cell proliferation. It has a poor prognosis and deaths occur frequently within 5 years from onset of pulmonary symptoms.[8] As cystic disease is difficult to diagnose on chest X-ray, it is imperative that every TSC patient should have a baseline chest CT scan, particularly women with TSC who are 18 years of age or older.[9] In our case, the patient expired due to pneumothorax few months from the time of LAM diagnosis owing to the lack of proper diagnostic evaluation and regular surveillance.

TSC is a multisystemic disease requiring multidisciplinary and symptomatic management. Dermatological lesions often require excision, curettage, chemical peel, cryosurgery, laser therapy, or dermabrasion as treatment. Anticonvulsants are mainstay medications for epileptic spasms with vigabatrin considered the first-line treatment.[10] Oral mTOR inhibitors have been approved by the U. S. Food and Drug Administration as treatment for TSC growths, such as sirolimus for LAMs and everolimus for refractory epilepsy, subependymal giant cell astrocytomas, and renal AML.[11] It acts to control the abnormal proliferation and growth of smooth muscle cells in the lung parenchyma and is effective and safe. Lung transplantation, however, remains the best option for patients with progressive pulmonary symptoms and poor lung function.[9] It is strongly recommended in TSC individuals with a baseline chest high-resolution CT scan not showing lung cysts to undergo imaging every 5–10 years; if cysts are present, the interval should be shortened to 2–3 years.[8]

The rarity and heterogeneity of TSC are a challenge in giving the best care to patients. Current recommendations for the delivery of services for TSC patients include diagnosis, surveillance, treatment, safe transition from pediatric to adult care, and collaboration with the family.[8] TSC treatment requires a multidisciplinary team to address its multisystemic nature.

Conclusion

Cutaneous lesions such as facial angiofibromas and ungual fibromas along with other systemic manifestations should alarm the clinician to TSC. Given its highly variable expressivity, awareness of TSC-associated manifestations is crucial to ensure that patients receive early diagnosis, timely initiation of treatment, and prompt referral to multidisciplinary team. Regular surveillance of various body systems is of great significance to avoid further debilitating complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given

her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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