DOI: 10.2478/v10249-011-0038-4

Tuberous Sclerosis Complex - A case report

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UDC 616.894-002.5-06:616.5-006

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Abstract

Tuberous sclerosis complex is a multisystem, autosomal dominant disorder affecting children and adults, which results from mutations in either of two genes, TSC1 (encoding hamartin) or TSC2 (encoding tuberin). Tuberous sclerosis complex often causes disabling neurologic disorders, including epilepsy, mental retardation, and autism. Major features of the disease include dermatologic manifestations, such as facial angiofibromas, renal angiomyolipomas, and pulmonary lymphangiomyomatosis.

We report a 20-year-old woman with epilepsy and subnormal intelligence, who was admitted for evaluation of multiple facial papules that have gradually increased in number over the past 15 years. She had been previously diagnosed with tuberous sclerosis complex based on findings of cardiac ventricular rhabdomyomas, tuberosclerotic nodules of glial proliferation in the cerebral cortex, and renal angiomyolipoma. The facial papules were angiofibromas, confirming the clinical presentation of tuberous sclerosis complex. Detailed examination of the skin and mucosa revealed Shagreen patches, nontraumatic subungual and gingival fibroma, all features of tuberous sclerosis complex.

A multidisciplinary team approach was used for diagnosis and medical care of tuberous sclerosis complex in order to treat many organ systems affected by tuberous sclerosis in our patient. The patient received antiepileptic medications, while rapamycin was recommended.

Key words

Tuberous Sclerosis; Comorbidity; Diagnosis; Anticonvulsants; Sirolimus; Adult

Tuberous sclerosis complex (TSC) is a multisystem, autosomal dominant disorder affecting children and adults which results from mutations in either of two genes, *TSC1* (encoding hamartin) or *TSC2* (encoding tuberin). TSC often causes disabling neurologic disorders, including epilepsy, mental retardation, and autism. Major features of the disease include dermatologic manifestations, such as facial angiofibromas, renal angiomyolipomas, and pulmonary lymphangiomyomatosis.

Though genetic testing for *TSC1* and *TSC2* mutations is commercially available, current diagnostic criteria are still based on clinical manifestations.

We describe the clinical and laboratory findings of a 21-year-old female patient with TSC.

Case presentation

A 21-year-old woman with epilepsy and subnormal intelligence, previously diagnosed with TSC, was admitted to University Clinic of Dermatology in Skopje for evaluation of multiple facial papules that have gradually increased in number over the past 15 years. Her facial papules were previously misdiagnosed as acne vulgaris and mollusca contagiosa. A diagnosis of facial angiofibromas (Fig. 1.), a major feature of TSC, was made. Detailed examination of the skin and mucosa revealed Shagreen patches in the lumbosacral region (Fig. 2.), nontraumatic subungual fibroma (Koenen tumor) (Fig. 3.) and gingival fibroma (Fig. 4.), all features of TSC.

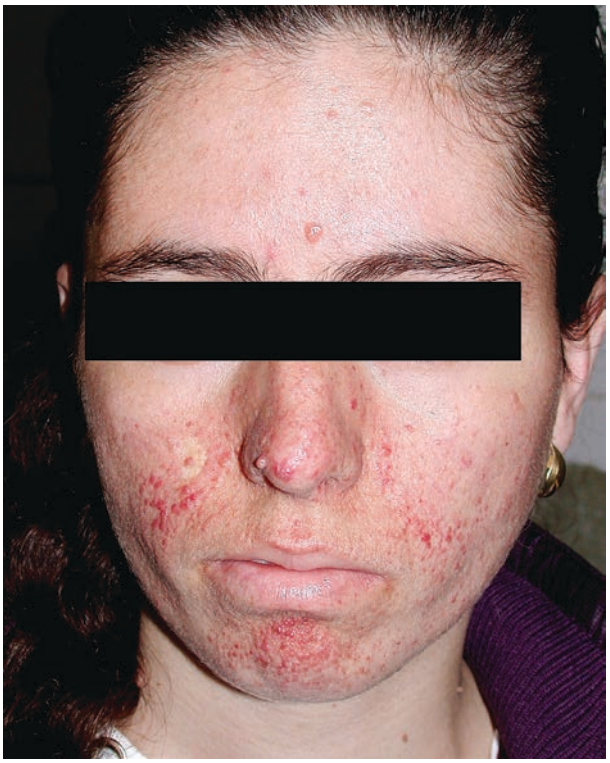

Figure 1. Multiple facial angiofibromas a major feature of TSC

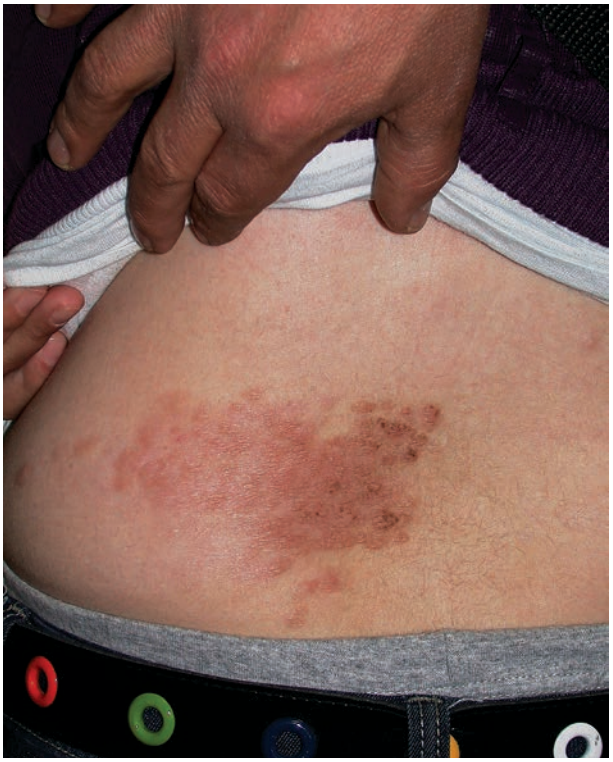

Figure 2. A chagreen patsh in lumbosacral region

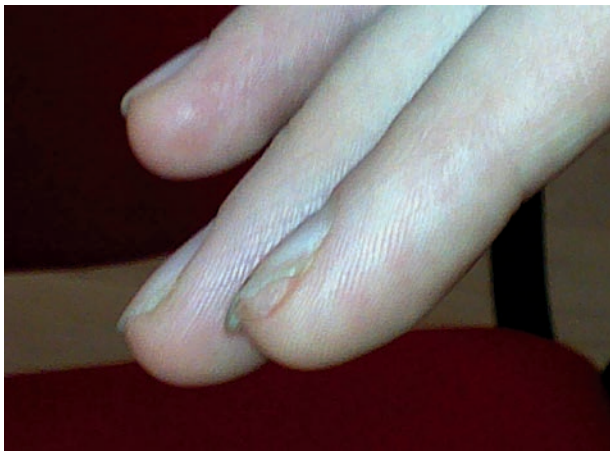

Figure 3. Nontraumatic subungual fibroma-Koenen tumor

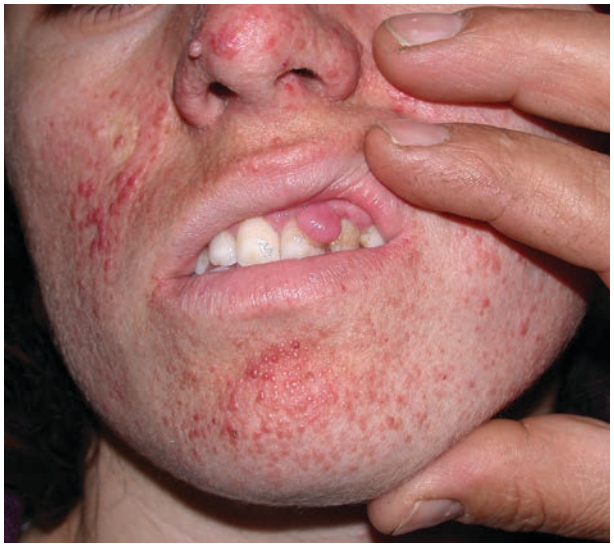

Figure 4. Gingival fibroma

A skin biopsy was obtained from facial papule for histopathologic analysis. It revealed dermal fibrosis, associated with vascular proliferation and dilatation. Also, compression of hair follicles was noted, which was due to growth of dermal fibrous tissue (Fig. 5.).

The diagnosis of TSC was previously made based on the presence of tuberosclerotic nodules of glial proliferation in the cerebral cortex - parietal, frontal and occipital lobes, cardiac ventricular rhabdomyomas and angiomyolipoma in the left kidney.

The patient was without significant family medical history; specifically, no family members suffered from mental retardation, seizures, skin lesions, or renal diseases.

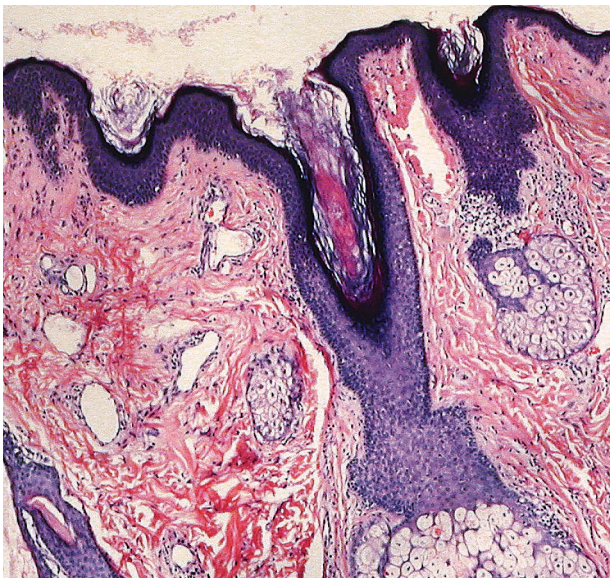

Figure 5. Histopathology pattern of skin biopsy showed abundant sebaceous glands, subepidermal fibroblast proliferation and associated vascular proliferation and dilatation.(H&E x 100)

Disscusion

Tuberous sclerosis complex is an autosomal dominant disorder characterized by the formation of hamartomatous lesions in multiple organ systems. It has a prevalence of about 1 in 6,000 newborns and affects approximately 1.5 million people worldwide, occurring in all races and both genders equally (1).

TSC is an autosomal-dominant disorder with high penetrance and variance (2). The mutation rate in TS is high, and 60-70% of cases seem to present with new mutations (3).

The diagnostic criteria for TSC consist of a set of major and minor diagnostic features (4). Cases meeting these criteria fulfill a clinical diagnosis of TSC; the results of molecular genetic testing of the *TSC1* or *TSC2* loci are currently viewed as corroborative (5).

Almost all patients with TSC have numerous cutaneous stigmata, some of which can be subtle (5, 6).

Hypopigmented macules, also known as ash-leaf spots, are generally detected in infancy or early childhood, whereas the so-called shagreen patches are identified with increasing frequency after the age of 5. Subungual fibromas typically appear after puberty, but may develop in adulthood. Facial angiofibromas, formerly called adenoma sebaceum, may be detected at any age, but they are generally more common in late childhood or adolescence (5). We found all cutaneous stigmata in our patient, including facial angiofibromas, shagreen patches and subungual fibroma with exception of hypopigmented macules.

Seizures are the most common symptoms of tuberous sclerosis. Epilepsy due to tuberous sclerosis usually starts in infancy or childhood, in 80-90% of cases (7). This applies to our patient as well. She has had epilepsy since her early childhood.

Neurologic manifestations of TSC, which include epilepsy, cognitive disability, and neurobehavioral abnormalities, such as autism, appear to be closely related to cerebral cortical tubers, that are present in over 80% of patients. Tubers are developmental abnormalities of the cerebral cortex histologically characterized by a loss of the normal six-layered structure of the cortex, and by dysmorphic neurons, large astrocytes, and a unique type of cells known as giant cells (8, 9).

Approximately half of the individuals diagnosed with tuberous sclerosis complex present with global intellectual impairment and developmental psychopathologies (10). In our patient it was subnormal intelligence.

Renal lesions commonly associated with tuberous sclerosis are angiomyolipomas (11). Angiomyolipomas, despite frightening histopathologic appearance, are benign (12). In our patient computerized tomography revealed an angiomyolipoma of the left kidney.

Up to two-thirds of newborns with TSC have rhabdomyomas, and they are often multiple (13). Cardiac rhabdomyomas are intracavitary or intramural tumors that are present in nearly 50 to 70% of infants with TSC. However, they cause important clinical problems in only a very small fraction of these patients (5). There are reports of complete regression of rhabdomyomas in patients with TSC (14). Using ultrasonography, cardiac ventricular rhabdomyomas were detected in our patient.

Conclusion

We report a case of tuberous sclerosis complex with 6 major features of tuberous sclerosis: facial angiofibromas, Shagreen patch, nontraumatic subungual fibroma, tuberosclerotic nodules of glial proliferation in the cerebral cortex, cardiac ventricular rhabdomyomas, renal angiomyolipoma, and 1 minor feature: gingival fibroma. The patient was treated with antiepileptic medications, while rapamycin was recommended.

A multidisciplinary team approach is needed for diagnosis and medical care of tuberous sclerosis complex in order to treat many organ systems that are affected. For diagnostic evaluation, full dermatological examination of the skin is necessary.

References

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Kompleks tuberozne skleroze – prikaz slučaja

Sažetak

Uvod: Kompleks tuberozna skleroza (*eng. tuberous sclerosis complex* – TSC), multisistemsko, autozomno dominantno oboljenje, kod dece i odraslih, rezultat je mutacija u jednom od dva gena, TSC1 (koji kodira hamartin) ili TSC2 (koji kodira tuberin). TSC često izaziva neurološke poremećaje koji dovode do invalidnosti, uključujući i epilepsiju, mentalnu retardaciju, i autizam. Dodatne glavne karakteristike bolesti su manifestacije na koži, npr. angiofibromi lica, angiomiolipomi bubrega i plućna limfangiomiomatoza.
Prikaz bolesnice: Prikazujemo 20-godišnju bolesnicu sa epilepsijom i potprosečnom inteligencijom, koja se javila na Kliniku za dermatologiju zbog većeg broja papula na licu, čiji se broj postepeno povećavao u poslednjih 15 godina. Kod nje je ranije bila postavljena dijagnoza TSC na osnovu nalaza rabdomioma srčanih komora, tuberosklerotskih nodula nastalih usled glijalne proliferacije u moždanoj kori i angiomiolipoma u levom bubregu. Papule na licu bile su dijagnostikovane kao angiofibromi, upotpunjavajući kliničku prezentaciju TSC-a. Detaljnim ispitivanjem kože i sluzokoža otkriveni su: šagrinska mrlja, netraumatski subungvalni fibrom i fibrom gingive, koji predstavljalju karakteristike kompleksa tuberozne skleroze.
Lečenje i nega: Kod prikazane bolesnice korišćen je multidisciplinarni timski pristup radi postavljanja korektne dijagnoze, lečenja i nege mnogih organskih sistema koji su bili pogođeni tuberoznom sklerozom. Bolesnica je lečena antiepilepticima sa preporukom da se u dalje lečenje uključi i imunomodulator rapamicin (poznat i pod nazivom sirolimus; po hemijskoj građi makrolidni antibiotik sa snažnim imunosupresivnim i antoproliferativnim dejstvom).

Ključne reči

Tuberozna skleroza; Komorbiditet; Dijagnoza; Antikonvulzivi; Sirolimus; Odrasli