CASE REPORT

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Brachial and subclavian arteries aneurysms due to tuberous sclerosis complex mechanisms – case report and literature review

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Abstract

Introduction: Tuberous sclerosis complex (TSC) is a rare autosomal dominant condition characterized by cutaneous, cerebral, and other multiorgan involvement. Aneurysms due to TSC pathogenic mechanism are rarely present, mainly aortic, renal, or intracranial and very few associated with peripheral circulation. A TSC patient, aged 31 years, who developed brachial and subclavian arteries aneurysms is presented. The question of a random association of the aneurysms with TSC *versus* aneurysms within pathogenic released mammalian target of rapamycin (mTOR) pathway effect was raised. *Case presentation*: Patient's file, available from the age of six months, was analyzed for demonstration of the TSC diagnosis. Patient was examined, and cerebral magnetic resonance imaging (MRI) was repeated. Surgery and angiographic reports and images were reviewed. Pathology of the aneurysmal wall available from surgery was reexamined and special stainings and immunohistochemistry markers were applied. Genetic characterization of the patient was performed. Definite TSC was diagnosed based on major criteria [ungual fibromas, shagreen patch, cortical tubers, subependymal nodules (SENs), subependymal giant cell astrocytoma (SEGA)], minor criteria (confetti skin lesions, dental enamel pits, gingival fibromas), genetic result showing heterozygous variant in exon 8 of *TSC1* gene (*c.733C>T-p.Arg245**). Pathology analysis revealed markedly thickened aneurysmal wall due to smooth muscle cells (SMCs) proliferation in media and neoformation vessels with similar characteristics in the aneurysmal wall. *Discussions and Conclusions*: This is a rare case with aneurysms related to TSC, with an exceptional peripheral localization. Pathology exam is the key investigation in demonstrating the TSC-related pathogenic mechanism. A literature review showed 73 TSC cases presenting aneurysms published until now.

Keywords: tuberous sclerosis complex, subclavian artery, aneurysms, heterozygous *TSC1* variant.

Introduction

Tuberous sclerosis complex (TSC) is a rare autosomal dominant disorder characterized by skin abnormalities (hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, ungual fibromas), brain involvement [cortical tubers, subependymal nodules (SENs) and subependymal giant cell astrocytoma (SEGA), seizures, intellectual disability], also affecting other organs, such as: kidneys [angiomyolipomas (AMLs)], cysts, renal cell carcinomas), heart (rhabdomyomas), lungs [lymphangioleiomyomatosis (LAM)], etc. [1]. Vascular involvement is rare and therefore less known and studied. Central and peripheral aneurysms and large and medium size arterial stenotic-occlusive disease have been reported in patients with TSC, as well as dysplasia of small vessels [2], including fibromuscular dysplasia [3].

Aim

We present the case of a 31-year-old TSC male patient with *TSC1* mutation diagnosed with two consecutive aneurysms of the right brachial and subclavian arteries,

respectively, raising the question of a random association of the aneurysms with TSC, *versus* aneurysms within pathogenic effect of the unsuppressed mammalian target of rapamycin (mTOR) pathway.

Case presentation

Patient's file, available from the age of six months was analyzed for demonstration of TSC diagnosis. Patient was clinically reexamined, and brain magnetic resonance imaging (MRI) was repeated. The *TSC1*, *TSC2* genes were analyzed by polymerase chain reaction (PCR) and next-generation sequencing of both deoxyribonucleic acid (DNA) strands of the entire coding region, and the highly conserved exon–intron splice junction analysis was performed. Multiplex ligation-dependent probe amplification (MLPA) analyses were performed to test for deletions or duplications within or including the *TSC1*, *TSC2* genes.

Surgery and angiography reports and films were reviewed together with the surgeon and the interventional radiologist. Pathology of the fragments of the aneurysmal wall available from the two surgical interventions were reexamined and special stainings for elastin, smooth muscle fibers and immunohistochemistry markers for vascular endothelium were applied: Hematoxylin–Eosin (HE), elastic van Gieson, alpha-smooth muscle actin (α-SMA), cluster of differentiation 34 (CD34) marker.

Cutaneous, mucosal, ungual and dental changes

Three ungual fibromas of the right- and left-hand fingers (Figure 1b) were documented in the patient's file at the age of 11 months; shagreen patch of the dorso-lumbar region, confetti white spots of the skin were noted at the age of four years, one dental enamel pit and gingival fibromas at the age of seven years.

Cerebral lesions

At the age of four years, a brain computed tomography (CT) scan revealed calcified SENs (Figure 1f); cerebral MRI performed at the age of 7, 11 and 26 years showed multiple bilateral cortical tubers and growing SENs; at the age of 26 years, SEGA was noted (Figure 1, g and h).

Epilepsy, intellectual disability, and autism spectrum disorder

Patient had West syndrome starting at the age of six months (epileptic spasms, hypsarrhythmia, developmental arrest), further evolving to Lennox–Gastaut syndrome, with multiple types of seizures: tonic seizures while awake and in sleep, generalized tonic-clonic seizures, atypical absences, focal seizures resistant to most antiseizure medications tried in monotherapy or different combinations. He had delayed milestones achievement and evolved to a profound intellectual disability [intelligence quotient (IQ)<20 at the age of 31], associating autism spectrum disorder with moderate aggressiveness from early childhood.

Other clinical changes

Bone changes (hypertrophic *digitus medius* of the right hand, with disorganized structure of the phalanges, thick bones cortex, osseous cysts, and periosteal apposition of the right forearm long and small bones) were noted starting around the age of four years (Figure 1, a–h). No cardiac, renal, pulmonary or eye changes were present.

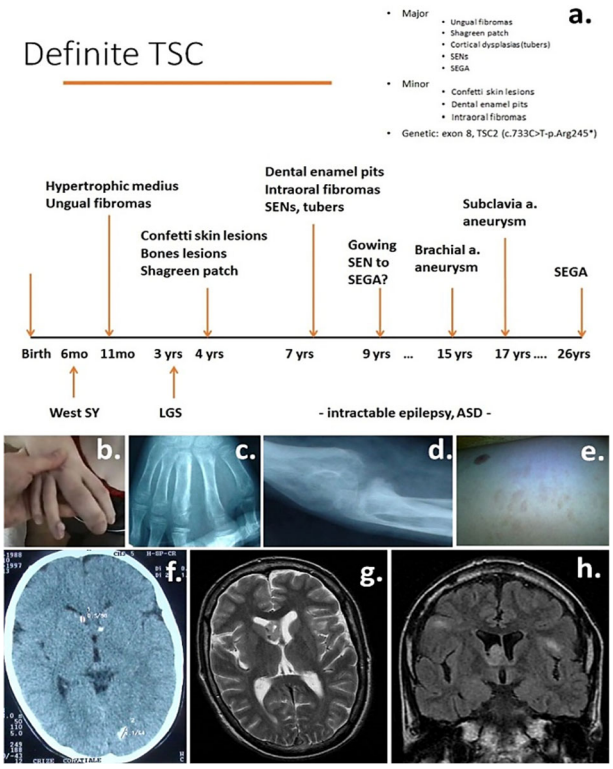

Figure 1 – ***(a) Chronological development of clinical features of the case; (b) Ungual fibromas; (c and d) Bone changes – hypertrophic digitus medius of the right hand with disorganized structure of the medius phalanges, thick bones cortex, osseous cysts, and periosteal apposition of the right forearm long and small bones; (e) Shagreen patch; (f) Calcified SENs and occipital tuber; (g) Right SEGA; (h) Bilateral cortical tubers and right SEGA. ASD: Autism spectrum disorder; LGS: Lennox–Gastaut syndrome; SEGA: Subependymal giant cell astrocytoma; SEN: Subependymal nodule; SY: Syndrome; TSC: Tuberous sclerosis complex.***

Aneurysms

Patient developed a growing tumor in the right arm starting at the age of 13 (Figure 2, a and b). Right arm MRI with Gadolinium and further angiography showed a giant aneurysmal dilatation of the brachial artery and important surrounding soft tissue changes secondary to local ischemia (Figure 2, c–f). Aneurysm and damaged tissue were surgically removed. Angiographic checkup after one year showed a second murine aneurysm at the right subclavian level (Figure 3a). Ligature and partial resection of the aneurysm were performed (Figure 3b). Angiography of the arms, neck and head arteries did not detect other aneurysms. Aortic, renal, or lower limb vessels were not investigated with angiography, but chest CT scan and abdominopelvic MRI with contrast agent were negative.

Genetics and clinical family examination

Genetic analysis showed a heterozygous mutation in exon 8 of the *TSC1* gene (*c.733C>T-p.Arg245**). Father, who had periungual fibromas, declined further assessment (clinical, imaging, or genetic). Mother stated that her husband had only one generalized tonic-clonic seizure at the age of 42 for which he didn't receive treatment. Other

family members (mother, sister) showed no TSC clinical signs.

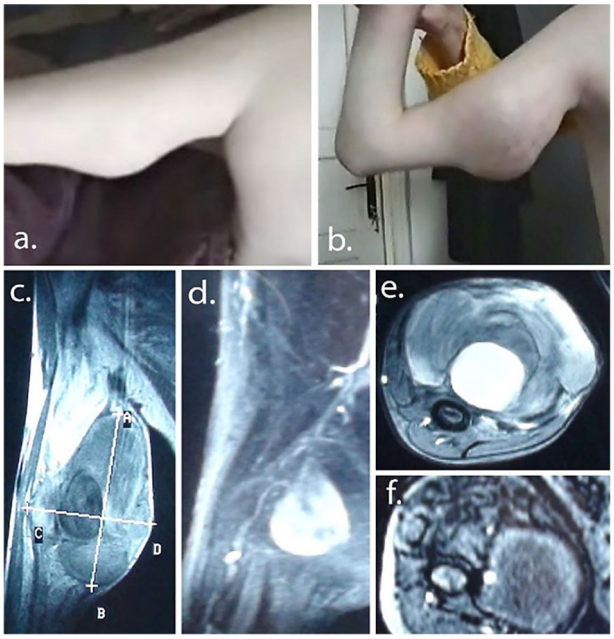

Figure 2 – ***(a and b) Brachial artery aneurysm: clinical progression (one year apart); (c–f) Preoperatory MRI with contrast agent showing massive saccular (5.5/6 cm) dilatation of middle part of brachial artery and destruction of surrounding tissue. MRI: Magnetic resonance imaging.***

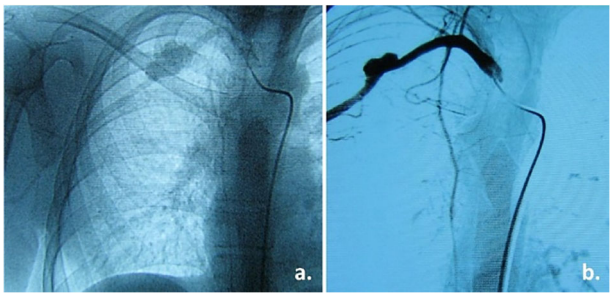

Figure 3 – ***(a) Angiography at one year after surgery for brachial aneurysm shows a second aneurysm – subclavian artery; (b) Same aneurysm after ligature (partial resection).***

Pathology examination

Pathology examination of the surgically removed fragments revealed a markedly thickened fibrous aneurysmal wall, with disorganized structure. Thickening was due to excessive proliferation of smooth muscle cells (SMCs) within media layer; the smooth muscle fibers were fragmented by overdeveloped collagen fibers, arranged in islands, and showing markedly disorganized arrangement. Middle tunic elastic layer was disorganized and fragmented by the collagen fibers. The intimate tunic showed large deposits of fibrin. Proliferation of small (neoformation) vessels in the outer tunic of the aneurysmal wall was observed (Figure 4, a–f).

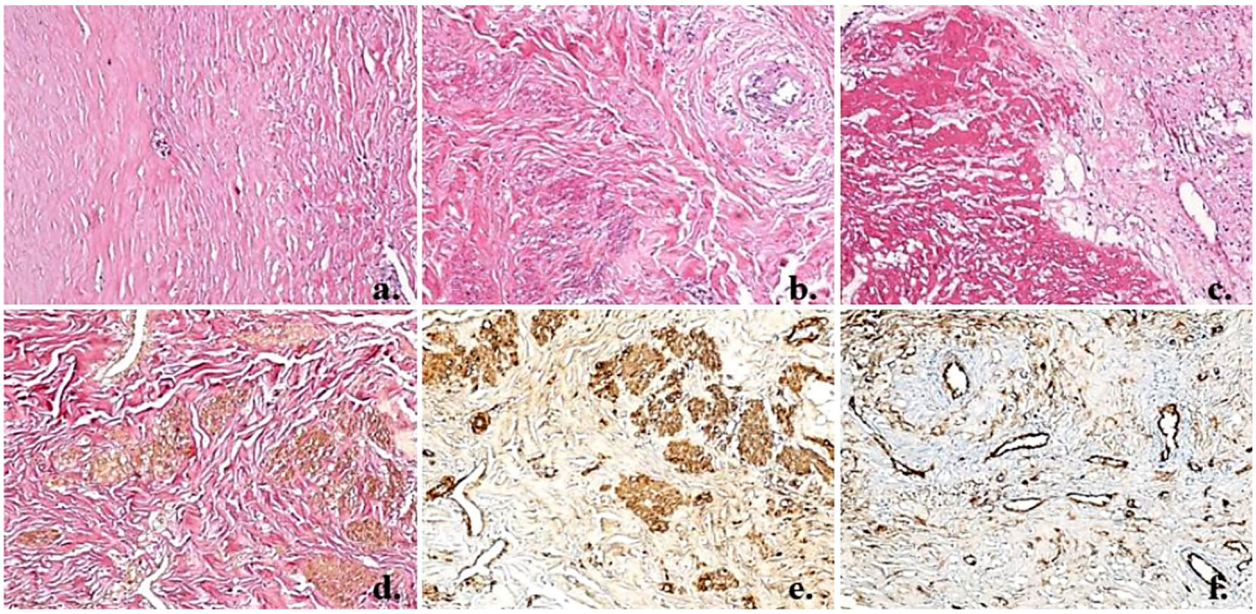

Figure 4 – ***(a) Markedly thickened fibrous aneurysmal wall; (b) Middle tunic of the vascular wall with markedly disorganized arrangement of the collagen fibers; (c) Large deposits of fibrin in the intimate tunic of the vascular wall; (d) Medium tunic elastic fibers, disorganized and fragmented by overdeveloped collagen fibers, with no visible continuous elastic layer; (e) Smooth muscle fibers proliferation in the middle tunic of the vascular wall, fragmented by collagen fibers, arranged in islands; (f) Microscopic image from the outer tunic of the vascular wall, which shows the presence of many blood vessels, including angiogenesis vessels. HE staining: (a–c) ×100. van Gieson staining: (d) ×100. Immunostaining with anti-α-SMA antibody: (e) ×100. Immunostaining with anti-CD34 antibody: (f) ×100. α-SMA: Alpha-smooth muscle actin; CD34: Cluster of differentiation 34; HE: Hematoxylin–Eosin.***

Discussions

This patient was diagnosed with definite TSC based on five major criteria (ungual fibromas, shagreen patch, cortical tubers, SENs, SEGA), three minor criteria (confetti skin lesions, dental enamel pits, gingival fibromas), the genetic result showing a heterozygous pathogenic variant in exon 8 of the *TSC1* gene (*c.733C>T-p.Arg245**). The disease was most probably transmitted by the father, who had periungual nodules and a single tonic-clonic epileptic seizure

at the age of 42, but no other clinical and genetic data are available; father declined treatment and investigations.

The case presented here showed two aneurysms in the arteries of the right arm, brachial and subclavian arteries. According to Boronat *et al.* (2014), aneurysms are rarely described, but twice more frequent in TSC patients (0.74%) compared to the general population (0.35%) [4]. Literature review underlines the rarity of TSC cases associating aneurysms – only 73 cases published since 1971 (Table 1). The most frequent arterial location is intracranial (53 aneurysms), usually involving the internal carotid artery (33 aneurysms); the second frequent aneurysmal location is aortic (36 aneurysms, 30 developed in the abdominal aorta). Peripheral aneurysms are very rare – only six cases have been previously described, presenting 10 aneurysms, in the iliac, iliofemoral, axillary, subclavian, or brachial arteries (Table 1). Patients usually have single aneurysms, only 12 cases presented multiple affected arteries and among these, only one in the arm. The patient discussed here presented two aneurysms in the arm, an exceptional aneurysmal location. Due to this rare disposition, an obvious question arose: are the aneurysms of the described case randomly associated with TSC or a direct result of the disturbed mTOR pathway and therefore a vascular TSC manifestation?

Table 1 – ***Location of TSC-associated aneurysms (literature review)***

Author(s), year	Ref. No.	Aneurysm location	No. of patients	Age	Genetics
Freycon *et al.*, 1971	5	Abdominal aorta	1		
Larbre *et al.*, 1971	6	Abdominal aorta	1		
Davidson, 1974	7	Multiple (2): internal carotid arteries (bilateral, fusiform)	1	Child	
Snowdon, 1974	8	Intracranial	1	Child	
Dutton & Singleton, 1975	9	Abdominal aorta	1	Child	
Hagood *et al.*, 1976	10	Abdominal aorta	1	Infant	
Ho, 1980	11	Intraventricular	1	26 years	
Beall & Delaney, 1983	12	Multiple (2): internal carotid; anterior communicating artery	1	17 years	
Guttman *et al.*, 1984	13	Giant intracranial	1	53 years	
Brill *et al.*, 1985	14	Giant intracranial	1	Child	
Copley, 1985	15	Intracranial	1		
Blumenkopf & Huggins, 1985	16	Multiple fusiform intracranial aneurysms	1	6 years	
Martin *et al.*, 1987	17	Giant intracranial	1		
Towbin *et al.*, 1987	18	Abdominal aorta	1	9 months	
Ng *et al.*, 1988	19	Abdominal aorta	1	24 years	
Libby *et al.*, 1989	20	Axillary	1		
Shepherd *et al.*, 1991	21	Thoracic aorta	1/355 (causes of death)	Child	
Occhionorelli *et al.*, 1991	22	Abdominal aorta	1	Adult	
van Reedt Dortland *et al.*, 1991	23	Abdominal aorta	1	5 years	
Lavocat *et al.*, 1992	24	Abdominal aorta (giant)	1	4.5 months	
Engel, 1992	25	Arterial circle of Willis	1	1 year	
Tsukui *et al.*, 1995	26	Abdominal aorta	1	4 years	
Paraf & Bruneval, 1996	3	Abdominal aorta (pathology – fibromuscular dysplasia)	1		
Spangler *et al.*, 1997	27	Multiple (3): internal carotid (fusiform), anterior cerebral (ectasia), middle cerebral (ectasia), all same side (left)	1	5 months	
Longa *et al.*, 1997	28	Middle cerebral (asymptomatic)	1	30 years	Large *TSC2/PKD1* deletion
Tamisier *et al.*, 1997	29	Abdominal aorta	1	Child	
Swarnkar *et al.*, 1998	30	Intracranial	1	Child	
Hite *et al.*, 1998	31	Multiple (2): axillary, brachial	1	10 months	
Jarrett *et al.*, 1998	32	Carotid	1		
Beltramello *et al.*, 1999	2	Internal carotid (giant)	1	11 years	
Ko *et al.*, 2000	33	Abdominal aorta (hamartomatous)	1	22 years	
Bavdekar *et al.*, 2000	34	Aorta	1	Child	
Baker & Furnival, 2000	35	Abdominal aorta	1	12 months	
Chen *et al.*, 2001	36	Internal carotid (paraclinoid)	1	19 years	
Jost *et al.*, 2001	37	Abdominal aorta	1	9 years	
		Thoracic aorta	1	41 years	
Patzer *et al.*, 2002	38	Internal carotid	1		
Jones *et al.*, 2002	39	Intracranial: midbasilar (giant)	1	19 months	
Burrows & Johnson, 2004	40	Pulmonary	1	52 years	

Author(s), year	Ref. No.	Aneurysm location	No. of patients	Age	Genetics
Lee *et al.*, 2004	41	Abdominal aorta	1	8 months	
Patiño Bahena *et al.*, 2005	42	Abdominal aorta (giant) and aortic dissection	1	8 months	
Kimura *et al.*, 2005	43	Descending aorta	1	2 years	
Wong *et al.*, 2006	44	Abdominal aorta (infradiaphragmatic)	1	4 years	
Araújo *et al.*, 1996	45	Internal carotid (giant)	1	9 years	*TSC2* deletion
Carette *et al.*, 2006	46	Pulmonary	1		
Koch *et al.*, 2008	47	Subclavian	1	4 years	
Calcagni *et al.*, 2008	48	Iliofemoral	1	20 months	
Hung *et al.*, 2008	49	Multiple intracranial (2): internal carotid and middle cerebral	1	8 months	
Moon *et al.*, 2009	50	Abdominal aorta	1	9 months	
Salerno *et al.*, 2010	51	Abdominal aorta	1	14 months	
Aissi *et al.*, 2010	52	Internal carotid (intracavernous)	1	34 years	
Sabat *et al.*, 2010	53	Multiple intracranial (2): posterior communicating (bilateral)	1	Adult	
Cao *et al.*, 2010	54	Multiple aortic (2): thoracoabdominal aorta and thoracic aorta	1	3 years	*TSC2 del.5340-5371*
Shelton *et al.*, 2011	55	Internal carotid (intracavernous)	1	9 months	
Denne *et al.*, 2011	56	Abdominal aorta	1	10 months	*TSC2*
Ye *et al.*, 2012	57	Abdominal aorta	1/6	17 months	
Yi *et al.*, 2012	58	Internal carotid	1	13 months	
Koroknay-Pál *et al.*, 2012	59	Multiple intracranial (4) fusiform aneurysms – three giant: one basilar, two internal carotid artery at bifurcation (bilateral), one posterior communicating artery	1/114	6 years	
Kirkwood *et al.*, 2013	60	Extracranial carotid	2/3 monozygotic twins	32 years	
		Intracranial	Maternal grandmother		
Bailey *et al.*, 2013	61	Thoracoabdominal aorta	1	3 years	
Dunet *et al.*, 2013	62	Multiple pulmonary artery	1	Adolescence	*TSC1* (exon 10, *c.990insT*)
Sawan *et al.*, 2015	63	Thoracoabdominal aorta	1	5 years	
Wang *et al.*, 2017	64	Superior mesenteric artery, right subclavian artery aneurysm	1	22 years	
Dueppers *et al.*, 2017	65	Abdominal aortic aneurysm	1	9 years	
Wang *et al.*, 2017	66	Carotid artery aneurysm	1	21 months	Large deletion 16p13.3. (*TSC2/PKD1* contiguous gene syndrome)
Geiger *et al.*, 2019	67	Thoracic aortic aneurysm	1	26 years	
Wiemer-Kruel *et al.*, 2020	68	Two aortic aneurysms and congenital segmental lymphedema of the left leg	1	7 years	*TSC2* (exon 38, *c.5024C>T*; *p.(Pro1675Leu)*
Hedin *et al.*, 2021	69	Abdominal aorta (infrarenal)	1	2 years	
Byrne *et al.*, 2022	70	Thoracic aorta	1	Pediatric patient	
Olvera *et al.*, 2022	71	Thoraco-abdominal aorta (three aneurysms)	1	4 years followed-up to 18 years	

PKD1: Polycystin 1, transient receptor potential channel interacting; TSC: Tuberous sclerosis complex.

The pathogeny of aneurysms formation in people without TSC is a complex remodeling process of synthesis and degradation of matrix proteins, the most striking feature being a thin media due to elastin fragmentation (leading to a compromised elastin network) [72, 73], decreased SMCs density by 74% by apoptosis, adventitial collagen synthesis, inflammation playing a role in the interaction between mesenchymal cells (SMCs and fibroblasts) and inflammatory cells (lymphocytes and macrophages) [74]. By contrast, TSC aneurysmal pathogeny is characterized by increased proliferation of the SMCs within the media, disorganized structure also involving the elastic layer [54]. The pathology examination of the aneurysmal wall of the patient showed characteristic changes for activation of the mTOR pathway, with the typical important thickening of the aneurysmal wall based on media SMCs proliferation.

We report a pathogenic variant in exon 8 of the *TSC1* gene (*c.733C>T-p.Arg245**). *c.733C>T* variant has been previously described; in the Leiden Open Variation Database (LOVD) (http://chromium.lovd.nl/LOVD2/TSC/home.php?select_db=*TSC1*&used_old_url), *c.733C>T* variant was reported 45 times. This was the only mutation in 40 reports,

another variant being associated in the rest of the five reports, including *TSC2* gene mutations. Usually, *TSC2* variants are associated with severe phenotypes [75]. Only 10 of the LOVD reports were published in five articles [76–80]. None of the published cases with *c.733C>T* variant associated aneurysms.

In the literature review of the published TSC cases associating aneurysms, very few discussed the causal variant (Table 1). Both *TSC1* and *TSC2* variants have been described in individuals with TSC and aneurysms. TSC pathogeny has a role in the genesis of aneurysms, considering that aneurysms are twice more frequent in the TSC population compared to the general population. Why are not all TSC patients presenting aneurysms? Why is this clinical manifestation so rare? Most probably other modifying genes and/or epigenetic factors are involved.

The patients with TSC and palpable vascular masses, hypertension, abdominal pain, or other symptoms, which may suggest aneurysms, should be screened using duplex ultrasound as the initial diagnostic approach of choice [51]. Multislice CT or MRI is recommended as a complementary screening and diagnostic tool [48]. Because TSC families with positive history of aneurysms do exist (although rare), it was suggested that systematic screening for aneurysms should be added as standard care of the asymptomatic TSC patients with vascular positive family history [60]. Routine screening for aneurysms is not recommended in patients with TSC and no positive history for aneurysms, due to the very low incidence of the aneurysms in the TSC population (0.74%) [4, 51].

Everolimus, an mTOR inhibitor, is now indicated for treatment of SEGA and AMLs, leading to their size reduction, but also has a favorable effect on other clinical elements of the disease, such as angiofibromas, or skin lesions [81]. mTOR is a serine/threonine kinase regulated by phosphoinositide-3-kinase (PI3K) and regulates cellular metabolism, cell growth, motility, angiogenesis. The PI3K-mTOR pathway members are implicated in the pathogeny of vascular anomalies by dysregulation of angiogenesis and lymphangiogenesis, protein overgrowth, cellular hyper-metabolism [82, 83]. It was shown in an experimental rat model that Rapamycin (mTOR inhibitor) suppressed the aortic aneurysm growth [84], but the pathogeny of this model may differ from that of the activated mTOR pathway. Therefore, mTOR inhibitors are predicted to be effective in other disorders in which the growth control factor is affected. There is no data in the literature presenting the effects of Everolimus treatment on aneurysms in TSC patients, but it is very tempting to think that Everolimus will have a favorable effect on TSC aneurysms, as Rapamycin (Sirolimus) proved to be effective in vascular anomalies such as vascular malformations or vascular tumors (Kaposiform hemangioendothelioma, capillary lymphatic venous malformation, diffuse microcystic lymphatic malformation), with significant response/improvement to Sirolimus [85]. In a recent published case of a 7-year-old TSC male patient with *TSC2* mutation, multiple aneurysms have been described: one growing aneurysm of the abdominal aorta near the emergence of both renal arteries, one of the common iliac, one of the left external iliac, two of the left internal iliac arteries. Because of an additional lymphatic malformation of the left leg, he was treated with Everolimus for six weeks, then stopped, four weeks before an urgent operation of the growing aortic aneurysm at the age of 17 months. One month after surgery, the treatment with Everolimus was resumed for the lymphatic malformation, without long-term side effects (more than 3.3 years with 3.5 mg/day). In a routine control of the aorta by CT angiography at five months, a new aneurysm was seen at the junction of the aorta and renal arteries, above the graft with Everolimus therapy. It remained stable over time, not growing with Everolimus treatment of 5 mg/day [68]. It is possible that the growth of the first aneurysm was due to an insufficient treatment duration. Arrest aneurysm growth in this single case report points at possible favorable effect of Everolimus for this pathology. It is known that in TSC aneurysms, massive SMCs proliferation within aneurysmal wall leads to elastic fibers fragmentation and impressive loss of organization of the trilaminar vascular wall structure [54]. Hypothetically, if Everolimus treatment is used and SMCs proliferation is stopped or even reversed, one may speculate that a thin and fragile aneurysmal wall (with damaged elastic layer) may result, and this might lead to an increased probability of rupture. Currently no proof exists on this effect of Everolimus treatment on SMCs. Further research is needed to clarify this issue.

Conclusions

A case with a severe phenotype having a *TSC1* gene mutation is presented; usually, the severe phenotype is associated with the *TSC2* variants. This is a rare case presenting aneurysms related to TSC, with an exceptional localization. Pathology examination is the key investigation for demonstrating TSC-related pathogenic mechanism. A literature review of TSC cases presenting with aneurysms was performed (73 cases). Very few TSC patients with aneurysms were genetically analyzed, and in most cases strict analysis of the *TSC1* and *TSC2* genes was performed. To determine if other modifying genes or epigenetic factors are involved in the pathogenesis of the TSC-associated aneurysms, further research is needed. The role of Everolimus in the treatment of TSC aneurysms must be unraveled.

Conflict of interests

The authors declare that they have no conflict of interests.

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