Two cases of Tuberous sclerosis complex with manifestation: Diagnosis and management

Tran Vu Minh Thu, MD

Patient's identification

- Patient's name: [redacted]
- Occupation:
- Address: Dak Nong province
- BMI: 18.7 kg/m^2
- Chief of complain: Heart tumor
- Date of admission: 23/10/2018
- Date of discharge: 27/10/2018

History of present illness

When she was 5 month old baby, she revealed convulsion after she fell down from a hammock . At that time, she was diagnosis generalized epilepsy. She was prescribed anticonvulsant medication. When she was an 2 year old child, she suffer from partial epilepsy (eye convulsion).

During 17 years, she was prescribed many kind of drugs for epilepsy treatment. There were about 8 – 10 episodes of convulsion/year. Medication are used sodium valproate and carbamazepine,

When she was 15 years old, she couldn't learn by heart. So, she stopped studying.

Before admission, she had a routine checkup in Vu Anh Hospital. Echocardiography showed abnormality. MSCT was indicated and concluded lipoma in heart wall. So, she went to Tam Duc hear hospital for further treatment.

Past medical history

2nd / 2 children – Normal delivery – full term – BW 3200g

Full vaccination.

No FHx of epilepsy

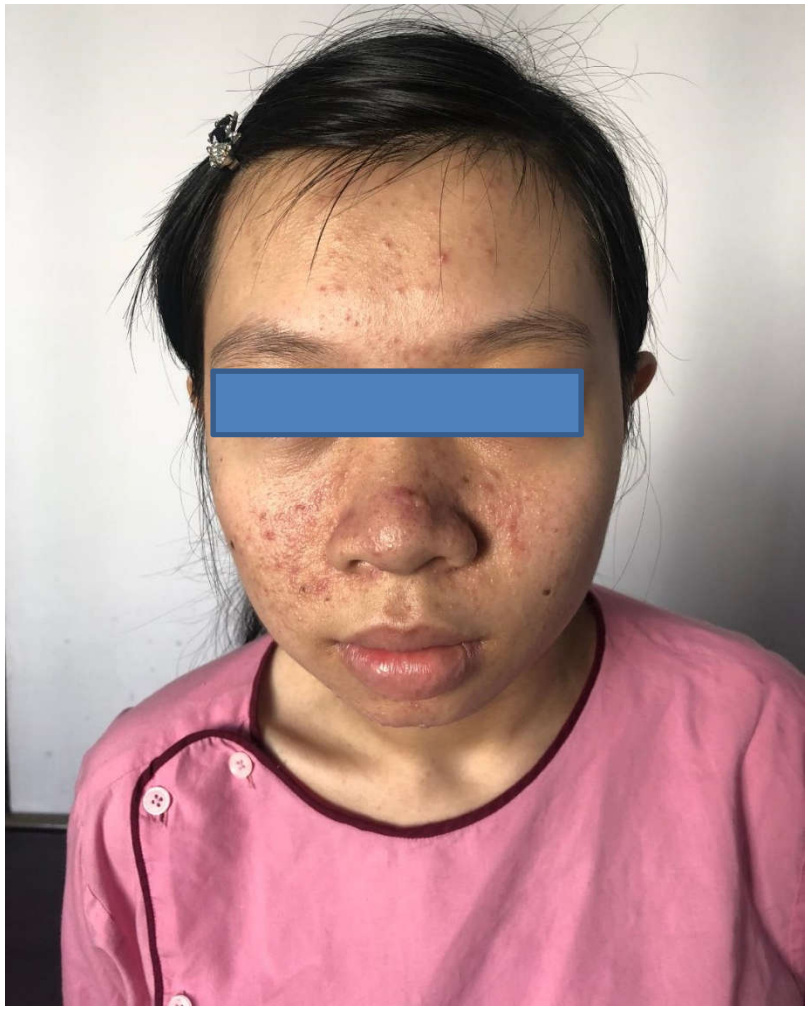
Physical examination

On admission

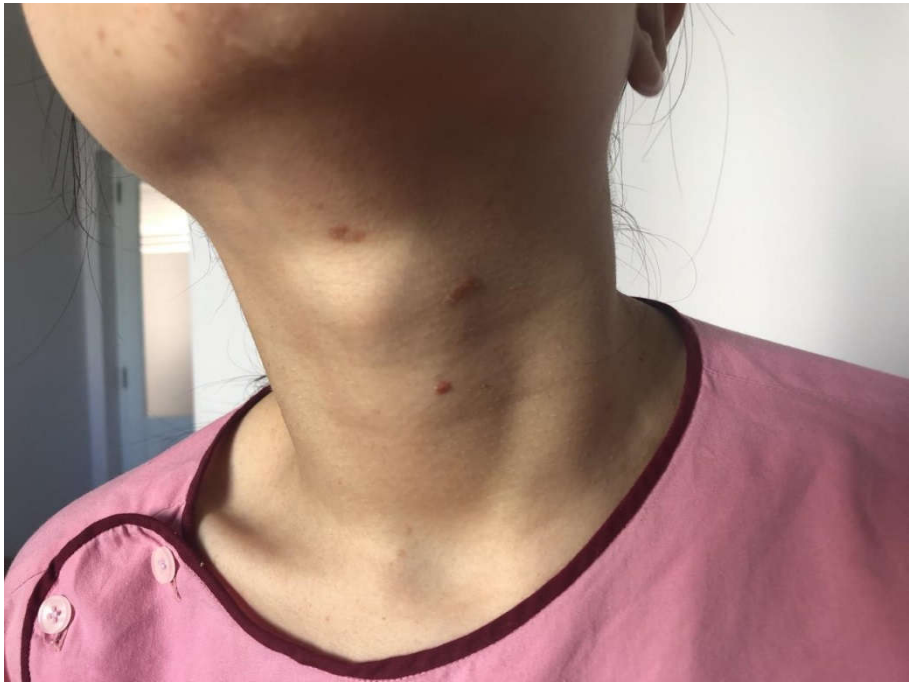
- Alert
- HR: 90 bpm BP: 110/60 mmHg T:37ºC RR:16 bpm
- Pulse at lower extremities (both sides): (+)
- Regular heart rate
- No carotid bruit
- No pulmonary rale or crackle
- Abdomen: tenderness. No hepatomegaly or splenomegaly.
- Other organs: unremarkable
- ABI R:1.0 L:1.0

Skin lesions

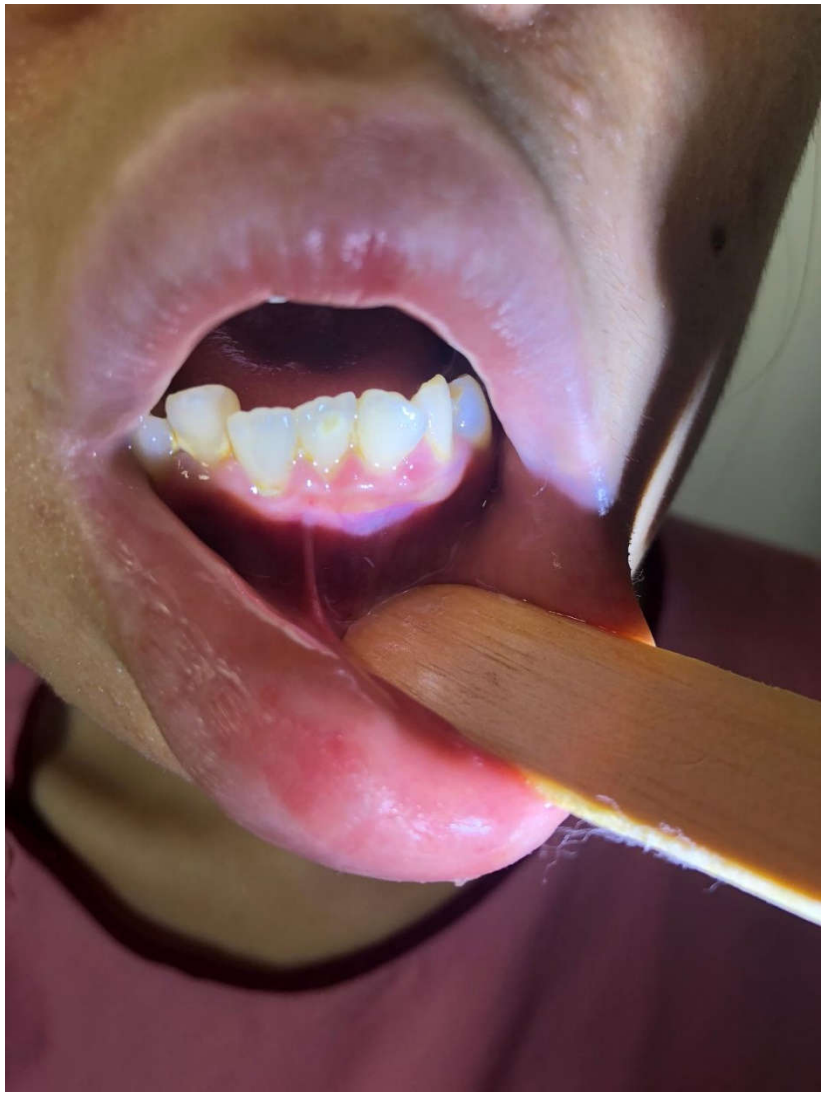
Facial angiofibromas



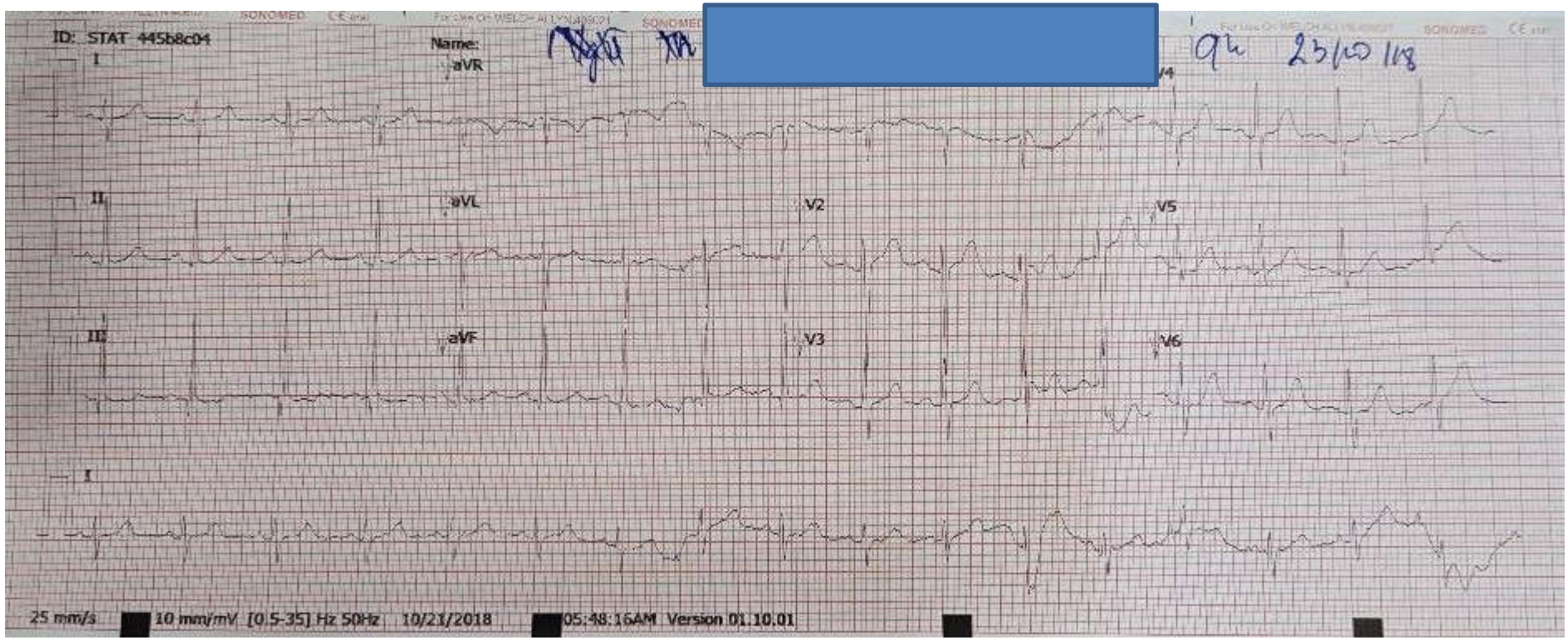
Shagreen patch



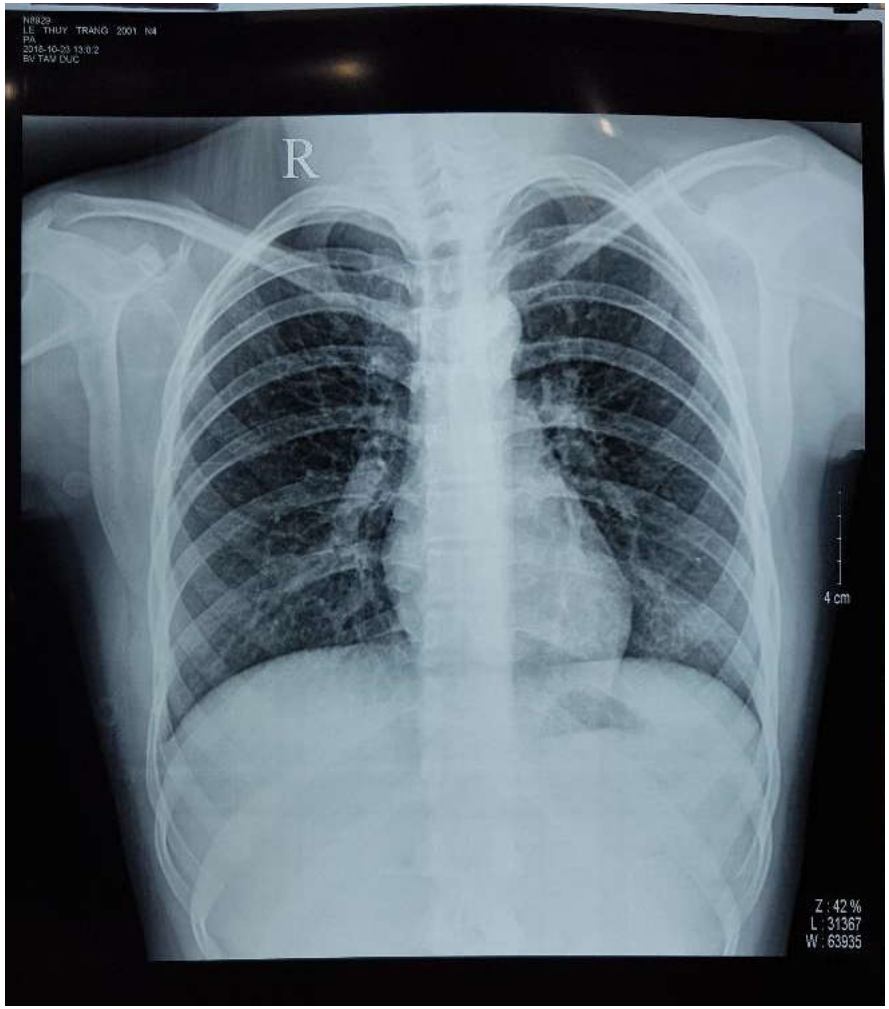
Intraoral fibromas



Eclectrocardiography

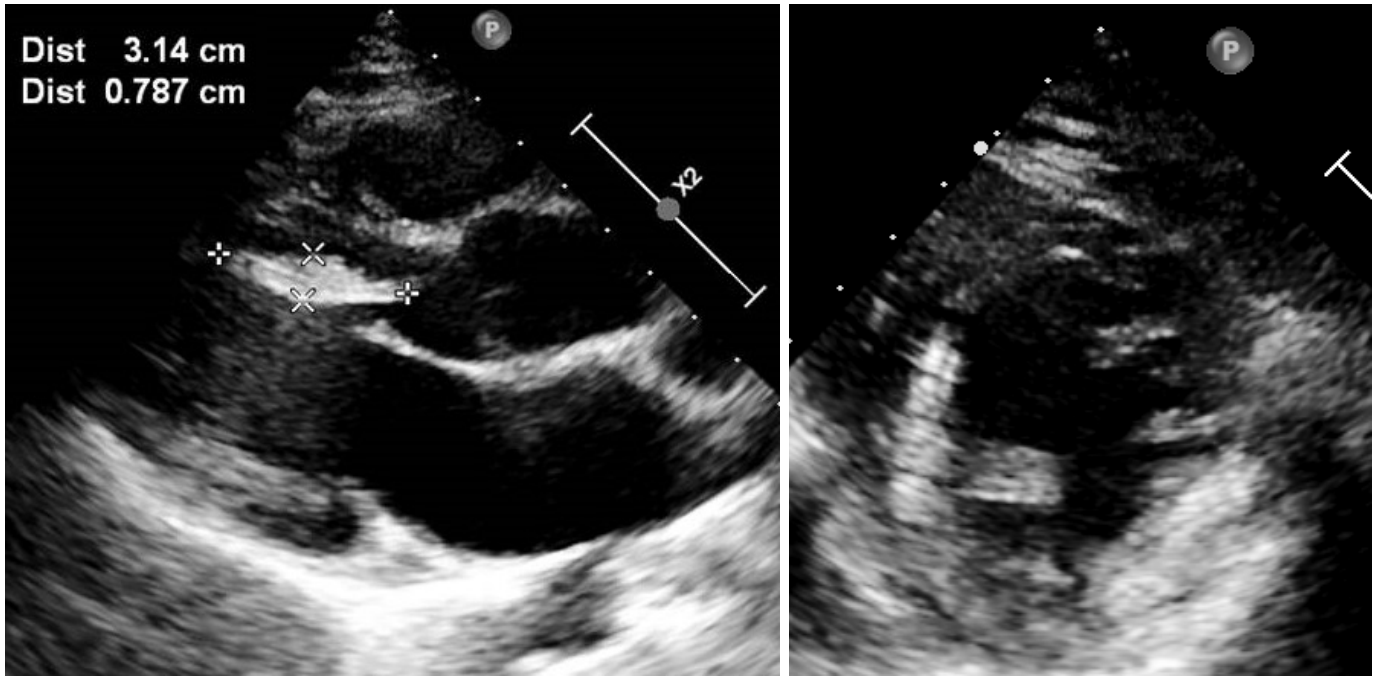


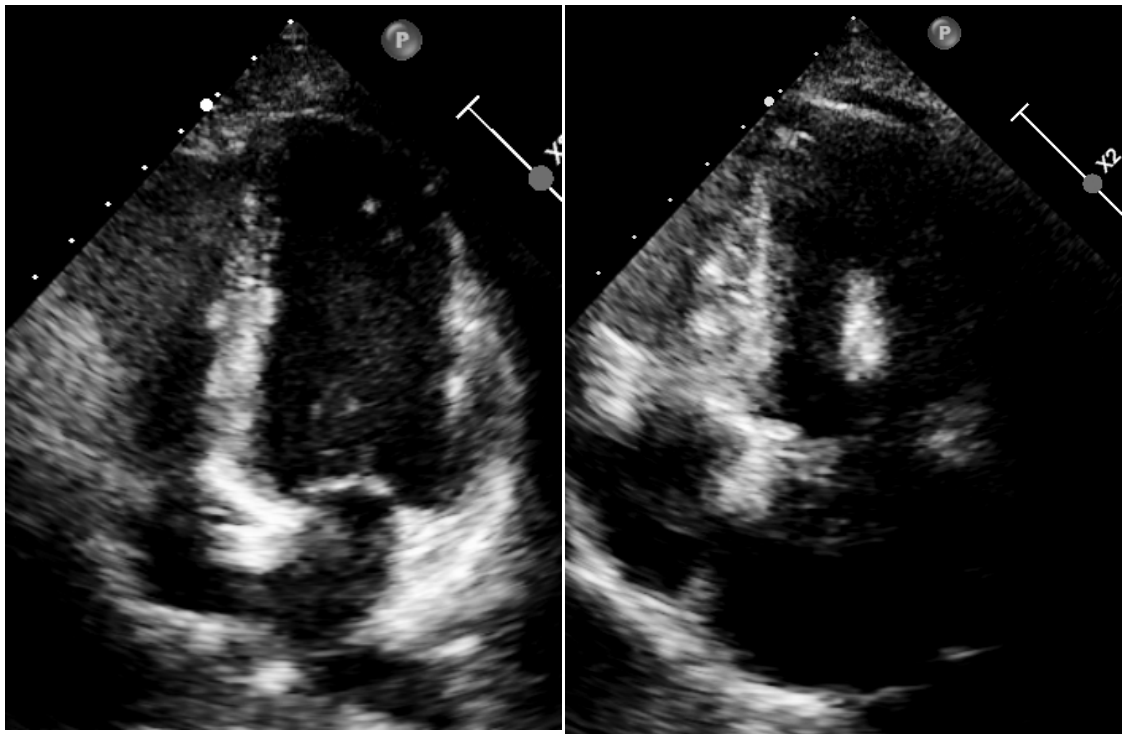
Chest Xray



Laboratory studies

Parameter		Parameter	
RBC (M/ul)	3.7	Serum creatinin (mmol/l)	58
Hb (g/dl)	11.7	GFR (ml/p/1,73m²)	
WBC (K/UI)	5.8	Na (mmol/l)	137
PLT (K/ul)	215	K (mmol/l)	3.8
CRP (mg/L)	0.7	Fasting glucose (mmol/l)	4.9
TC (mmol/l)	4.7	TSH (mUI/l)	2.4
HDL-C (mmol/l)	2.3	FT3	2.7
LDL-C (mmol/l)	1.7	FT4	0.7
TG (mmol/l)	0.8	NT-proBNP (pg/ml)	58
AST (U/L)	5	hsTnT	5
ALT(U/L)	20	Urine analysis	
		Protein (g/l)	-
		Glucose (mmol/l	-





Echocardiography

Normal motion of heart walls.
LVEF: 68%

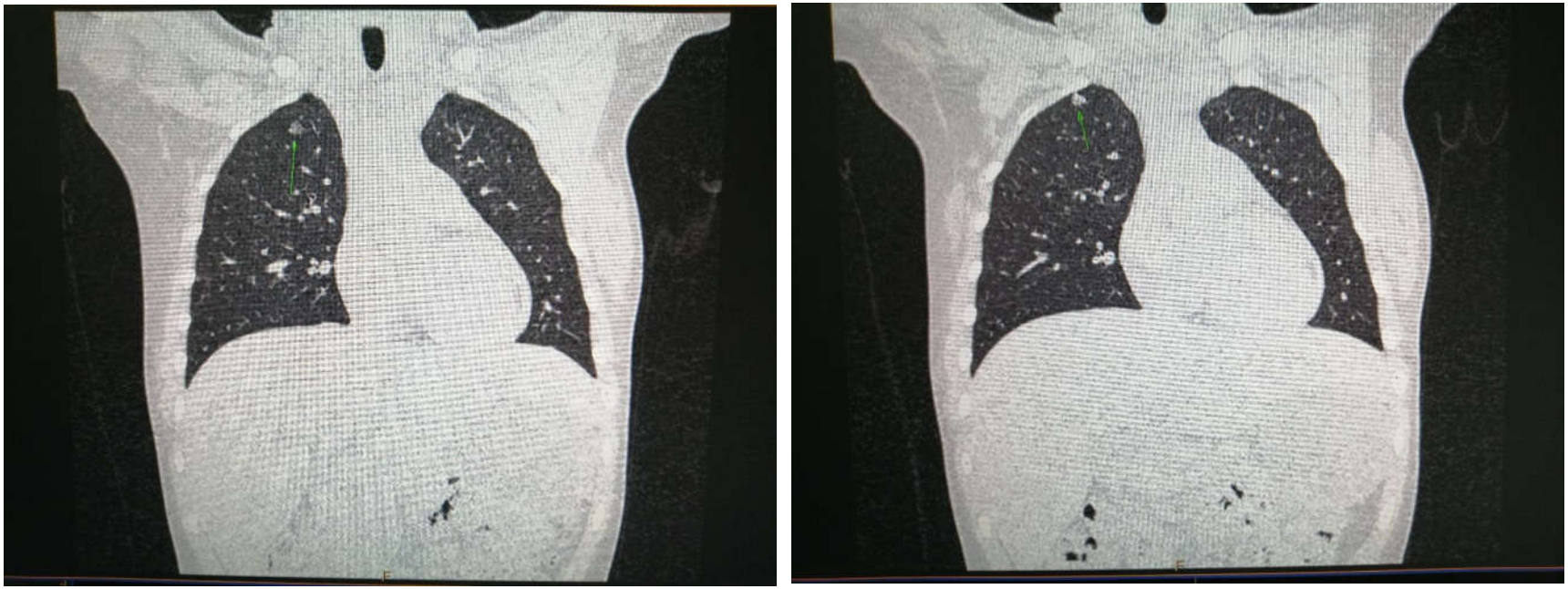
Holter ECG

- Premature ventricular contraction

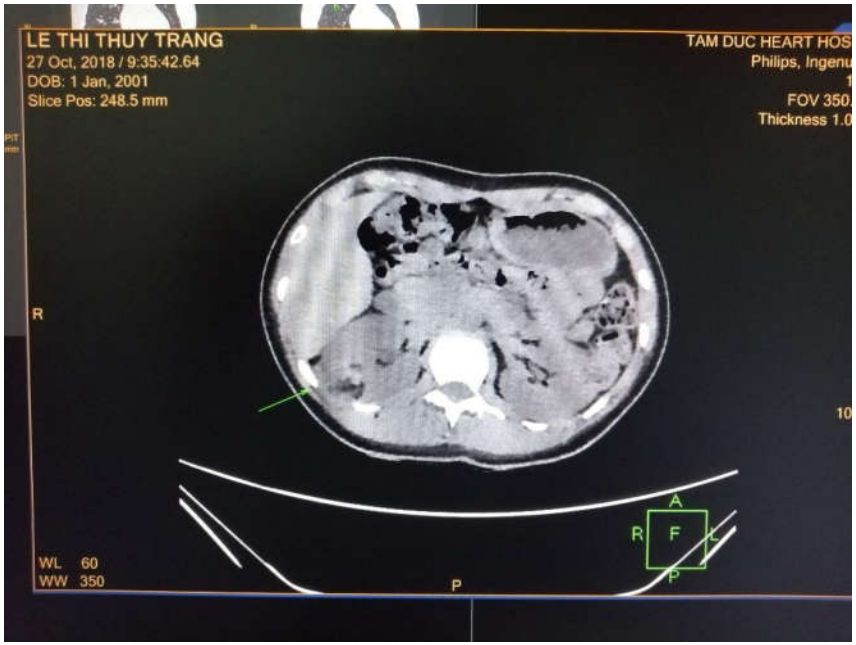
Cerebral MRI

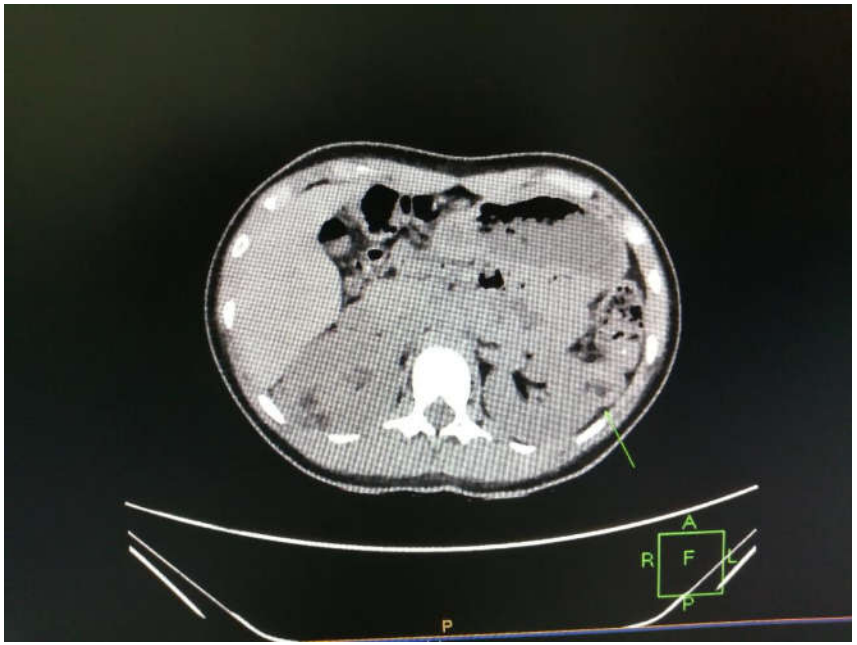
- Nodules 5 – 7 mm in brain cortex
- Subependymal nodules

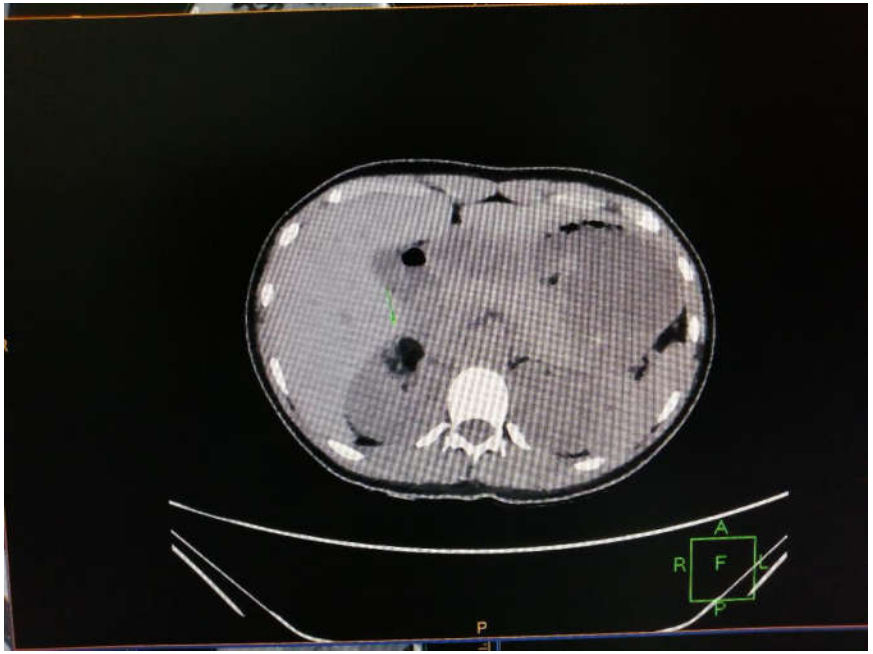
Thoracic MSCT



Nodules 3 - 5 mm in lungs







Angiomyolipoma 50 x 50 mm in two kidneys

Cardiac MRI

- Lipoma 6 x 22 x 32 mm in mid segment of LV lateral wall
- Sclerosis chordae tendinae

Genetic testing

Likely pathogenic mutation TSC2 c.2626delA

In summary

- Female patient, 17yrs
- Partial epilepsy
- Decrease learning skill
- Skin lesions: Facial angiofibromas, Shagreen patch, Intraoral fibromas
- Brain: Nodules in brain cortex, subependymal zone
- Lung: nodules
- Heart: Lipoma 6 x 22 x 32 mm in mid segment of LV lateral wall. Sclerosis chordae tendina
- Kidney: Angiomyolipoma 50 x 50 mm in two kidneys
- Likely pathogenic mutation TSC2 c.2626delA

Updated diagnostic criteria for tuberous sclerosis complex 2012

A. Genetic diagnostic criteria

The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al., 2012 and 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

B. Clinical diagnostic criteria

Major features

1. Hypomelanotic macules (≥3, at least 5-mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)†
11. Angiomyolipomas (≥2)†

Minor features

1. "Confetti" skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with ≥2 minor features

Possible diagnosis: Either one major feature or ≥2 minor features

* Includes tubers and cerebral white matter radial migration lines.

† A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

Northrup H et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243-254

Updated diagnostic criteria for tuberous sclerosis complex 2012

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Major features	Minor features
Hypomelanotic macules (≥ 3, at least 5 mm in diameter)	"Confetti" skin lesions
Angiofibromas (≥ 3) or fibrous cephalic plaque	Dental enamel pits (> 3)
Ungual fibromas (≥ 2)	Intraoral fibromas (≥ 2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasias	Nonrenal hamartomas
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis	
Angiomyolipomas (≥ 2)	

Definite diagnosis: Two major features or 1 major feature with ≥ 2 minor features. Possible diagnosis: Either 1 major feature or ≥ 2 minor features.

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Diagnosis

Tuberous sclerosis complex

- Partial epilepsy
- Decrease learning skill
- Skin lesions: Facial angiofibromas, Shagreen patch, Intraoral fibromas
- Brain: Nodules in brain cortex, subependymal zone
- Lung: nodules
- Heart: Lipoma 6 x 22 x 32 mm in mid segment of LV lateral wall. Sclerosis chordae tendina
- Kidney: Angiomyolipoma 50 x 50 mm in two kidneys

Treatment

Tuberous sclerosis complex

- Partial epilepsy
- Decrease learning skill
- Skin lesions: Facial angiofibromas, Shagreen patch, Intraoral fibromas
- Brain: Nodules in brain cortex, subependymal zone
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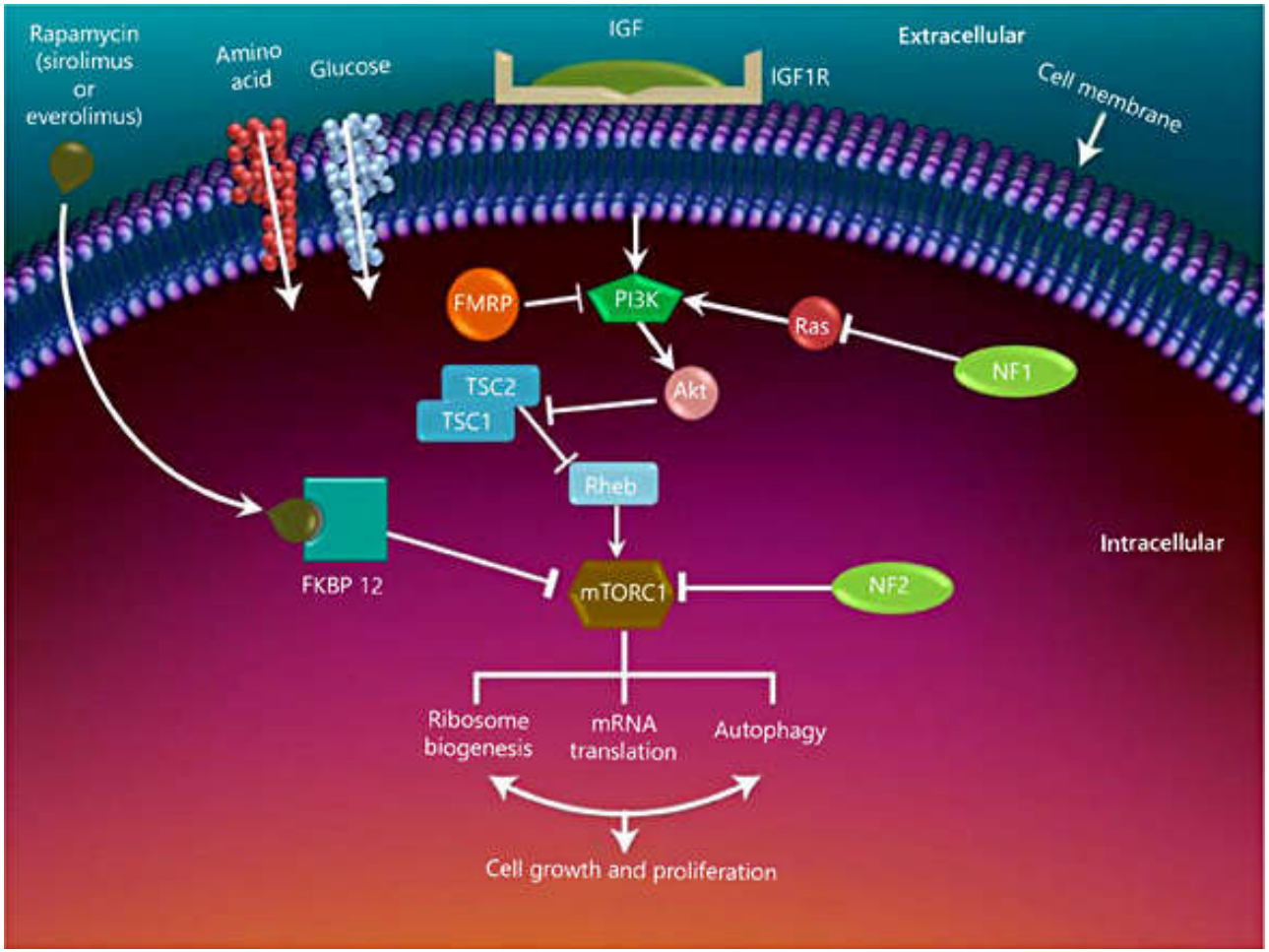
Renal angiomyolipoma

Management recommendations for renal angiomyolipoma	
Angiomyolipoma with acute hemorrhage	Embolization (followed by corticosteroids for 7 days to mitigate postembolization syndrome) [14]. Embolization should be as selective as technically feasible to preserve renal parenchyma. Avoid nephrectomy.
Asymptomatic, growing angiomyolipoma > 3 cm in diameter.	First-line: mTOR inhibitor. Second-line: selective embolization or kidney-sparing resection.

GFR = glomerular filtration rate; MRI = magnetic resonance imaging; mTOR = mammalian target of rapamycin; TSC = tuberous sclerosis complex.

Krueger DA et al. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference.Pediatr Neurol 2013; 49: 255-265

The mTOR pathway



In TSC, the growth of benign tumors in various organs occurs from loss of TSC1 or TSC2 genes and subsequent overactivation of mammalian target of rapamycin (mTOR), a kinase responsible for regulating cell growth, proliferation, and angiogenesis

J. Chris Kingswood. Review of the Tuberous Sclerosis Renal Guidelines from the 2012 Consensus Conference: Current Data and Future Study. Nephron 2016;134:51–58

PLoS One. 2016 Jun 28;11(6):e0158476. doi: 10.1371/journal.pone.0158476. eCollection 2016.

Long-Term Use of Everolimus in Patients with Tuberous Sclerosis Complex: Final Results from the EXIST-1 Study.

Franz DN[1], Belousova E[2], Sparagana S[3], Bebin EM[4], Frost MD[5], Kuperman R[6], Witt O[7], Kohrman MH[8], Flamini JR[9], Wu JY[10], Curatolo P[11], de Vries PJ[12], Berkowitz N[13], Niolat J[14], Jóźwiak S[15].

Author information

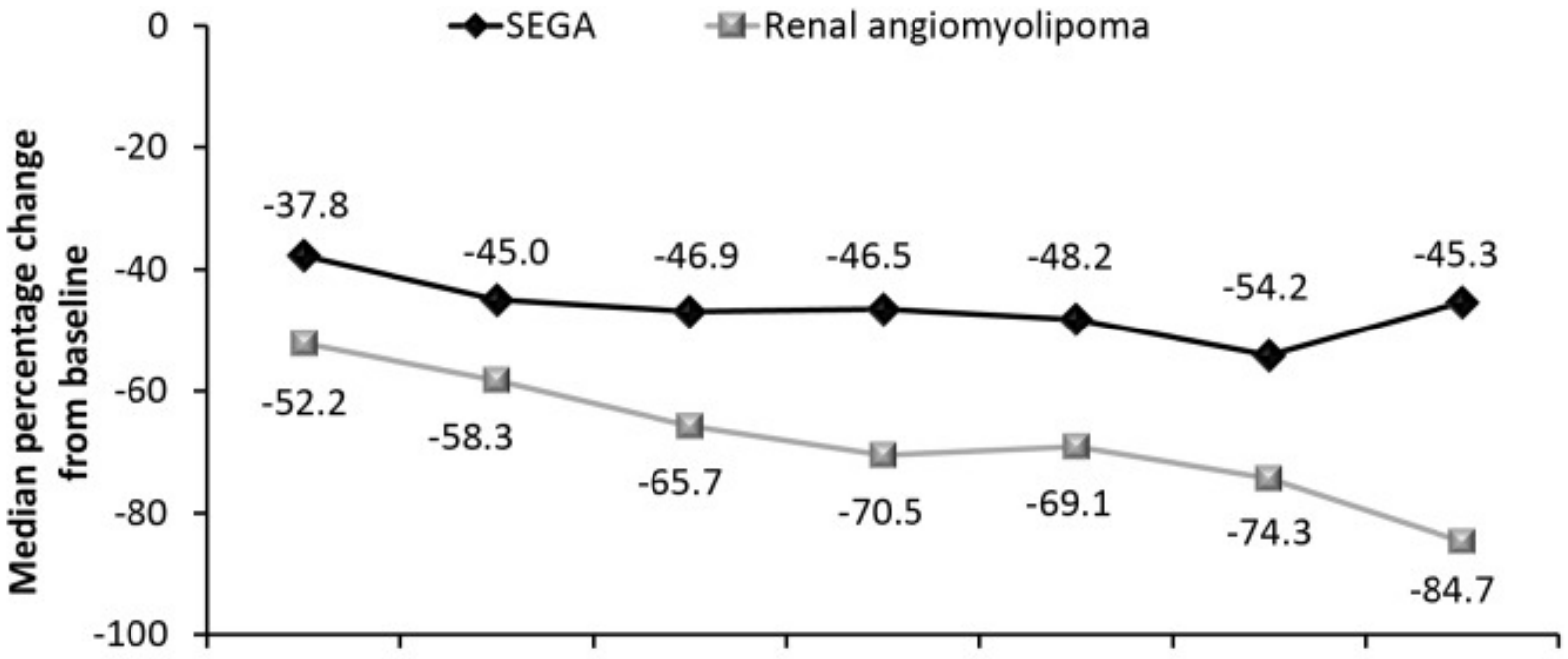
Abstract

BACKGROUND: Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has demonstrated efficacy in treating subependymal giant cell astrocytomas (SEGAs) and other manifestations of tuberous sclerosis complex (TSC). However, long-term use of mTOR inhibitors might be necessary. This analysis explored long-term efficacy and safety of everolimus from the conclusion of the EXIST-1 study (NCT00789828).

METHODS AND FINDINGS: EXIST-1 was an international, prospective, double-blind, placebo-controlled phase 3 trial examining everolimus in patients with new or growing TSC-related SEGA. After a double-blind core phase, all remaining patients could receive everolimus in a long-term, open-label extension. Everolimus was initiated at a dose (4.5 mg/m2/day) titrated to a target blood trough of 5-15 ng/mL. SEGA response rate (primary end point) was defined as the proportion of patients achieving confirmed ≥50% reduction in the sum volume of target SEGA lesions from baseline in the absence of worsening nontarget SEGA lesions, new target SEGA lesions, and new or worsening hydrocephalus. Of 111 patients (median age, 9.5 years) who received ≥1 dose of everolimus (median duration, 47.1 months), 57.7% (95% confidence interval [CI], 47.9-67.0) achieved SEGA response. Of 41 patients with target renal angiomyolipomas at baseline, 30 (73.2%) achieved renal angiomyolipoma response. In 105 patients with ≥1 skin lesion at baseline, skin lesion response rate was 58.1%. Incidence of adverse events (AEs) was comparable with that of previous reports, and occurrence of emergent AEs generally decreased over time. The most common AEs (≥30% incidence) suspected to be treatment-related were stomatitis (43.2%) and mouth ulceration (32.4%).

CONCLUSIONS: Everolimus use led to sustained reduction in tumor volume, and new responses were observed for SEGA and renal angiomyolipoma from the blinded core phase of the study. These findings support the hypothesis that everolimus can safely reverse multisystem manifestations of TSC in a significant proportion of patients.

Median percentage reduction in SEGA and renal angiomyolipoma volume over time

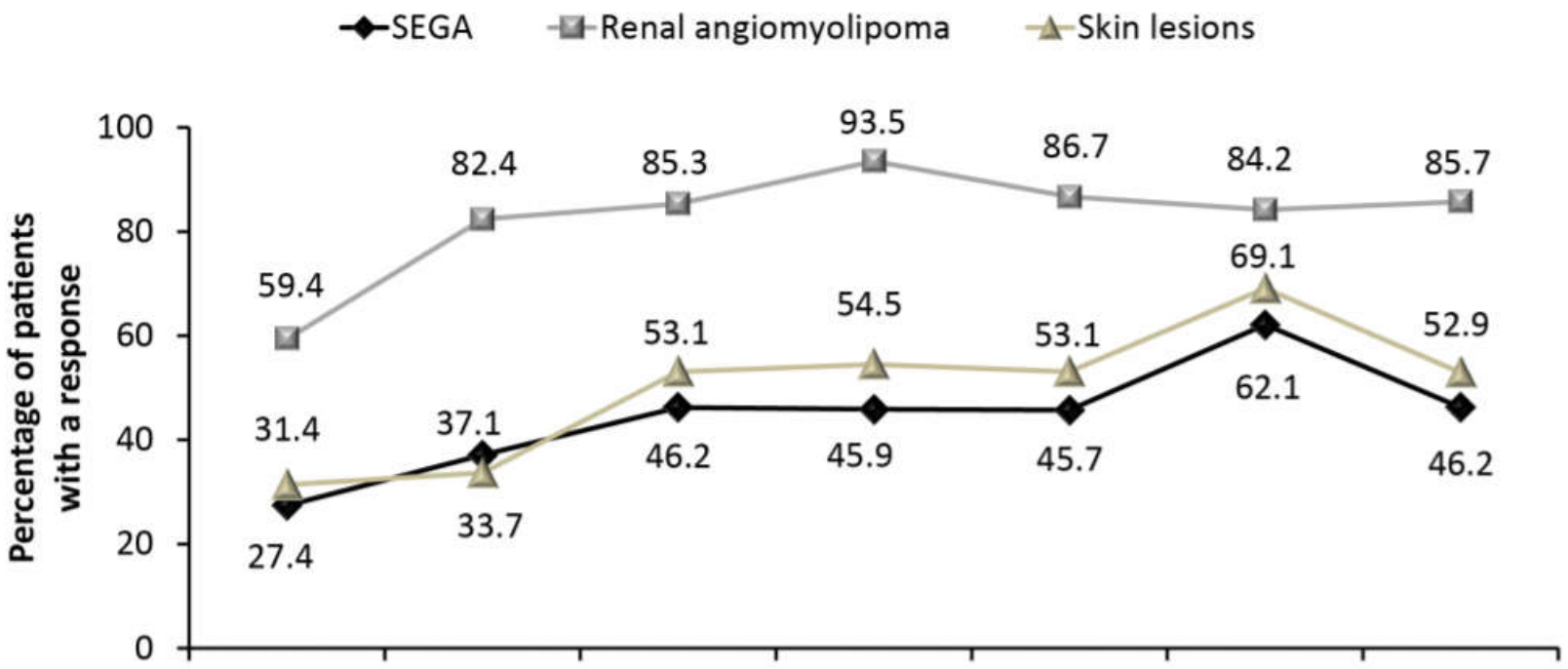


Time, weeks	12	24	48	96	144	192	240
Patients w/ SEGA, n	106	105	104	98	92	66	26
Patients w/ renal angiomyolipoma, n	32	34	34	31	30	19	7

SEGA, subependymal giant cell astrocytomas

Franz DN, et al. Long-Term Use of Everolimus in Patients with Tuberous Sclerosis Complex: Final Results from the EXIST-1 Study. PloS One. 2016; 11(6): e0158476

Final 4-Year Results from the Clinical Trial, EXIST-1
Proportion of patients with ≥ 50% reduction/improvement



Time, weeks	12	24	48	96	144	192	240
Patients w/ SEGA, n	106	105	104	98	92	66	26
Patients w/ renal angiomyolipoma, n	32	34	34	31	30	19	7
Patients w/ skin lesions, n	102	95	96	88	81	55	17

Franz DN, et al. Long-Term Use of Everolimus in Patients with Tuberous Sclerosis Complex: Final Results from the EXIST-1 Study. PloS One. 2016; 11(6): e0158476

AEs by Preferred Term Regardless of Relationship to Study Drug and by Year of Emergence Occurring in >10% of Patients

	Everolimus				
AEs, n (%)	**≤12 months (N = 111)**	**13–24 months (n = 106)**	**25–36 months (n = 98)**	**37–48 months (n = 88)**	**>48 months (n = 57)**
Any AE	108 (97.3)	93 (87.7)	84 (85.7)	66 (75.0)	28 (49.1)
Stomatitis	44 (39.6)	13 (12.3)	11 (11.2)	6 (6.8)	5 (8.8)
Mouth ulceration	32 (28.8)	15 (14.2)	10 (10.2)	7 (8.0)	1 (1.8)
Convulsion	24 (21.6)	15 (14.2)	13 (13.3)	10 (11.4)	4 (7.0)
Pyrexia	22 (19.8)	18 (17.0)	12 (12.2)	5 (5.7)	1 (1.8)
Vomiting	21 (18.9)	8 (7.5)	5 (5.1)	3 (3.4)	0
Cough	21 (18.9)	7 (6.6)	6 (6.1)	4 (4.5)	2 (3.5)
Nasopharyngitis	19 (17.1)	12 (11.3)	10 (10.2)	9 (10.2)	2 (3.5)
Diarrhea	18 (16.2)	9 (8.5)	3 (3.1)	2 (2.3)	3 (5.3)
Upper respiratory tract infection	16 (14.4)	9 (8.5)	4 (4.1)	6 (6.8)	1 (1.8)
Pharyngitis	13 (11.7)	5 (4.7)	8 (8.2)	4 (4.5)	4 (7.0)
Ear infection	12 (10.8)	5 (4.7)	6 (6.1)	1 (1.1)	0
Pneumonia	7 (6.3)	12 (11.3)	10 (10.2)	3 (3.4)	2 (3.5)

AE, adverse event.

Franz DN, et al. Long-Term Use of Everolimus in Patients with Tuberous Sclerosis Complex: Final Results from the EXIST-1 Study. PloS One. 2016; 11(6): e0158476

Lancet. 2013 Mar 9;381(9869):817-24.

Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial.

Bissler JJ[1], Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, Nonomura N, Brakemeier S, de Vries PJ, Whittemore VH, Chen D, Sahmoud T, Shah G, Lincy J, Lebwohl D, Budde K.

Author information

Abstract

BACKGROUND: Angiomyolipomas are slow-growing tumours associated with constitutive activation of mammalian target of rapamycin (mTOR), and are common in patients with tuberous sclerosis complex and sporadic lymphangioleiomyomatosis. The insidious growth of these tumours predisposes patients to serious complications including retroperitoneal haemorrhage and impaired renal function. Everolimus, a rapamycin derivative, inhibits the mTOR pathway by acting on the mTOR complex 1. We compared the angiomyolipoma response rate on everolimus with placebo in patients with tuberous sclerosis or sporadic lymphanioleiomyomatosis-associated angiomyolipomata.

METHODS: In this double-blind, placebo-controlled, phase 3 trial, patients aged 18 years or older with at least one angiomyolipoma 3 cm or larger in its longest diameter (defined by radiological assessment) and a definite diagnosis of tuberous sclerosis or sporadic lymphangioleiomyomatosis were randomly assigned, in a 2:1 fashion with the use of an interactive web response system, to receive oral everolimus 10 mg per day or placebo. The primary efficacy endpoint was the proportion of patients with confirmed angiomyolipoma response of at least a 50% reduction in total volume of target angiomyolipomas relative to baseline. This study is registered with ClinicalTrials.gov number NCT00790400.

RESULTS: 118 patients (median age 31·0 years; IQR 18·0–61·0) from 24 centres in 11 countries were randomly assigned to receive everolimus (n=79) or placebo (n=39). At the data cutoff, double-blind treatment was ongoing for 98 patients; two main reasons for discontination were disease progression (nine placebo patients) followed by adverse events (two everolimus patients; four placebo patients). The angiomyolipoma response rate was 42% (33 of 79 [95% CI 31–53%]) for everolimus and 0% (0 of 39 [0–9%]) for placebo (response rate difference 42% [24–58%]; one-sided Cochran-Mantel-Haenszel test p<0·0001). The most common adverse events in the everolimus and placebo groups were stomatitis (48% [38 of 79], 8% [3 of 39], respectively), nasopharyngitis (24% [19 of 79] and 31% [12 of 39]), and acne-like skin lesions (22% [17 of 79] and 5% [2 of 39]).

INTERPRETATION: Everolimus reduced angiomyolipoma volume with an acceptable safety profile, suggesting it could be a potential treatment for angiomyolipomas associated with tuberous sclerosis.

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Consequences of delay in screening, monitoring, and treatment of angiomyolipoma and tuberous sclerosis: A case report

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TSC Center of Excellence, LeBonheur Children's Hospital, Boling Center for Developmental Disabilities, Memphis, TN, USA

Abstract. Background: Tuberous sclerosis complex (TSC) is a multisystem disorder that results in tumor growth in various organs. TSC can affect the kidneys in the form of renal angiomyolipomas and cysts that can lead to chronic kidney disease. Case presentation: A 38-year-old woman was referred to Kennedy Krieger Institute for comprehensive TSC management. Before referral, the patient had gone most of her life without a definite diagnosis of TSC despite visually-prominent signs such as forehead plaques, facial angiofibromas, and ungual fibromas. Eventually, complications of the disease led to the patient requiring hemodialysis at age 34 and a complete bilateral nephrectomy at age 36. However, the patient was not diagnosed with TSC until an evaluation at the National Institutes of Health at age 37. After becoming a patient at our clinic, a multidisciplinary approach was taken to provide comprehensive care by including various disciplines such as nephrology, neurology, pulmonology, ophthalmology, dentistry, dermatology, and cardiology. Discussion and conclusion: TSC consensus recommendations aid in diagnosis, monitoring, and treatment of TSC and its associated manifestations, including those involving the kidneys. Our case underscores the importance of early identification of TSC to prevent future complications and promotes use of a multidisciplinary team to provide comprehensive care.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFINITOR/AFINITOR DISPERZ safely and effectively. See full prescribing information for AFINITOR/AFINITOR DISPERZ.

AFINITOR® (everolimus) tablets, for oral use

AFINITOR DISPERZ® (everolimus tablets for oral suspension)

Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.6)	4/2018
Dosage and Administration (2.7, 2.8)	4/2018
Warnings and Precautions (5.2, 5.3, 5.9, 5.10)	4/2018

----------INDICATIONS AND USAGE----------

AFINITOR is a kinase inhibitor indicated for the treatment of:

- Postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole. (1.1)
- Adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic.
  Limitation of Use: AFINITOR is not indicated for the treatment of patients with functional carcinoid tumors. (1.2)
- Adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. (1.3)
- Adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. (1.4)

Treatment?

- Biopsy renal tumor
- Everolimus if renal angiomyolipoma is confirmed

The 2nd patient

- Patient's name: [redacted]
- Address: HCM city
- Chief of complain: convulsion

History of present illness

When he was 8 month old baby, he revealed convulsion. At that time, he was diagnosis generalized epilepsy. He was prescribed anticonvulsant medication. When he was an 3 year old child, he suffer from absence epilepsy .

During 4 years, he was prescribed many kind of drugs for epilepsy treatment. There were about 10 episodes of convulsion/month. Medication are used

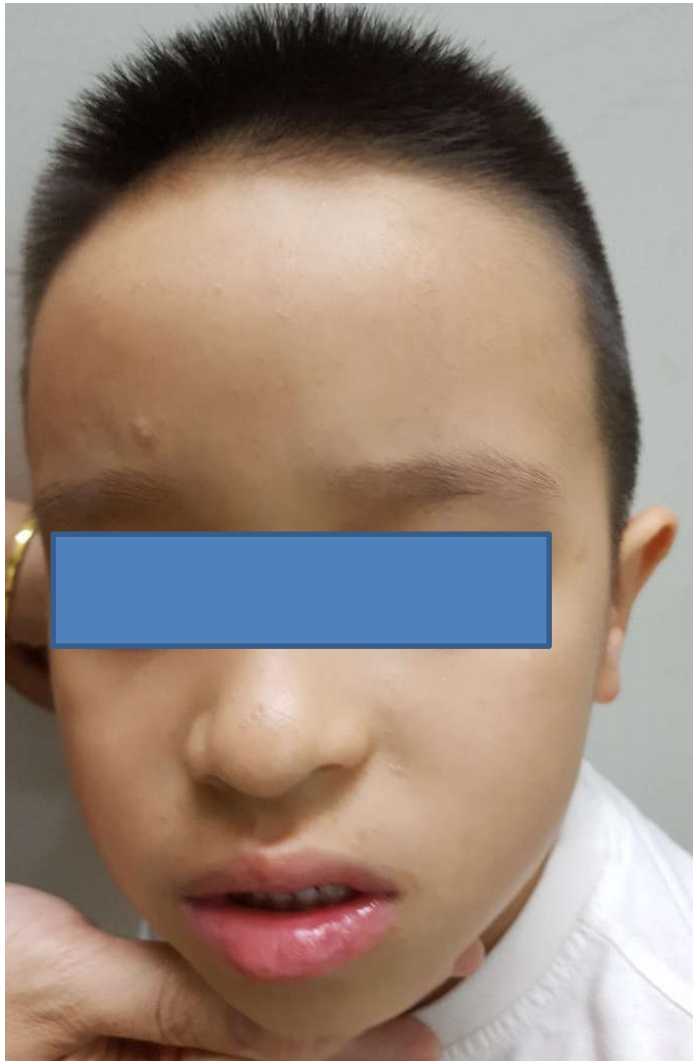
Past medical history

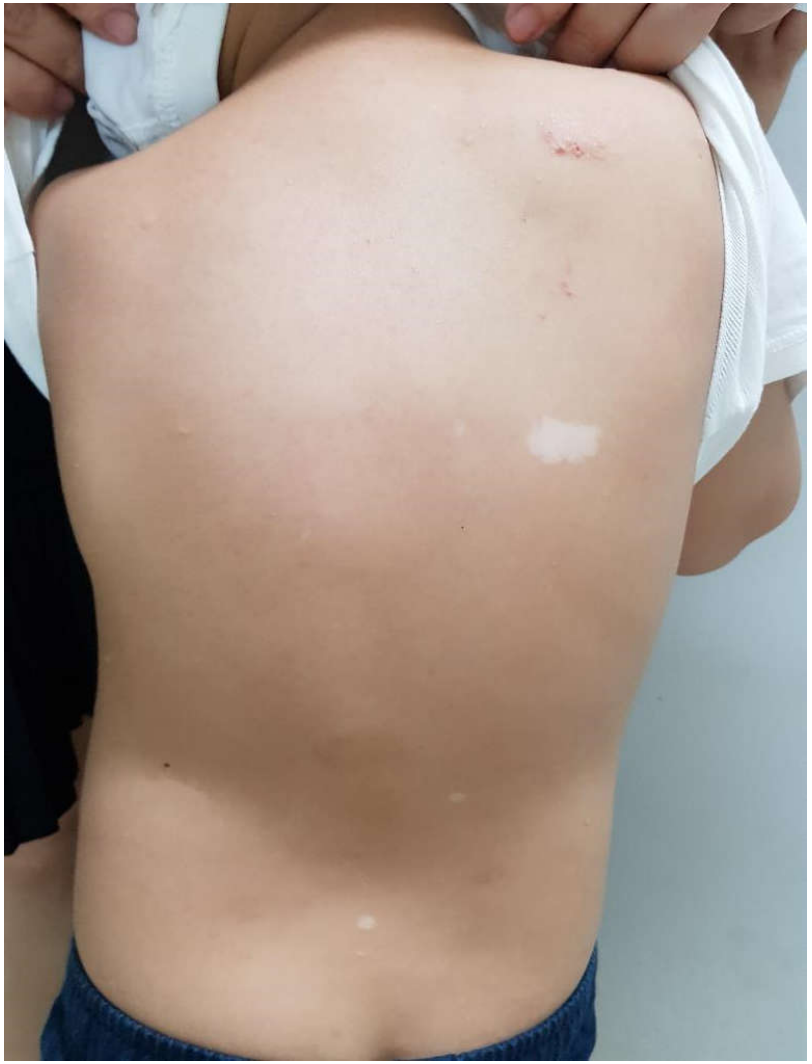
1st / 2 children – Normal delivery – full term – BW 3500g

Full vaccination.

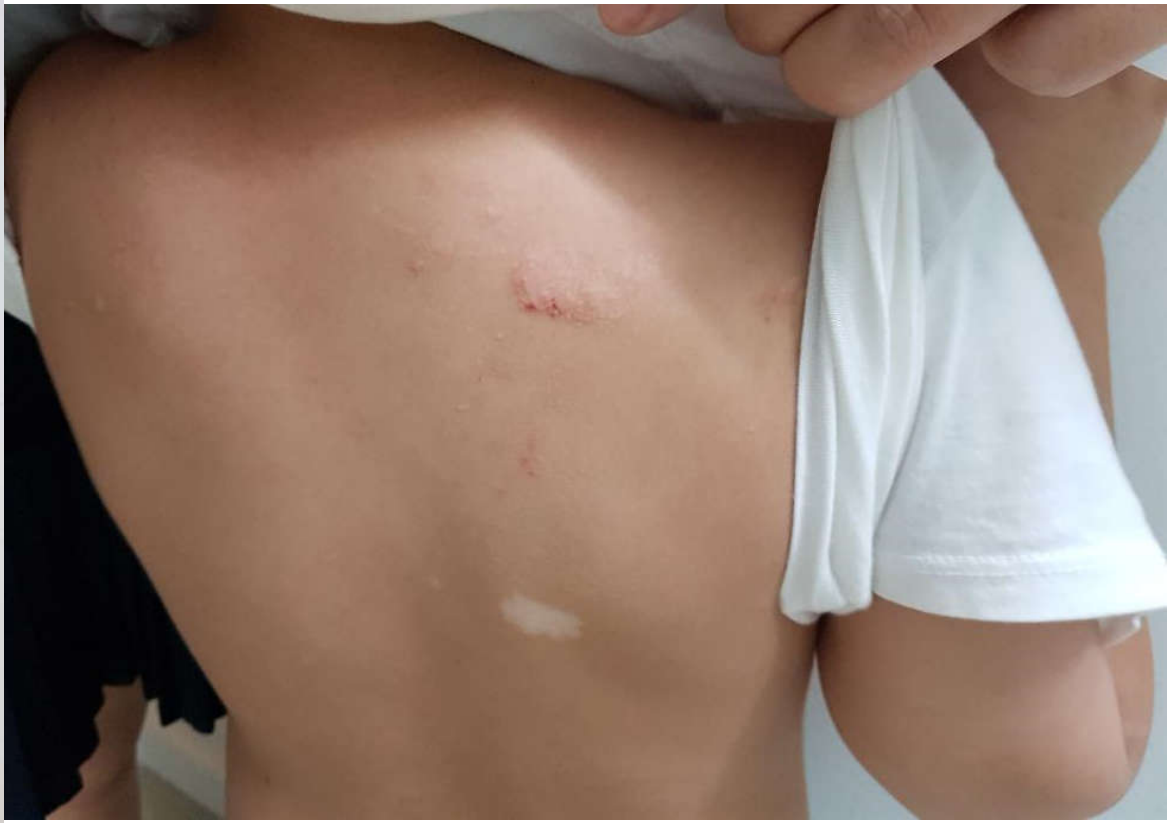
No FHx of epilepsy

Skin lesion

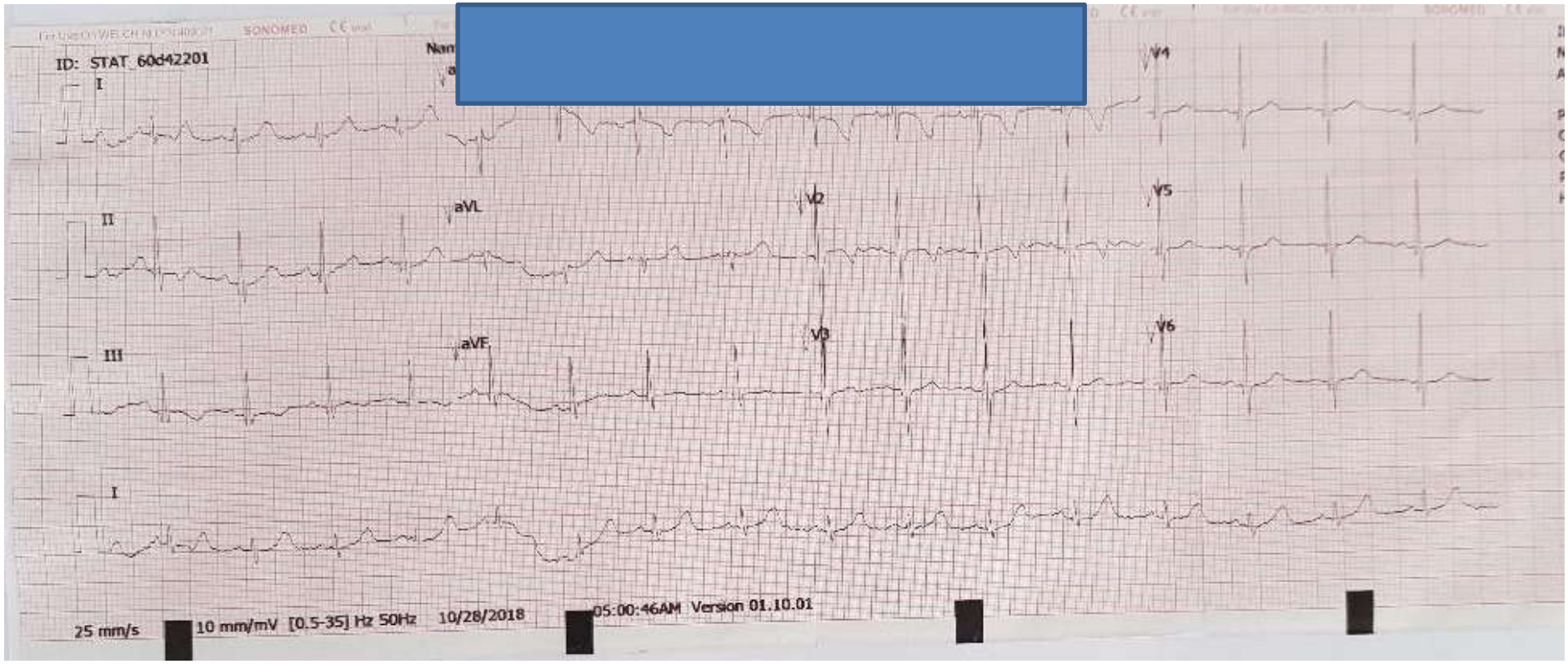




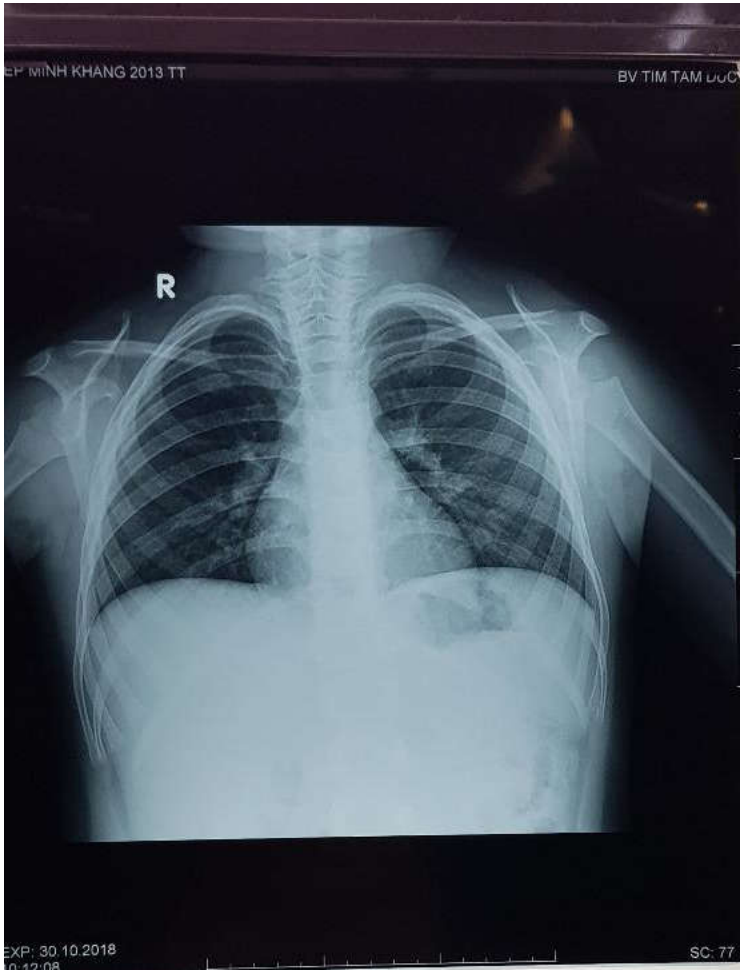
Shagreen patch
Hypopigmented macules



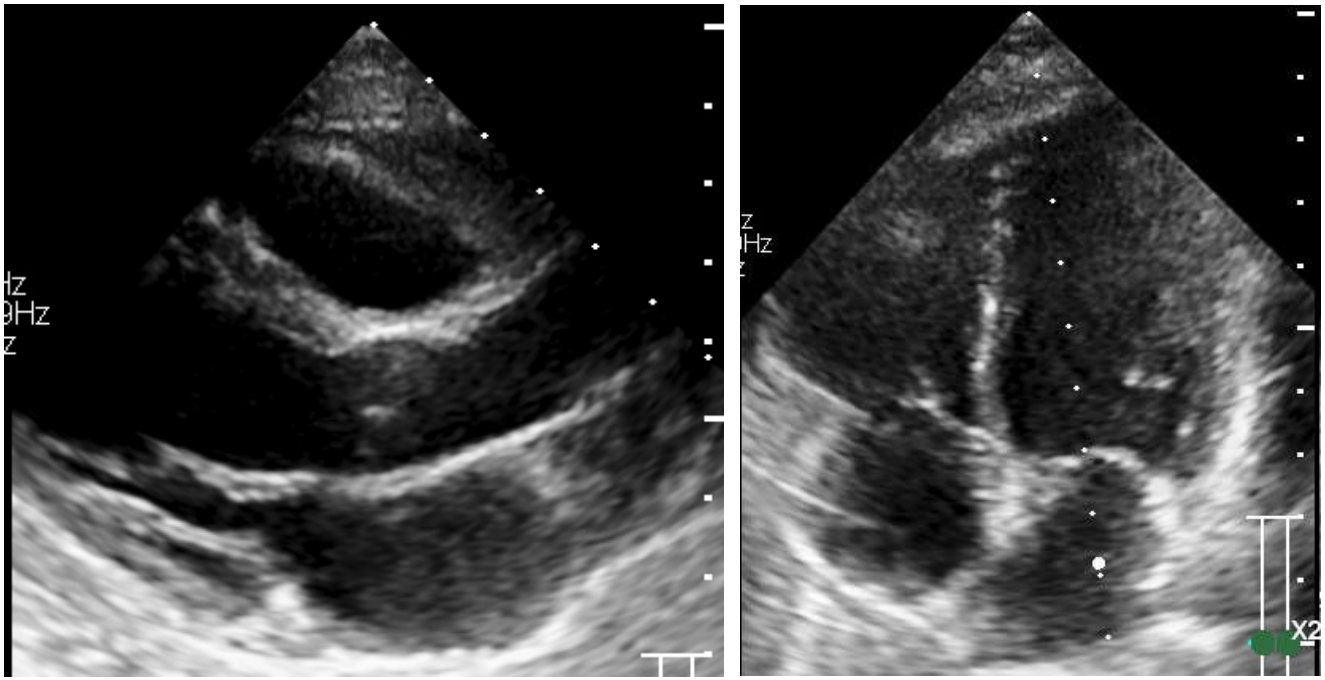
Electrocardiography

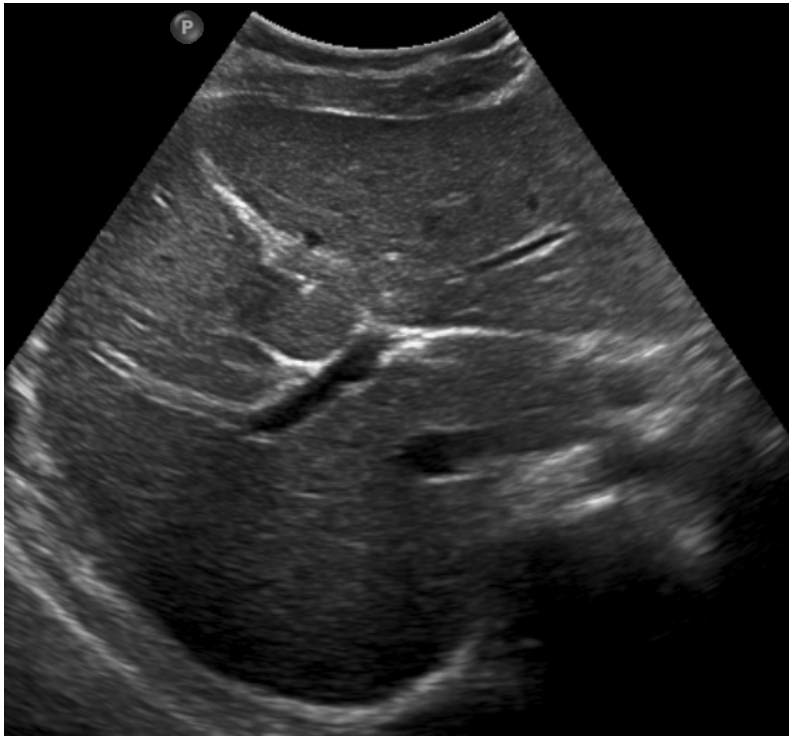


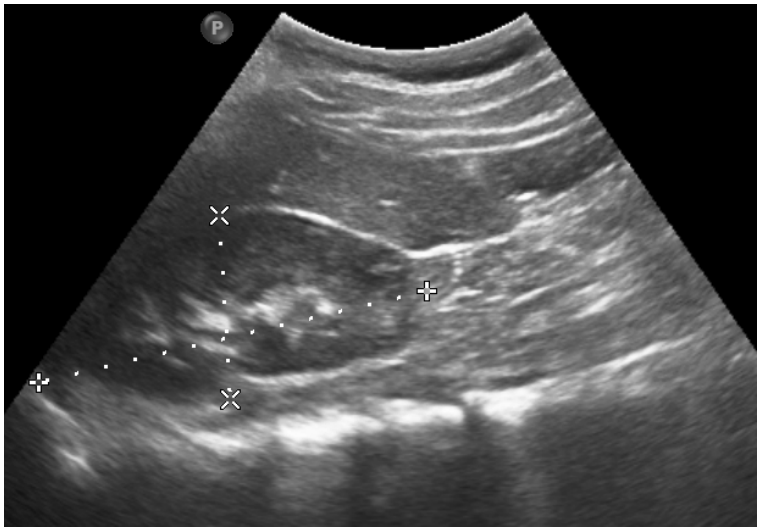
Chest X-ray

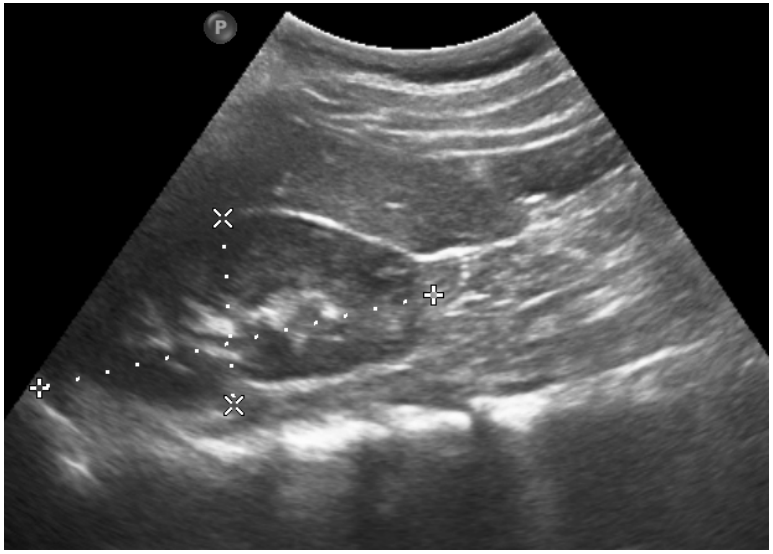


Echocardiography









Cerebral MRI

- Nodules 2 – 3 mm in brain cortex
- Subependymal nodules

Genetic testing

Pathogenic mutation TSC2c.1372C>T

Diagnosis

Tuberous sclerosis complex

- Absence epilepsy
- Decrease learning skill
- Skin lesions: Facial angiofibromas, Shagreen patch,
- Brain: Nodules in brain cortex, subependymal zone
- Pathogenic mutation TSC2c.1372C>T

Thank you

Tuberous Sclerosis Complex

- TSC occurs in approximately 1:6000 live births affecting approximately1 million people worldwide
- Autosomal dominant syndrome with variable expressivity.
- Manifested by hamartomatous tumors in multiple organs, including brain (causing seizures), eyes, heart, kidneys, lungs, and skin.

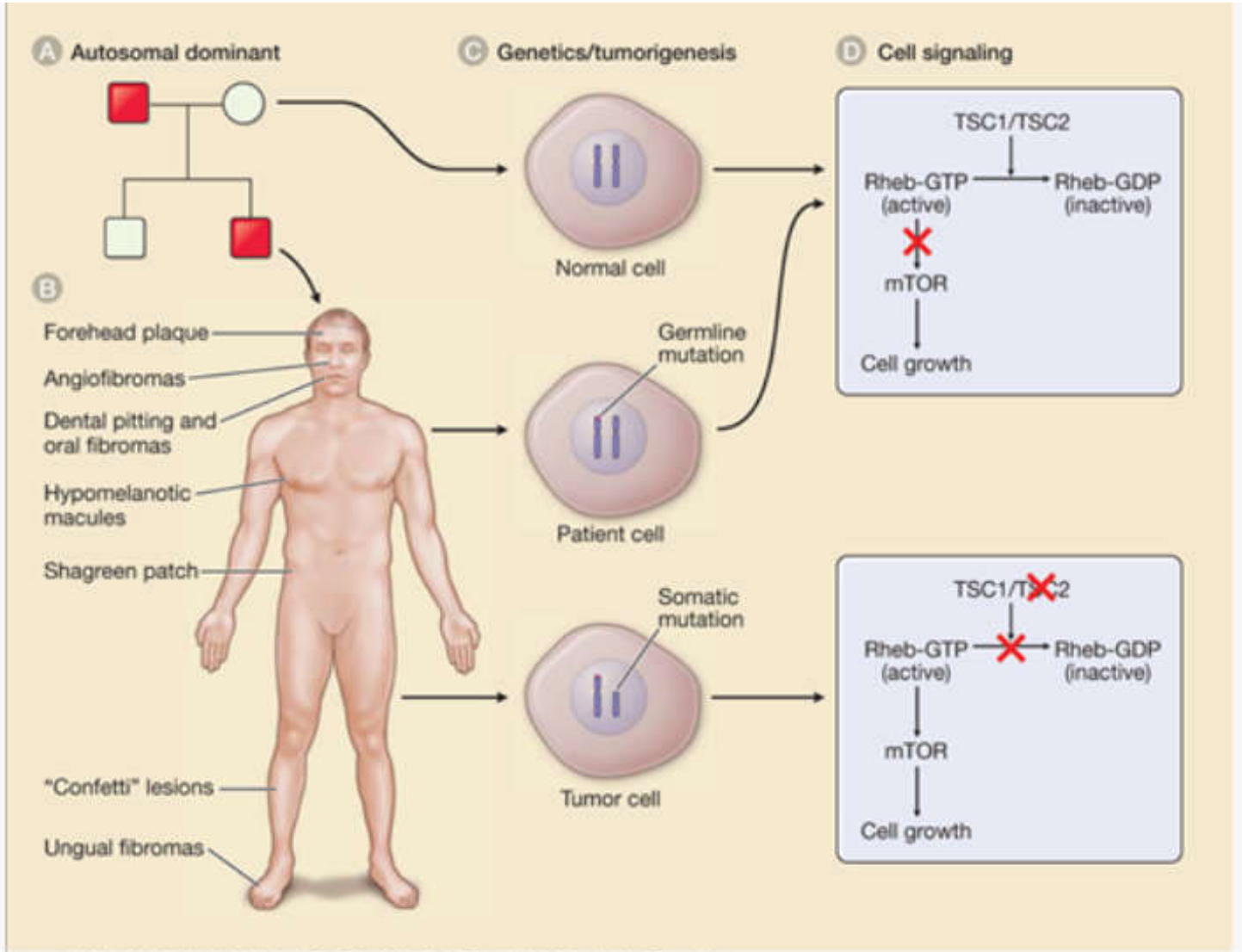
Molecular pathogenesis of tuberous sclerosis complex

In TSC, the growth of benign tumors in various organs occurs from loss of TSC1 or TSC2 genes and subsequent overactivation of mammalian target of rapamycin (mTOR), a kinase responsible for regulating cell growth, proliferation, and angiogenesis

Molecular pathogenesis of tuberous sclerosis complex

- TSC is caused by mutations in a tumor suppressor gene, either *TSC1* or *TSC2*. Mutations in *TSC2* are observed in about three-fourths of patients, and even more commonly in de novo cases. Patients with mutations in *TSC2* tend to exhibit a more severe phenotype
- *TSC1* maps to chromosome band 9q34. The 8.6-kb full-length transcript encodes a protein called *hamartin* or TSC1. *TSC2*maps to chromosome band 16p13.3. The 5.5-kb transcript encodes a protein called *tuberin* or TSC2. Immediately adjacent to *TSC2* on chromosome 16 is *PKD1*, the gene mutated in polycystic kidney disease. Some patients with TSC have severe, early-onset renal cystic disease, and most of these patients have a contiguous deletion of *TSC2* and *PKD1*.
- Typical of mutations in tumor suppressor genes, the mutations observed in patients with TSC are inactivating mutations located anywhere along the sequence of *TSC1* or *TSC2*. Consistent with Knudson's two-hit hypothesis, most TSC tumors show a second somatic mutation that inactivates the wild-type allele. TSC1 and TSC2 form a complex that inhibits signaling through the mammalian target of rapamycin (mTOR) pathway . Loss of TSC1/TSC2 function leads to increased mTOR signaling and increased cell growth. Rapamycin is a drug that inhibits mTOR and may be useful for the treatment

Molecular pathogenesis of tuberous sclerosis complex



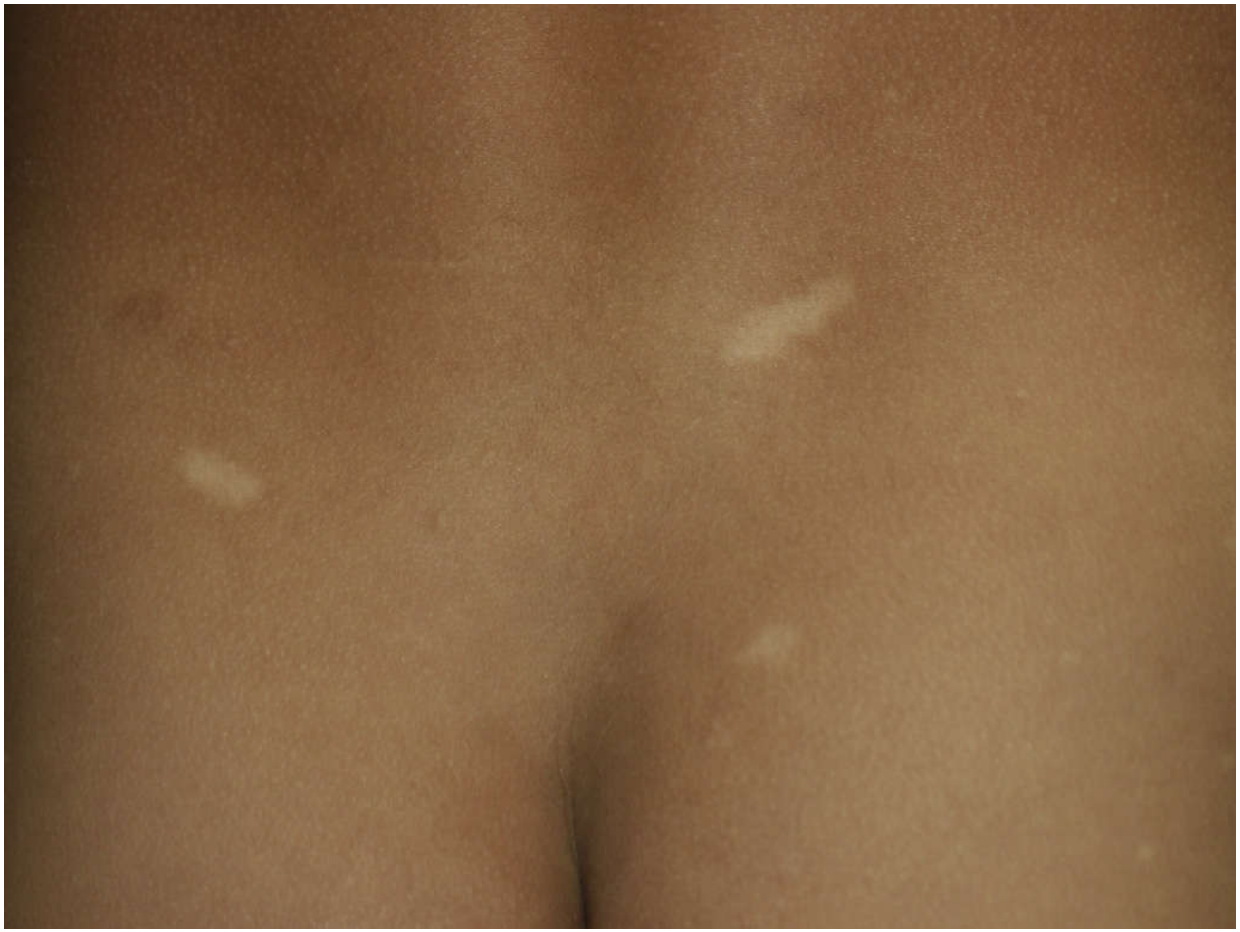
Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

Findings in TSC

- Neurologic findings: Abnormal neurologic findings result from the location, size, and growth of tubers and the presence of subependymal nodules (SENs) and subependymal giant cell astrocytomas (SEGAs)
- Cutaneous findings: adenoma sebaceum, which often does not appear until late childhood or early adolescence
- Cardiac findings: mostly rhabdomyomas.
- Ophthalmic findings: At least 50% of patients have ocular abnormalities; retinal astrocytomas

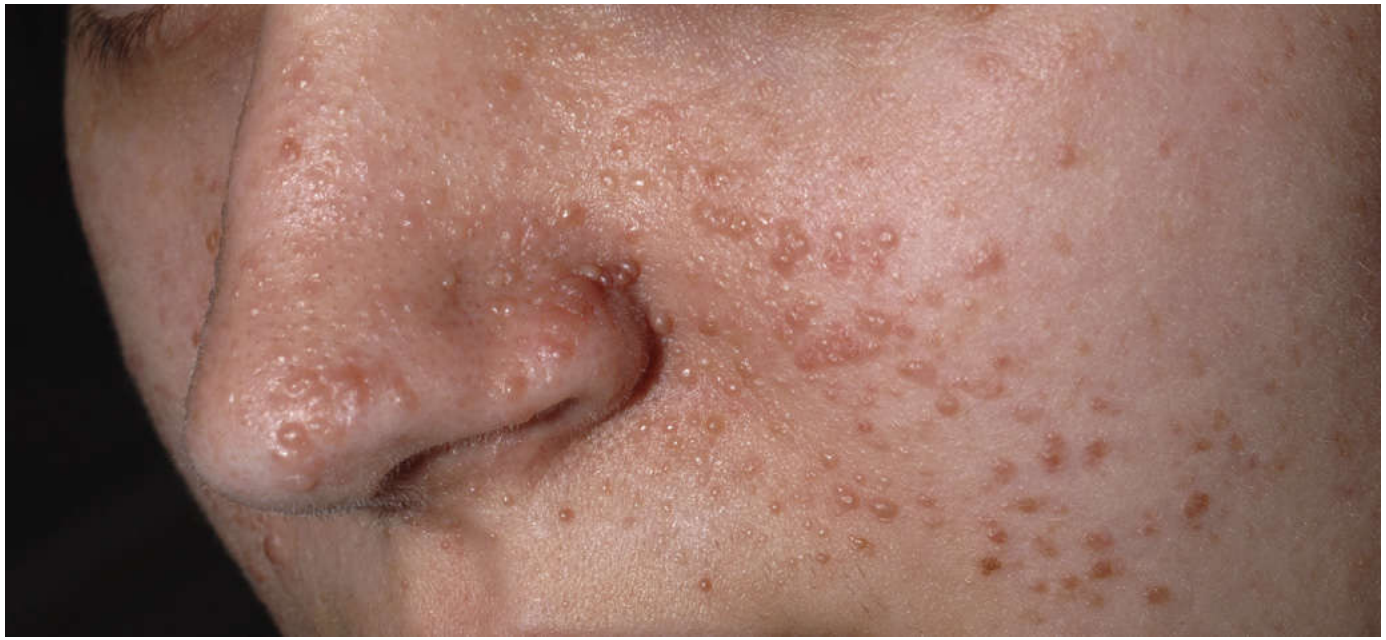
- Pulmonary findings: cystic pulmonary abnormalities in as many as 40% of women with TSC
- Renal findings: Renal manifestations of TSC are the second most common clinical feature; 4 types of lesions can occur: autosomal dominant polycystic kidney disease lesions, isolated renal cyst(s), angiomyolipomas (AMLs), and renal cell carcinomas
- Dental findings: Pitting of the dental enamel is invariably present in the permanent teeth of patients with TSC [1] ; gingival fibromas occur in 70% of adults with TSC, in 50% of children with mixed dentition (primary and permanent teeth), and in 3% of children with only primary teeth
- Gastrointestinal findings: Hamartomas and polyposis of the stomach, intestine, and colon may occur
- Hepatic findings: Hepatic cysts and hepatic AML, as 24% of patients with TSC, with a marked female predominance (female-to-male ratio 5:1)
- Skeletal findings: Sclerotic and hypertrophic lesions of bone may be found incidentally on radiography performed for other indications

Three hypopigmented macules the lower back/upper buttocks



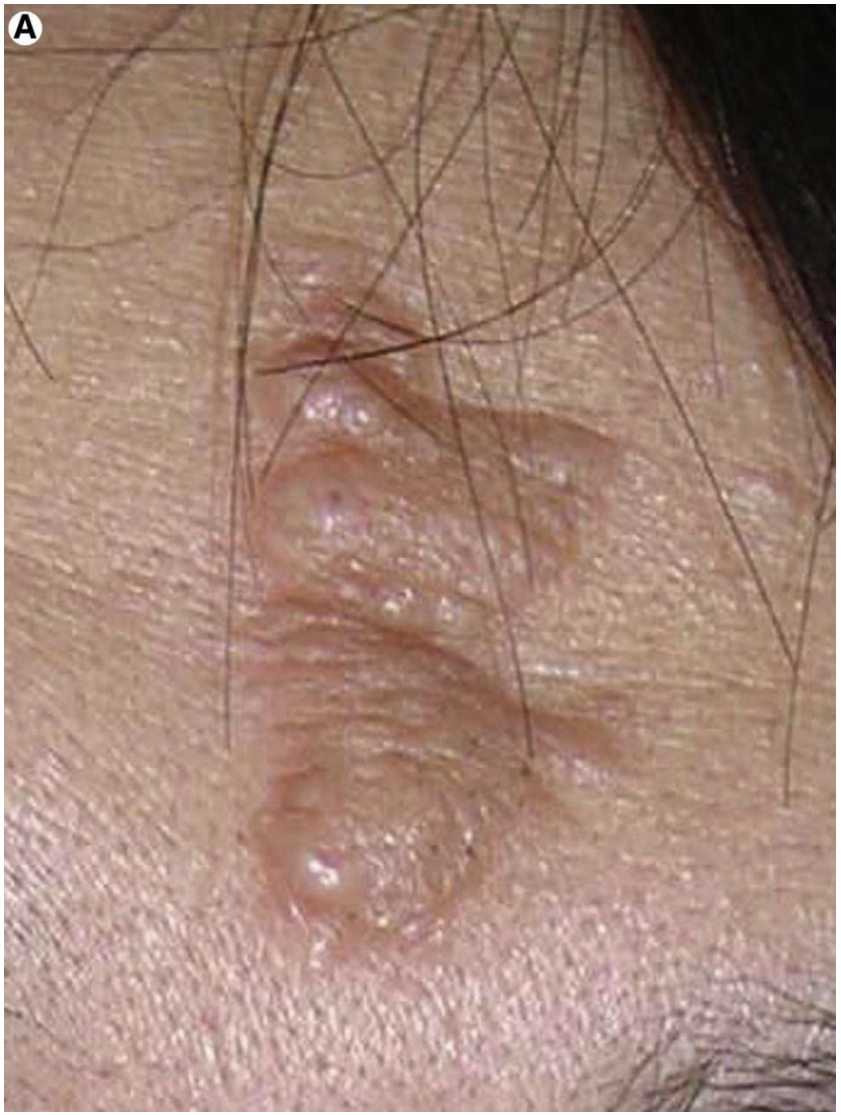
Northrup H et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243-254

Facial angiofibromas

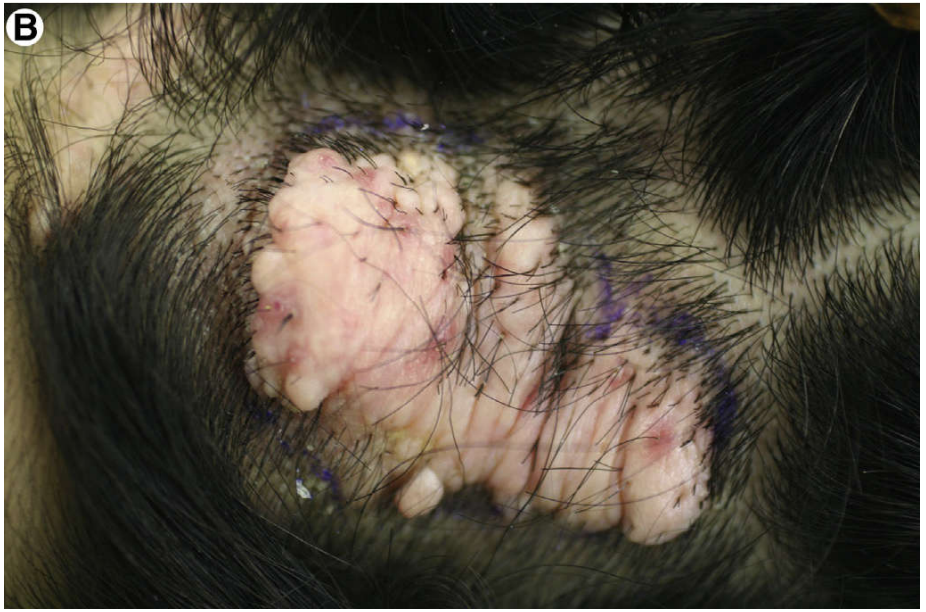


Northrup H et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243-254

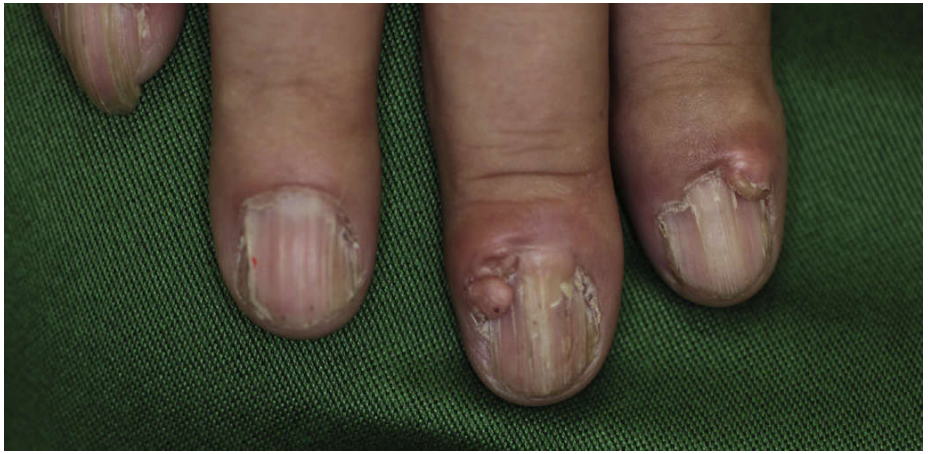
Fibrous plaque on face



Fibrous plaque on scalp

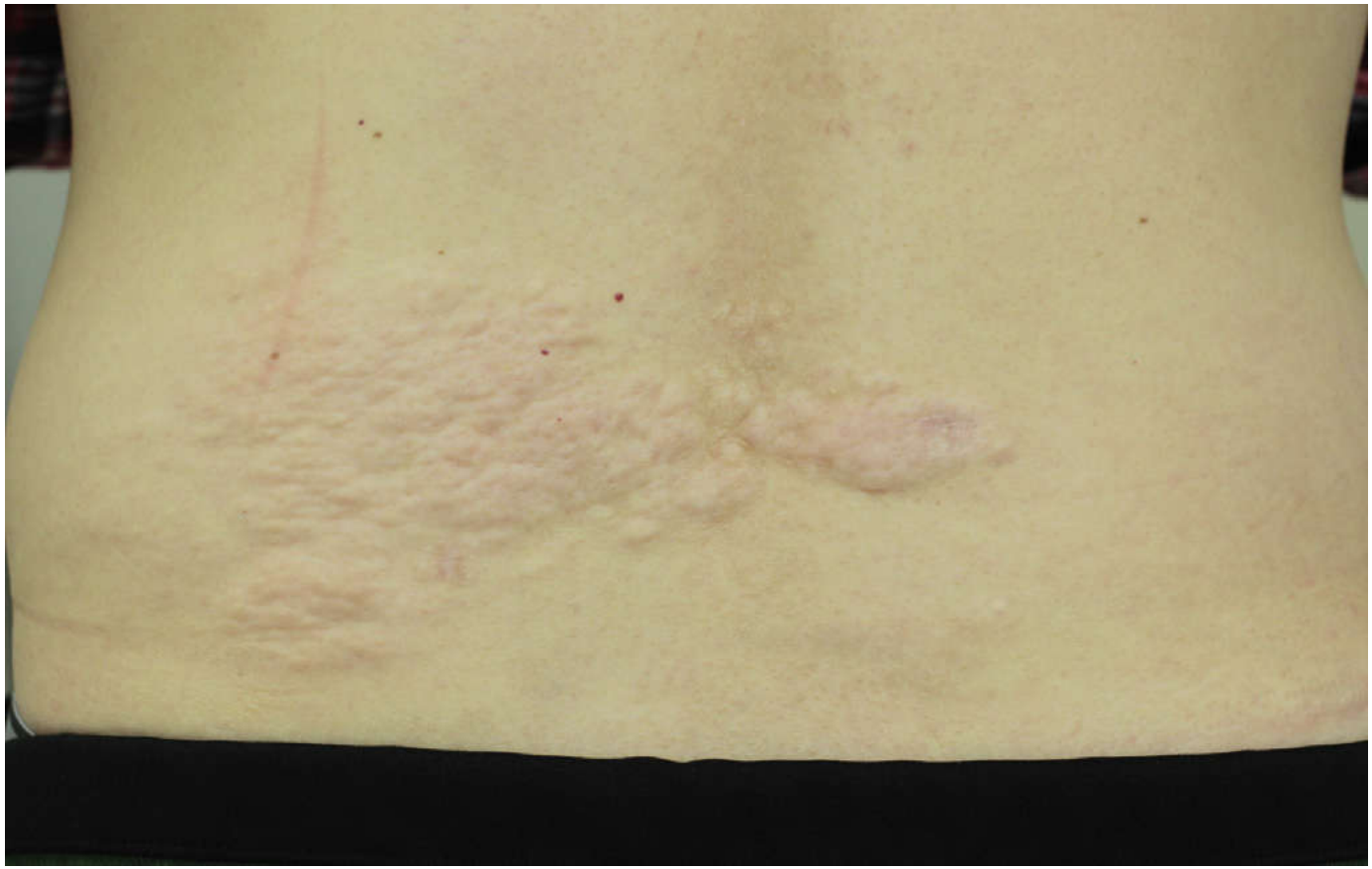


Ungual fibromas



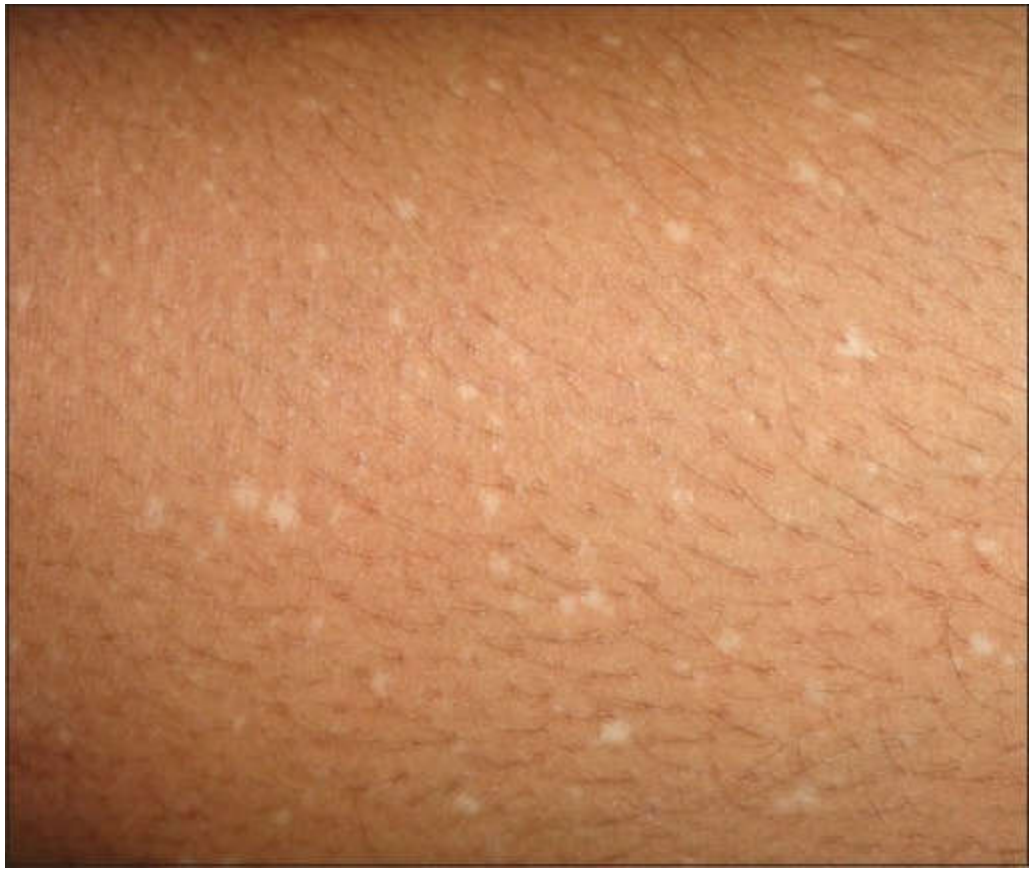
Northrup H et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243-254

Shagreen patch on dorsolumbar area



Northrup H et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243-254

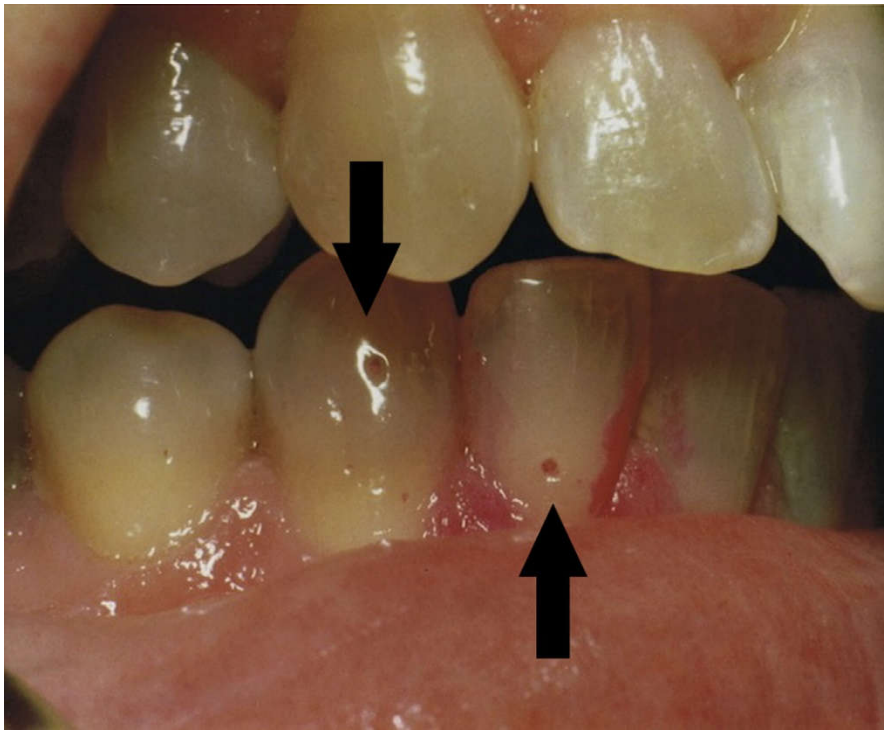
“Confetti” skin lesions



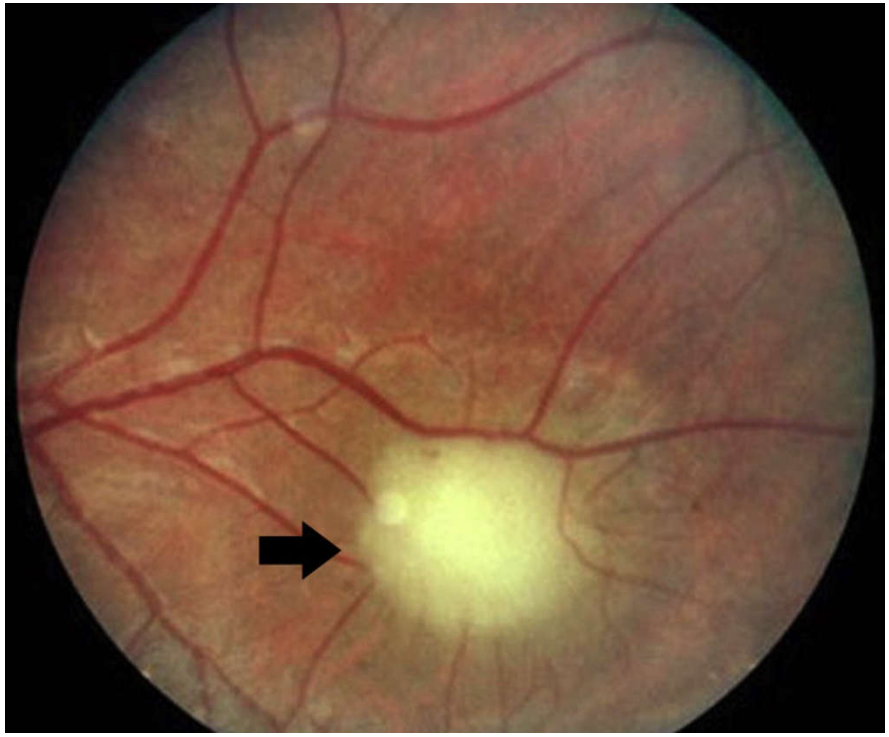
Confetti skin lesions are numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs.

Northrup H et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243-254

Dental pits

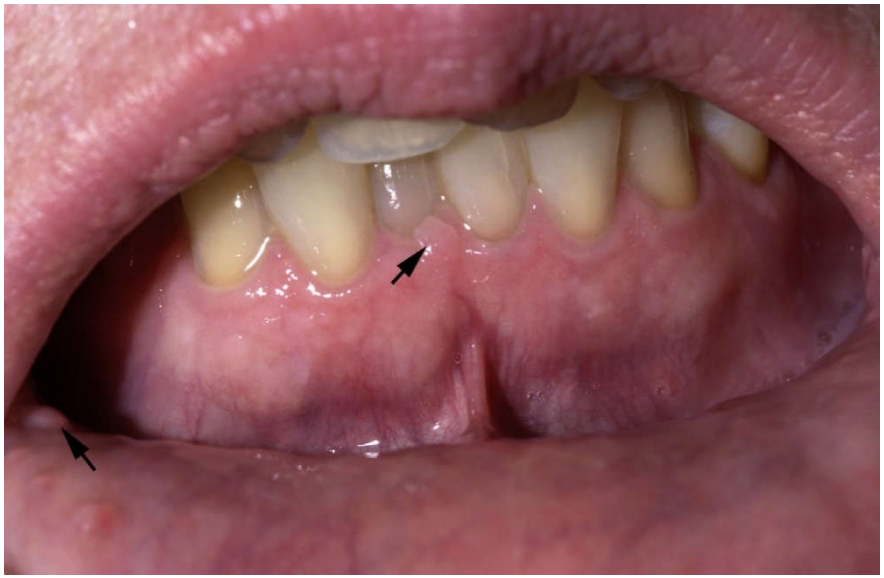


Retinal hamartoma

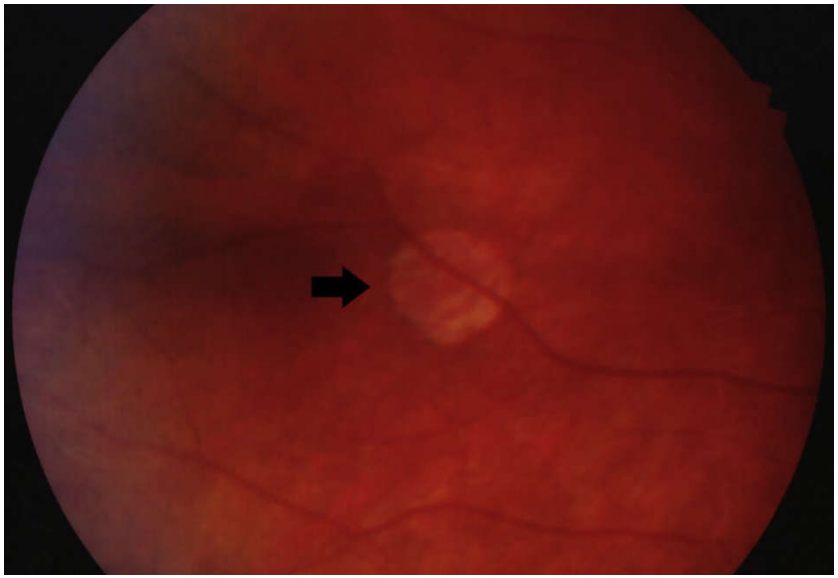


Northrup H et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243-254

Intraoral fibromas



Retinal achromic patch

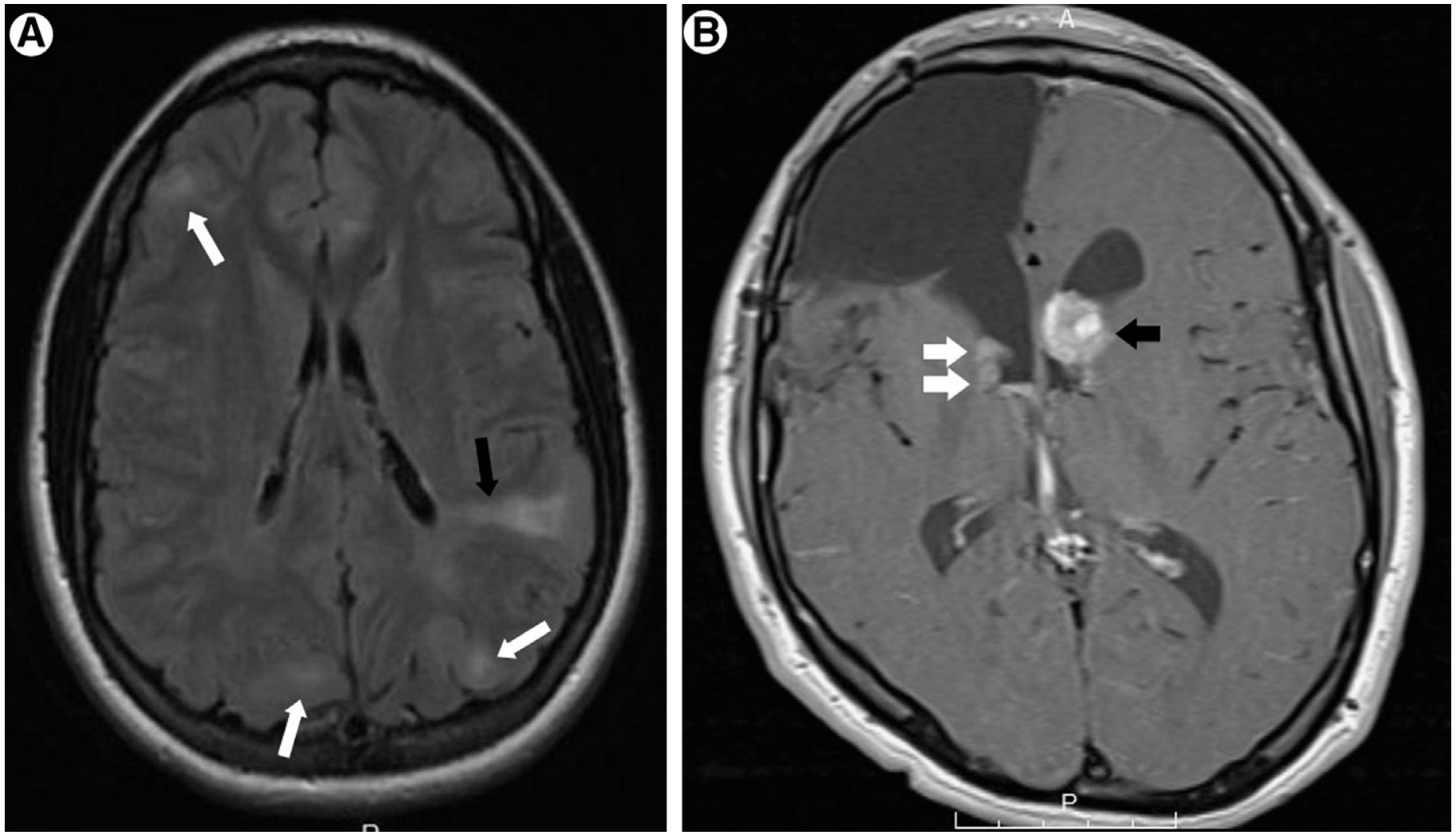


Northrup H et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243-254

cortical dysplasia

subependymal nodules

subependymal giant cell astrocytoma



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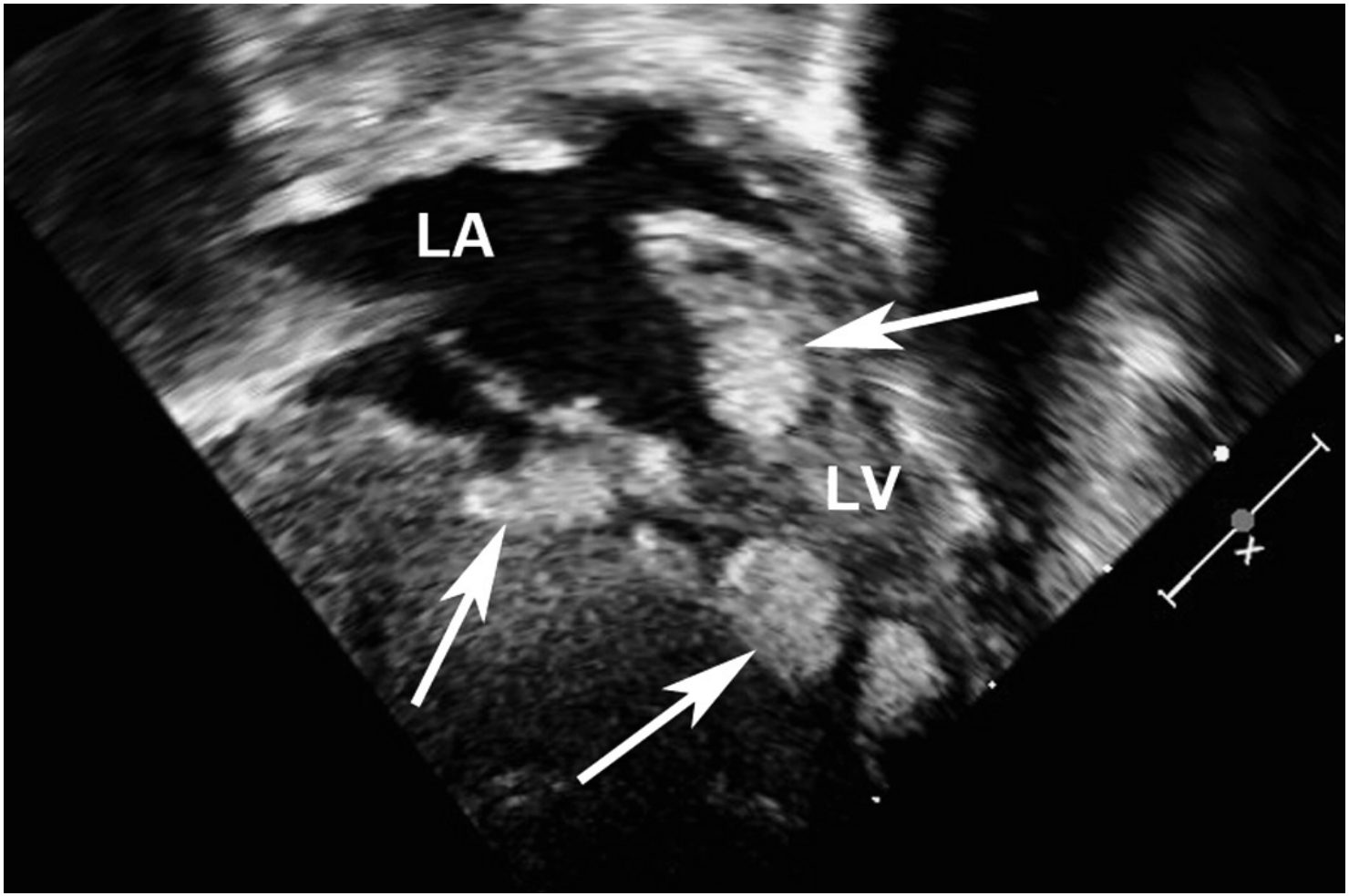
Cardiac rhabdomyomas

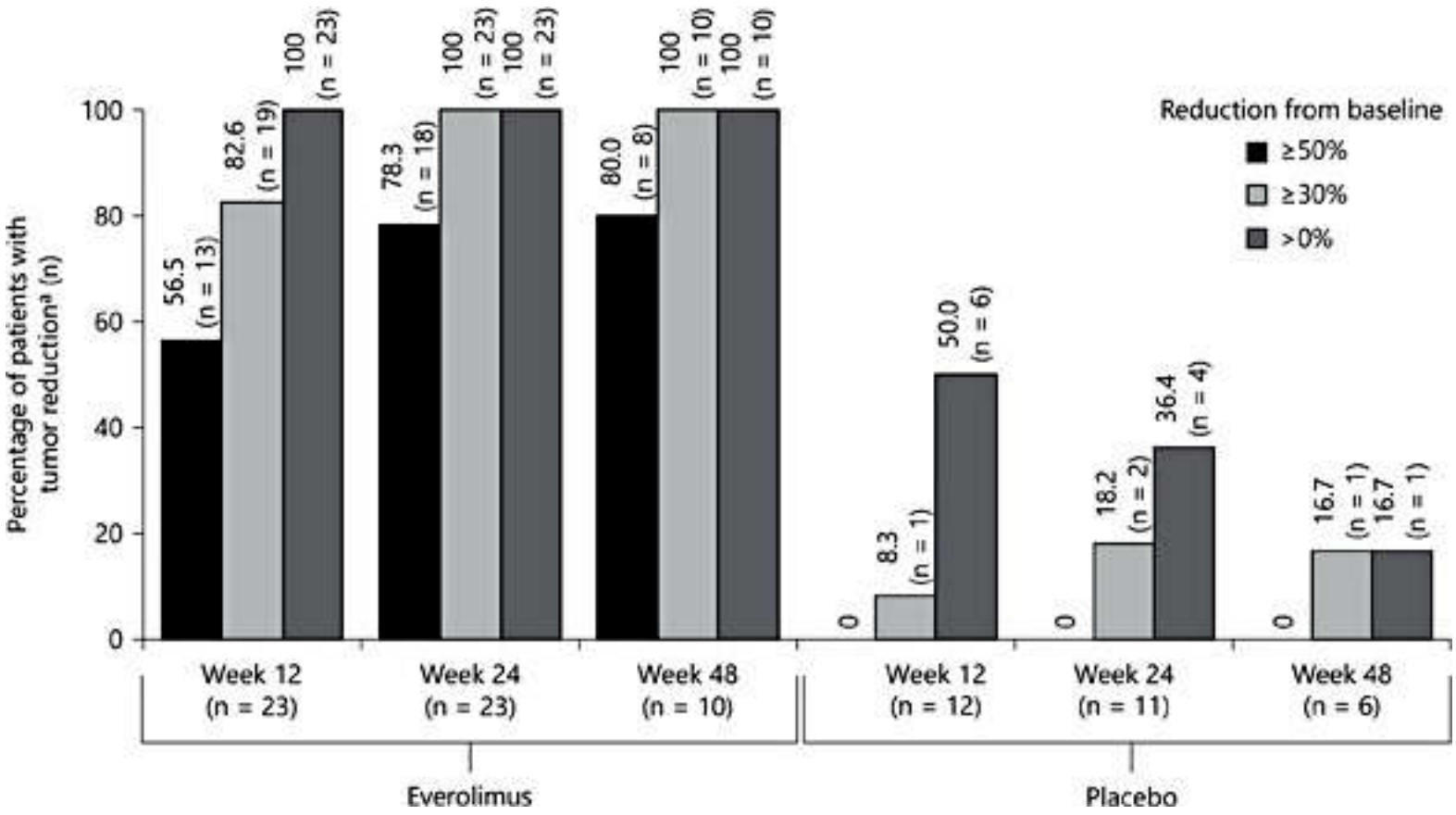


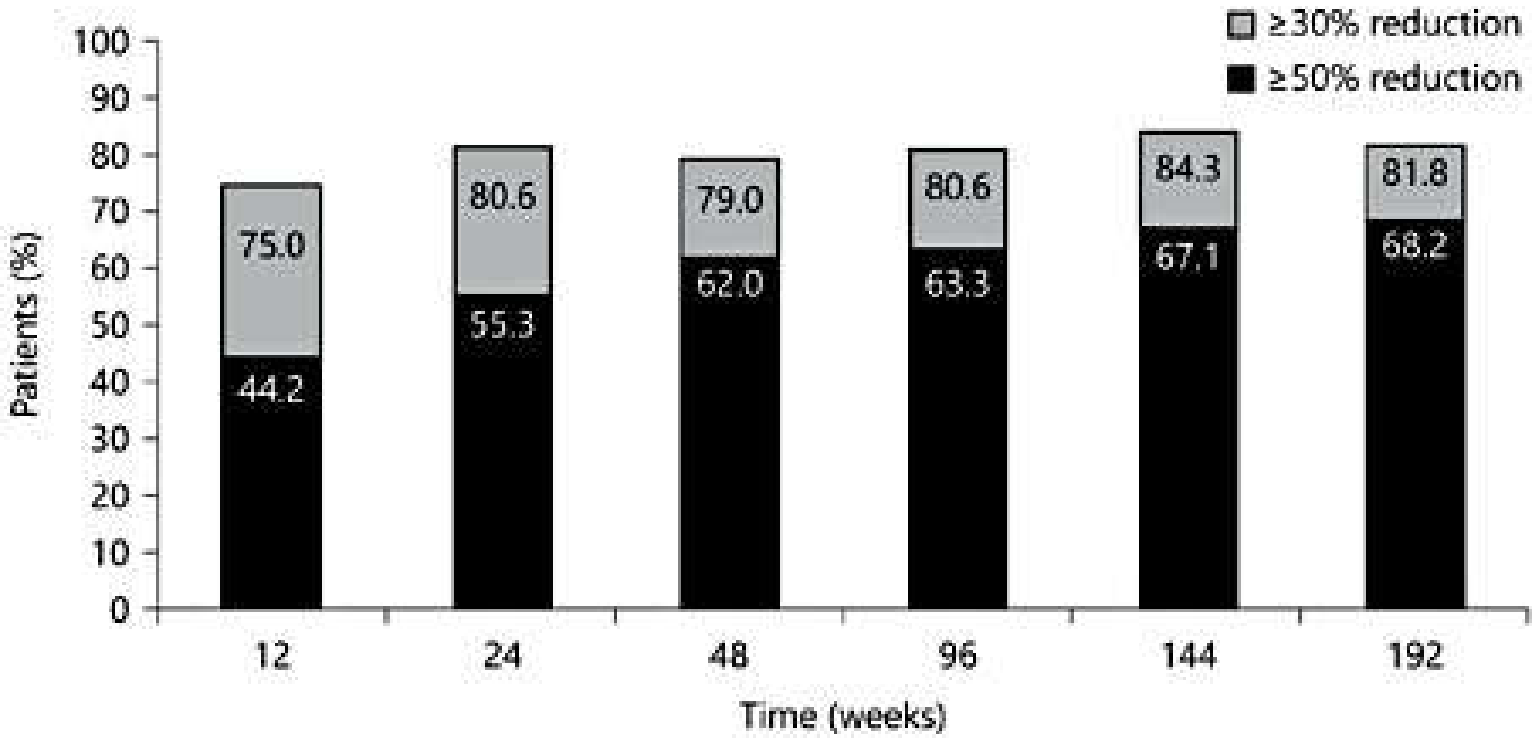
Northrup H et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243-254

Surveillance and management recommendations for newly diagnosed or suspected TSC

Organ System or Specialty Area	Recommendation
Genetics	• Obtain three-generation family history to assess for additional family members at risk of TSC • Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed
Brain	• Perform magnetic resonance imaging (MRI) of the brain to assess for the presence of tubers, subependymal nodules (SEN), migrational defects, and subependymal giant cell astrocytoma (SEGA) • Evaluate for TSC-associated neuropsychiatric disorder (TAND) • During infancy, educate parents to recognize infantile spasms, even if none have occurred at time of first diagnosis • Obtain baseline routine electroencephalogram (EEG). If abnormal, especially if features of TAND are also present, follow-up with a 24-hr video EEG to assess for subclinical seizure activity
Kidney	• Obtain MRI of the abdomen to assess for the presence of angiomyolipoma and renal cysts • Screen for hypertension by obtaining an accurate blood pressure • Evaluate renal function by determination of glomerular filtration rate (GFR)
Lung	• Perform baseline pulmonary function testing (pulmonary function testing and 6-minute walk test) and high-resolution chest computed tomography (HRCT), even if asymptomatic, in patients at risk of developing lymphangioleiomyomatosis (LAM), typically females 18 years or older. Adult males, if symptomatic, should also undergo testing • Provide counsel on smoking risks and estrogen use in adolescent and adult females
Skin	• Perform a detailed clinical dermatologic inspection/exam
Teeth	• Perform a detailed clinical dental inspection/exam
Heart	• Consider fetal echocardiography to detect individuals with high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound • Obtain an echocardiogram in pediatric patients, especially if younger than 3 yr of age • Obtain an electrocardiogram (ECG) in all ages to assess for underlying conduction defects
Eye	• Perform a complete ophthalmologic evaluation, including dilated funduscopy, to assess for retinal lesions and visual field deficits

Krueger DA et al. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference.Pediatr Neurol 2013; 49: 255-265


Percentage of patients with tumor reduction[a] (n)
100
80
60
40
20
0
Reduction from baseline
≥50%
≥30%
>0%
56.5 (n = 13)
82.6 (n = 19)
100 (n = 23)
78.3 (n = 18)
100 (n = 23)
100 (n = 23)
80.0 (n = 8)
100 (n = 10)
100 (n = 10)
0
8.3 (n = 1)
50.0 (n = 6)
0
18.2 (n = 2)
36.4 (n = 4)
0
16.7 (n = 1)
16.7 (n = 1)
Week 12 (n = 23)
Week 24 (n = 23)
Week 48 (n = 10)
Week 12 (n = 12)
Week 24 (n = 11)
Week 48 (n = 6)
Everolimus
Placebo



Time (months)	3	6	11	22	33	44
All patients (n)	104	103	100	98	70	22