Case presentation TSC

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Disclosures

- Investigator on clinical trials sponsored by:
  - Astra-Zeneca
  - Janssen
  - BMS
  - Viventia Biotech
  - Bayer
  - Medivation
- Sit on advisory boards for:
  - Roche
  - Merck
  - Amgen

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Objectives

- Recognize the criteria for clinical diagnosis of TSC
- Know the percentage of subjects with a clinical diagnosis of TSC who have negative genetic testing
- Recognize side effects related to mTOR therapy

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Presentation

- 43 YO male presenting in 2007
- Known since age 5 with a clinical diagnosis of TSC but no genetic documentation
- Accountant
- Asthma
- Referred by neurology for multiple renal lesions

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- 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.

Pediatr Neurol. 2013 Oct; 49(4): 243–254.

- Clinical diagnostic criteria
  - Major features
    - Hypomelanotic macules (≥3, at least 5-mm diameter)
    - Angiofibromas (≥3) or fibrous cephalic plaque
    - Ungual fibromas (≥2)
    - Shagreen patch
    - Multiple retinal hamartomas
    - Cortical dysplasias*
    - Subependymal nodules
    - Subependymal giant cell astrocytoma
    - Cardiac rhabdomyoma
    - Lymphangioleiomyomatosis (LAM)†
    - Angiomyolipomas (≥2)†

Pediatr Neurol. 2013 Oct; 49(4): 243–254.

- Minor features
  - “Confetti” skin lesions
  - Dental enamel pits (>3)
  - Intraoral fibromas (≥2)
  - Retinal achromic patch
  - Multiple renal cysts
  - 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

Pediatr Neurol. 2013 Oct; 49(4): 243–254.

Overall picture

- Does not have neurologic or psychiatric symptoms
  - Brain scan shows multiple frontal calcified tubers
- Multiple facial lesions
  - Used to have dermabrasion sessions at a younger age to treat them
  - Biopsied at our center: anfgiofibromas
- Ungeal painful nodules that were finally treated by radical onycectomy at our center
- No cardiac manifestation
  - ECG in 2008 at our center shows left axial deviation

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Renal involvement

- Patient remembers having been told that he had renal lesions but was lost to follow up at a very young age
- Imaging in 2008 shows multiple renal lesions of which majority were AML but one was enhancing lesions suspicious of RCC
- Biopsy was not possible radiologically

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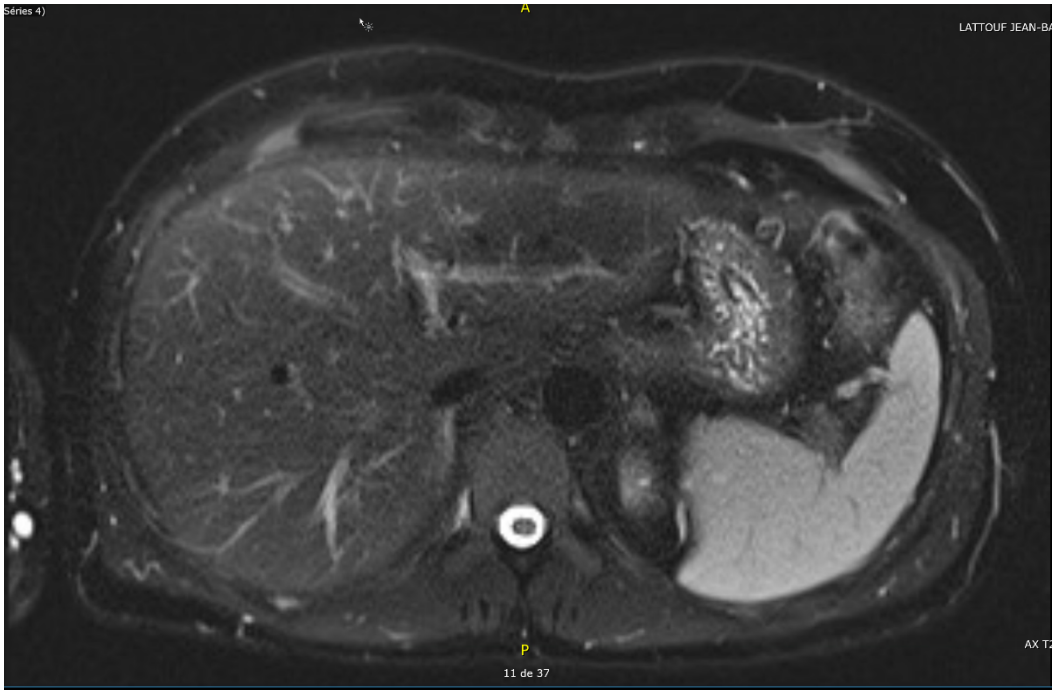
MRI abdomen



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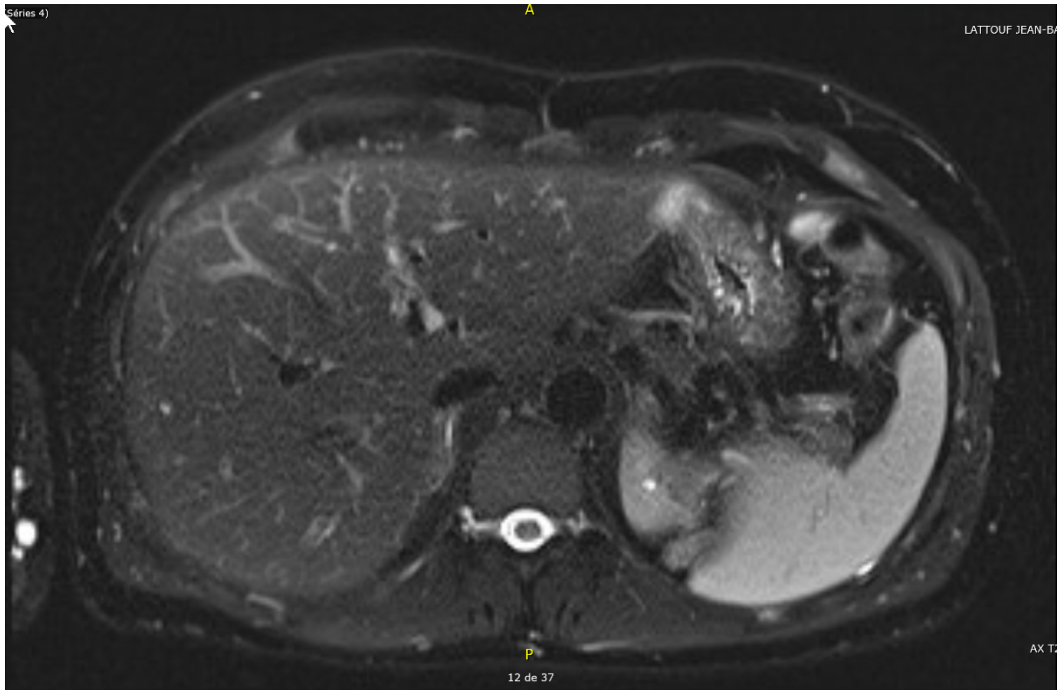

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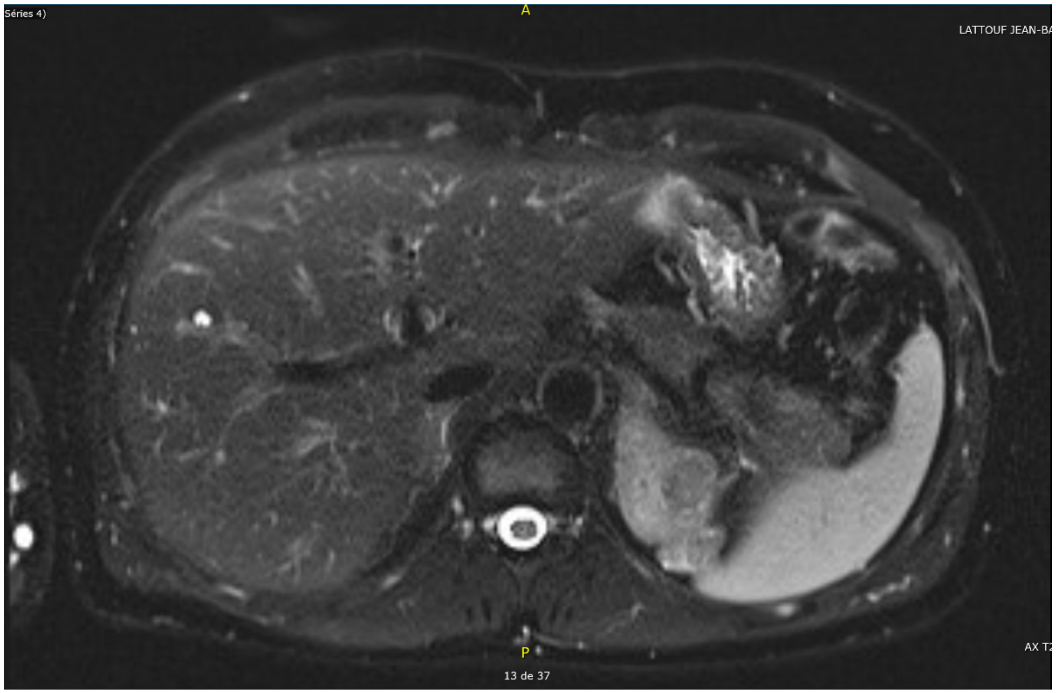

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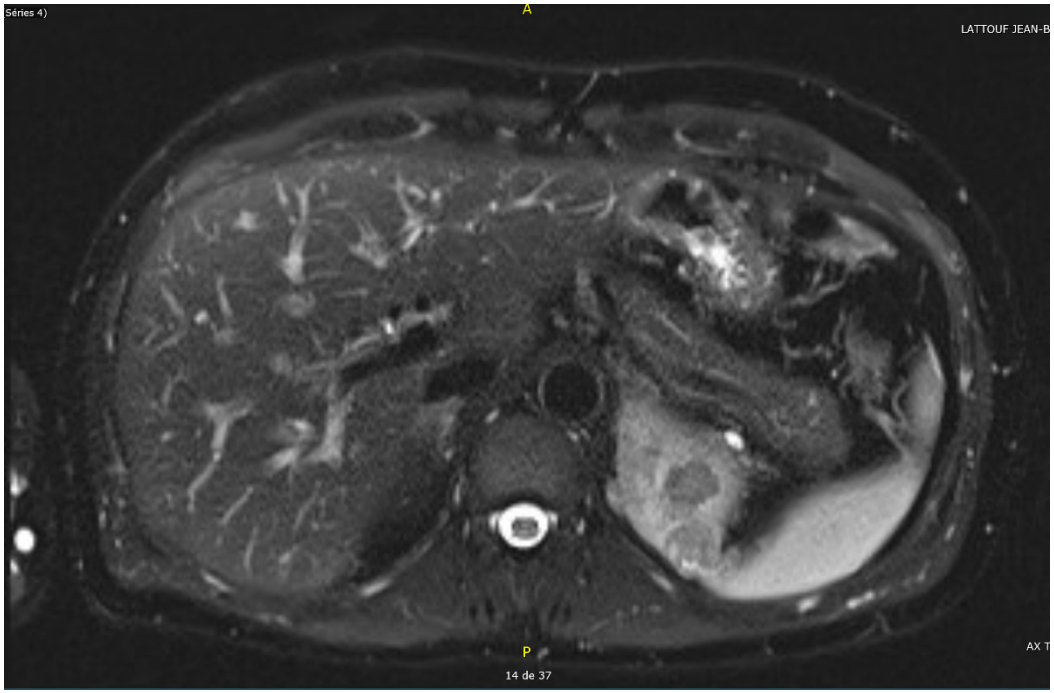

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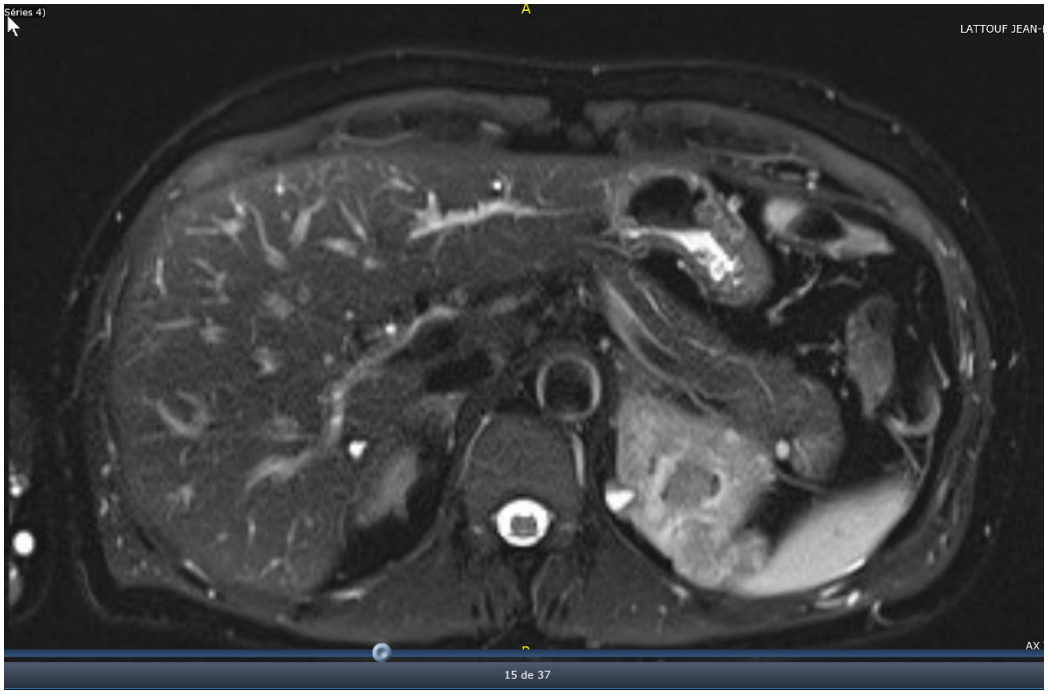

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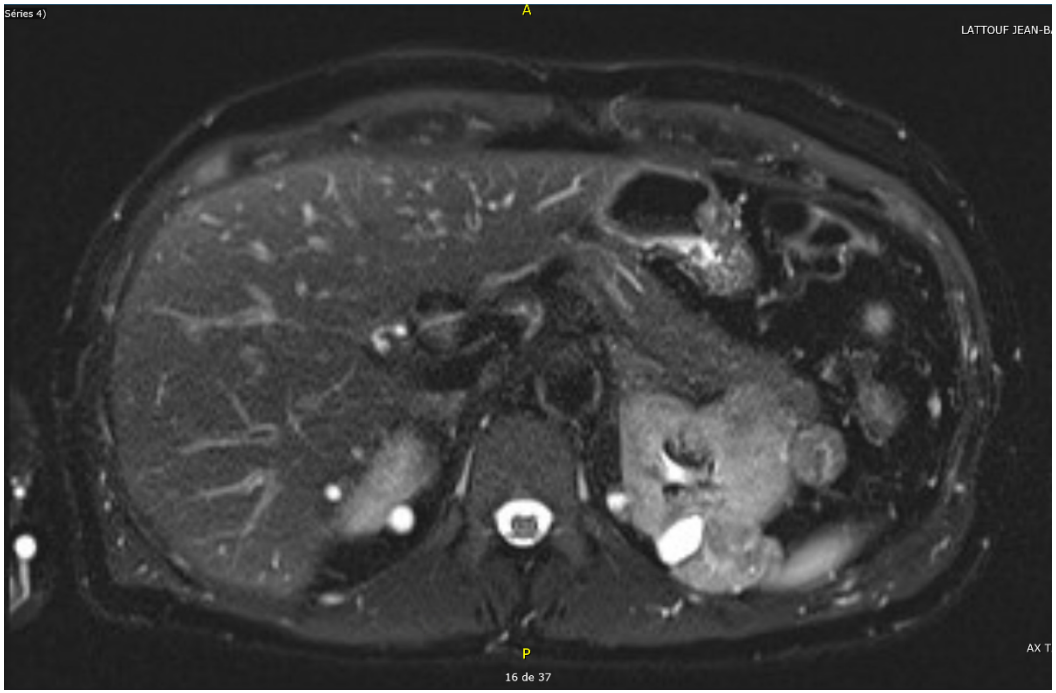
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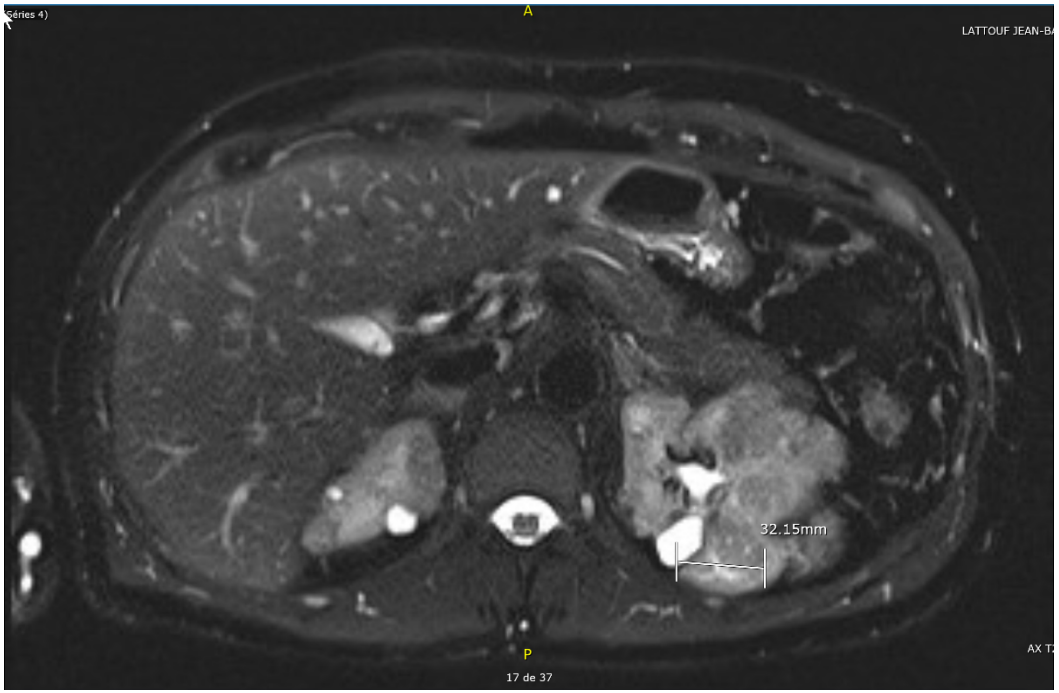

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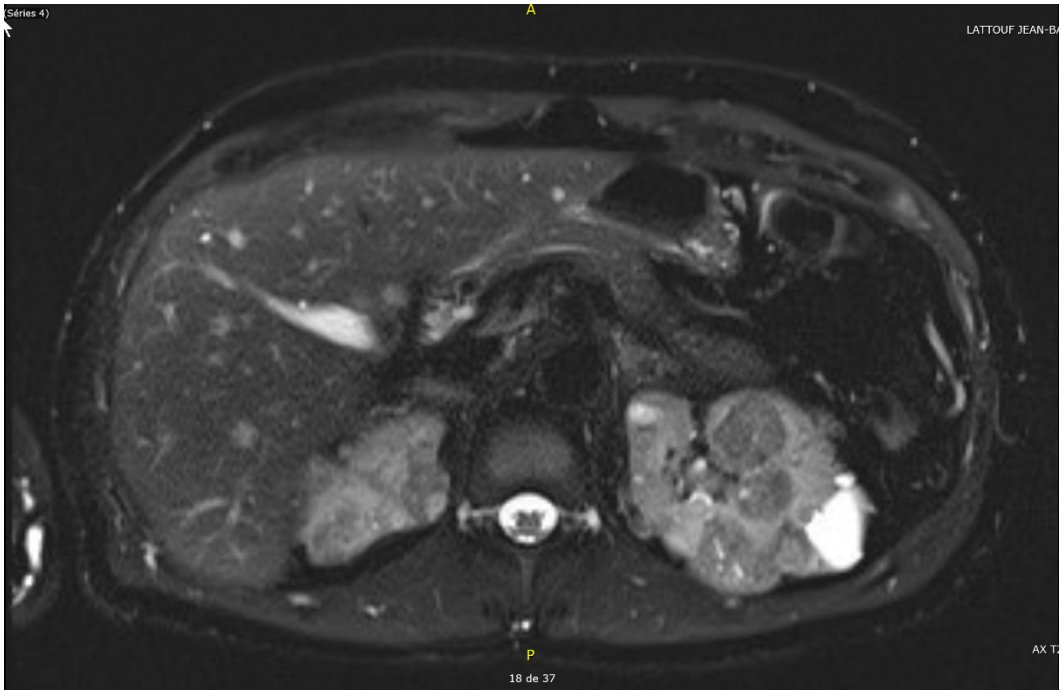

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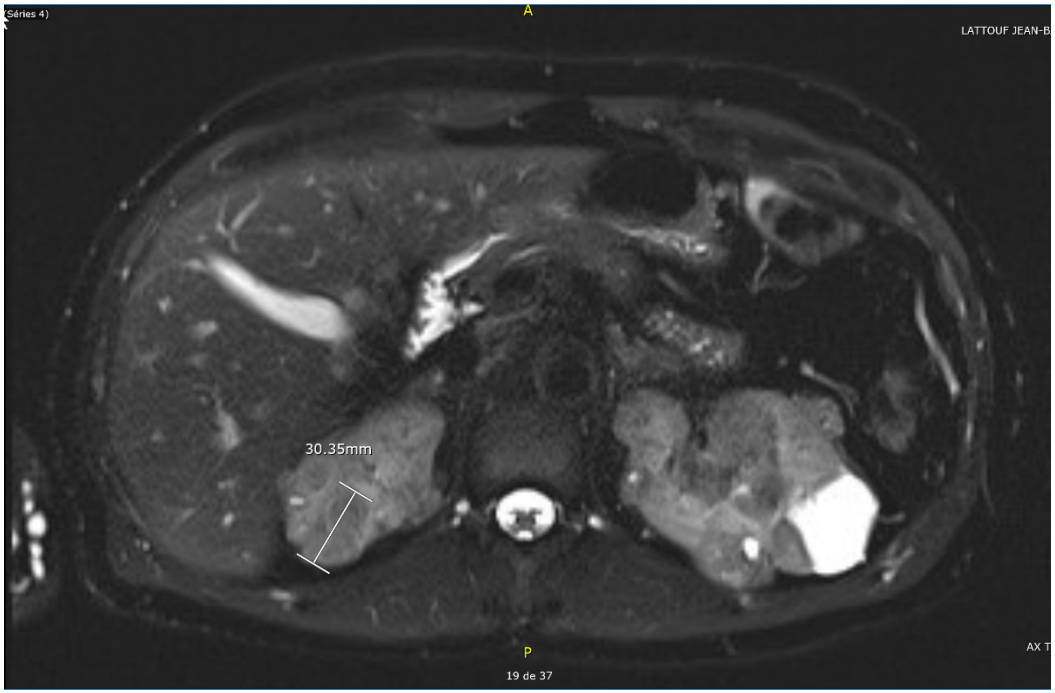
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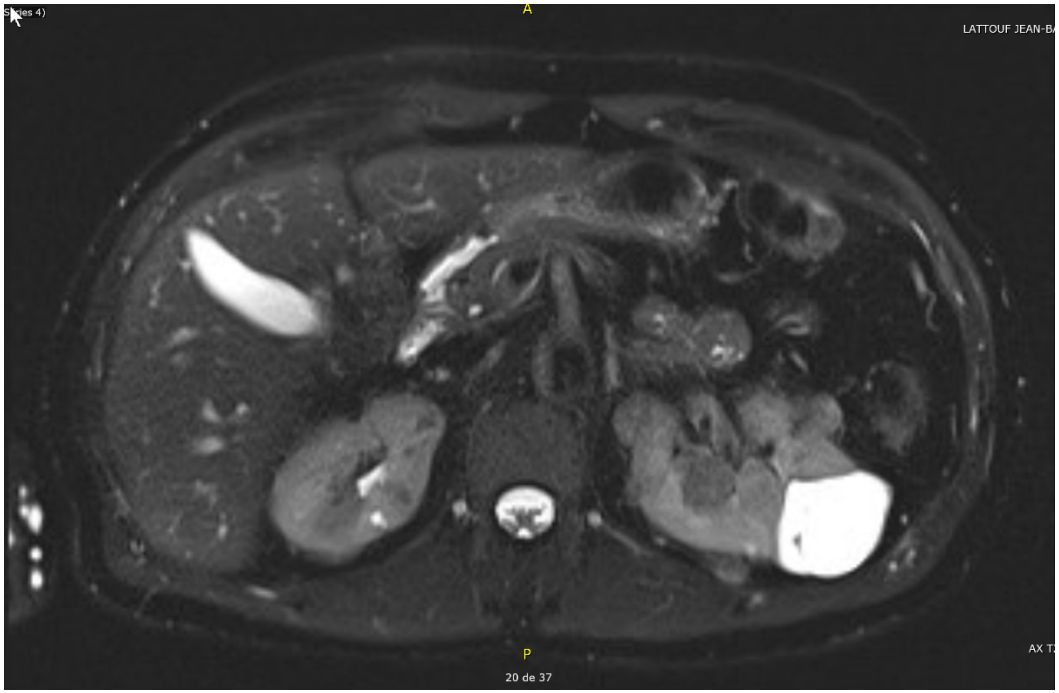
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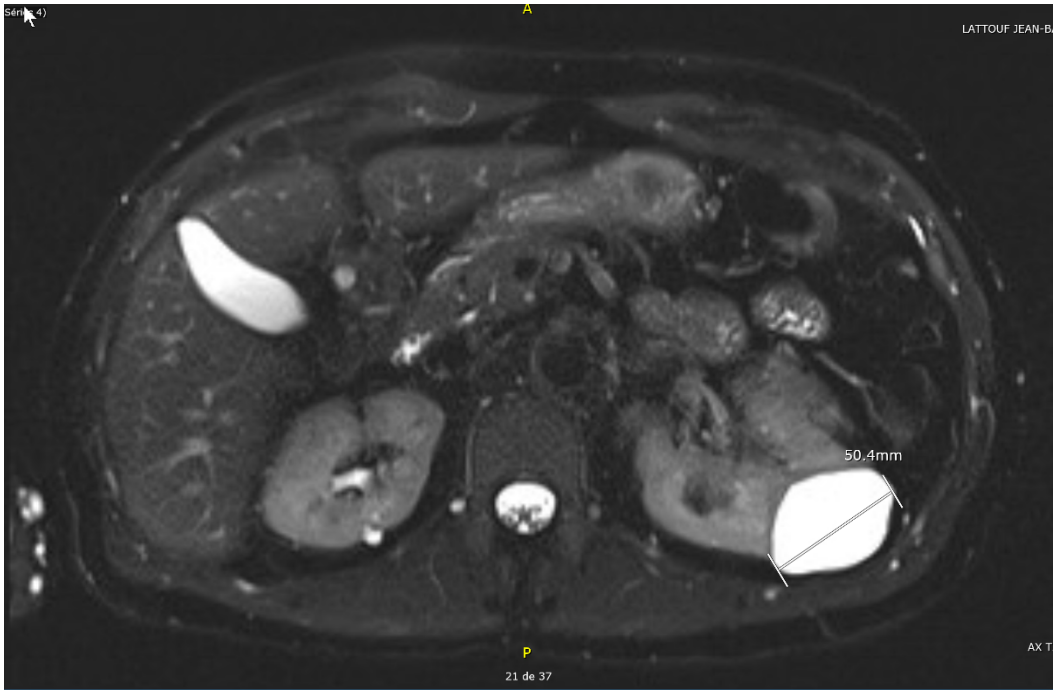

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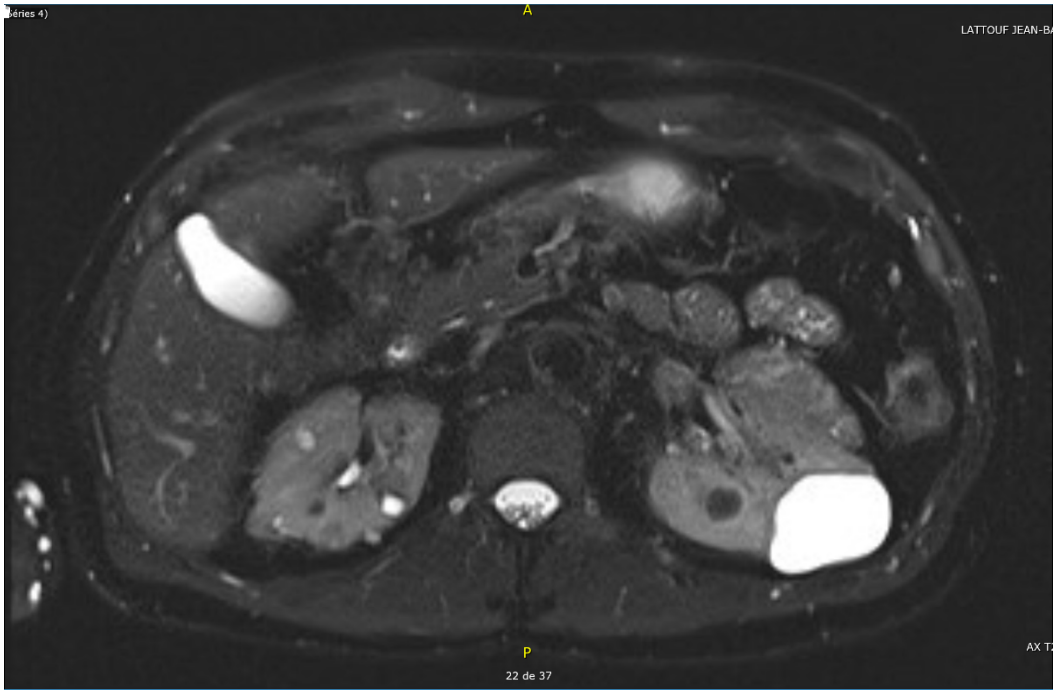
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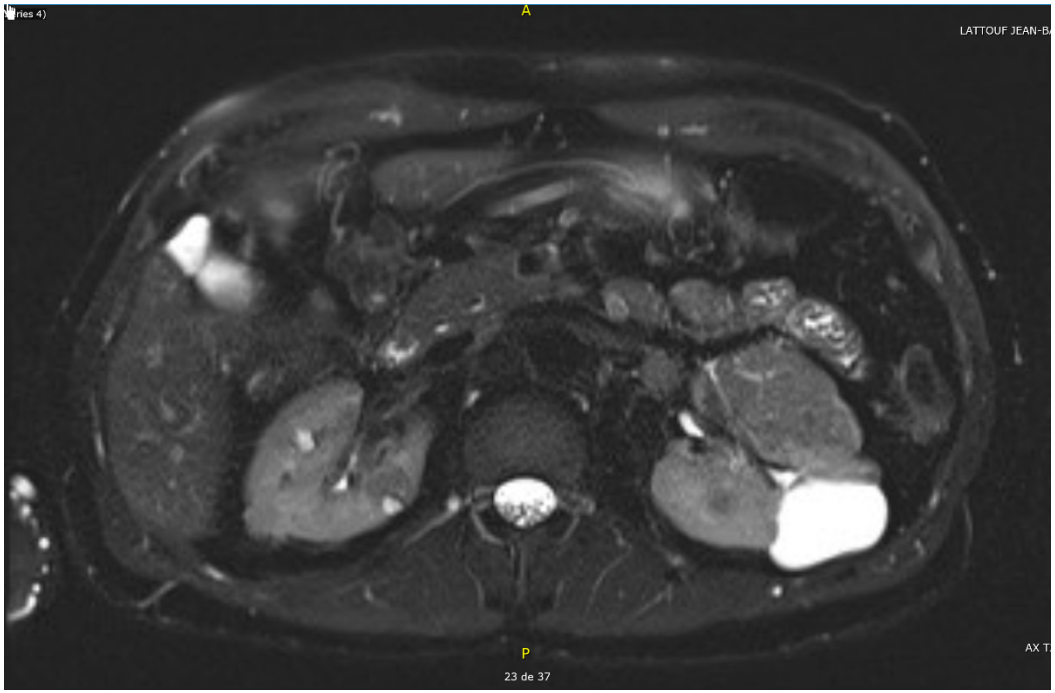
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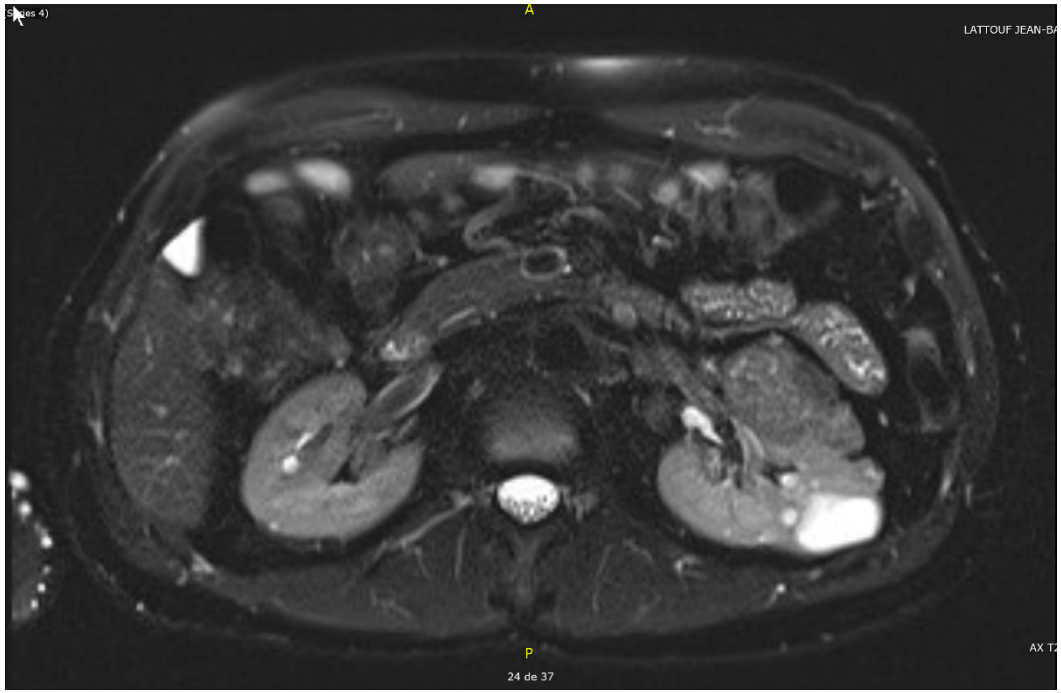
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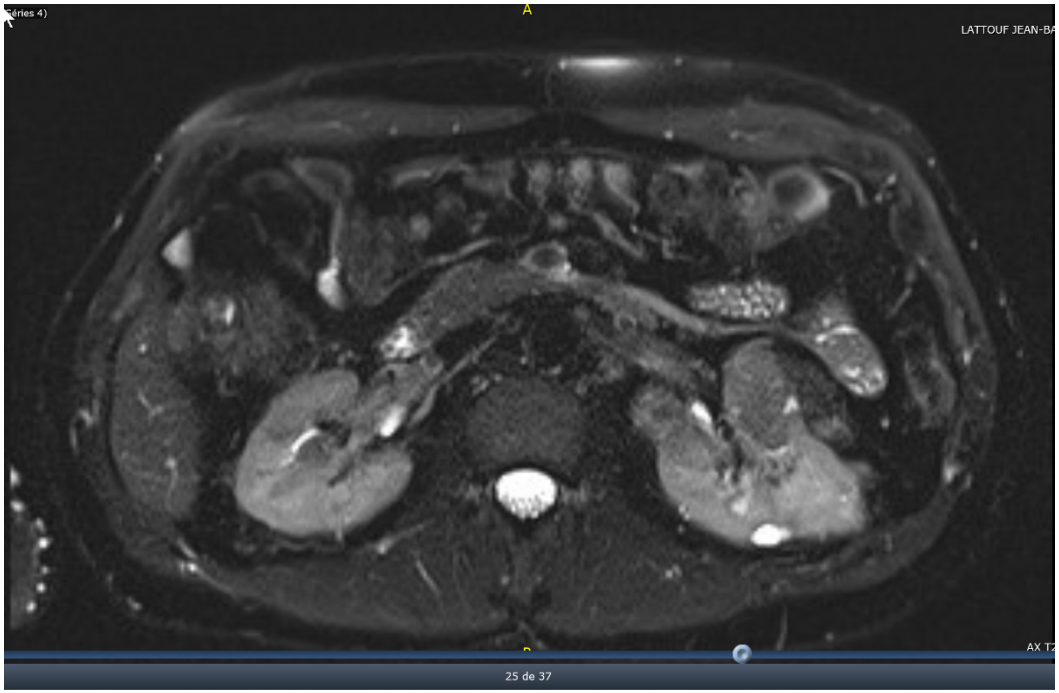
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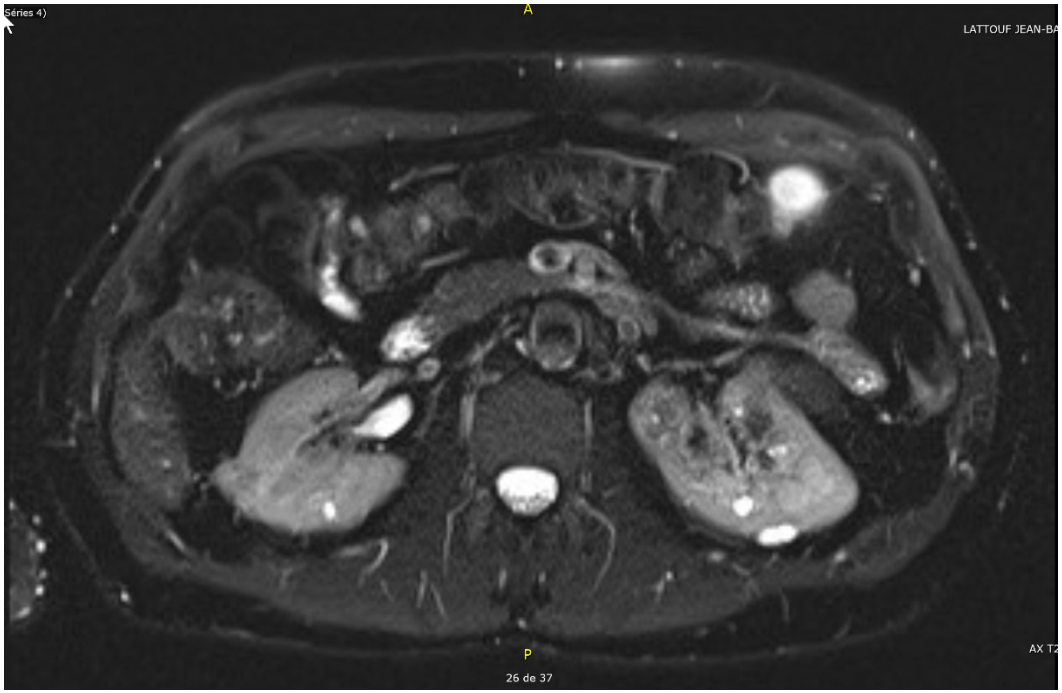

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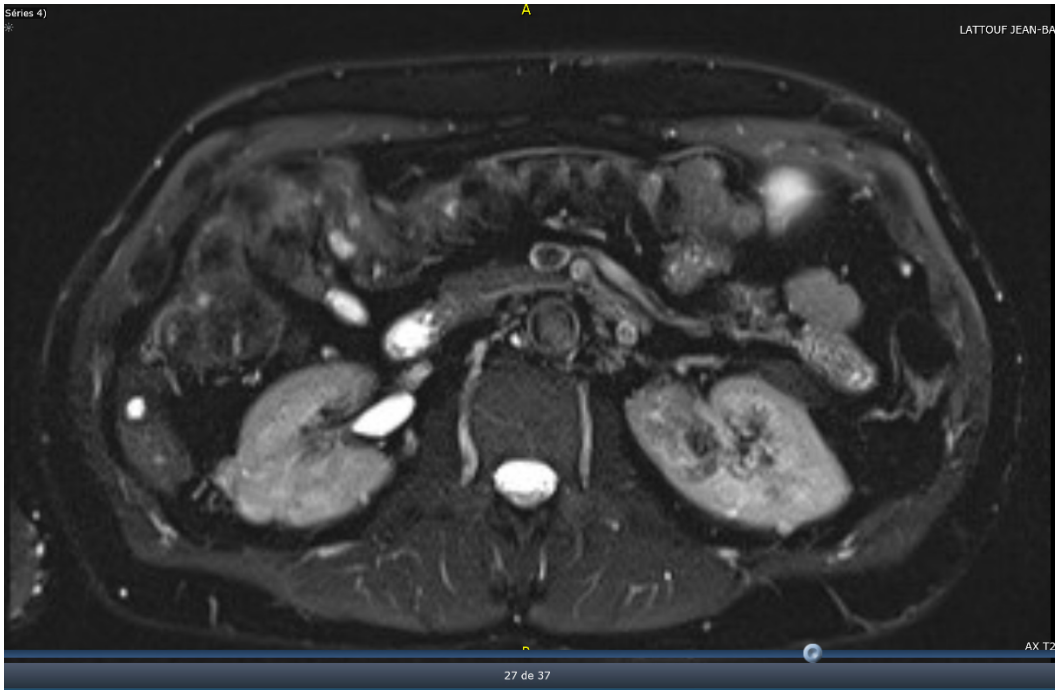

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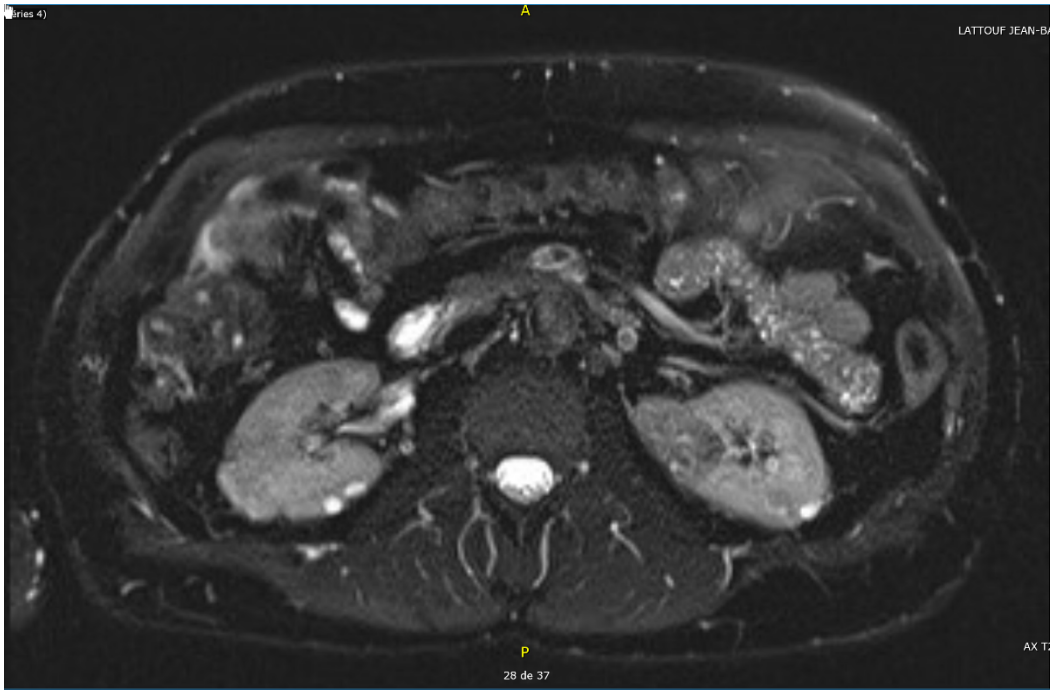
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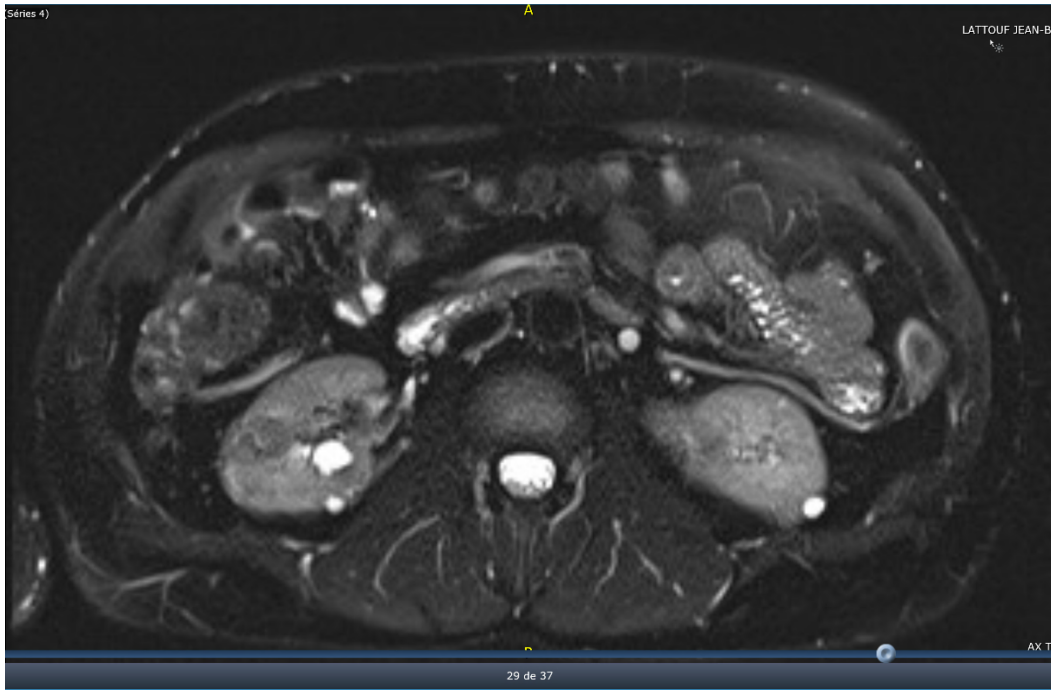

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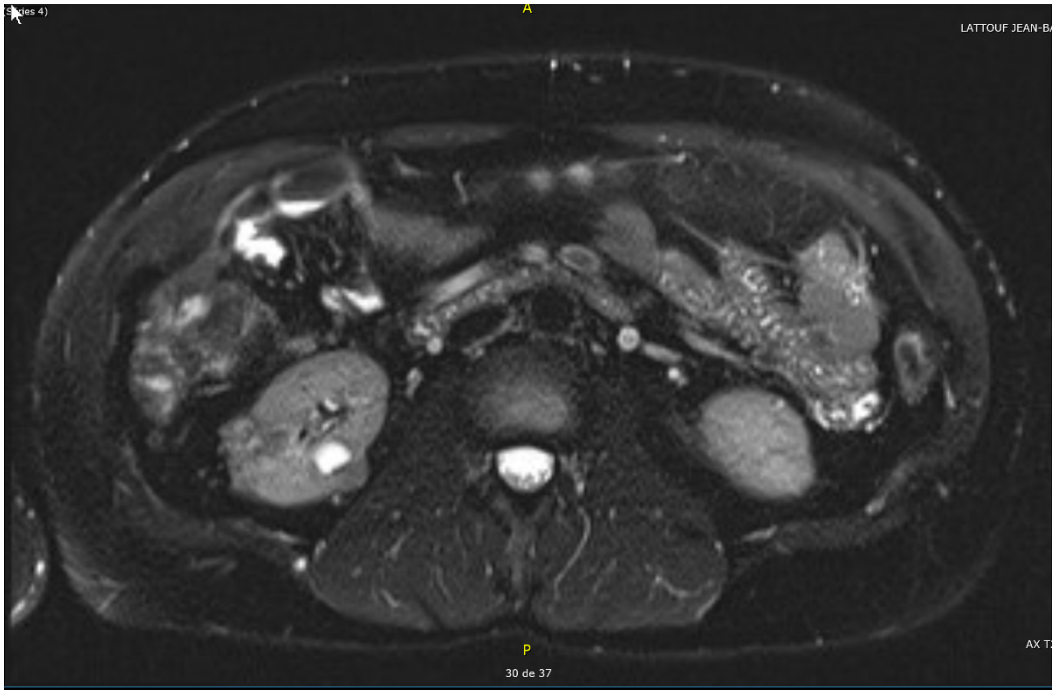
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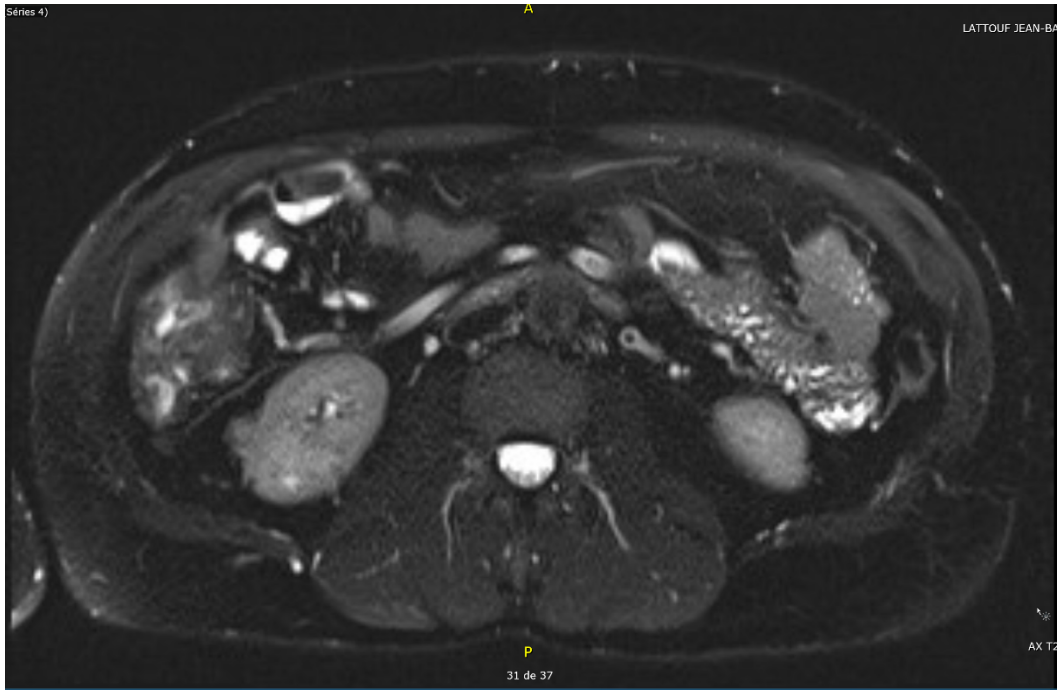

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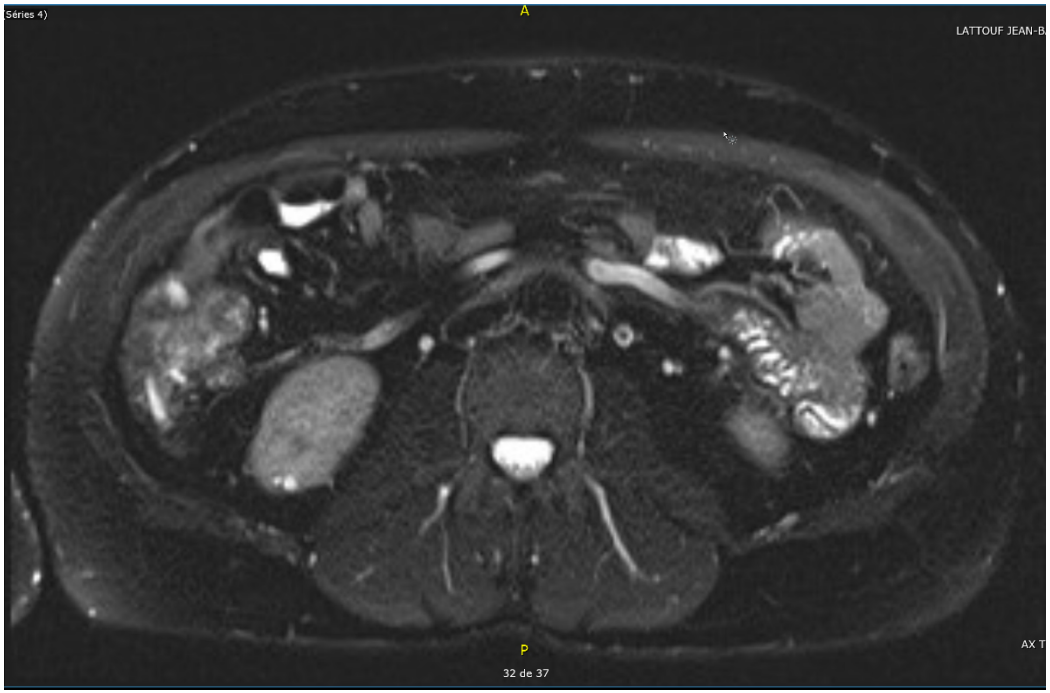

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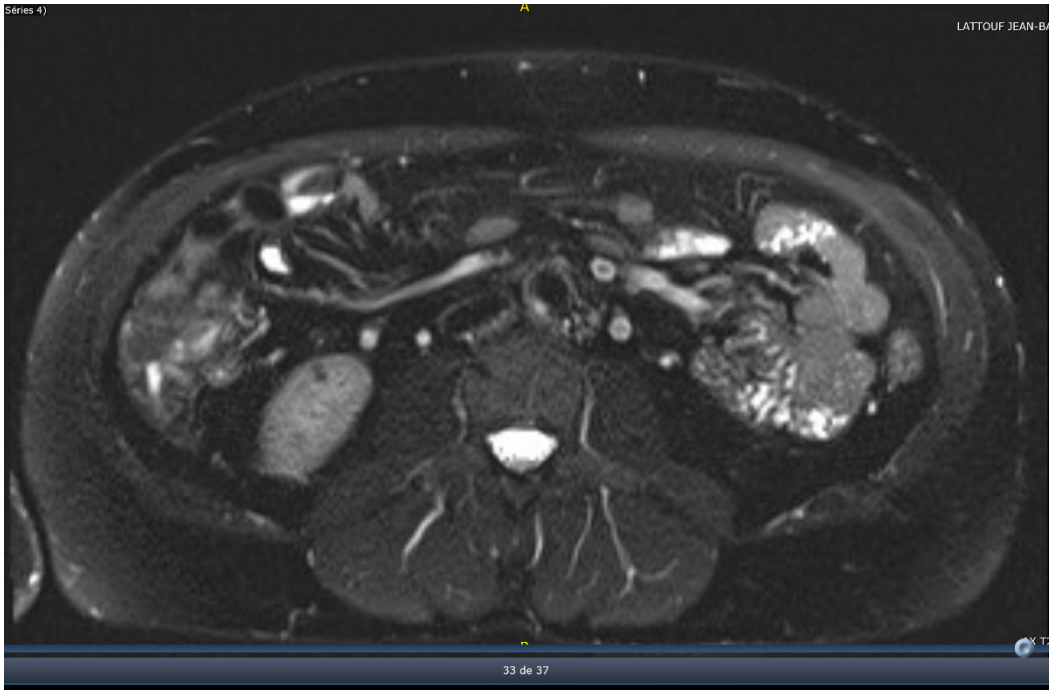

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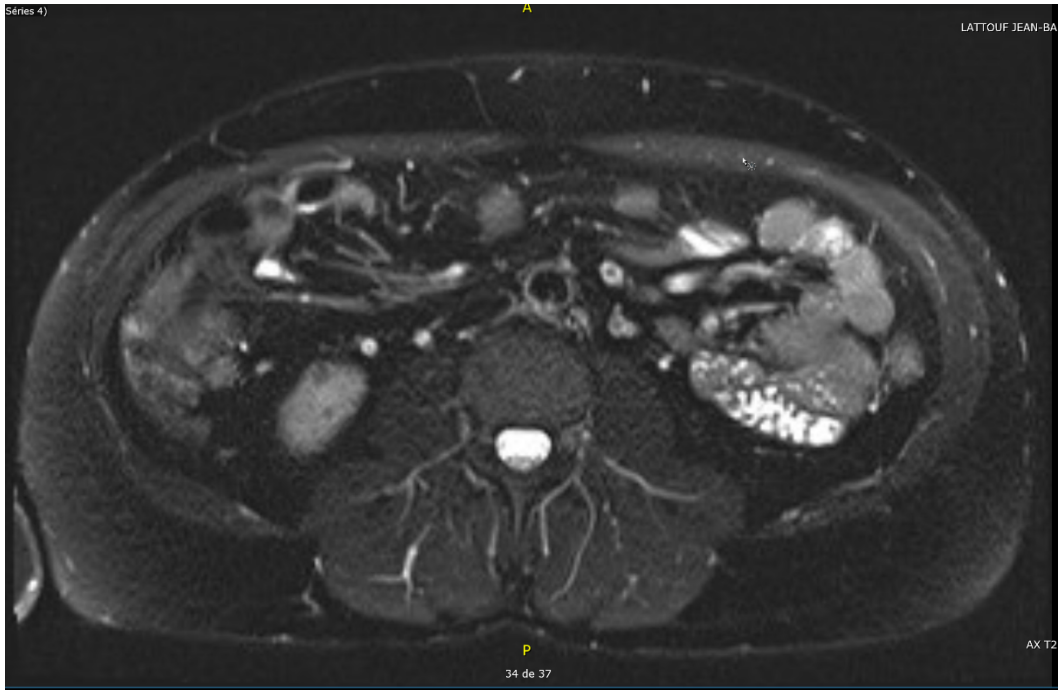

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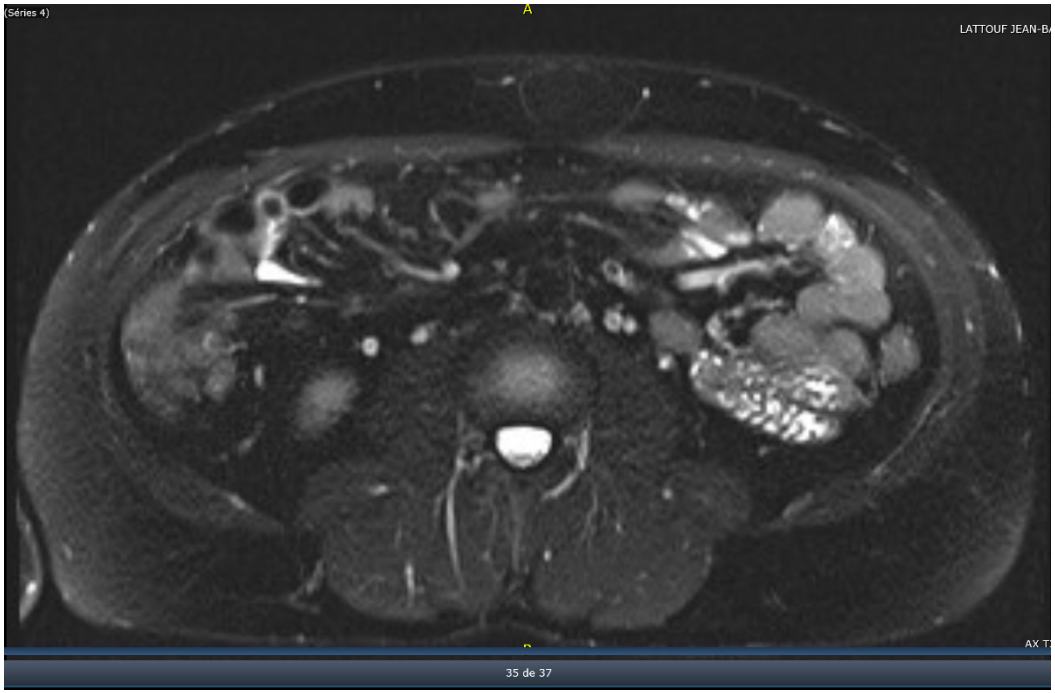

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Diagnosis of indeterminate lesion

- Biopsy of left anterior hilar lesion was performed laparoscopically
- Diagnosis: AML with dominant muscle component
- Follow thereafter took place yearly with MRI abdomen
  - Stability of all lesions for 4 consecutive years
- Followup was reduced to every other year in 2012
- Incidentally, genetic testing at our center was NEGATIVE for a TSC1 or TSC2 mutation

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Slow increase of largest AML over time

- 2012 5,6cm
- 2014 6,1cm
- 2016 6,5cm

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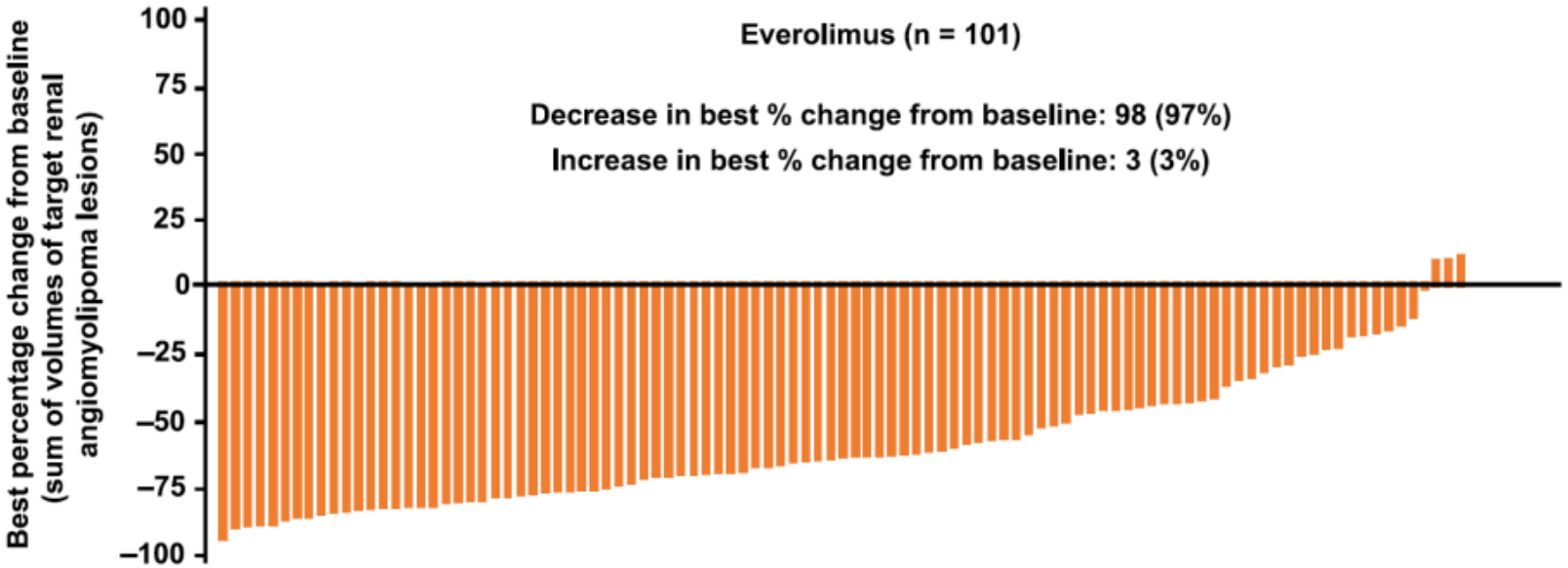

Fig 2. Best percentage reduction in the sum volume of target renal angiomyolipomas each individual patient reported at any time point in the study in 101 evaluable patients.[a] [a]11 patients were considered "non-evaluable" due to missing overall angiomyolipoma response status at each radiological assessment. Among the 12 patients with a best overall response with the status "not evaluable", only one patient reported at least one radiological assessment with a non-missing overall angiomyolipoma response status.

https://doi.org/10.1371/journal.pone.0180939.g002

Bissler JJ. 2017. PLOS

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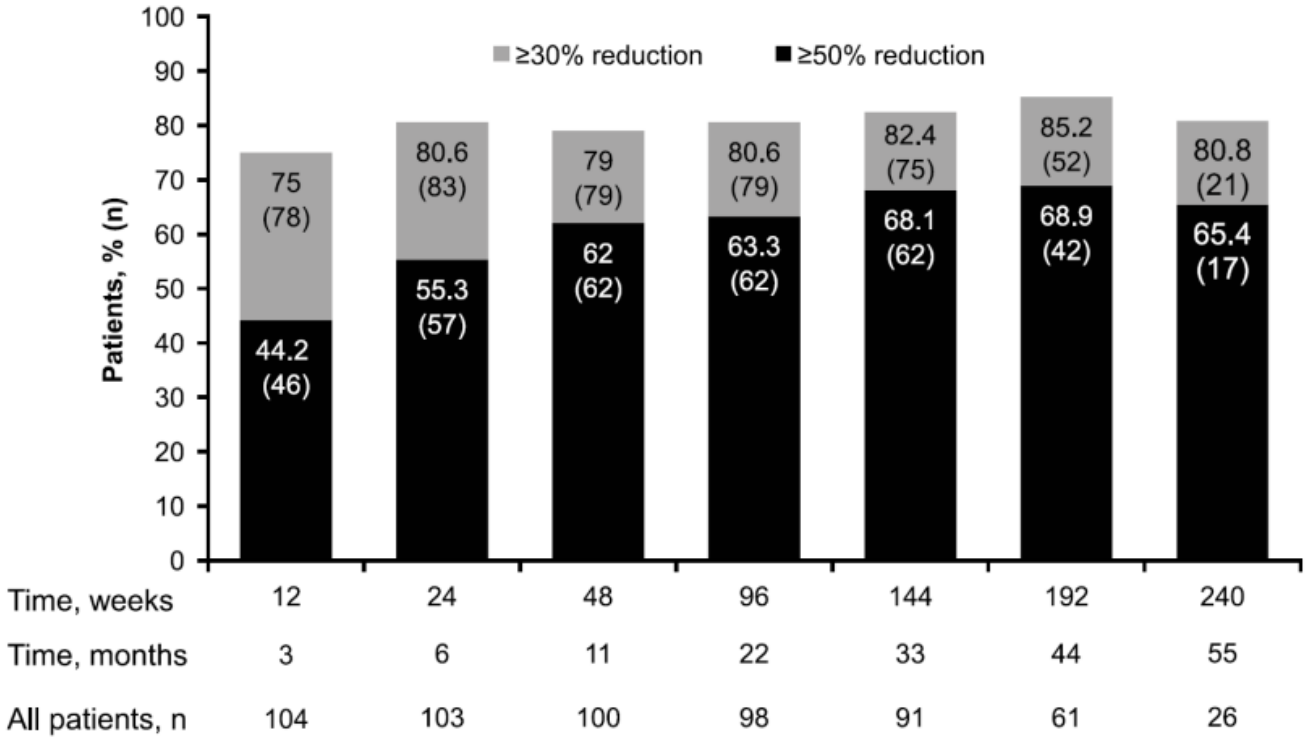

Fig 3. Renal angiomyolipoma response rate with everolimus over time.

https://doi.org/10.1371/journal.pone.0180939.g003

Bissler JJ. 2017. PLOS

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Consensus statement

Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference

Darcy A. Krueger MD PhD [a,*], Hope Northrup MD [b], on behalf of the International Tuberous Sclerosis Complex Consensus Group

[a] *Division of Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio*
[b] *Division of Medical Genetics, Department of Pediatrics, University of Texas Medical School at Houston, Houston, Texas*

Kidney

- Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1-3 yr throughout the lifetime of the patient.
- Assess renal function (including determination of glomerular filtration rate [GFR]) and blood pressure at least annually.
- Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy is to be avoided. For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first-line therapy. Selective embolization or kidney-sparing resection are acceptable second-line therapy for asymptomatic angiomyolipoma.

Pediatric Neurology 49 (2013) 255–265

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Indication for MTOR therapy

- Started everolimus at 10mg daily on may 2017
- Patient developed pulmonary symptoms of cough that interfered with daily activities.
- Labs remained normal (CBC; TSH; Lipid profile; UA)
- Dose needed to be reduced to 5mg daily on june 2017

FUP on everolimus

- Proteinuria appeared in urine on july 2017
- Imaging on July 2017:
  - Reduction in almost all AML from 5 mm to 10 mm each
- Everolimus discontinued

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Table 3. Adverse events by preferred term regardless of relationship to study drug and by year of emergence (>15% of patients).

Adverse events, n (%)	≤12 months N = 112	13–24 months n = 101	25–36 months n = 100	37–48 months n = 91	49–60 months n = 52
Stomatitis	46 (41.1)	9 (8.9)	5 (5.0)	5 (5.5)	2 (3.8)
Nasopharyngitis	36 (32.1)	21 (20.8)	20 (20.0)	20 (22.0)	6 (11.5)
Acne	28 (25.0)	8 (7.9)	6 (6.0)	2 (2.2)	0
Headache	26 (23.2)	11 (10.9)	6 (6.0)	4 (4.4)	1 (1.9)
Hypercholesterolemia	25 (22.3)	13 (12.9)	11 (11.0)	7 (7.7)	1 (1.9)
Aphthous stomatitis	21 (18.8)	15 (14.9)	9 (9.0)	5 (5.5)	2 (3.8)
Fatigue	19 (17.0)	2 (2.0)	4 (4.0)	4 (4.4)	2 (3.8)
Cough	18 (16.1)	4 (4.0)	4 (4.0)	3 (3.3)	0
Diarrhoea	17 (15.2)	7 (6.9)	7 (7.0)	4 (4.4)	1 (1.9)
Mouth ulceration	17 (15.2)	6 (5.9)	5 (5.0)	2 (2.2)	0
Nausea	17 (15.2)	5 (5.0)	2 (2.0)	3 (3.3)	0

https://doi.org/10.1371/journal.pone.0180939.t003

Bissler JJ. 2017. PLOS

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