Angiomyolipomas:
Current evidence and its effect on management

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OBJECTIVES

• Epidemiology & Etiology
• Presentation
• Diagnosis
• Natural history
• Intervention options
• Intervention indications
Introduction

- Angiomyolipomas have 2 main clinical subtypes:
  - Sporadic
  - Tuberous Sclerosis Complex and/or Lymphangioleiomyomatosis

Prevalence of sporadic renal angiomyolipoma: a retrospective analysis of 61,389 in- and out-patients

- 49.7% women and 50.3% men consecutively scanned between Sep 1999 to Dec 2012
- Incidental finding
- Sporadic AML prevalence 0.44%
- 3:1 ratio F:M
Hormone receptor expression in renal angiomyolipoma: clinicopathologic correlation

- Retrospective
- 1970-2004 Mayo Clinic Nephrectomy registry
- 110 patients
- 90F, 20M
- 56% symptomatic

<table>
<thead>
<tr>
<th>Table, Patient demographics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>90(81.8)</td>
</tr>
<tr>
<td>Male</td>
<td>20(18.2)</td>
</tr>
<tr>
<td>Symptoms at presentation</td>
<td></td>
</tr>
<tr>
<td>Painless flank/abdominal mass</td>
<td>3(2.7)</td>
</tr>
<tr>
<td>Discomfort</td>
<td>48(43.6)</td>
</tr>
<tr>
<td>Ipsilateral/contralateral side</td>
<td>15(13.6)</td>
</tr>
<tr>
<td>Rash, sweats, weight loss, fatigue, early safety</td>
<td></td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>8(7.3)</td>
</tr>
<tr>
<td>Any symptoms at presentation Ipsilateral AMLs (n)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>97(88.2)</td>
</tr>
<tr>
<td>2</td>
<td>8(7.3)</td>
</tr>
<tr>
<td>3</td>
<td>2(1.8)</td>
</tr>
<tr>
<td>4</td>
<td>1(0.9)</td>
</tr>
<tr>
<td>5</td>
<td>1(0.9)</td>
</tr>
<tr>
<td>6</td>
<td>8(7.3)</td>
</tr>
<tr>
<td>Bilateral AMLs Histologic subtype of AML</td>
<td></td>
</tr>
<tr>
<td>Triphasic</td>
<td>77(70)</td>
</tr>
<tr>
<td>Lipomatous</td>
<td>20(18.2)</td>
</tr>
<tr>
<td>Leiomymomatous</td>
<td>7(6.4)</td>
</tr>
<tr>
<td>Epithelioid</td>
<td>4(3.6)</td>
</tr>
<tr>
<td>Typical</td>
<td>2(1.8)</td>
</tr>
</tbody>
</table>

TSC AML

- Tuberous Sclerotic Complex
  - Affects 1,600-10,000 births
- Mutations in TSC1 – hamartin - and TSC2 genes – tuberin
- Autosomal dominant
- Classic Dx includes triad of facial angiofibromas, intellectual disability, and epilepsy
TSC AML

Clinical correlates of renal angiomyolipoma subtypes in 209 patients: classic, fat poor, tuberous sclerosis associated and epithelioid
Presentation

• Clinical Manifestations
  – Flank pain
  – Palpable mass
  – Hematuria
  – Hemorrhage/Aneurysmal vessel rupture
  – Retroperitoneal hemorrhage (Wunderlich syndr)

The radiological diagnosis and treatment of renal angiomyolipoma—current status

• Ultrasound
  – Appearance overlaps with RCC in up to ~12%
    • 21-33% in RCC <3cm
  – strongly hyper-reflective lesion with acoustic shadowing

• Computed tomography
  – 4-5% unable to detect intra-tumoral fat
    • Up to 33% in TSC
  – hyper-attenuating, homogeneously enhanced masses with prolonged enhancement

• MRI
  – Chemical shift MRI T1-weighted and T2-weighted
  – India ink artifacts
  – Similar sensitivity to CT, with improved specificity

Role of MRI in indeterminate renal mass: diagnostic accuracy and impact on clinical decision making


Treatment

- Active surveillance
- Medical management
- Nephron sparing
  - Partial nephrectomy
  - Embolization
  - RFA
  - Cryo
- Radical nephrectomy

Table 1. Patient and tumor characteristics according to CT diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>120</td>
<td>78 (65.0)</td>
<td>25 (20.0)</td>
<td>17 (14.2)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>66 (26-85)</td>
<td>55 (28-85)</td>
<td>52 (29-74)</td>
<td>53 (28-85)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>76 (60.0)</td>
<td>55 (68.0)</td>
<td>12 (48.0)</td>
<td>11 (66.4)</td>
</tr>
<tr>
<td>Male</td>
<td>44 (40.0)</td>
<td>21 (32.0)</td>
<td>13 (52.0)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Female</td>
<td>16.4 ± 10.9</td>
<td>18.5 ± 9.9</td>
<td>18.2 ± 13.8</td>
<td>14.0 ± 10.3</td>
</tr>
<tr>
<td>Mean tumor size (range), cm</td>
<td>1.4 (0.5-8.5)</td>
<td>1.4 (0.5-8.5)</td>
<td>1.8 (0.5-4.6)</td>
<td>1.5 (0.5-4.6)</td>
</tr>
<tr>
<td>Size category (%)</td>
<td>&lt;2</td>
<td>40 (55.1)</td>
<td>14 (56.0)</td>
<td>11 (66.4)</td>
</tr>
<tr>
<td>2 to &lt;3</td>
<td>22 (18.5)</td>
<td>15 (19.2)</td>
<td>4 (16.0)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td>17 (14.2)</td>
<td>13 (16.7)</td>
<td>4 (16.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>4 or greater</td>
<td>13 (10.8)</td>
<td>7 (9.0)</td>
<td>3 (12.0)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>p value</td>
</tr>
<tr>
<td>Type of tumor (%)</td>
<td>Solid</td>
<td>105 (87.5)</td>
<td>70 (99.7)</td>
<td>23 (92.0)</td>
</tr>
<tr>
<td>Cystic</td>
<td>15 (12.5)</td>
<td>8 (10.3)</td>
<td>2 (8.0)</td>
<td>5 (21.6)</td>
</tr>
<tr>
<td>Pathological diagnosis (%)</td>
<td>Yes</td>
<td>89 (74.2)</td>
<td>62 (79.4)</td>
<td>21 (84.4)</td>
</tr>
<tr>
<td>No</td>
<td>31 (25.8)</td>
<td>16 (20.6)</td>
<td>4 (16.0)</td>
<td>11 (66.4)</td>
</tr>
<tr>
<td>Total diagnosis (%)</td>
<td>RCC</td>
<td>73 (60.6)</td>
<td>57 (73.3)</td>
<td>12 (48.0)</td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>32 (26.7)</td>
<td>14 (18.0)</td>
<td>9 (36.0)</td>
<td>5 (23.3)</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>5 (4.2)</td>
<td>3 (3.8)</td>
<td>2 (8.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Complicated cyst</td>
<td>10 (8.3)</td>
<td>4 (5.3)</td>
<td>2 (8.0)</td>
<td>4 (23.5)</td>
</tr>
</tbody>
</table>
Active Surveillance for renal angiomyolipoma: outcomes and factors predictive of delayed intervention

- Retrospective
- Glickman Urological and Kidney Institute, and Imaging Institute, Cleveland Clinic
- 400 patients
- Database search including patients with the final diagnosis of renal mass
- AML identified by fat content on CT scan
- 270 treated, 130 active surveillance (10 TSC)
- 17 required delayed treatment
- Follow-up physical exam and imaging at 6mo, 12mo and then annually

Active Surveillance for renal angiomyolipoma: outcomes and factors predictive of delayed intervention

Trends of presentation and clinical outcome of treated renal angiomyolipoma

- Retrospective between Mar ‘98 & Oct ‘08
- Yonsei University College of Medicine, Seoul
- AML identified by CT scan fat component or pathology after surgery
- 254 patients
- 129 treated
Trends of presentation and clinical outcome of treated renal angiomyolipoma

### Table 2. Differences of Patient Characteristics between Sporadic and Tuberous Sclerosis (TS)-Associated AML

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sporadic AML (n = 117)</th>
<th>TS-associated AML (n = 12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>52.6 ± 12.1</td>
<td>30.1 ± 12.1</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>No. of female (%)</td>
<td>92 (78.6)</td>
<td>8 (66.7)</td>
<td>0.273</td>
</tr>
<tr>
<td>Mean tumor size (cm)</td>
<td>3.7 ± 2.5</td>
<td>7.6 ± 4.3</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Size range (cm)</td>
<td>0.8 - 11.7</td>
<td>1.1 - 16</td>
<td></td>
</tr>
<tr>
<td>Symptomatic at presentation (%)</td>
<td>21 (17.9)</td>
<td>11 (91.7)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Multiple (%)</td>
<td>8 (6.8)</td>
<td>9 (75.0)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Bilateral (%)</td>
<td>3 (2.6)</td>
<td>8 (66.7)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Radiologic appearance (%)</td>
<td></td>
<td></td>
<td>0.238</td>
</tr>
<tr>
<td>Classic AML</td>
<td>78 (66.7)</td>
<td>10 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Fat poor AML</td>
<td>39 (33.3)</td>
<td>2 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Surgical intervention (%)</td>
<td>96 (82.1)</td>
<td>7 (58.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Nephron sparing surgery (%)</td>
<td>67 (69.7)</td>
<td>1 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Radical nephrectomy (%)</td>
<td>29 (30.3)</td>
<td>6 (85.8)</td>
<td></td>
</tr>
<tr>
<td>Embolization (%)</td>
<td>21 (17.9)</td>
<td>5 (41.7)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Lymph node involvement (%)</td>
<td>5 (4.3)</td>
<td>4 (33.3)</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

### Table 3. Differences of Patient Characteristics According to Tumor Size

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt; 4 cm</th>
<th>≥ 4 cm</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>82</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Age at presentation (yrs)</td>
<td>52.4 ± 12.7</td>
<td>47.1 ± 14.8</td>
<td>0.034*</td>
</tr>
<tr>
<td>Mean tumor size (cm)</td>
<td>2.2 ± 0.8</td>
<td>7.3 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Size range (cm)</td>
<td>0.8 - 3.7</td>
<td>4 - 16</td>
<td></td>
</tr>
<tr>
<td>Symptomatic at presentation (%)</td>
<td>12 (14.6)</td>
<td>20 (42.5)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Tuberous sclerosis complex (%)</td>
<td>3 (3.6)</td>
<td>9 (19.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Surgical intervention (%)</td>
<td>66 (80.0)</td>
<td>32 (68.0)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Nephron sparing surgery (%)</td>
<td>61 (92.4)</td>
<td>6 (18.8)</td>
<td></td>
</tr>
<tr>
<td>Radical nephrectomy (%)</td>
<td>5 (7.6)</td>
<td>26 (81.2)</td>
<td></td>
</tr>
<tr>
<td>Embolization (%)</td>
<td>16 (19.5)</td>
<td>15 (31.9)</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>
Natural history of renal angiomyolipoma (AML):
most patients with large AMLs >4cm can be
offered active surveillance as an initial
management strategy

- Retrospective
- Princess Margaret cancer centre from 2002-2013
- Patients undergoing abdominal imaging for any reason
- AMLs identified by report indicating fat in lesion
- 2741 patients identified, 447 patients with 582 tumors followed for median 43
months
- 2294 had fewer than 3 images, only 13 had intervention (0.56%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>No intervention, n (%)</th>
<th>Intervention, n (%)</th>
<th>Total, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, yr</td>
<td>Median</td>
<td>58.1 (range)</td>
<td>69 (20-66)</td>
<td>58.1 (18.5-90.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>336 (79.0)</td>
<td>22 (88)</td>
<td>358 (85.1)</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>400 (95.5)</td>
<td>5 (24)</td>
<td>405 (96.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>TSC status</td>
<td>Known</td>
<td>411 (97.5)</td>
<td>10 (76)</td>
<td>421 (94.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>11 (2.7)</td>
<td>5 (24)</td>
<td>17 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Incidental</td>
<td>394 (91)</td>
<td>12 (48)</td>
<td>406 (90.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td>20 (7)</td>
<td>13 (52)</td>
<td>43 (93)</td>
<td></td>
</tr>
<tr>
<td>Initial size</td>
<td>&lt;4 cm</td>
<td>393 (91.1)</td>
<td>7 (28)</td>
<td>400 (95.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>&gt;4 cm</td>
<td>30 (6.8)</td>
<td>13 (77)</td>
<td>43 (93)</td>
<td></td>
</tr>
<tr>
<td>Growth rate</td>
<td>&gt;0.25 cm/yr</td>
<td>388 (92)</td>
<td>17 (77)</td>
<td>406 (91.8)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>&gt;0.35 cm/yr</td>
<td>33 (8)</td>
<td>5 (21)</td>
<td>38 (8.2)</td>
<td></td>
</tr>
</tbody>
</table>

TSC = tuberous sclerosis complex.

[Table 4 - Demographic comparison of 422 patients who did not have intervention with 25 patients who had an intervention]

Renal angiomyolipoma: relationships between tumor size, aneurysm formation and rupture

- Retrospective series of 23 patients
- Aug 1990 – May 2001
- Examined with CT and angiography

Microaneurysms in renal angiomyolipomas: can clinical and computed tomography features predict their presence and size?

- Retrospective
- Two French hospitals’ records
- Patients undergoing RAE between Jan 2005 and Feb 2015
- Preoperative CT imaging
- 31 patients
  - Total of 54 AMLs
  - 15 TSC and/or LAM
  - 5 patients referred for urgent RAE due to hemorrhage (2 TSC/LAM)
Treatment

- mTOR inhibitors
- Ablation
  - RFA
  - Cryo
  - Microwave
- Embolization
- NSS
- Radical

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

- 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
- Assigned in a 2:1 fashion to receive either everolimus or placebo
Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial

- Angiomyolipoma response rates by subgroup
- The difference in response rates is everolimus minus placebo
- Best percentage change from baseline in the sum of volumes of target angiomyolipoma lesions

Each bar represents one patient

<table>
<thead>
<tr>
<th>Difference in response rate (95% CI)</th>
<th>Everolimus response rate (95% CI)</th>
<th>Placebo response rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=133)</td>
<td>45 (34-58)</td>
<td>45 (37-54)</td>
</tr>
<tr>
<td>Male (n=77)</td>
<td>41 (30-54)</td>
<td>43 (34-54)</td>
</tr>
<tr>
<td>Female (n=56)</td>
<td>45 (33-58)</td>
<td>45 (37-54)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 years (n=25)</td>
<td>45 (38-58)</td>
<td>45 (37-54)</td>
</tr>
<tr>
<td>≥10 years (n=8)</td>
<td>46 (38-53)</td>
<td>44 (34-54)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (n=99)</td>
<td>45 (34-58)</td>
<td>44 (34-54)</td>
</tr>
<tr>
<td>Non-white (n=34)</td>
<td>46 (38-53)</td>
<td>45 (34-54)</td>
</tr>
</tbody>
</table>

Sirolimus Therapy for Angiomyolipoma in Tuberous Sclerosis and Sporadic Lymphangioleiomyomatosis: A Phase 2 Trial

- Prospective multicentre
- Phase 2 study
- Conducted in UK and Switzerland
- Patient age 18-65 years of age
- 1 AML 2cm or more in diameter
- 2 years of sirolimus treatment
- At baseline, angiomyolipomas were visualized by abdominal MRI without contrast media and measured
Sirolimus Therapy for Angiomyolipoma in Tuberous Sclerosis and Sporadic Lymphangioleiomyomatosis: A Phase 2 Trial

- Of 23 angiomyolipomas evaluated at 24 months, 21 were smaller and 2 were unchanged
- Overall response rate by RECIST criteria was 50% (8 of 16) and in the per protocol group it was 80% (8 of 10)
- At 24 months, a partial response was present in 4 of 10 patients (40%) remaining in the trial


Interventional Radiology

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Embolization of AML

• Treatment of choice with acute bleeding
• Rationale: Decrease vascularity, secondary ischemic effects on parenchyma
• No size limitation, anatomy generally doesn’t matter
• Doesn’t interfere with other treatments
• Minimally invasive, wide expertise

Embolization (cont.)

• Meta-analysis n=31 studies, 524 patients
• Post embo syndrome 36%, other complications 7%. No deaths
• Unplanned re-embo or surgery 21% (revascularization, bleeding, symptoms)

Murray TE, et al. J Urol 2015;194

Courtesy Dr Fred Lee
C7 - KUB

If the patient does not speak English, an interpreter MUST accompany the patient.

PERTINENT HISTORY / MEDICATIONS:

- UGI steadies d-lactic flux gran.
- urine 200 RBC/mL
- likely metastasis
- stage of location?
Ablation for AML: Rationale

- Stakes are different than for RCC
- Destroy blood vessels to decrease bleed risk
- Destroy parenchyma, no potential for revascularization (but getting every cell not critical)
- Percutaneous-avoid surgery, etc.
- Not for all patients: tumor location, size
- Cryoablation, RF, and MW have all been tried with success

Courtesy Dr Fred Lee
Ablation for AML

- Studies are small, all positive
  - Cryoablation n=3 (perc) n=7 (lap)
  - RF ablation n=15 (perc + lap)
    - Castle, et al. BJUI 2011;109
  - MW ablation n=14 (perc)

Ablation technologies

- Not enough data to declare one superior to others
- All effected by intratumoral fat (insulator): need to treat harder than for RCC
- We use MW due to deep penetration into tissue, hotter temps
MW of AML, UW Results

- N=11, mean diameter 3.4 cm, 15.5 mo f/u
- Two patients failed embolization
- Hydrodissection used in all cases
- eGFR 95 (pre) to 87 (post), p=0.15
- No complications, no bleeds
- Volume: -44.3% decrease
- Enhancement (HU): 44.1 (pre) vs. 14.6 (post)

Cristescu M, et al. CVIR 2015;epub

Technique: CT+US monitoring

Courtesy Dr Fred Lee
Devascularization by MW

Volume change: -61%
Enhancement (pre)=74 HU vs. 6.2 (post)

Technique: Target feeding vessel

Feeding vessel

Courtesy Dr Fred Lee
Treated vs. untreated AML

Diameter: 4.9 vs. 2.4 cm
Volume: -90%

Diameter: 4.3 vs. 5.2 cm
Volume: +21%

Courtesy Dr Fred Lee

Nephron Sparing Surgery Associated With Better Survival Than Radical Nephrectomy in Patients Treated for Unforeseen Benign Renal Tumors

- Retrospective cohort
- Jan 1, '05 – Dec 31, '12
- 506 consecutive patients
  - 256 men and 250 women
  - 58% Oncocytoma, 24% AML, 11% Cystic and 8% diverse benign path
Nephron Sparing Surgery Associated With Better Survival Than Radical Nephrectomy in Patients Treated for Unforeseen Benign Renal Tumors


Treatment of angiomyolipoma at a tertiary care centre: the decision between surgery and angioembolization

Indications for Treatment

- Wunderlich syndrome
- Hemorrhage/Aneurysm rupture
- Aneurysm size
- Suspicion of malignancy
- Symptomatic
- Size
- Multiplicity
- Epitheloid variant
- Young female of reproductive age*

Conclusion

- AML are uncommon, though not rare
- Can present as diagnostic dilemmas, as imaging imperfect for differentiating AML from RCC
- Our understanding of the Natural history is still evolving but appearing relatively benign course in absence of RF for rupture
- Treatment is advancing
  - Further studies required for differentiating role for each modality
- Guidelines required
  - With focus on when to surveil, when treatment is required and with which modality
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